BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

bjhbs.hupe.uerj.br

Vol. 19, número 2, julho-dezembro/2020

Editorial

81 Mario Bernardo-Filho

Artigos originais/Original articles/Artículos originales

83 **Vitamin D levels and risk of COVID-19 infection: A systematic review**
Ana C. Coelho-Oliveira, Bruno B. Monteiro-Oliveira, Rebeca B. M. Cavalcante, Daniel B. Santos, Anelise Sonza, Danúbia C. de Sá-Caputo, Mario Bernardo-Filho

91 **N-acetylcysteine+nimesulide: An association strategy aiming to prevent nimesulide-induced hepatotoxicity**
Amanda G. Elias, Julia S. da Silva, Rafaela L. Klein, Francieli U. I. Amaral, Marcelo D. Arbo, Fernanda M. Conte, Solange C. Garcia, Eliane Dallegrave, Janaine R. Martins, Charise D. Bertol, Diorges H. Setim, Adriana C. da Motta, Romulo P. Barcelos, Luciana G. R. Grando

100 **The effect of long-term whole-body vibration on muscular performance**
Yossef Haleva, Ayelet Dunsky, Yoav Meckel, Heinz Kleinöder, Michael Bar-Eli, Joachim Mester

108 **Evaluation of residues of pesticides on humans from medium plant of Rio Grande do Sul, Brazil**
Vitória A. Rosano, Gabriela E. Dal Pizzol, Maria T. Friedrich, Charise D. Bertol, Luciana G. R.-Grando

Revisão/Review Article/Artículo de revisión

114 **Keep your droplets to yourself: Universal use of face masks along with social**
Helena Carvalho, Daniel Contaifer Jr., Renata N. Aranha, Juliana A. de Matos

124 **Pulmonary and central nervous system infiltration of chronic lymphocytic leukemia with concomitant diffuse large B-cell lymphoma: Case report and review of literature**
Saulo F. D. Batista, Karina V. de Melo, Patricia Horn, Vinicius da C. Lisboa, Ana Sheila Cypriano, Andrea Pires, Marilza de M. Ribeiro-Carvalho, Fábio Santiago, Maria Helena F. O. de Souza

130 **Legal and biological safety of legal reprocessing of medical-hospital materials**
Paula Z. P. F. Pinto, Nelson Massini

142 **Benefícios motores da Realidade Virtual na Encefalopatia Crônica da Infância: uma revisão narrativa**
Rebeca C. L. de Oliveira, Priscila S. Cardoso, Ingridi M. B. Almeida, Francisco J. S. da Silva, Leissa da S. Melo-Figueiredo, Bruno B. M. de Oliveira, Danúbia da C. de Sá-Caputo, Laisa L. Paineiras-Domingos

Caso clínico/Clinical Case/Caso clínico

151 **Basilar dolichoectasia with otorhinolaryngological symptoms: A case report**
Tuani A. Stroke, Ana Cristina C. Martins, Lucas A. L. T. Silva, Henrique José C. Artigoza, Annelise O. A. B. Figueira, Fernando José M. Mendes, Rafael Hollanda

BRAZILIAN JOURNAL BJHBS OF HEALTH AND BIOMEDICAL SCIENCES

Vol. 19, número 2, julho-dezembro/2020

Rio de Janeiro

Correspondência/*Mail*

Comissão Científica Pedro Ernesto (COCIPE)
Endereço: *Boulevard* 28 de Setembro, 77
Rio de Janeiro – RJ. CEP: 20551-030.

Telefone/*Telephone*

(55 21) 2868 8586 | 2868 8108

Internet

bjhbs.hupe.uerj.br
E-mail: bjhbs.uerj@gmail.com

Assistente editorial, preparação, normalização:

Michelle Borges Rossi

Revisão:

Michelle Borges Rossi

Diagramação:

2ml design

CATALOGAÇÃO NA FONTE
UERJ/REDE SIRIUS/CBA

Brazilian Journal of Health and Biomedical Sciences. – V. 18, n. 2 (jul.-dez.2019) . – Rio de Janeiro: HUPE, 2002-
v. : il. (algumas color.)

Semestral 2019-.
Disponível em: bjhbs.hupe.uerj.br
Título anterior: Revista Hospital Universitário Pedro Ernesto.

1. Ciências médicas – Periódicos. 2. Saúde – Periódicos. I. Hospital Universitário Pedro Ernesto.

CDU 61

Bibliotecária: Thais Ferreira Vieira - CRB - 5302

Universidade do Estado do Rio de Janeiro

Ricardo Lodi Ribeiro
Reitor

Mario Sergio Alves Carneiro
Vice-Reitora

Tania Maria de Castro Carvalho Netto
Sub-Reitoria de Graduação – SR1

Egberto Gaspar de Moura
Sub-Reitoria de Pós-Graduação e Pesquisa – SR2

Elaine Ferreira Torres
Sub-Reitoria de Graduação e Cultura – SR3

Mário Sérgio Alves Carneiro
Diretor do Centro Biomédico

Centro Biomédico

Hospital Universitário Pedro Ernesto

Ronaldo Damião
Diretor

José Luiz Muniz Bandeira Duarte
Vice-Diretor

Faculdade de Ciências Médicas

Albanita Viana de Oliveira
Diretora

Marcos Junqueira do Lago
Vice-Diretor

Escola de Enfermagem

Norma Valéria Dantas de Oliveira Souza
Diretora

Eloa Carneiro Carvalho
Vice-Diretora

Instituto de Biologia Roberto Alcântara Gomes

Jorge José de Carvalho
Diretor

Norma Albarello
Vice-Diretora

Instituto de Nutrição

Inês Rugani Ribeiro de Castro
Diretora

Flávia Fioruci Bezerra
Vice-Diretora

Instituto de Medicina Social

Gulnar Azevedo e Silva
Diretora

Rossano Cabral Lima
Vice-Diretor

Faculdade de Odontologia

Ricardo Guimarães Fischer
Diretor

Brazilian Journal of Health and Biomedical Sciences
Corpo Editorial

Corpo Editorial Internacional

Assistente Editorial

Editorial

There is consistent and strong scientific evidence about the numerous health benefits related to the physical activity (PA). Regular PA can improve physical fitness and health and assist in the prevention of various diseases. In general, physically active adults are healthier and present higher physical performance in comparison with inactive adults worldwide. Among some desirable behaviors, PA can be considered as part of a healthy lifestyle and can be categorized into occupational, sports, conditioning, household, or other activities involving movement of the body generated by skeletal muscles with energy expenditure. Aligned with that, it is undeniable the relevance of the physical inactivity as a risk factor for premature mortality and for cardiovascular disease and a variety of other chronic diseases, including diabetes mellitus, cancer (colon and breast), obesity, hypertension, bone and joint diseases (osteoporosis and osteoarthritis), and depression. Moreover, exercise in patients with hematologic cancer, like leukemia, could improve immune function.

Due to the relevance of the PA, it is important to stimulate behaviors involving the physical practice. There are several factors that can influence these behaviors, such as: personal (biological, health and psychological attributes), social (family, affiliation group, and work factors), and environmental (contexts for different forms of PA and policy factors that could determine availability of relevant settings and opportunities).

The outbreak of the coronavirus disease 19 (COVID-19) has interfered in different factors of the PA behaviors. Depending of the severity of the COVID-19 in an individual, there are limitations to performed PA. Furthermore, aiming to contain the COVID-19 infections and to reduce interaction between infected and non-infected individuals, strategies and restrictive policies have been suggested, such as quarantine, local confinement, lockdown and isolation. It is clear that, while the individuals are confined at home the level of PA, in general, decreases, due to the reduction of (i) daily activities outside, (ii) the participation in social events and, (iii) sometimes, of laboral activities. This may have a negative impact in general heath because it can contribute to sedentary behaviors. Besides the confinement, it is important to consider other actions to protect against the COVID-19 infection that is the universal use of masks.

In addition to those facts, as an environmental factor, in confinement, the sunlight exposure is reduced. The relevance of the ultraviolet B radiation present in sunlight to the active production of vitamin D in the organisms is well known. This vitamin has a relevant role to metabolic responses and protection against diseases, including cancer. Vitamin D deficiency has been recognized as an undesirable global public health problem and it plays a wide role in health and in the prevention of several diseases, including the COVID-19.

As the reduction of the muscle strength is observed in the individuals that had COVID-19, PA or exercises could be important for their rehabilitation. There are different modalities of exercises that could be also used for them, including the whole-body vibration exercises to improve the muscular performance.

Putting together, people in the world is living, or is trying to live, in conditions to maintain a minimal, but convenient level of PA to have health to contercouse the bad situation of the COVID-19 up to a definitive and confident vaccin be available to the human beings. The researchers are working hard to aid the world population to win this fight against the COVID-19 and the sedentary behaviors.

Naturally, COVID-19 and the sedentarism are problems for the world, but the continuous education about the importance of PA, the studies about the effects of medications that can be used in the treatments of diseases, the control of use of drugs, as the pesticides, and the discussion about the biological and legal aspects of reprocessing of medical-hospital material are welcome to contribute to improve the health.

Mario Bernardo-Filho

Editor In Chief

Editorial

There is consistent and strong scientific evidence about the numerous health benefits related to the physical activity (PA). Regular PA can improve physical fitness and health and assist in the prevention of various diseases. In general, physically active adults are healthier and present higher physical performance in comparison with inactive adults worldwide. Among some desirable behaviors, PA can be considered as part of a healthy lifestyle and can be categorized into occupational, sports, conditioning, household, or other activities involving movement of the body generated by skeletal muscles with energy expenditure. Aligned with that, it is undeniable the relevance of the physical inactivity as a risk factor for premature mortality and for cardiovascular disease and a variety of other chronic diseases, including diabetes mellitus, cancer (colon and breast), obesity, hypertension, bone and joint diseases (osteoporosis and osteoarthritis), and depression. Moreover, exercise in patients with hematologic cancer, like leukemia, could improve immune function.

Due to the relevance of the PA, it is important to stimulate behaviors involving the physical practice. There are several factors that can influence these behaviors, such as: personal (biological, health and psychological attributes), social (family, affiliation group, and work factors), and environmental (contexts for different forms of PA and policy factors that could determine availability of relevant settings and opportunities).

The outbreak of the coronavirus disease 19 (COVID--19) has interfered in different factors of the PA behaviors. Depending of the severity of the COVID-19 in an individual, there are limitations to performed PA. Furthermore, aiming to contain the COVID-19 infections and to reduce interaction between infected and non-infected individuals, strategies and restrictive policies have been suggested, such as quarantine, local confinement, lockdown and isolation. It is clear that, while the individuals are confined at home the level of PA, in general, decreases, due to the reduction of (i) daily activities outside, (ii) the participation in social events and, (iii) sometimes, of laboral activities. This may have a negative impact in general heath because it can contribute to sedentary behaviors. Besides the confinement, it is important to consider other actions to protect against the COVID-19 infection that is the universal use of masks.

In addition to those facts, as an environmental factor, in confinement, the sunlight exposure is reduced. The relevance of the ultraviolet B radiation present in sunlight to the active production of vitamin D in the organisms is well known. This vitamin has a relevant role to metabolic responses and protection against diseases, including cancer. Vitamin D deficiency has been recognized as an undesirable global public health problem and it plays a wide role in health and in the prevention of several diseases, including the COVID-19.

As the reduction of the muscle strength is observed in the individuals that had COVID-19, PA or exercises could be important for their rehabilitation. There are different modalities of exercises that could be also used for them, including the whole-body vibration exercises to improve the muscular performance.

Putting together, people in the world is living, or is trying to live, in conditions to maintain a minimal, but convenient level of PA to have health to contercouse the bad situation of the COVID-19 up to a definitive and confident vaccin be available to the human beings. The researchers are working hard to aid the world population to win this fight against the COVID-19 and the sedentary behaviors.

Naturally, COVID-19 and the sedentarism are problems for the world, but the continuous education about the importance of PA, the studies about the effects of medications that can be used in the treatments of diseases, the control of use of drugs, as the pesticides, and the discussion about the biological and legal aspects of reprocessing of medical-hospital material are welcome to contribute to improve the health.

Mario Bernardo-Filho

Editor In Chief

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Original article

Vitamin D levels and risk of COVID-19 infection: A systematic review

Ana C. Coelho-Oliveira,[1, 2]* Bruno B. Monteiro-Oliveira, [1, 2, 3] Rebeca B. M. Cavalcante,[1] Daniel B. Santos,[2] Anelise Sonza,[4] Danúbia C. de Sá-Caputo,[2, 3] Mario Bernardo-Filho [2]

Abstract

Objective: Consistent independent associations between low serum 25-hydroxyvitamin D concentrations and susceptibility to acute respiratory tract infections have suggested a possible involvement of vitamin D in reducing the risk of respiratory infections and proposing its replacement as a potential strategy for prevention or treatment in this context. However, the role of vitamin D supplementation in the infection by the novel coronavirus named SARS-CoV-2 is still under investigation and no clinical evidence has been reported to date. Methods: Electronic searches in Pubmed, Embase and Scopus databases were conducted and three cohort studies that analyzed the effects of interaction of vitamin D with COVID-19, published only in English, were included. Two reviewers, which independently examined titles and abstracts, identified records through database search and reference screening and irrelevant studies were excluded based in eligibility criteria. Relevant full texts were analyzed for eligibility, and all relevant studies were included in the systematic review. Results: Three cohort studies were included in this systematic review with a mean methodological quality low. Only one study demonstrated interaction of low vitamin D concentration in patients with a positive diagnosis for COVID-19. Randomized clinical trials and studies of good methodological quality are necessary to confirm the findings of this systematic review. Conclusions: This systematic review has not demonstrated consistent associations between low levels of vitamin D and susceptibility to COVID-19 infection. Further studies on vitamin D supplementation for the prevention of COVID-19 infection should be conducted..

Keywords: Vitamin D; COVID-19; Public health.

1. Programa de Pós-Graduação em Fisiopatologia Clínica e Experimental, Instituto de Biologia Roberto Alcântara Gomes. Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
2. Departamento de Biofísica e Biometria, Laboratório de Vibrações Mecânicas e Práticas Integrativas, Instituto de Biologia Roberto Alcantara Gomes. Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.
3. Faculdade Bezerra de Araújo, Rio de Janeiro, RJ, Brazil.
4. Universidade do Estado de Santa Catarina, Florianópolis, SC, Brazil.

***Correspondence address:**
UERJ, PPC, LAVIMP
Avenida Marechal Rondon, 381
Rio de Janeiro, RJ, Brasil
CEP: 20950-003
E-mail: anacarol_coelho@hotmail.com
ORCID https://orcid.org/0000-0002-5491-6060

BJHBS, Rio de Janeiro, 2020;19(2):83-90

Received on 03/11/2020. Approved on 10/11/2020.

Resumo

Níveis de vitamina D e risco de infecção por COVID-19: Uma revisão sistemática

Objetivo: Associações independentes consistentes entre baixas concentrações séricas de 25-hidroxivitamina D e suscetibilidade a infecções agudas do trato respiratório sugeriram um possível envolvimento da vitamina D na redução do risco de infecções respiratórias e propuseram sua substituição como uma estratégia potencial para prevenção ou tratamento neste contexto. No entanto, o papel da suplementação de vitamina D na infecção pelo novo coronavírus denominado SARS-CoV-2 ainda está sob investigação e nenhuma evidência clínica foi relatada até o momento. Métodos: Foram realizadas buscas eletrônicas nas bases de dados Pubmed, Embase e Scopus e incluídos três estudos de coorte que analisaram os efeitos da interação da vitamina D com o COVID-19, publicados apenas em inglês. Dois revisores, que examinaram de maneira independente títulos e resumos, identificaram registros por meio de pesquisa de banco de dados e triagem de referência e foram excluídos estudos irrelevantes com base em critérios de elegibilidade. Textos completos relevantes foram analisados para elegibilidade, e todos os estudos relevantes foram incluídos na revisão sistemática. Resultados: Três estudos de coorte foram incluídos nesta revisão sistemática com uma qualidade metodológica média baixa. Apenas um estudo demonstrou interação de baixa concentração de vitamina D em pacientes com diagnóstico positivo para COVID-19. Ensaios clínicos randomizados e estudos de boa qualidade metodológica são necessários para confirmar os achados desta revisão sistemática. Conclusões: Esta revisão sistemática não demonstrou associações consistentes entre baixos níveis de vitamina D e susceptibilidade à infecção por COVID-19. Mais estudos sobre a suplementação de vitamina D para a prevenção da infecção por COVID-19 devem ser realizados..

Descritores: Vitamina D; COVID-19; Saúde pública.

Resumen

Niveles de vitamina D y riesgo de infección por COVID-19: Una revisión sistemática

Objetivo: Las asociaciones independientes consistentes entre las concentraciones séricas bajas de 25-hidroxivitamina D y la susceptibilidad a las infecciones respiratorias agudas han sugerido una posible participación de la vitamina D en la reducción del riesgo de infecciones respiratorias y proponen su reemplazo como una estrategia potencial de prevención o tratamiento en este contexto. Sin embargo, el papel de la suplementación con vitamina D en la infección por el nuevo coronavirus llamado SARS-CoV-2 todavía está bajo investigación y hasta la fecha no se ha informado de evidencia clínica. Métodos: Se realizaron búsquedas electrónicas en las bases de datos Pubmed, Embase y Scopus y se incluyeron tres estudios de cohortes que analizaron los efectos de la interacción de la vitamina D con COVID-19, publicados solo en inglés. Dos revisores, que examinaron de forma independiente los títulos y los resúmenes, identificaron los registros mediante la búsqueda en la base de datos y la selección de referencias y se excluyeron los estudios irrelevantes según los criterios de elegibilidad. Se analizaron los textos completos pertinentes para determinar su elegibilidad y todos los estudios relevantes se incluyeron en la revisión sistemática. Resultados: En esta revisión sistemática se incluyeron tres estudios de cohortes con una calidad metodológica media baja. Solo un estudio demostró la interacción de una concentración baja de vitamina D en pacientes con un diagnóstico positivo de COVID-19. Se necesitan ensayos clínicos aleatorios y estudios de buena calidad metodológica para confirmar los hallazgos de esta revisión sistemática. Conclusiones: Esta revisión sistemática no ha demostrado asociaciones consistentes entre niveles bajos de vitamina D y susceptibilidad a la infección por COVID-19. Deben realizarse más estudios sobre la suplementación con vitamina D para la prevención de la infección por COVID-19.

Palabras clave: Vitamina D; COVID-19; Salud pública.

Introduction

The 2019 coronavirus disease global pandemic (COVID-19), caused by the SARS-CoV-2 coronavirus, has resulted in more than 6 million cases, has caused 376,000 deaths worldwide, and generally produces severe lower respiratory symptoms, according to the World Health Organization (WHO).[1] However, to this date, there is no specific treatment recommended to help alleviate the symptoms of patients affected with COVID-19 and SARS-COV-2, and some non-pharmacological interventions during the hospitalization,[2] the confinement[3] and post-COVID-19 infection have been suggested.[4]

COVID-19 is more prevalent among African-Americans,[5] persons living in northern cities in the late winter,[6] older adults,[7] nursing home residents,[8] health care workers,[9] and populations at increased risk of vitamin D deficiency.

Since COVID-19 can manifest with different intensity of symptoms (from asymptomatic to severe symptoms), recently, some studies have reported consistent independent associations between low serum concentrations of 25-hydroxyvitamin D (the major circulating vitamin D metabolite) and susceptibility to acute respiratory tract infection,[10] suggesting a possible involvement of vitamin D in reducing the risk of respiratory tract infections and proposing its replacement as a potential strategy for prevention or treatment, especially in the context of influenza and COVID-19. However, the role of vitamin D supplementation in the context of virus infection is still under investigation, and no clinical evidence has been reported yet.

Although vitamin D deficiency is common in a large part of the general population, disparities in socioeconomic standards, housing conditions, socialization habits and risk perception, people living in higher latitudes, and especially ethnic conditions, have potential implications for the risk of COVID-19 exposure and transmission, presenting higher rates among people with darker skin or reduced exposure to ultraviolet (UV) radiation from the sun.[11, 12]

Authors describe vitamin D hormone as having important functions – including immunomodulant, anti-inflammatory and anti-infective roles.[13] It acts via monocyte and cell-mediated immunity stimulation, suppression of lymphocyte proliferation, antibody production and cytokine synthesis.[10] Human lung cells are able to intracellularly convert the inactive 25(OH)D to its active form 1,25(OH)D, which reduces proinflammatory cytokines and increases peptides (e.g. the innate antimicrobial peptide cathelicidin). Cathelicidin has direct antiviral activity against enveloped respiratory viruses such as hepatitis B, influenza, respiratory syncytial virus and possibly the COVID-19 as well.[10] Nevertheless, evidence of whether vitamin D deficiency is associated with COVID-19 infection is lacking and/or could help

establish vitamin D as an evidence-based approach to decrease the burden and potentially the spread of COVID-19. Considering this rationale, the aim of this systematic review is to assess the effects of the association of vitamin D and COVID-19.

Methods

The review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[14] and the methods were prespecified in a protocol that was registered under number CRD42020196135 in the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO).[15]

Search Strategy: It was conducted an electronic search in Pubmed, Embase and Scopus databases in June 22th 2020, using the following search string ("covid 19" OR "covid-19" OR "coronavirus" OR "SARS-Cov-2") AND ("vitamin D"). The keywords used in the search were defined based on the PICO strategy, focusing on patients with COVID-19 (Participants) and its relationship with vitamin D (Intervention) without restrictions regarding comparisons (Comparison). All reported outcomes (Outcomes) were allowed if considered relevant to the studied population.[16]

Eligibility Criteria

Inclusion criteria: To be included in this review, the works must be full articles, meet the search criteria and investigate effects of vitamin D on COVID-19 patients, independent of the year of the publication. A flowchart (Figure 1), based in the PRISMA analysis was done to show the steps in the selection of the full papers analyzed in this review.[14]

Exclusion criteria: Exclusion criteria allowed the elimination of unnecessary publications. Papers were excluded if: (i) published in a language other than English; (ii) with findings not related to COVID-19 and vitamin D; (iii) being replies, editorials, letters, abstracts, reviews, commentary's or short communications; and (iv) being conducted with animal, or with combined treatments.

Level of evidence of the selected papers: The level of evidence of each selected publication was individually assessed by using the National Health and Medical Research Council hierarchy of evidence.[17] The level of evidence was defined as follows: (i) I, the systematic review of level II studies; (ii) II, the randomized clinical trial (RCT); (iii) III-1, the pseudo-randomized controlled trial (alternate allocation, as a crossover study or some other similar method); (iv) III-2, the comparative study with concurrent controls (non-randomized experimental trial, cohort study, case control study, interrupted time series with a control group); (v) III-3, the comparative study without concurrent control (historical control, two or more single arm study, interrupted time series without a parallel control group; and (vi) IV, the case series with either post-test or pretest/post-test outcomes.

Study Selection and Data Extraction: All references were exported to a data management software (EndNote X9), and duplicates were removed. The review was conducted following four steps. Records were identified through database search and reference screening (Identification), and two reviewers independently examined titles and abstracts and irrelevant studies were excluded based in eligibility criteria (Screening). Relevant full texts were analyzed for eligibility (Eligibility), and all relevant works were included in the systematic review. The disagreement was resolved by a third reviewer. The same researchers were responsible for the data extraction from the included studies. Data regarding study information (author and year), study design, objectives, and outcomes were extracted.

Results

A total of 277 studies were identified through a database search and, after the removal of 138 duplicates, 139 studies were identified. During the screening process, 127 publications were excluded for not being related to the research question and the full text of 11 articles was reviewed in detail. After careful analysis, 8 studies were excluded (5 review articles, 2 commentaries and 1 vitamin D and other treatment). Finally, three publications were included in the systematic review. The selection process is summarized in Figure 1.

Table 1 shows the characteristics of the participants, the aims of the studies, the outcomes of the selected articles and the level of evidence of the selected papers. The levels of evidence[17] for all studies included in the current review were considered LE III -2.

Several outcomes have been assessed in the matter of whether (i) vitamin D reduces the risk of infection, (ii) vitamin D deficiency is associated with COVID-19 infection and (iii) there is a correlation between vitamin D and COVID -19 in black and South Asian people.

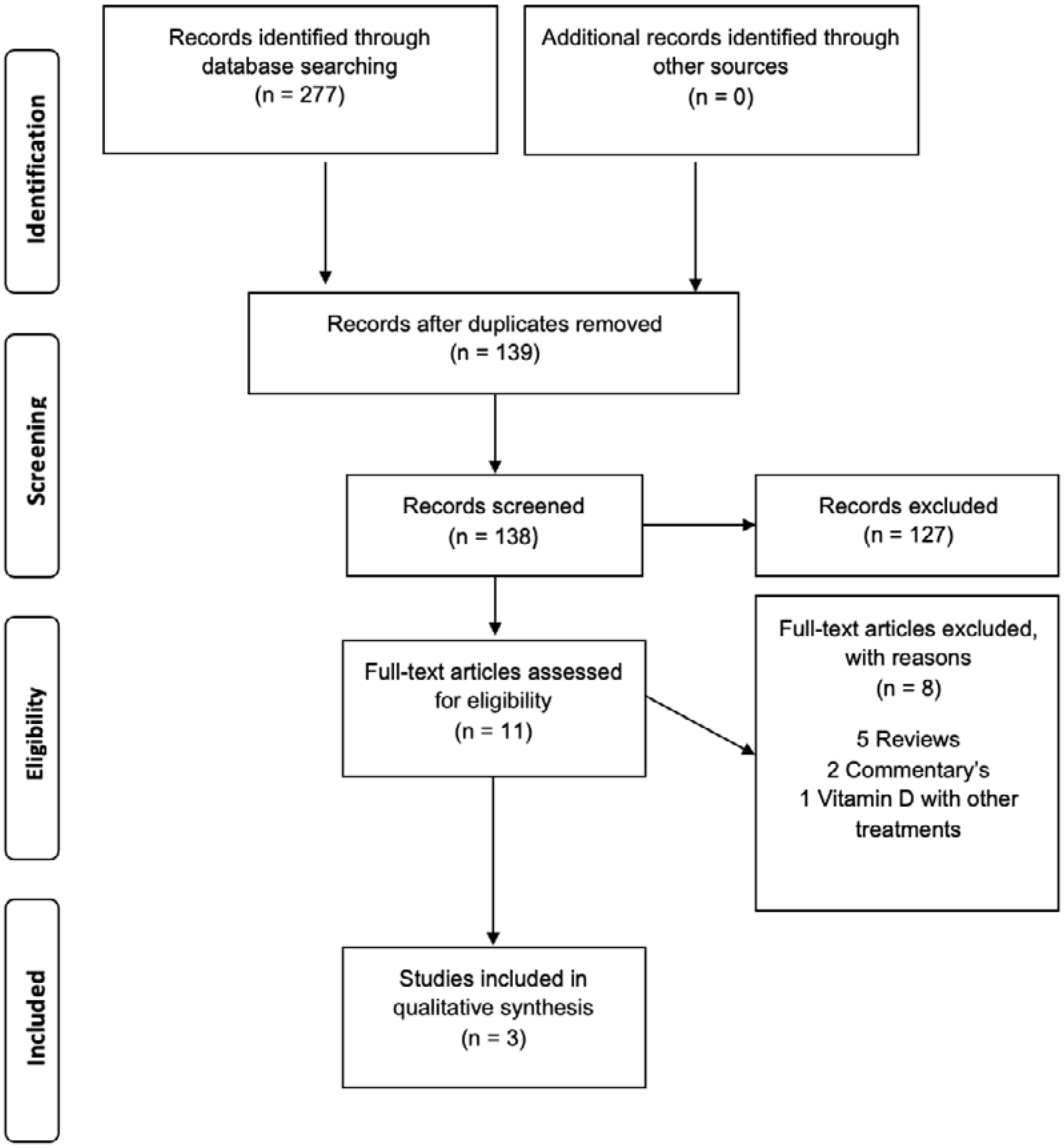


Figure 1. PRISMA flow diagram of the literature selection process

Regarding the main findings based on the results, vitamin D was lower in patients positive for SARS-CoV-2 PCR compared to negative patients.[18]

The works used populations of three countries, UK, USA, and Switzerland. The studied population ranged from 107 to 348,598 individuals with an average age ranging from 45.7 to 73 years and the concentration of vitamin D ranged from 22 to 32.7 ng/mL. One work[18] evaluated two groups: 27 individuals SARS-CoV2 positive (54,2% males) with median age of 73 years and median vitamin D of 22 ng/mL and 80 individuals SARS-Cov2 negative (48.8% males) with median age of 73 years and median vitamin D of 24.6 ng/mL; one work[19] evaluated 4,314 individuals with median age

Table 1. Description of the selected studies

Study	Demograph	Type of study	Objective	Results	Level of Evidence
D'Avolio et al, 2020	**Total 107 patients in 2 groups.** male = 54.2%; median age = 73 years 25(OH)D = 22.0 ng/mL. **27 SARS-CoV-2 PCR-positive** male = 70.4%; Median age = 74 years 25(OH)D = 11.1 ng/mL **80 SARS-CoV-2 PCR-negative** male = 48.8%; median age = 73 years median 25(OH)D = 24.6 ng/mL Switzerland	**Cohort retrospective study**	**The involvement of vitamin D in reducing the risk of infections.**	Statistically significant (p = 0.004) lower 25(OH)D levels (11.1 ng/mL) in patients positive for the SARS-CoV-2 PCR compared with the negative patients (24.6 ng/mL) was observed. When stratifying the 2020 patients by age (0–70 years and >70 years) and PCR positivity, and considering only patients with age >70 years (n = 43 vs. n = 18), the vitamin D concentrations are significantly different (p = 0.037), with median values of 23.1 ng/mL in PCR-negative patients vs. 9.3 ng/mL in PCR-positive patients.	**III - 2**
D'Meltzer et al, 2020	Total 4,314 patients. male = 35%, females (65%); median age = 45.7 years **SARS-CoV-2 positive and deficiency Vitamin D** 32 of 178 (18%) **SARS-CoV-2 positive and non-deficient patients** 40 of 321(11%) USA	**Cohort retrospective study**	**Deficiency analysis and vitamin D treatment are associated with a positive test for COVID-19.**	The Vitamin D dose was not significantly associated with testing positive for COVID-19.	**III - 2**
Hastie et al, 2020	**Total 348,598** **SARS-CoV-2 positive** Male 265 (59.02%) Female 184 (40.98%) Mean Age 49 25(OH)D = 28.7 ng/mL **SARS-CoV-2 negative** Male 168,391 (48.37) Female 179,758 (51.63) Mean Age 49 25(OH)D = 32.7 ng/mL UK	**Cohort Prospective study**	**The objective of the study was to assess whether there is an association between (25 (OH) D) and the risk of COVID-19 and explaining the higher incidence of COVID-19 in black and South Asian people**	Did not find a potential between vitamin D concentrations and risk of COVID-19 infection, nor that vitamin D concentration can explain ethnic differences Contagion of COVID-19.	**III - 2**

Legends: 25(OH)D: Vitamin D; UK: United Kindon; USA: United States of America.

of 45.7 years and a greater number of females (65%) than males (35%); and one work[20] evaluated 348,598 individuals in two groups: 449 individuals SARS-CoV2 positive (59.02% males) with median age of 49 years and median vitamin D of 28.7 ng/mL, and 348.149 individuals SARS-Cov2 negative (48.37% males) with median age of 49 years and median vitamin D of 32.7 ng/mL.

Discussion

The main goal of this systematic review was to assess the effects of the association of vitamin D and COVID-19. After analyzing the included studies and considering their limitations, it was clear that studies with better quality are lacking, indicating a promising field of study. The methodological quality and level of evidence of the included studies in this review were low, mainly regarding the lack of experimental studies with interventions on this context. So far, only observational studies have been carried out.

The results of the works included in this review are not sufficient to establish the association between the vitamin D concentration and the predisposition to COVID-19 infection, but this correlation may be possible. Two retrospective studies found this association. D'Avolio et al.[18] found that individuals with a positive diagnosis of SARS-CoV-2 had lower plasma concentrations of 25-hydroxyvitamin D, compared to individuals with a negative diagnosis. Meltzer et al.[19] observed that vitamin D deficiency that is not sufficiently treated is associated with COVID-19 risk. In the other hand, Hastie et al.,[20] in a prospective study, did not find this association.

Few reviews consider the mechanisms through which vitamin D reduces the risk of viral infections.[21,22] It is believed that vitamin D, being a fat-soluble vitamin, is activated in the lung and acts in the modulation of the renin-angiotensin system, decreasing the release of the ECA2 enzyme, which is a gateway to COVID-19 in the lung.[23] Additionally, Martineau et al.[24] concluded in a meta-analysis that vitamin D supplementation was safe and protective against acute respiratory tract infections. However, although there are studies suggesting that this supplementation may also be effective for COVID-19, only one article included in this review suggests vitamin D as a protective factor for this virus.

According to the literature, vitamin D deficiency is highly prevalent around the world, as around 7% of the world population has severe deficiency and about 40% live with modest deficiency.[25] Individuals from colder regions, higher latitudes, and the elderly, who experience little exposure to sunlight, are also more vulnerable to vitamin D deficiency and consequently to more respiratory symptoms,[12] as well as COVID-19.

Most vitamin D results from production in the skin following exposure to ultraviolet (UV) radiation from the sun; therefore, UV radiation is the main source of vitamin D, providing around 80% of its production. Individuals with dark skin have, on average, lower concentrations of blood vitamin D because the melanin in dark skin does not absorb as much UV radiation.[26] These findings corroborate with two studies in this review that suggest an association between deficiency of vitamin D and the development of COVID-19.

A recent population-based study utilizing data from a large health maintenance organization in Israel that evaluated associations of plasma 25(OH)D status with the likelihood of coronavirus disease infection and hospitalization concluded that low plasma 25(OH) D level appears to be an independent risk factor for COVID-19 infection and hospitalization, after adjusting for age, gender, socioeconomic status (SES) and chronic, mental and physical disorders.[27] The discrepancy between the results of Hastie et al.[20] and the findings of the Israeli population study can be explained by a smaller sample size, by the elderly population and by the inability to control various confounding factors in the first study, like SES and chronic medical conditions.

A review article on the plausible mechanisms that link vitamin D deficiency to increased susceptibility to severe COVID-19 infection in patients with diabetes found sufficient evidence of a shared pathophysiological and mechanistic link between diabetes and COVID-19 infection most evident in presence of vitamin D levels below 10 ng/mL, pointing out that health care providers need to ensure adequate level of vitamin D in such situation.[28]

The present systematic review has some limitations and therefore the results should be interpreted with caution. It was not possible to assess the risk of bias, due to the design of the studies included in the review. Only cohort studies were included, the searches were performed only in three databases and in the English language.

The strength of this work is related to the identification of acceptable, relatively safe and inexpensive intervention (i.e., vitamin D) able to

determine improvements and reducing COVID-19 infection rate.

Conclusion

Vitamin D deficiency and insufficiency is a worldwide issue and adequate levels of this fat-soluble vitamin are required for the proper functioning of the body's defense system. This systematic review has not demonstrated widely consistent associations between low levels of vitamin D and susceptibility to COVID-19. Further placebo-controlled randomized clinical trials on vitamin D supplementation for the prevention of this infection should be conducted in populations with a high prevalence of vitamin D deficiency, addressing the impact of the replacement regimen and aiming to detect effects in different subgroups. Studies will require careful consideration to adapt this treatment to the specific needs of each patient.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors of this study would like to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação Carlos Chagas filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

References

1. World Health Organization. Coronavirus disease (COVID-19) Situation Report-134 [Internet]. 2020 [cited 2020 Jul 7]. Available from: https://www.who.int/docs/default-source/coro%0D%0Anaviruse/situation-reports/20200602-covid-19-sitrep-134.pdf %0D%0A
2. Sañudo B, Seixas A, Gloeckl R, et al. Potential application of whole body vibration exercise for improving the clinical conditions of covid-19 infected individuals: A narrative review from the world association of vibration exercise experts (wavex) panel. International Journal of Environmental Research and Public Health. 2020.
3. da Cunha de Sá-Caputo D, Taiar R, Seixas A, et al. A Proposal of Physical Performance Tests Adapted as Home Workout Options during the COVID-19 Pandemic. Appl Sci [Internet]. 2020 Jul 10 [cited 2020 Jul 24];10(14):4755. Available from: https://www.mdpi.com/2076-3417/10/14/4755
4. Li Z, Zheng C, Duan C, et al. Rehabilitation needs of the first cohort of post-acute COVID-19 patients in Hubei, China. Eur J Phys Rehabil Med [Internet]. 2020 Jul [cited 2020 Jul 24];56(3):339–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32672029
5. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 Apr 17 [cited 2020 Jul 7];69(15):458–64. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm
6. JC U. Casting Sunlight on an Epidemic [Internet]. MedPage Today. 2020 [cited 2020 Jul 7]. Available from: https://www.medpagetoday.com/infectiousdisease/covid19/85596
7. National Center for Health Statistics. Provisional Death Counts for Coronavirus Disease (COVID-19) [Internet]. U.S. Department of Health and Human Services. 2020 [cited 2020 Jul 7]. Available from: https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm
8. Prevention C for DC and. Preparing for COVID-19 in Nursing Homes [Internet]. 2020 [cited 2020 Jul 7]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/long-term-care.html
9. Burrer SL, de Perio MA, Hughes MM, et al. Characteristics of health care personnel with Covid-19 - United States, February 12-April 9, 2020. Morb Mortal Wkly Rep [Internet]. 2020 Apr 17 [cited 2020 Jul 7];69(15):477–81. Available from: http://www.cdc.gov/mmwr/volumes/69/wr/mm6915e6.htm?s_cid=mm6915e6_w
10. Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. J Clin Virol [Internet]. 2011 Mar 1 [cited 2020 Jul 7];50(3):194–200. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1386653210004932
11. Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. Health Technol Assess (Rockv) [Internet]. 2019 Jan 1 [cited 2020 Jul 7];23(2):1–44. Available from: https://pubmed.ncbi.nlm.nih.gov/30675873/
12. Forrest KYZ, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res [Internet]. 2011 Jan [cited 2020 Jul 7];31(1):48–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0271531710002599
13. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin d supplementation could reduce risk of influenza and covid-19 infections and deaths [Internet]. Vol. 12, Nutrients. MDPI AG; 2020 [cited 2020 Jul 7]. p. 988. Available from: https://www.mdpi.com/2072-6643/12/4/988
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ [Internet]. 2009 Dec 4;339(jul21 1):b2700–b2700. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.b2700
15. Pacheco RL, Latorraca C de OC, Martimbianco ALC, et al. PROSPERO: base de registro de protocolos de revisões sistemáticas. Estudo descritivo. Diagnóstico Trat [Internet]. 2018;23(3):101–4. Available from: http://docs.bvsalud.org/

biblioref/2019/01/969297/rdt_v23n3_101-104.pdf
16. Costantino G, Montano N, Casazza G. When should we change our clinical practice based on the results of a clinical study? The hierarchy of evidence. Intern Emerg Med [Internet]. 2015 Sep 10 [cited 2020 Jul 7];10(6):745–7. Available from: https://pubmed.ncbi.nlm.nih.gov/25860505/
17. Merlin T, Weston A, Tooher R, Australian Government. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. BMC Med Res Methodol. 2009;9(34):1–23.
18. D'Avolio A, Avataneo V, Manca A, et al. 25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. Nutrients [Internet]. 2020 May 9;12(5):1359. Available from: https://www.mdpi.com/2072-6643/12/5/1359
19. Meltzer DO, Best TJ, Zhang H, et al. Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence. medrxiv. 2020;
20. Hastie CE, Mackay DF, Ho F, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr Clin Res Rev [Internet]. 2020 Jul;14(4):561–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1871402120301156
21. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D [Internet]. Vol. 7, Nutrients. MDPI AG; 2015 [cited 2020 Jul 15]. p. 4240–70. Available from: www.mdpi.com/journal/nutrients
22. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. Nutrients [Internet]. 2020 Jan 16 [cited 2020 Jul 15];12(1):236. Available from: https://www.mdpi.com/2072-6643/12/1/236
23. Malek Mahdavi A. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19. Rev Med Virol [Internet]. 2020;(April):1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32584474
24. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ [Internet]. 2017 Feb 15 [cited 2020 Jul 15];356:i6583. Available from: http://dx.doi.org/10.1136/bmj.i6583
25. Bouillon R. Vitamin D status in Africa is worse than in other continents. Lancet Glob Heal [Internet]. 2020 Jan 1 [cited 2020 Jul 15];8(1):e20–1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2214109X19304929
26. Nair R, Maseeh A. Vitamin D: The sunshine vitamin [Internet]. Vol. 3, Journal of Pharmacology and Pharmacotherapeutics. Wolters Kluwer -- Medknow Publications; 2012 [cited 2020 Jul 15]. p. 118–26. Available from: /pmc/articles/PMC3356951/?report=abstract
27. Merzon E, Tworowski D, Gorohovski A, et al. Low plasma 25(OH) vitamin D3 level is associated with increased risk of COVID-19 infection: an Israeli population-based study. medRxiv [Internet]. 2020 Jan 1;2020.07.01.20144329. Available from: http://medrxiv.org/content/early/2020/07/03/2020.07.01.20144329.abstract
28. Singh SK, Jain R, Singh S. Vitamin D deficiency in patients with diabetes and COVID- 19 infection. Diabetes Metab Syndr Clin Res Rev [Internet]. 2020 Sep 3 [cited 2020 Jul 15];14(5):1033–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32640414

BRAZILIAN JOURNAL BJHBS OF HEALTH AND BIOMEDICAL SCIENCES

Original article

N-acetylcysteine+nimesulide: An association strategy aiming to prevent nimesulide-induced hepatotoxicity

Amanda G. Elias,[1] Julia S. da Silva,[2] Rafaela L. Klein,[1] Francieli U. I. Amaral,[3] Marcelo D. Arbo,[4] Fernanda M. Conte,[5] Solange C. Garcia,[4] Eliane Dallegrave,[5] Janaine R. Martins,[5] Charise D. Bertol,[6] Diorges H. Setim,[1] Adriana C. da Motta,[1] Romulo P. Barcelos,[1,2] Luciana G. R. Grando[1*]

Abstract

Introduction: Nimesulide is a potent anti-inflammatory with rapid and long-lasting effects, but also with a high risk of hepatotoxicity. Objective: This work aimed to prevent nimesulide-induced hepatotoxicity through the association of nimesulide with a hepatoprotective agent. Materials and Methods: First, we tested three hepatoprotective agents: N-acetylcysteine, L-carnitine, and *Gingko biloba* extract in an *in vitro* hepatic cell model. Both N-acetylcysteine and *G. biloba* showed promisor results. We selected N-acetylcysteine to continue the studies in an animal model. *In vivo* study was performed using male Wistar rats divided in 4 groups: control, nimesulide (100mg/kg/day), nimesulide (100mg/kg/day) + N-acetylcysteine (100mg/kg/day) and N-acetylcysteine alone (100mg/kg/day). Treatments were given by gavage, daily, for 15 days. Results: Animals receiving nimesulide alone showed lower body weight gain compared to control. Body weight gain in the nimesulide + N-acetylcysteine group was higher than nimesulide alone, evidencing lower toxicity. However, the body weight gain of the nimesulide + N-acetylcysteine group was still lower than the control animals. Animals treated with nimesulide alone presented an increased relative mass of heart, liver, and spleen and significant hepatic damage seen in microscopy when compared to other groups. N-acetylcysteine co-administered with nimesulide prevented the increased heart mass, but the same was not true with liver and spleen. Conclusions: This work evidence partial protection elicited by the association of N-acetylcysteine and nimesulide against nimesulide-induced hepatotoxicity.

Keywords: Nimesulide; N-acetylcysteine; Safety; Hepatotoxicity; Anti-inflammatory.

1. Graduate Program in Bioexperimentation. University of Passo Fundo, Brazil.
2. Graduate Program in Toxicological Biochemistry. Federal University of Santa Maria, Brazil.
3. Biotério. University of Passo Fundo, Brazil.
4. Graduate Program in Pharmaceutical Sciences. Federal University of Rio Grande do Sul, Brazil.
5. Federal University of Health Sciences of Porto Alegre, Brazil.
6. Graduate Program in Human Aging. University of Passo Fundo, Brazil.

***Correspondence address:**
BR 285, São José
Passo Fundo, RS, Brazil.
CEP: 99052-900.
Email: rossatoluciana@upf.br
ORCID: https://orcid.org/0000-0003-4574-855X

BJHBS, Rio de Janeiro, 2020;19(2):91-99

Received on 22/07/2020. Approved on 23/11/2020.

Resumo

N-acetilcisteína + nimesulida: Estratégia de associação com o objetivo de prevenir a hepatotoxicidade induzida por nimesulida

Introdução: A nimesulida é um potente anti-inflamatório com efeitos rápidos e duradouros, mas também com alto risco de hepatotoxicidade. Objetivo: Este trabalho teve como objetivo prevenir a hepatotoxicidade induzida pela nimesulida por meio da associação de nimesulida a um hepatoprotetor. Materiais e Métodos: Primeiro, testamos três possíveis hepatoprotetores: N-acetilcisteína, L-carnitina e extrato de *Gingko biloba* em um modelo de células hepáticas *in vitro*. N-acetilcisteína e *G. biloba* apresentaram bom potencial hepatoprotetor. Selecionamos a N-acetilcisteína para continuar os estudos em um modelo animal. O estudo *in vivo* foi realizado com ratos Wistar machos divididos em 4 grupos: controle, nimesulida (100 mg/kg/dia), nimesulida (100 mg/kg/dia) + N-acetilcisteína (100 mg/kg/dia) e N-acetilcisteína isolada (100 mg/kg/dia). Os tratamentos foram realizados por gavagem, diariamente, por 15 dias. Resultados: Os animais que receberam nimesulida isoladamente apresentaram menor ganho de peso corporal em comparação ao controle. O ganho de peso corporal no grupo nimesulida + N-acetilcisteína foi maior que o nimesulida isolado, evidenciando menor toxicidade. No entanto, o ganho de peso corporal do grupo nimesulida + N-acetilcisteína ainda era menor do que os animais controle. Os animais tratados com nimesulida isoladamente apresentaram aumento da massa relativa do coração, fígado e baço e dano hepático significativo observado na microscopia quando comparados a outros grupos. A N-acetilcisteína co-administrada com nimesulida impediu o aumento da massa cardíaca, mas tal fato não ocorreu com o fígado e o baço. Conclusões: Este trabalho evidencia proteção parcial provocada pela associação

de N-acetilcisteína e nimesulida contra hepatotoxicidade induzida por nimesulida.

Descritores: Nimesulide; N-acetilcisteína; Segurança; Hepatotoxicidade; Anti-inflamatório.

Resumen

N-acetilcisteína + nimesulida: Una estrategia de asociación dirigida a prevenir la hepatotoxicidad inducida por nimesulida

Introducción: La nimesulida es un potente antiinflamatorio con efectos rápidos y duraderos, pero también con un alto riesgo de hepatotoxicidad. Objetivo: Este estudio tuvo como objetivo prevenir la hepatotoxicidad inducida por nimesulida combinando nimesulida con un medicamento hepatoprotector. Materiales y métodos: Primero, probamos tres candidatos: N-acetilcisteína, L-carnitina y extracto de *Gingko biloba* en un modelo de células hepáticas *in vitro*. N-acetilcisteína y *G. biloba* mostraron buen potencial. A continuación, seleccionamos N-acetilcisteína para continuar los estudios en un modelo animal. El estudio *in vivo* se realizó con ratas Wistar machos divididas en 4 grupos: control, nimesulida (100 mg/kg/día), nimesulida (100 mg/kg/día) + N-acetilcisteína (100 mg/kg/día) y N-acetilcisteína aislada (100 mg/kg/día). Los tratamientos se realizaron por sonda, diariamente, durante 15 días. Resultados: Los animales que recibieron nimesulida sola mostraron menos aumento de peso corporal en comparación con el control. El aumento de peso corporal en el grupo de nimesulida + N-acetilcisteína fue mayor que el de nimesulida sola, mostrando menos toxicidad. Sin embargo, el aumento de peso corporal del grupo nimesulida + N-acetilcisteína fue aún menor que el de los animales de control. Los animales tratados con nimesulida sola mostraron un aumento en la masa relativa del corazón, el hígado y el bazo y un daño hepático significativo observado al microscopio en comparación con otros grupos. La N-acetilcisteína administrada conjuntamente con nimesulida evitó el aumento de la masa cardíaca, pero no sucedió lo mismo con el hígado y el bazo. Conclusiones: Este trabajo muestra una protección parcial causada por la asociación de N-acetilcisteína y nimesulida contra la hepatotoxicidad inducida por la nimesulida.

Palabras clave: Nimesulida; N-acetilcisteína; La seguridad; Hepatotoxicidad; Antiinflamatorio.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) reduces inflammation, pain, and fever processes by decreasing the synthesis of prostaglandins by blocking cyclooxygenases.[1, 2] Nimesulide is a NSAID marketed for the first time in Italy, in 1985, and now it is present in more than 50 countries. In some joint diseases such as osteoarthritis and arthrosis nimesulide is a more effective alternative than other NSAIDs because it presents faster and long-lasting analgesic effect.[3, 4]

Easy access to NSAIDs contributes to the occurrence of adverse effects related to these drugs.[1, 5, 6] NSAIDs, along with antibiotics, are the most common cause of drug-induced hepatotoxicity, being responsible for about 10% of the cases.[7] Clinical manifestations of NSAIDs- induced hepatotoxicity vary between low aminotransferase increases until fulminant hepatitis with a high mortality rate.[8]

The World Health Organization registered more than 320 cases of nimesulide-induced hepatotoxicity a year. These hepatic disturbances related to nimesulide raise concern about its safety profile. In 2002, the Spanish Agency for Medicines and Health Products suspended nimesulide due to high hepatotoxic risks. Ten years later, the European Medicine Agency declared that nimesulide presents a higher risk to induce hepatotoxicity when compared to other NSAIDs.[9] Nimesulide was never approved in the USA, United Kingdom, Canada, and New Zeeland.[9] Considering Latin America, Argentina suspended nimesulide in all forms of presentation while in Brazil is widely prescribed and only contraindicated to children under 12 years old because of Reye Syndrome risk.[9]

Mechanisms related to nimesulide-induced hepatotoxicity are not fully understood. It might involve an increased rate of nimesulide retention in the hepatobiliary compartment, adducts formed after metabolism that causes cell injury, and the inhibition of mitochondrial function with consequent oxidative stress and ATP depletion.[10, 11]

This work aimed to enhance nimesulide safety profile through the association with a hepatoprotective agent. We tested three different candidates *in vitro*: N-acetylcysteine (potent antioxidant and glutathione precursor, well known as an antidote to hepatic intoxication related to other drugs),[12-14] L-carnitine (a mitochondrial function enhancer),[15, 16] and *Ginkgo biloba* extract (selected due to its natural antioxidant effects).[17, 18] After the selection of the best candidate in the *in vitro* challenge, we performed an *in vivo* study.

Materials and methods

Chemicals

Nimesulide, N-acetylcysteine, L-carnitine, Dulbecco's modified eagle's medium (DMEM) with phenol and 4,500 mg/L glucose, fetal bovine serum (FBS), sodium bicarbonate, antibiotic (10,000 U/mL penicillin, 10,000 µg/mL streptomycin), trypsin, 3-(4,5-dimethyltiazol-2-il)-2,5-diphenyltetrazol bromide (MTT) and dimethyl Sulfoxide (DMSO) were purchased from Sigma-Aldrich (São Paulo, Brazil), The standardized extract of *Ginkgo biloba L.* (leaves, Ginkgoaceae) was obtained from Martins Bauer Group - Finzelberg GmbH & Co. KG (Germany), according to the European Pharmacopoeia.

The extract contains between 22 and 27% flavonoid glycosides, between 5 and 7% terpenolactones, between 2 and 6% bilobalide, between 2.8 and 3.4% ginkgolides A, B, C and at most 5 ppm of ginkgolic acids.

Experimental Design

We aim to prevent nimesulide-induced hepatotoxicity through the association with a hepatoprotective agent. We tested three possible hepatoprotective (N-acetylcysteine, L-carnitine, and *Gingko biloba* extract) in an *in vitro* hepatic cell model. After the *in vitro* challenge, we selected the most promisor hepatoprotective to continue the study in rats. *In vivo* study was performed using male Wistar rats divided into four groups: control, nimesulide, nimesulide+hepatoprotector (simultaneously administered), and hepatoprotective drug alone. Treatments were given by gavage, daily, for 15 days. Hepatotoxicity was monitored during the study. Protection was evaluated by the comparison of body weight gain, organ relative mass, and liver microscopy between groups.

In vitro model: HepG2 cell culture

The HepG2 cell line is derived from human hepatocyte carcinoma and it has been accepted as a good *in vitro* model to study hepatotoxicity. Cells were gently provided by Dr. Marcelo Dutra Arbo, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil. Cells were cultured in 75 cm^2 tissue culture flasks using DMEM supplemented with 10% FBS and 1% antibiotic solution. Cells were kept in a humidified 5% CO_2 - 95% air atmosphere, at 37 °C, and the medium was replaced every 2-3 days. Cells were subcultured once 70-80% confluence was reached.

Cytotoxicity assays

Cells were seeded at a density of 50,000 cells/plate in 96-well plates to obtain confluent monolayers in 24 h. Nimesulide (20 µM, 50 µM, 100 µM, 250 µM, 500 µM, 1 mM and 2 mM) was incubated for 48 h, in 6 replicates of 3 independent experiments. Concentration-response curves were evaluated through 3-(4,5-dimethyltiazol-2-il)-2,5-diphenyltetrazol bromide (MTT) reduction assay and neutral red uptake assay. Considering cytotoxicity results, we selected 100 µM nimesulide as the working concentration. Nimesulide was co-incubated with N-acetylcysteine (25µM, 50µM and 100µM), L-carnitine (100 µM), or *Gingko biloba* extract (25 µM, 50 µM and 100 µM). Hepatoprotective concentrations were selected following previously described works using hepatoprotective approaches in cell models.[14-16, 19]

Stock solutions of nimesulide were prepared in DMSO. Thus, 0.1% DMSO in culture medium was used as vehicle control. All stock solutions were stored at -20 °C and freshly diluted on the day of the experiment.

MTT reduction assay

Cell viability was assessed through MTT reduction assay.[20] After the treatment incubation period, cell culture medium was removed, and a fresh medium containing 0.5 mg/L MTT in HBSS was added and incubated for two hours. After the formed formazan crystals were dissolved in DMSO, the absorbance was measured at 550 nm in a multi-well plate reader. Results were graphically presented as the percentage of cell death *vs.* concentration.

Neutral red uptake assay

After the treatment incubation period, the medium was replaced by phosphate buffer saline containing 50 µg/mL neutral red. Cells were incubated at 37 °C for two hours, allowing lysosomes from viable cells to uptake the dye. Cells were gently washed with HBSS to eliminate extracellular dye and lysed with 50% ethanol in acetic acid solution 1%. Absorbance was read at 540 nm in a multi-plate reader. The percent cell death relative to that of the control cells was used as the cytotoxicity measure.[20]

In vivo assay

Animals were acclimated for two weeks before the study. Food and water were provided *ad libitum*; animals

were subjected to a 12 h light/dark cycle, controlled room temperature 22 °C (±3 °C). Experiments were approved by the Ethical Committee on the use of animals from the University of Passo Fundo (Protocol nº 020/2018).

Adult male Wistar rats (± 300 g, 8 week old) were divided into four groups (6 animals/group) and were treated by oral gavage, for 15 days. Treatment groups were control (saline solution), nimesulide group (100 mg/kg/day), nimesulide + N-acetylcysteine group (both administered at 100 mg/kg/day) and N-acetylcysteine group (100 mg/kg/day).

During the experiment, body mass gain and daily clinical evaluations were performed. Systemic toxicity was evaluated through the occurrence of piloerection, dehydration, bleeding and diarrhea, motor function (tone and movement coordination), breathing (rate and depth, gasping), mucosal color (pale, cyanotic), and clinical signals of abdominal pain.[22] Animals were euthanized through intraperitoneal injection of Ketamine/xylazine (100mg/kg/20mg/kg, respectively).

Biochemical analysis

Blood was collected by cardiac puncture and was used to assess serum hepatic biomarkers bilirubin, hepatic transaminases (ALT and AST), and gamma-GT, using commercial kits.

Organ-target toxicity

Organs (heart, liver, kidneys, and spleen) were removed from animals washed with saline solution and dried in order to remove residual blood. After macroscopic evaluation, organs were weighted to assess the relative mass (calculated as the percentage of the total body weight) as a toxicity parameter.[22]

Liver microscopy

During necropsy, two fragments from two hepatic lobes from all animals were collected and immediately kept in a solution containing buffered formalin (10%). After fixing, liver pieces were cut and mounted in slides. Samples were stained with hematoxylin/eosin and analyzed under a light microscope.

Hepatic oxidative stress evaluation

The occurrence of oxidative stress in the liver was evaluated in hepatic tissue. Liver samples were homogenized [1:4 (m/v)] in ice-cold phosphate-buffered saline solution, pH7.4, with an Ultra-Turrax homogenizer and centrifuged (3000 g, 10 min).[22] Aliquots of supernatant were taken to assess hepatic protein levels,[23] lipid peroxidation,[24] and non-proteic thiols content.[25]

Statistical analysis

Results were presented as mean±standard deviation from independent experiments. Normality distribution was assessed through the Shapiro-Wilk test. Relative body mass gain was analyzed through two-way ANOVA. Statistical comparisons between groups that presented normal distribution were performed by One-Way ANOVA followed by Tukey *post hoc* test (organ relative weights and hepatic oxidative stress) and Kruskal-Wallis followed by Dunn's *post hoc* (biochemical parameters) was used to compare variables without normal distribution.

Results

Hepatoprotector selection

After analyzing the concentration-response curves of nimesulide (Figure 1), we selected the concentration of 100 μM to further studies. This concentration was chosen because it kills cells around 60 % when compared to control conditions, as evidenced in Figure 1.

Both N-acetylcysteine and *Ginkgo biloba* extract significantly protected cells from nimesulide-induced cytotoxicity, as demonstrated by both cytotoxicity assays (Figure 2). L-carnitine did not counteract nimesulide damage (Figure 2). Thus, we chose N-acetylcys-teine to continue the study, considering significant clinical experience using this drug as an antidote to revert hepatotoxicity of other drugs such as acetaminophen.[12-14]

N-acetylcysteine partially protects against nimesulide-induced toxicity

During *in vivo* study, control and N-acetylcysteine groups increased relative body weight gain similarly, evidencing the lack of systemic toxicity. Animals receiving nimesulide alone showed lower body weight gain compared to control ($p<0.0001$). Animals treated nimesulide + N-acetylcysteine significantly increased body weight gain compared to nimesulide alone ($p<0.05$), evidencing lower toxicity obtained with this association. However, systemic toxicity was not fully antagonized because the body weight gain of the nimesulide + N-acetylcysteine group was still lower than control animals ($p<0.001$) (Figure 3).

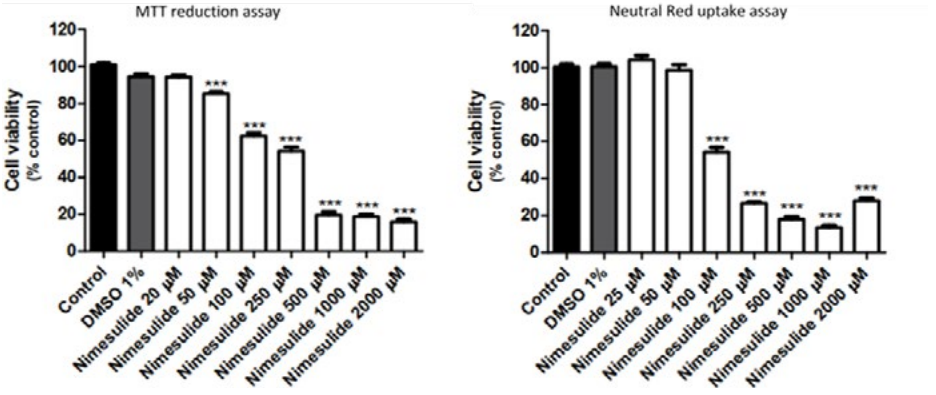


Figure 1. Effect of different concentrations of nimesulide after 48 h incubation at 37 °C with HepG2 cells evaluated through A) MTT reduction assay and B) Neutral red uptake assay. Results are presented as means (%) ±standard deviation of 3 independent experiments. Statistical comparison were made using one-way ANOVA test followed by Tukey post hoc test (* p<0.001 vs control)**

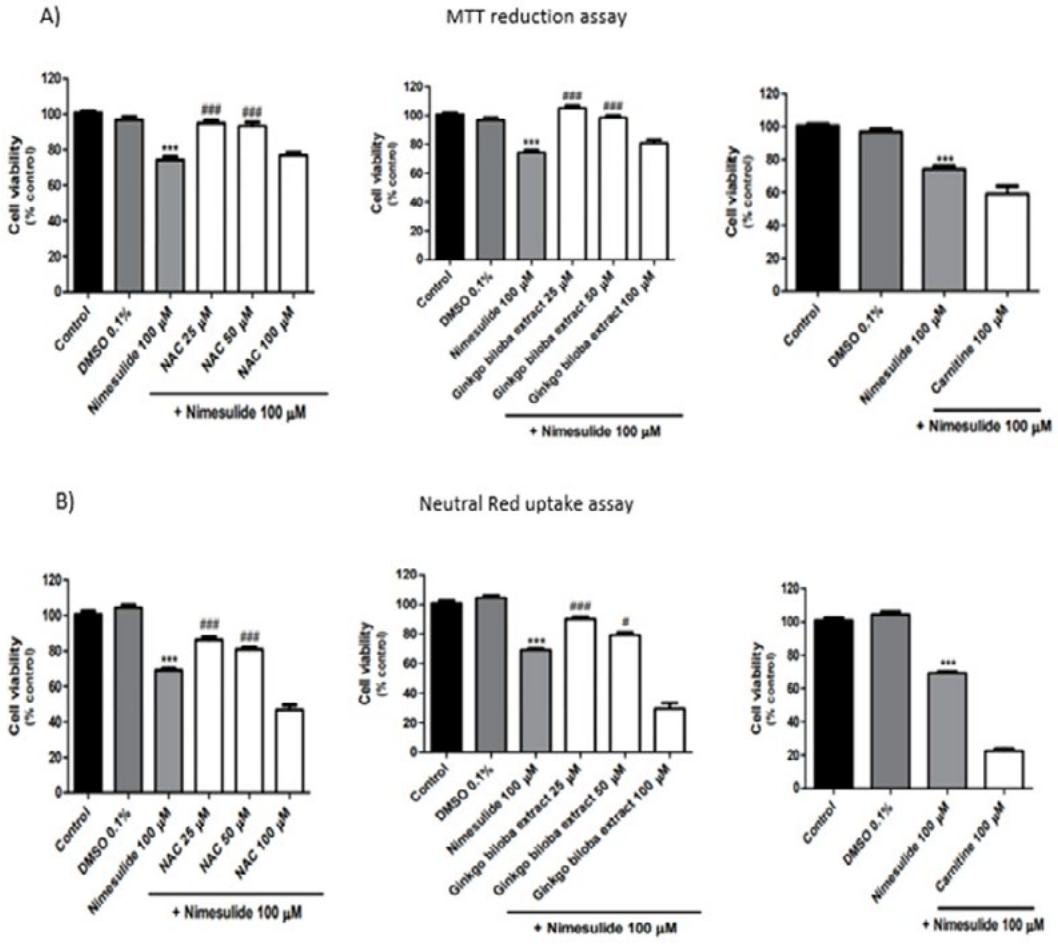


Figure 2. Citotoxicity results after co-exposure of nimesulide and 3 different hepatoprotectors after 48 h at 37 °C. Results are presented as means (%) ±standard deviation of 3 independent experiments. Statistical comparison were made using one-way ANOVA test followed by Tukey post hoc test (* p<0.001 vs control; ### p<0.001 vs nimesulide group)**

Two animals from the nimesulide group died before the end of the study (on day 7 and day 9). Necropsy revealed hepatic changes such as degeneration, diffuse centrilobular necrosis, peritonitis, and tubular necrosis on kidneys (Figure 4).

Hepatic microscopic lesions

The typical hepatic lesions seen in nimesulide groups were hepatocellular degeneration and necrosis. Animals treated with nimesulide alone presented more significant hepatic damage than other groups and when compared to control. Despite of that, the nimesulide + N-acetylcysteine group also showed injuries (Figure 4).

Organ-target toxicity

Nimesulide alone caused an increased relative mass of heart, liver, and spleen when compared to control groups. N-acetylcysteine co-administered with nimesulide reverted the increased heart mass but failed to revert increased hepatic or spleen mass compared to nimesulide alone group (Figure 5). Treatments did not cause any change in the relative weight of kidneys (*data not shown*).

Biochemical and oxidative stress results

It was not observed significant differences between groups in biochemical biomarkers or oxidative stress parameters (hepatic lipid peroxidation, total hepatic protein level, and non-protein thiols on the liver) (*data not shown*).

Discussion

The major finding of this work is to evidence that N-acetylcysteine partially reverts nimesulide-induced hepatotoxicity. We aimed to simulate the hepatotoxicity observed as an adverse effect obtained in therapeutic doses and not in anoverdose context. Thus, the selected dose would not be too far from the pharmacological dose. Then we extended treatment to 15 days. Nimesulide scheme dose regimen was also supported by previous studies in rats.[21] The N-acetylcysteine dose was selected considering hepatoprotective results observed in rats when associated with other hepato-toxicity drugs.[22]

N-acetylcysteine was selected as the most promising hepatoprotective drug after *in vitro* studies. Cytotoxicity results demonstrate that both N-acetylcysteine and *G. biloba* extract revert cell death obtained with nimesulide alone. We invested in N-acetylcysteine to continue *in vivo* studies considering the clinical experience and consolidated studies using this antidote in the hepatotoxicity of other drugs such as acetaminophen.[27-30] After being absorbed, N-acetylcysteine is biotransformed by acetyltransferases to L-cysteine, which is subtract to glutathione synthesis. Thus, N-acetylcysteine presents a direct free species scavenger effect and also acts as a glutathione precursor, being recognized as a board antioxidant.[13,14,31] This mechanism may contribute to protective results against nimesulide-induced oxidative stress.[10,11]

In the *in vivo* study, N-acetylcysteine partially protected animals treated with nimesulide, as demonstrated

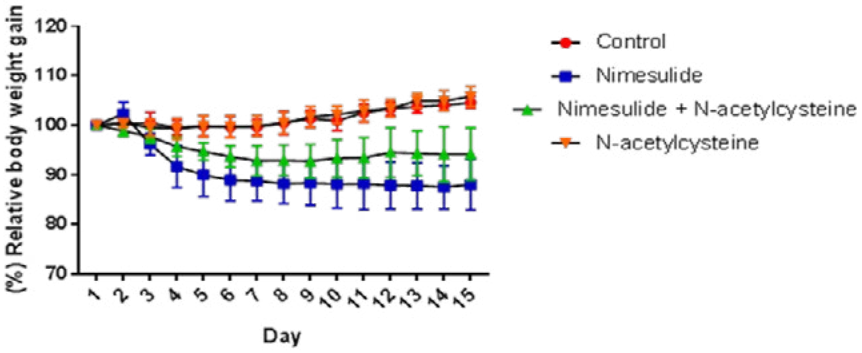


Figure 3. Relative body weight gain. Results are presented as mean ± standard deviation. Significant results were seen between nimesulide (100mg/kg) and control groups and nimesulide (100mg/kg) and nimesulide (100mg/kg) + N-acetylcysteine (100mg/kg) groups (p<0.05)

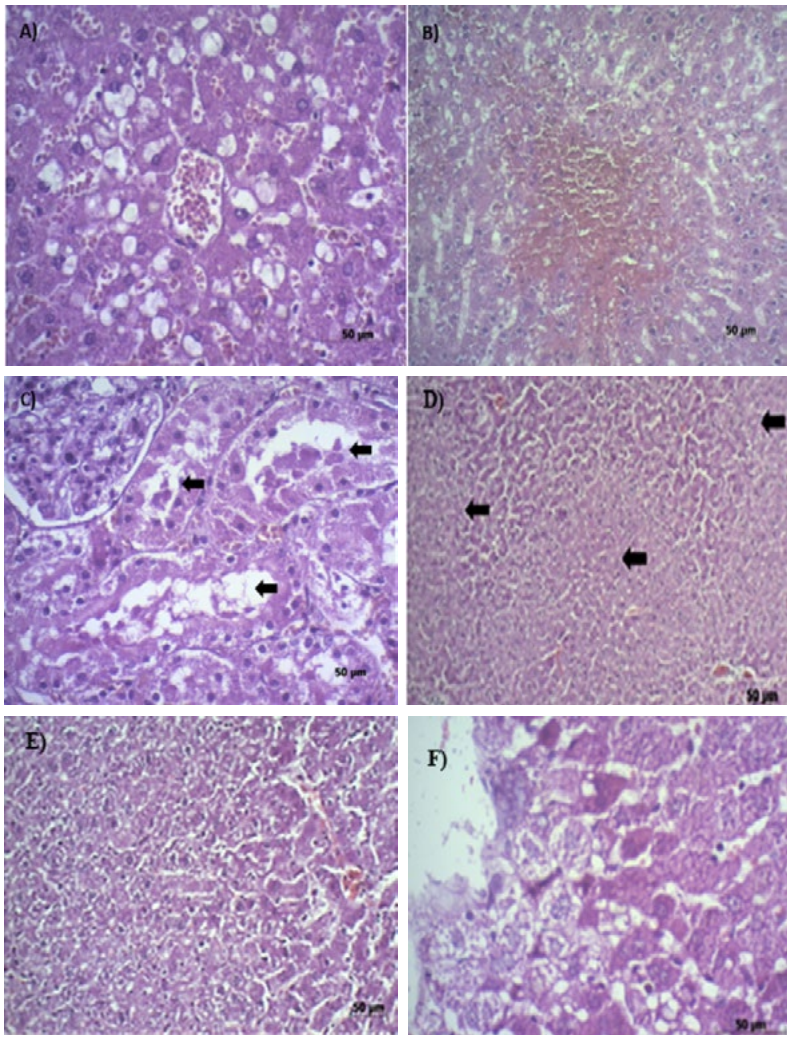


Figure 4. A), B) e C) Liver from nimesulide treated rat died on day 7. A) Hepatic centrolobullar region showing degeneration and necrosisHE, 400X. B). Hepatic centrolobullar region showing degeneration and hemorrhagic necrosis. HE, 200X. C) Kidney, córtex, showing degeneration and tubular necrosis with hyaline cylinders (arrow).HE, 400X. D) and E) Liver from nimesulide group presenting D) hepatocellular degeneration and necrosis. (arrows) HE, 100x. E) HE, 200x. F) Liver from nimesulide + N-acetylcysteine group presenting hepatocellular degeneration and necrosis.(arrows) HE, 400x

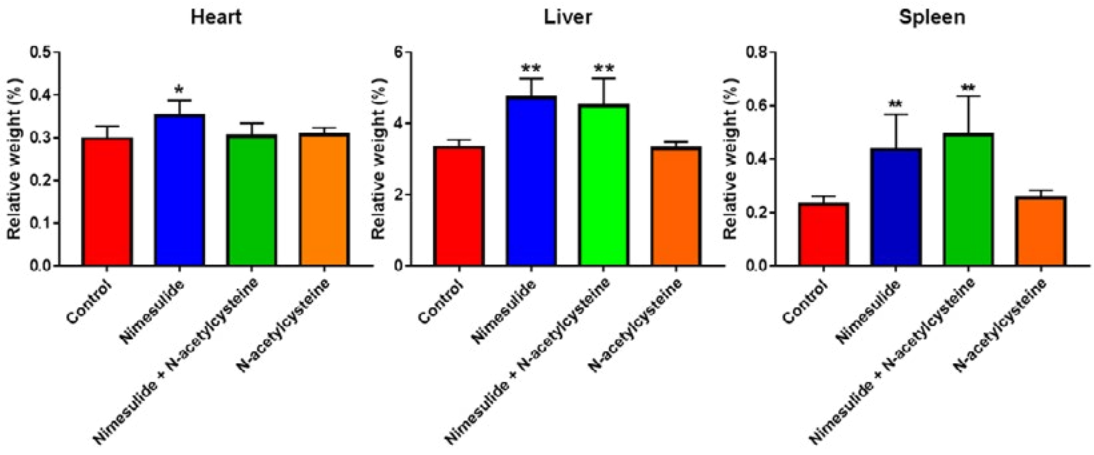


Figure 5. Relative mass of heart, liver and spleen after in vivo study. Results are presented as mean ± standard deviation (N= 6 rats per group). Statistical comparison were made using one-way ANOVA test followed by Tukey post hoc test (* p<0.05 vs. control; ** p<0.01 vs. control)

by the recovery in relative body weight gain observed in nimesulide + N-acetylcysteine rats compared to nimesulide group. However, co-administration of N-acetylcysteine with nimesulide was not enough to fully revert toxicity, considering body weight gain in this group is still lower than control animals. The partial protection obtained with N-acetylcysteine is also proved in microscopic results since both groups receiving nimesulide presented hepatic lesions, but more pronounced when nimesulide is given alone.

Increases in the relative mass of livers from the nimesulide group are related to hepatocyte commitment showed in microscopy. One hypothesis to increased heart volume observed here is a secondary effect to progressive hepatic decompensation. In this scenario, blood volume is redistributed, decreasing central circulation, and increasing water retention.[32, 33] However, we cannot exclude a direct effect since COX-2 inhibitors are related to a higher risk of a heart attack.[1]

Here we did not show changes in biochemical biomarkers or hepatic oxidative stress. The absence of these expected alterations might be related to an *in vivo* endpoint (15 days). Apparently, 15 days is enough for cellular adaptations to restore these transient markers. This is a reliable hypothesis considering the plasticity/adaptation ability of the liver.[34] Moreover, similarly to what is observed in nimesulide in humans, it seems that hepatotoxicity is strongly dependent of individual susceptibility.[32] Thus, in our study, two rats treated with nimesulide alone died on days 7 and 9. The other rats, which also presented lower body weight gain and apathy, recovered until the end of the experiment. Necropsy of animals found dead revealed hepatic injury and even renal changes that deserve to be highlighted in future approaches.

G. biloba extract is also an excellent candidate to be employed as a hepatoprotective agent against nimesulide-induced hepatotoxicity, as suggested by our *in vitro* preliminary study. This extract increases prostacyclin synthesis and inhibits oxidative stress associated with inflammation.[17] Flavonoids and terpenes present in this plant are related to antiapoptotic effects, which might contribute to hepatoprotection.[17, 18]

L-carnitine does not seem to attenuate nimesulide-induced cell damage in our hepatic cell model. The mechanism of action of L-carnitine is focused on mitochondria.[15] L-carnitine and acetyl-L-carnitine enhance mitochondrial function because of their key-role in β-oxidation and removal of toxic substrates from mitochondria.[35-37] However, the injury caused by nimesulide involves more complex mechanisms.[11]

To the best of our knowledge, we show for the first time, the protection elicited by N-acetylcysteine against nimesulide-induced hepatotoxicity. Despite the excellent effects of N-acetylcysteine used as an antidote in another drug-induced hepatotoxicity, the protection obtained here is only partial.

Acknowledgments

This work received financial support from FAPERGS (Fundação de Amparo a Pesquisa do Rio Grande do Sul), Project ARD 17/2551-000804-9.

References

1. Risser A, Donovan D, Heintzman J, et al. NSAID prescribing precautions. Am Fam Physician. 2009;80(12):1371–8.
2. Sousa JM de, Neto MF de A, et al. Ação Anti-inflamatória da Nimesulida e seu grau de Hepatotoxidade. Revista Científica do ITPAC. 2016 Feb;
3. Bianchi M, Ferrario P, Balzarini P, et al. Plasma and synovial fluid concentrations of nimesulide and its main metabolite after a single or repeated oral administration in patients with knee osteoarthritis. J Int Med Res. 2006;34(4):348–54.
4. Silva NA da, Marczyk LRS. Eficácia e tolerabilidade da nimesulida versus celecoxib na osteoartrite. Acta Ortopédica Bras. 2006;9(1):42–54.
5. Adams RJ, Appleton SL, Gill TK, et al. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community -A population-based study. BMC Family Practice. 2011;12(1):70.
6. Arrais PSD, Fernandes MEP, Pizzol T da SD, et al. Prevalence of self-medication in Brazil and associated factors. Revista de Saude Publica. 2016;50(supl 2):1–11.
7. Bessone F. Non-steroidal anti-inflammatory drugs: What is the actual risk of liver damage? World J Gastroenterol. 2010;16(45):5651–61.
8. Licata A, Calvaruso V, Cappello M, et al. Clinical course and outcomes of drug-induced liver injury : Nimesulide as the first implicated medication. 2010;42:143–8.
9. OPAS. Hepatotoxicidad grave asociada con el uso de nimesulida. Bol Inf la Red Centros Inf Medicam Lat y el Caribe, Organ Pan-Americana da Saúde. 2017;(5):1–12.
10. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354(7):731–9.

11. Edited by Rainsford KD. Nimesulide - Actions and Uses. Birkhäuser Verlag, P.O. Box 133, CH-4010 Basel, Switzerland; 2005. 1–445 p.
12. Benlamkaddem S, Iken I, Houari N, et al. Paracetamol self-poisoning: When oral N-acetylcysteine saves life? A case report. Pan Afr Med J. 2018;29:1–5.
13. Yesil Y, Ozdemir AA. Evaluation of the children with acute acetaminophen overdose and intravenous N-acetylcysteine treatment. 2018;34(3):590–4.
14. Heil J, Schultze D, Schemmer P, et al. N-acetylcysteine protects hepatocytes from hypoxia-related cell injury. Clin Exp Hepatol. 2018;4(4):260–6.
15. Masi F, Leggio B, Nanni G, et al. Effects of long-term acetyl-L-carnitine administration in rats—II: Protection against the disrupting effect of stress on the acquisition of appetitive behavior. Neuropsychopharmacology. 2003;28(4):683–93.
16. Rebouche CJ. Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. Ann N Y Acad Sci. 2004;1033:30–41.
17. Diamond BJ, Bailey MR. Ginkgo biloba. Indications, Mechanisms, and Safety. Psychiatr Clin North Am. 2013;36(1):73–83.
18. Waidyanatha S, Mutlu E, Gibbs S, et al. Systemic exposure to Ginkgo biloba extract in male F344/NCrl rats: Relevance to humans. Food Chem Toxicol. 2019;131:110586.
19. Rossato LG, Costa VM, Vilas-Boas V, et al. Therapeutic concentrations of mitoxantrone elicit energetic imbalance in H9c2 cells as an earlier event. Cardiovasc Toxicol. 2013;13(4):413–25.
20. Arbo MD, Silva R, Barbosa DJ, et al. Piperazine designer drugs induce toxicity in cardiomyoblast h9c2 cells through mitochondrial impairment. Toxicol Lett. 2014;229(1):178–89.
21. Patel PB, Patel TK, Patni S, et al. Hepatotoxicity Studies of Nimesulide in Litters of Rat. 364001.
22. Calegari EM, Endres HC, Dallegrave E, et al. Silymarin elicits partial protection against methotrexate-induced hepatotoxicity in wistar rats. Int J Pharm Pharm Sci. 2015;7(9):462–5.
23. Bradford MM. A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding. 1976;254:481.
24. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351–8.
25. Elmann GL. Tissue sulfhydryl groups. Arch Biochem Biophys 1959;82:70-7.
26. Raza M, Ahmad M, Gado A. A comparison of hepatoprotective activities of aminoguanidine and N -acetylcysteine in rat against the toxic damage induced by azathioprine. 2003;134:451–6.
27. Prescott LF, Illingworth RN, Adam RD. Intravenous N-acetylcysteine : the treatment of choice for paracetamol poisoning. 1979;(November):1097–100.
28. Mumtaz K, Azam Z, Hamid S, et al. Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. Hepatology International. 2009;3(4):563–70.
29. Al C, Gluud C, Brok J, et al. Interventions for paracetamol (acetaminophen) overdose (Review) Summary of Findings for the main Comparison. Cochrane Database Syst Rev. 2018;(2):1–90.
30. Athuraliya TNC, Jones AL. Prolonged N-acetylcysteine therapy in late acetaminophen poisoning associated with acute liver failure – a need to be more cautious? Crit Care. 2009;13(3):144.
31. Whillier S, Raftos JE, Chapman B, et al. Role of N-acetylcysteine and cystine in glutathione synthesis in human erythrocytes. 2013;0002.
32. Traversa G. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ. 2003;327(7405):18–22.
33. Liu H, Lee SS. Cirrhotic cardiomyopathy. Cirrhosis A Pract Guid to Manag. 2015;56(7):225–35.
34. Tao Y, Wang M, Chen E, et al. Liver Regeneration: Analysis of the Main Relevant Signaling Molecules. Mediators Inflamm. 2017;2017:4256352. doi: 10.1155/2017/4256352.
35. Tolu P, Masi F, Leggio B, et al. Effects of long-term acetyl-L-carnitine administration in rats: I. Increased dopamine output in mesocorticolimbic areas and protection toward acute stress exposure. Neuropsychopharmacology. 2002;27(3):410–20.
36. Hoang BX, Graeme Shaw D, Pham P, et al. Restoration of cellular energetic balance with l-carnitine in the neuro-bioenergetic approach for cancer prevention and treatment. Med Hypotheses. 2007;69(2):262–72.
37. Bovell DL, Clunes MT, Elder HY, et al. L-carnitine prevents increase in diastolic [Ca2+] induced by doxorubicin in cardiac cells. 2000;45–8.

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND BIOMEDICAL SCIENCES

Original article

The effect of long-term whole-body vibration on muscular performance

Yossef Haleva,[1,2]* Ayelet Dunsky,[2] Yoav Meckel,[2] Heinz Kleinöder,[1] Michael Bar-Eli,[2] Joachim Mester[1]

Abstract

Introduction: The whole-body vibration (WBV) approach is considered to be a unique training method for physical rehabilitation, injury preventions, and improving physical performance in athlete. The scientific literature about WBV is well documented and presents different vibration protocols, different measurements and, as a consequence - different results. Objectives: To explore the effect of a strengthening program with WBV on several muscular strength variables among physical education students in comparison to a control passive group of students. Methods: Thirty-eight healthy male physical education students were randomly allocated into Vibration Group (VG, n=13) - who underwent strengthening program with WBV and external load, and Control Group (CG, n=25), that received no treatment. The study included pre-test assessments, 4-week intervention phase and post-test assessments. During the intervention phase VG performed three training sessions per week that included six sets of 30 sec squats with external loads on a WBV platform. Assessments included maximal muscle strength, power, reactive strength and endurance. Results: Significant improvements were shown in all components among the VG from pre to post-tests ($p<0.001$), with no significant change among the CG. Conclusions: A 4-week strengthening program with WBV and medium external load improves different components of strength among healthy physical education students.

Keywords: Whole body vibration; Strength; Power; Reactive strength.

1. The Institute of Training Science and Sport Informatics. German Sport University Cologne, Germany.
2. The Academic College at Wingate. Wingate Institute, Netanya, Israel.

***Correspondence address:**
The Academic College at Wingate
Wingate Institute 4290200, Israel
E-mail: yossihaleva@gmail.com
ORCID: https://orcid.org/0000-0002-9228-7007

BJHBS, Rio de Janeiro, 2020;19(2):100-107

Received on 26/10/2020. Approved on 08/12/2020.

Resumo

O efeito de um programa de fortalecimento que consiste em exercícios de vibração de corpo inteiro no desempenho muscular

Introdução: A técnica de vibração de corpo inteiro (WBV) é considerada como um método de treino único para reabilitação física, prevenção de lesões e melhoria do desempenho físico do atleta. A literatura científica sobre a WBV está bastante documentada e apresenta diferentes protocolos de vibração, diferentes medições e, consequentemente - diferentes resultados. Objetivos: explorar o efeito do programa de fortalecimento com WBV em várias variáveis de força muscular entre os estudantes de educação física, em comparação com um grupo de controlo passivo de estudantes. Métodos: Trinta e oito estudantes de educação física saudáveis do sexo masculino foram distribuídos aleatoriamente num Grupo de Vibração (VG, n=13) - os quais foram submetidos a um programa de fortalecimento com WBV e carga externa - e num Grupo de Controlo (CG, n=25) - que não receberam tratamento. O estudo incluiu avaliações pré-teste, fase de intervenção de 4 semanas e avaliações pós-teste. Durante a fase de intervenção, o VG realizou três sessões de treino por semana que incluíram seis séries de agachamentos de 30 segundos com cargas externas numa plataforma WBV. As avaliações incluíram a força muscular máxima, potência, força reativa e resistência. Resultados: Foram apresentadas melhorias significativas em todos os componentes do VG, desde os pré-testes até aos pós-testes ($p<0,001$), sem qualquer alteração significativa por parte do CG. Conclusões: Um programa de 4 semanas de fortalecimento com WBV e carga externa média melhora diversos elementos de força entre os estudantes de educação física saudáveis.

Descritores: Vibração de corpo inteiro; Força; Potência; Força reativa.

Resumen

El efecto de un programa de fortalecimiento en el rendimiento muscular que consiste en ejercicios con vibración transmitida en todo el cuerpo

Introducción: El enfoque de la vibración transmitida en todo el cuerpo (VBM) se considera un método de entrenamiento

único para la rehabilitación física, la prevención de lesiones y la mejora del rendimiento físico en el atleta. La literatura científica sobre la VBM está bien documentada y presenta diferentes protocolos de vibración, diferentes mediciones y, como consecuencia – diferentes resultados. Objetivos: explorar el efecto del programa de fortalecimiento con VMB en varias variables de fuerza muscular entre los estudiantes de educación física en comparación con un grupo pasivo de referencia de estudiantes. Métodos: Treinta y ocho estudiantes masculinos de educación física sanos fueron asignados al azar en el grupo de Vibración (VG, n=13) – que se sometieron a un programa de fortalecimiento con VMB y carga externa –, y el Grupo de Referencia (CG, n=25) – que no recibió ningún tratamiento. El estudio incluyó evaluaciones previas a la prueba, fase de intervención de 4 semanas y evaluaciones posteriores a la prueba. Durante la fase de intervención, el VG realizó tres sesiones de entrenamiento por semana que incluyeron seis series de sentadillas de 30 segundos con cargas externas en una plataforma WBV. Las evaluaciones incluyeron fuerza muscular máxima, potencia, fuerza reactiva y resistencia. Resultados: Se mostraron mejoras significativas en todos los componentes entre el VG desde el pre y el post test (p<0,001), sin cambios significativos entre el CG. Conclusiones: Un programa de fortalecimiento de 4 semanas con VBV y carga externa media, mejora los diferentes componentes de fuerza entre los estudiantes de educación física sanos..

Palabras clave: Vibración transmitida al cuerpo entero; Fuerza; Potencia; Fuerza reactiva.

Introduction

Muscle strength is of primary importance in human life, particularly in elite, amateur, and leisure sport, but also in prevention and rehabilitation training. Among athletes, strength and relevant strength training are preconditions for high performance, thus they are practicing different protocols in order to increase the effectiveness of those strength trainings. Additionally, there is a trend towards shorter training times in modern strength training at different achievement levels.[1, 2]

In the last twenty years one of the training approaches, that tries to answer these standards, is based on whole-body vibrations (WBV). This approach is based on a mechanical stimulus generated by motors underneath a platform, which are subsequently transmitted to the human body via feet when standing on the platform. Cardinale and Pope (2003)[1] defined these mechanical vibrations as deterministic sinusoidal motions in two dimensions: side-to-side alternating and vertical. The effect of WBV is dependent on the magnitude of the biomechanical loading parameters, such as working time interspersed with rest time, frequency, amplitude and peak acceleration, as well as the positioning of the individual.[2] The WBV approach with different vibration-producing devices and its effect on humans have been under examination in the training sciences for several years.[3, 4] It was found to produce neuromuscular adaptation which enhances the tonic vibration reflex that stimulates the muscular reflex for contraction, and improve the function of the neuromuscular systems.[5, 6] When combined with strength training, it provided additional improvements in power and RM1, however, in comparison to maximum voluntary contraction, WBV based on bodyweight produced lower EMG (electromyogram) activity, thus it was suggested that additional external load must be introduced for further improvements.[7–13] WBV for long-term had significantly higher improvement on strength and jump performance in comparison to a passive control group, and had small higher effect on those variables compared to a control group performing the same exercise without WBV.[14] It is important to note that the effects of long-term WBV on muscle strength and power are inconclusive, as different studies report diverse methods, different vibration protocols, and different measurements.[15, 16] Thus, the purpose of the current study was to explore the effect of strengthening program with WBV on several muscular strength variables among physical education students in comparison to a control passive group of students.

Materials and methods

Ethics

The study was performed in consensus with all Helsinki requirements and was conducted with the understanding and the consent of the human subject. The Ethical Committee of the responsible University faculty (German Sport University Cologne) has approved the study.

Inclusion criteria for participating in the study were: 1) Registered to the sport university at the time of the study, 2) Training regularly (at least twice a week), and 3) have experience in training with free weights. None of the participants took any prescription medications or food supplements during the study.

Participants with a previous history of fractures or bone injuries were excluded from the study.

Participants

Thirty-eight healthy male physical education students volunteered to take part in the study. Their mean age was 24.95 ± 3.44 years, mean weight was 79.86 ± 9.41 kg, and mean height was 183.14 ± 7.61 cm. Standard calibrated scales and stadiometers (Seca, 707, Germany) were used to determine body mass and height. The participants were informed of the experimental procedures, and signed an informed consent prior to participation.

Study design

The study lasted six weeks. On the first week participant partook in two pre-testing assessments, followed by four weeks of intervention phase, and one week in which they partook in two post-testing assessments. Using a controlled study design, participants were randomly assigned to one of two study groups, after matching for strength assessments according to the pre-test assessments:[14] Vibration Group (VG) – performed WBV during the intervention phase (n=13) –, and Control Group (CG), that kept their physical activity routine (as physical education students) with no specific program during the intervention period (n=25). Participants were asked to avoid any additional physical activity during the study (other than the study program). During the study 16 participants dropout due to missed follow-up tests, injuries, or absence from more than 10% of the training sessions. Out of these 16, 10 participants from the CG were excluded as they did not keep their physical activity routine and added different training methods during the study period.

Thus, only 22 participants were included in the final analysis: 12 in VG and 10 in CG.

Training protocol

During the 4-week intervention phase, participants in the VG performed three training sessions per week, with a minimum of 48 hours between sessions. All training sessions were performed at a gym with sportswear and sneakers, during morning hours (2-3 hours after breakfast), with an average air temperature of about 18–22 °C. Participants were instructed to drink 500cc of water 30 min before each training session. The training protocol was based on traditional strength training method[17] with additional vibration loads. Each training session lasted approximately 40-50 min, beginning with a standard warm-up, followed by the training phase, and a recovery phase. The training phase was composed of six sets of 30 sec exercise and one-minute rest of dynamic squats in shoulder-width apart (between 10-12 repetitions) with external loads using a special barbell (the hands could touch the support handle of the device lightly, in order to maintain stability), while standing on WBV platform (Power Plate©) with constant vibration amplitudes in a vertical direction, at 4 mm. The external load was adjusted to 40% of 1RM (that was based on a Maximum strength evaluation that was measured prior training phase), that is considered a medium training intensity for athletes.[18] Additionally, the frequency of the vibrations was constant during the training session and increased from 30 to 40 Hz after every four sessions. It should be noted that during the training session a supervision was always present. Table 1 presents the training progress over the 6-week program.

Strength Assessments

Based on the Bührle's (1989) model[19] the strength components that were measured in the current study were: isomeric maximal strength, power, reactive

Table 1. The Training Protocol Sessions for the experimental/Vibrations Group

Groups	Pre test		Standard loads	Meso cycle of 4 weeks			Post test	
				Sessions 1-4	Sessions 5-8	Sessions 9-12		
VG	1	2	Exe: back squat Train-freq: 3 X wk -1, 6 sets, 1 Set: 10-12 rep/30 sec External loads: 40% 1RM Pause between Sets: 60 sec	30Hz	35Hz	40Hz	1	2
CG	1	2	No treatment				1	2

Legend: VG = WBV group; CG = control group; Train-freq = training frequency; Exe = Exercise.

strength, and muscular endurance. Accordingly, pre- and post-training assessments included the following tests:

Maximal isomeric strength – It was measured by Static leg press on the isokinetic "Desmotronic" Function, which was performed in an upright sitting position (seat-back angle 85°), with knee angle at 120°. During three successive measurements (with 30-60 s break) the participant had to produce maximum static contraction against rigid resistance. The measuring period of individual attempts lasted up to 5 s.

Power assessment – It was measured by Squat Jump (SJ) – a vertical jump performed from a squatting position (knee angle 90°) with feet at approximately hip width, and without swinging the arms. Each participant performed three SJ with a 1-min break in between. After each jump participants received feedback about jump height (cm) and jump technique. The highest achievement was used for analysis.

Reactive strength assessment – It was measured by Counter Movement Jump (CMJ) and Drop Jump (DJ). CMJ is performed like the SJ with a "dip" just prior the vertical jump, thus momentarily stretching the involved muscles (long S.C.C according to Young et al. 1999)[20] and producing a more powerful movement. Each participant performed three CMJ with a 1-min break in between. After each jump, participants received feedback about jump height (cm) and jump technique. The highest achievement was used for analysis. During DJ participants dropped from a box 40 cm high and upon landing, they were instructed to jump for maximum vertical height and minimum ground contact time. Height jump (cm), contact time (ms), and height/contact time (cm*s-1) were immediately displayed on the computer screen, and feedback was provided after each trial. This was considered important so that subjects could determine the optimum combination of height and contact time to produce the best height/contact time ratio. The best height/time score for each DJ was used for analysis. Due to the relatively short contact time and the need to quickly shift from the eccentric phase to the concentric phase, this test is considered a measure of reactive strength (short S.C.C) of leg capacity.[20, 21]

Maximum strength evaluation (10RM) – This test was obtained by knee extensions (the distance between bench and ground was to 52 cm, with the aim that all participants perform the same range) with a special barbell with angled iron strips. Additional load was then increased every 2 min up to individual maximum. Maximum strength with additional load was regarded as the load at which 10RM could be performed. The goal was to determine maximum efficiency of trunk and leg musculature, in order to subsequently adjust the additional load for training.

Muscular endurance assessment – It was measured based on the Maximum strength evaluation (10RM), in which, 40% of 1RM was calculated.[22] Participants performed the strength endurance test – maximum repetition number of knee extensions that they could perform with 40% of 1RM.

Each assessment session began with a warm-up that was divided into a 5-min general and 5-min of specific warm-up for the respective jumps (SJ, CMJ and DJ). Subsequently, participants performed 5-min flexibility exercises.

During each two assessment timepoints all tests were performed but the Muscular Endurance Assessment that was not performed during Pre-test 1, and Post-test 1 assessments, and the 10RM that was not performed during Pre-test-2, and Post-test-2 assessments.

Statistical analysis

The assumptions of the current study were that the strengthening program consisting exercise with WBV will improve muscular strength in comparison to the passive control group that will have no change in the assessed variables. Data were subjected to analysis of variance (One-way ANOVA) followed by the Tukey's post-hoc test (using the program SPSS 25 statistical computer program). Differences between groups were considered significant at a level of $p \leq 0.05$ for all comparisons.

Results

Pre-test assessments

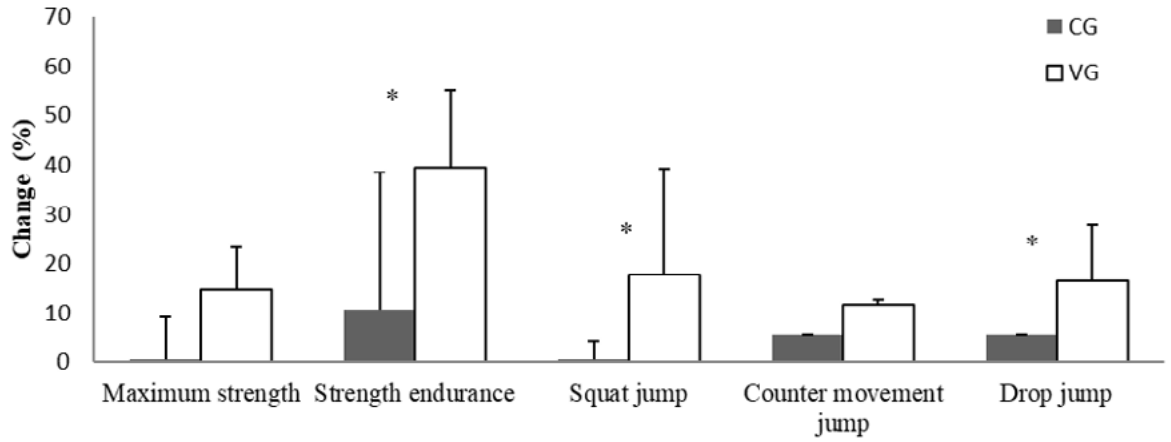
There were no differences in any of the strength assessments achievements between the groups, prior the training phase ($p > 0.05$).

Post-test assessments

Changes in strength performances following the training program of VG are presented in Table 2 and

Figure 1. As it can be seen in Table 2, all strength components improved significantly from pre-test to post-test among the VG (p<0.001), but not among the CG (Table 2). More specifically, at the SJ test, the VG had significant 17.7% improvement (p<0.001) with no significant change among CG. Additionally, significant groups X time interaction was found (F1, 20=32.94, p<0.001). At the CMJ test, the VG had significant 11.66% improvement (p<0.001) with no significant change among CG. At the DJ, test the VG had significant 16.53% improvement (p<0.01) with no significant change among CG. Additionally, significant groups X time interaction was found (F1, 20=5.05, p<0.05). At the Maximum strength test, the VG had significant 14.74%

Figure 1. Changes on strength performance among the VG versus CG following the intervention phase



*** Significant differences between groups (p<0.01).**

Table 2. Changes in strength components among VG versus CG (means ± SD)

Variable	Vibration Group (VG) N=12			Control Group (CG) N=10			time F (1, 20)	p	time*-group F (1, 20)	p
	Pre	Post	ES	Pre	Post	ES				
Maximal Strength [N]	4439.20 ± 1058.43	5093.60 ± 1149.15*	0.62	5031.50 ± 837.35	5058.30 ± 879.46	0.03	3.31	0.09	2.81	0.11
Maximal Repetition Number [t]	27.82 ± 9.58	38.82 ± 11.05**	1.15	25.00 ± 11.38	27.6 ± 11.58	0.23	15.46	0.001	5.90	0.03*
Squat Jump [cm]	38.70 ± 4.68	45.56 ± 3.68**	1.47	36.74 ± 6.33	36.91 ± 6.08	0.03	36.40	>0.001	32.94	>0.01**
Counter Movement Jump [cm]	41.89 ± 4.86	46.77 ± 3.62**	1.01	38.39 ± 7.04	40.59 ± 7.99	0.31	18.91	>0.001	2.69	0.12
Drop Jump [cm]	31.55 ± 4.19	36.76 ± 4.66**	1.24	29.42 ± 5.60	31.08 ± 4.96	0.30	18.89	>0.001	5.05	0.04*

Legend: ES: effect size (Cohen's d).

* Significant differences between groups (p<0.05).

** Significant differences between groups (p<0.01).

improvement ($p<0.05$) with no significant change among CG. And at the Muscular endurance test, the VG had significant 39.54% improvement ($p<0.01$) with no significant change among CG. Additionally, significant groups X time interaction was found ($F1, 20=5.90$, $p<0.05$).

Discussion

The purpose of the current study was to compare the effect of 4 weeks of strengthening program with WBV on strength components of the lower limb among a group of physical education students in comparison to a passive control group (who kept their physical activity routine). The main findings of this study point to the significant improving effect of the strengthening program with WBV approach on strength components among the VG with no significant changes among participants in the CG.

The effect of WBV on power

The current results are in line with previous results about the effect of long-term WBV on power as represented by SJ achievements.[15,21,23-25] Possible explanation for the positive effect of the strengthening program with WBV on power is based on the fact that the SJ is mainly achieved by fast twitch (FT) muscle fibers requitement.[26] The higher the proportion of FT muscle fibers that are activated in a specific movement, the higher the jump is. In the current study the VG, showed 17.7% improvement on that measure, suggesting that the mechanical vibration movement during the WBV training produced neuromuscular adaptation to enhance better recruitment of the FT muscle fibers.[5,14,27] Our results are in contrast to the findings of Spitzenpfeil (2000)[28] Cochrane (2004)[29] and Rittweger et al.[30,31] that reported a decline in performance among the WBV groups. It is possible that differences in the WBV protocols led to the different effects.

The effect of WBV on reactive strength

Reactive strength is of particular importance for athletes in sports that includes high jumps such as gymnastics, high jump and volleyball. The CMJ and the DJ resemble those skills, and are based on optimal use of the stretch-shortening cycle.[20] The positive effect of WBV training on those tests found in the current study are in line with several previous studies Torvinen et al. (2002a&b),[27,32] Ziegler (2003)[25] and Berschin et al.,[18] who found that strength training with vibration loads were more effective in comparison to traditional training (the same training program without vibration loads) on CMJ performance, and on DJ performance.[23,33,34] On the contrary, Spitzenpfeil (2000)[28] found no improvements of DJ following long term WBV training, while Ziegler (2003)[25] reported a decline of about 4% in DJ following WBV. DJ performance is based upon the ability to recruit concentric contraction following landing from a drop of 40 cm, and a very short ground contact time,[35] thus the musculo-neural system has to adjust to changes in direction of contractions very fast. One possible explanation for changes in that ability following WBV training is based upon the possible change it creates in the neural system,[5,20,21] thus enabling higher jump through improved biomechanical means (better storage of kinetic energy over the flexible muscle component) and neurophysiological means (improved stretch-shortening cycle).

Regarding the results of maximal strength, the current study found significant 14.74% improvement among the VG following the strengthening program with WBV. Rønnestad (2009)[36] reported that WBV loading showed improvement in squat 1 repetition maximum (1RM) compared with no vibration in both trained and untrained participants. Such evidence was also suggested in a systematic review from Rehn et al (2006).[26] As for the effect of WBV on muscular endurance, Güllich and Schmidtbleicher (1999)[37] suggested that improvements in maximal strength correlate with improvement in endurance, and our results are in accordance with this suggestion. However, no previous study showed improvements in muscular endurance following strengthening program with WBV.

There are several limitations to the current study, the first one is the fact that the CG did not receive any strengthening program. If they did, it could be suggested that the differences found between the groups occurred specifically due to the WBV. Second, the fact that the WBV protocol used in the current study was based certain vibration amplitudes and frequencies. It is possible that changes in these parameters would lead to higher improvements in the assessed variables.

Conclusion

Based on the results of the current study, we can conclude that a 4-week strengthening program with WBV and medium external load improves differ-

ent components of strength. Future studies should evaluate the effect of the same training protocol in comparison to a same strengthening program without vibrations, and, in comparison, to other amplitudes or frequencies.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The researchers would like to express gratitude to the participants who partook in the study and to Efi Haleva who helped throughout the study.

Article highlights

Research background

The whole-body vibration (WBV) approach is considered to be a unique training method for physical rehabilitation, injuries prevention, and improving physical performance in athlete.

Research motivation

The scientific literature about WBV is documented with inconclusive methods, different vibration protocols, different measurements and, as a consequent – different results.

Research objectives

To explore the effect of strengthening program with WBV on several muscular strength variables among physical education students in comparison to a control passive group of students.

Research methods

Thirty-eight healthy male physical education students were randomly allocated into Vibration Group (VG, n=13) – who underwent strengthening program with WBV and external load, and Control Group (CG, n=25), that kept their physical activity routine. The study included pre-test assessments, 4-week intervention phase and post-test assessments. During the intervention phase, VG performed three training sessions per week that included six sets of 30 sec squats with external loads on a WBV platform. Assessments included maximal muscle strength, power, reactive strength and endurance.

Research results

Significant improvements were shown in all components among the VG from pre to post-tests ($p<0.001$), with no significant change among the CG.

Research conclusions

A 4-week strengthening program with WBV and medium external load improves different components of strength among healthy physical education students.

Research perspectives

Future studies should evaluate the effect of the same training protocol in comparison to a same strengthening program without vibrations, and, in comparison, to other amplitudes or frequencies.

References

1. Cardinale M, Pope M. The effects of whole body vibration on humans: Dangerous or advantageous? Acta Physiologica Hungarica. 2003;90(3):195–206.
2. Marín P, Rhea M. Effects of vibration training on muscle strength: A meta-analysis. J. Strength Cond. Res. 2010;24(2):548–556.
3. Morel DS, Dionello CdF, Moreira-Marconi E, et al. Relevance of Whole Body Vibration Exercise in Sport: a Short Review With Soccer, Diver and Combat Sport. African J. Tradit. Complement. Altern. Med. 2017;14(s):19-27.
4. Moreira-Marconi E, Moura-Fernandes MC, Teixeira-Silva Y, et al. Whole-body vibration exercises benefit individuals with knee osteoarthritis: a narrative review. Rev. Hosp. Univ. Pedro Ernesto. 2018;17(1):44–50.
5. Bosco C, Iacovelli M, Tsarpela O, et al. Hormonal responses to whole-body vibration in men. Eur J Appl Physiol. 2000;81:449–454.
6. Torvinen S, Kannus P, Sievänen H, et al. Effect of 8-month vertical whole body vibration on bone, muscle performance, and body balance: A randomized controlled study. J Bone Min. Res. 2003;18(5):876–884.
7. Wilcock IM, Whatman C, Harris N, et al. Vibration training: Could it enhance the strength, power, or speed of athletes? J Strength Cond Res. 2009;23(2):593–603.
8. Goodwill A, Kidgell D. The effects of whole-body vibration on the cross-transfer of strength. Sci. World J. 2012;1-11.
9. Caserotti P, Madsen K. Effects of vibration and resistance training on neuromuscular and hormonal measures. Eur J Appl Physiol. 2006;96:615–625.
10. Preatoni E, Colombo A, Verga M, et al. The effects of whole-

body vibration in isolation or combined with strength training in female athletes. J Strength Cond Res. 2012;26(9):2495–2506.
11. Rønnestad BR, Holden G, Samnøy L, et al. Acute effect of whole-body vibration on power, one-repetition maximum, and muscle activation in power lifters. J. Strength Cond. Res. 2012;26(2):531–539.
12. Rosenberger AB, Johannes J, Schoenau E, et al. Changes in muscle cross-sectional area, muscle force, and jump performance during 6 weeks of progressive whole-body vibration combined with progressive, high intensity resistance training. J Musculoskelet Neuronal Interact. 2017;17(2):38–49.
13. Weier A, Kidgell D. Strength training with superimposed whole body vibration does not preferentially modulate cortical plasticity. Sci World J. 2012;1-9.
14. Nordlund M M, Thorstensson A. A Strength training effects of whole-body vibration? Scand J Med Sci Sports. 2007;17(2):38-49.
15. Hamlin MJ, Manimmanakorn A. Long-term effect of whole body vibration training on jump height: Meta-analysis. J Strength Cond Res. 2014;28(6):1739–1750.
16. Wuestefeld A, Fuermaier A B, Bernardo-Filho M, et al. Towards reporting guidelines of research using whole-body vibration as training or treatment regimen in human subjects-A Delphi consensus study. PLoS One 15. 2020;1-24.
17. Ehlenz H, Grosser M, Zimmermann E. Krafttraining: Grundlagen, Methoden, Übungen, Leistungssteuerung, Trainingsprogramme. BLV. 2003.
18. Berschin G, Schmiedeberg I, Sommer HM, et al. Zum einsatz von vibrationskrafttraining als spezifisches schnellkrafttrainingsmittel in sportspielen. Leistungssport. 2003;4:11–13.
19. Bührle M. Maximalkraft–Schnellkraft–Reaktivkraft. Sportwissenschaft. 1989;4:311–325.
20. Young WB, Wilson GJ, Byrne C, et al. A comparison of drop jump training methods: Effects on leg extensor strength qualities and jumping performance massage and rolling massage view project resistance training responses and adaptations view project. Int J Sport Med. 1999;20:295–303.
21. Serge SC, Manuela P, Julien E, et al. Whole-body vibrtation training effects on the physical performance of basketball players. J Strength Cond Res. 2010;24(4):999–1006.
22. Baechle T, Groves B. Weight training instruction: Steps to success. Human Kinetics Pub. 1994.
23. Knauf A. Muskuläre annpassungen des Körpers auf Ganzkörpervibrationen im Krafttraining. DSHS. 1999.
24. Schlumberger A, Salin D, Schmidtbleicher D, et al. Krafttraining unter vibrationseinwirkung. Sportverletzung Sportschaden. 2001;15:1–7.
25. Ziegler J. Einzelfallstudie über den Einfluss eines Vibrationskrafttrainings in der Saisonvorbereitung eines professionellen Eishockeyspielers. DSHS. 2003.
26. Rehn B, Lidström J, Skoglund J, et al. Effects on leg muscular performance from whole-body vibration exercise: A systematic review. Scand J Med Sci Sports. 2006;17(1):2–11.
27. Torvinen S, Kannus P, Sieva H, et al. Effect of four-month vertical whole body vibration on performance and balance. Med Sci Sport Exerc. 2002;34:1523–1528.
28. Spitzenpfeil P. Vibrationsbelastungen im alpinen Skirennlauf: Analyse – Simulation. DSHS. 2000.
29. Cochrane DJ, Legg SJ, Hooker MJ, et al. The short-term effect of whole-body vibration training on vertical jump, sprint, and agility performance. J Strength Cond Res. 2004;18(4):828–832.
30. Rittweger J, Beller G, Felsenberg D, et al. Acute physiological effects of exhaustive whole-body vibration exercise in man. Clin. Physiol. 2000;20(2):134–142.
31. Rittweger J, Mutschelknauss M, Felsenberg D, et al. Acute changes in neuromuscular excitability after exhaustive whole body vibration exercise as compared to exhaustion by squatting exercise. Clin Phy Func Im. 2003;23(2):81–86.
32. Torvinen S, Kannus P, Sievähen H, et al. Effect of four-month vertical whole body vibration on performance and balance. Physical Fitness and Performance. 2002;1523-1528.
33. Kube J. Die einsetzbarkeit und wirkung von vibrationskrafttraining in verbindung mit konventionellen methoden der kraft- und schnellkraftentwicklung innerhalb einer vorbereitungsperiode im kurzsprint. DSHS. 2002.
34. Mahieu NN, Witvrouw E, Van De Voorde D, et al. Improving strength and postural control in young skiers: whole-body vibration versus equivalent resistance training. J Ath Train. 2006;41(3):286–293.
35. Bauersfeld M, Voß G. Neue wege im schnelligkeitstraining. Philippka Verlag. 1992.
36. Rønnestad B. Acute effects of various whole-body vibration frequencies on lower-body power in trained and untrained subjects. J Strength Cond Res. 2009;23(7):1309–1315.
37. Güllich A, Schmidtbleicher D. struktur der kraftfähigkeiten und ihrer trainingsmethoden. Dtsch. Z. Sportmed. 1999;50(7+8):223–234.

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND BIOMEDICAL SCIENCES

Original article

Evaluation of residues of pesticides on humans from medium plant of Rio Grande do Sul, Brazil

Vitória A. Rosano,[1] Gabriela E. Dal Pizzol,[2] Maria T. Friedrich,[3] Charise D. Bertol,[1,4] Luciana G. Rossato-Grando[1,2]*

Abstract

Introduction: Pesticide use in Brazil is widespread. General population is concerned about the risks of consuming food containing pesticide residues. Objective: The greatest contribution of this work is to highlight the absence of blood residual contamination in the population of medium plant of Rio Grande do Sul, Brazil, by the pesticides: atrazine, abamectin, chlorpyriphos and diuron. Materials and methods: Pesticide residues were extracted using QuEChERS approach and were quantified by liquid chromatography-mass spectrometry. Results: Most volunteers (92.75%) present normal levels of plasma cholinesterase and all volunteers do not present residues of any pesticide tested. Conclusion: This study demonstrates that even though the use of pesticides is widespread in our region, the population did not present blood residues or enzymatic changes suggestive of acute intoxication..

Keywords: Pesticides; Toxicity; Atrazine; Abamectin; Chlorpyriphos; Diuron.

1. Institute of Biological Sciences, University of Passo Fundo. Passo Fundo, RS, Brazil.
2. Graduate Program in Bioexperimentation. University of Passo Fundo, Passo Fundo, RS, Brazil.
3. Graduate Program in Food Science and Technology. University of Passo Fundo, Passo Fundo, RS, Brazil.
4. Human Aging Graduate Program. University of Passo Fundo, Passo Fundo, RS, Brazil.

***Correspondence address:**
Av. Brasil Leste, 285
Passo Fundo, RS, Brasil.
CEP: 99052-900.
E-mail: rossatoluciana@upf.br
ORCID: https://orcid.org/0000-0003-4574-855X

BJHBS, Rio de Janeiro, 2020;19(2):108-113

Recebido em 18/08/2020. Aprovado em 27/10/2020.

Resumo

Avaliação de resíduos de pesticidas em humanos do planalto médio do Rio Grande do Sul, Brasil

Introdução: O uso de agrotóxicos no Brasil é bastante difundido. A população em geral está preocupada com os riscos do consumo de alimentos com resíduos de agrotóxicos. Objetivo: A maior contribuição deste trabalho é destacar a ausência de contaminação residual sanguínea na população do plantalto médio do Rio Grande do Sul, Brasil, pelos pesticidas atrazina, abamectina, clorpirifós e diuron. Materiais e métodos: Os resíduos de pesticidas foram extraídos usando a abordagem QuEChERS e quantificados por cromatografia líquida-espectrometria de massa. Resultados: A maioria dos voluntários (92,75%) apresenta níveis normais de colinesterase plasmática e todos os voluntários não apresentam resíduos de nenhum pesticida testado. Conclusão: Esse estudo demonstra que mesmo o uso de pesticidas sendo amplo na nossa região, a população não apresentou resíduos no sangue ou alterações enzimáticas sugestivas de intoxicação aguda.

Descritores: Pesticidas; Toxicidade; Atrazina; Abamectina; Clorpirifós; Diuron.

Resumen

Evaluación de residuos de plaguicidas en humanos de planta mediana de Rio Grande do Sul, Brasil

Introducción: El uso de pesticidas en Brasil está muy extendido. La población en general está preocupada por los riesgos de consumir alimentos con residuos de plaguicidas. Objetivo: La principal contribución de este trabajo es resaltar la ausencia de contaminación sanguínea residual en la población de plantas medianas de Rio Grande do Sul, Brasil, por los pesticidas atrazina, abamectina, clorpirifos y diurón. Materiales y métodos: Los residuos de plaguicidas se extrajeron mediante el método QuEChERS y se cuantificaron mediante cromatografía líquida-espectrometría de masas. Resultados: La mayoría de los voluntarios (92,75%) tienen niveles normales de colinesterasa plasmática y todos los voluntarios no tienen residuos de ningún pesticida probado. Conclusión: Este estudio demuestra que a pesar de que el uso de plaguicidas está muy extendido en nuestra región, la población no presenta residuos sanguíneos ni cambios enzimáticos sugestivos de intoxicación aguda.

Palabras clave: Pesticidas; Toxidad; Atrazina; Abamectina; Clorpirifós; Diuron.

Introduction

Pesticides are extensively used to pest and ectoparasites control in agriculture and livestock. At domestic environment, they are employed as desiccants and repellents.[1] Between 2007 and 2014, pesticide sales increased 149,14%.[2]

The South of Brazil is a region where great part of the economy revolves around agribusiness. Currently, general population is concerned about food contamination by agrochemical residues and its consequences for human health. Thus, consumers are looking for organic diets to reduce this possible contamination.[3]

Human widespread exposure to pesticides is evidenced by the presence of organophosphate and pyrethroid metabolites and phenoxyacid herbicides in urine from people from Asia, Europe, North and Central America,[4,5] evidencing that human blood contamination are not restricted to agro-professionals.[6]

Population studies carried out in Brazil are also worrying. Between 2012 and 2013 organochlorine residues were described in blood from human population resident in Farroupilha, Rio Grande do Sul. Results suggest that chronic exposure to organochlori-nes are associated with immunosuppression.[7] Although this is a study also performed in Rio Grande do Sul, it only evaluated the presence of organochlorines, which have been gradually replaced to safer and non-persistent alternatives.

This study aims to evaluate the presence of abamectin, atrazine, chlorpyriphos, and diuron residues in human blood in the population from medium plant of Rio Grande do Sul, South of Brazil. We also evaluated plasmatic cholinesterase levels as a biomarker of organophosphate/carbamate intoxication.

Materials and Methods

Sample

The number of volunteers were defined through Simple Random Sample calculation. The equation considered the population from Passo Fundo, Rio Grande do Sul (200 thousand inhabitants). The confidence interval used was 99% with margin of error of 0.1%.

Two hundred volunteers are considered a number representative of this population. We recruited 207 volunteers, aging between 18 to 65 years old. Participants signed a free and informed consent. Blood (5 mL) was collected in EDTA tube, in 8 hours fasting condition and volunteers answered a short questionnaire containing basic personal information. Samples were collected between August and November 2018. This work was approved by the Ethics Commitee on Human Research (Protocol 2.802.812).

Plasma cholinesterase evaluation

Plasmatic cholinesterase (BuChE) was quantified using comercial kit (BioTécnica®, Brazil).

Pesticide residues

Pesticides evaluated in this work were selected due to their toxicological profile and widespread use in the studied region. General information about pesticides is summarized in Table 1.

Table 1. General information of agrochemicals evaluated in this work

Agrochemical	Class	Group	Toxicological class
Abamectin	Inseticide	Avermectin	Extremely toxic
Atrazine	Herbicide	Triazine	Moderately toxic
Chlorpiryphos – ethyl	Inseticide	Organophophate	Highly toxic
Diuron	Herbicide	Urea	Moderately toxic

Extraction of pesticide residues from human blood

The extraction of pesticide residues from human blood was performed using QuEChERS (Quick, Easy, Cheap, Effective, Rugged, Safe) approach.[8] The protocol used here was previously developed and validated to blood samples.

Extraction was performed adding 2 mL of extraction solution containing methanol: acetonitrile (30:70 + acidophormic acid 0.4%) to 1 mL total blood. After 1 min homogenization, 500 mg of a mixture containing 6 g magnesium sulphate and 1.5 g sodium acetate was added. Samples were centrifuged (5 min, 500 g) and 50 mg of a mixture containing 50 mg PSA and 150 mg magnesium sulphate was added to the supernatant. After 30 min homogenization, the supernatant was removed, filtered and freezed at -80 ºC until liquid chromatography coupled with mass spectrometry (LC/MS-MS) analysis.

LC/MS-MS analysis

A triple quadrupole Shimadzu LC/MS-MS 8040 equipped with a XR-ODS (150 x 2 mm, 2.2 µm) column and binary pump was used. The mobile phase consisted in water: methanol containing ammonium acetate (5 mmol L^{-1}).[9] Analysis was performed using a flow rate of 0.3 mL/min and 10 µL of injection volume. Mass detector was triple quadrupole equipped with electrospray ionization (ESI) in the positive mode operating in MS-MS scanning mode. Total run time is 15 min.[8] In Table 2, the chromatographic conditions are described.

Table 2. Chromatographic conditions such as retention time, precursor and product ions, collision, and cone energies from pesticides analyzed by LC/MS-MS

Pesticides	Retention Time (min)	Quantifications transition			Confirmations transition			Limits of detection/ quantification (ppb)
		Precurson ion	Production ion	Energy	Precurson ion	Production ion	Energy	
Abamectin	12.01	890.7	305.2	28	890.7	567.40	15	143.01/433.36
Atrazine	7.39	216.1	174.1	17	216.1	96.10	25	114.10/345.77
Chlorpiryphos-ethyl	11.11	349.8	97.0	34	349.8	198.00	48	56.09/169.97
Diuron	7.62	233.0	72.0	21	233.0	160.10	26	127.18/385.39

Results & Discussion

The major finding of this work is to evidence the absence of blood contamination and cholinesterase changes induced by pesticides in general people from medium plant, Rio Grande do Sul, Brazil. To the best our knowledge, this is the first report of blood contamination in this population. The characteristics of studied population are summarized on Table 3.

Organophosphates and carbamates inhibit acetylcholinesterase. This inhibition causes acetylcholine accumulation and, consequently, nicotinic (muscle stiffness, paresis, paralysis) and muscarinic (bradycardia, sudoresis, high intestinal motility) effects. Severe poisoning is associated with central symptoms such as seizures.[10] The majority of volunteers (92.75%) presented normal levels of cholinesterase (Figure 1). This result was expected since this is a populational study and enzyme inhibition occurs only in acute exposure compatible with occupational exposure. However, ten individuals (nine women and one man) presented cholinesterase inhibition, but none of them reported having daily contact with pesticides beyond the possible food contamination. This decrease can be related to verminosis, hepatic disorders[11] and when estrogen is high during fertile period.[12] Other five volunteers presented elevated cholinesterase levels. This change might be related to pathologies such as diabetes and hypertension.[11]

We did not detect any of the researched pesticides in blood. This is an important finding, since it enhances the safety to consumers. In Brazil, despite popular concerns, the Program for Analysis of Pesticide Residues in Food (PARA, from ANVISA), revealed that between 2013 and 2015, 80.3% of analyzed food was considered satisfactory for pesticide waste. It was not

Table 3. Studied population (n=207)

	N	%
Age, years*		
Mean(SD)	33.47 (±13.14)	
Sex		
Male	66	31.88
Female	141	68.12
Profession		
Rural workers	14	6.76
Students	78	37.68
Non rural workers	16	7.73
Organic food consumers		
Yes	104	50.24
Sometimes	35	16.91
Few times	4	1.93
No	50	24.15
Iindifferent	14	6.76

***Mean**

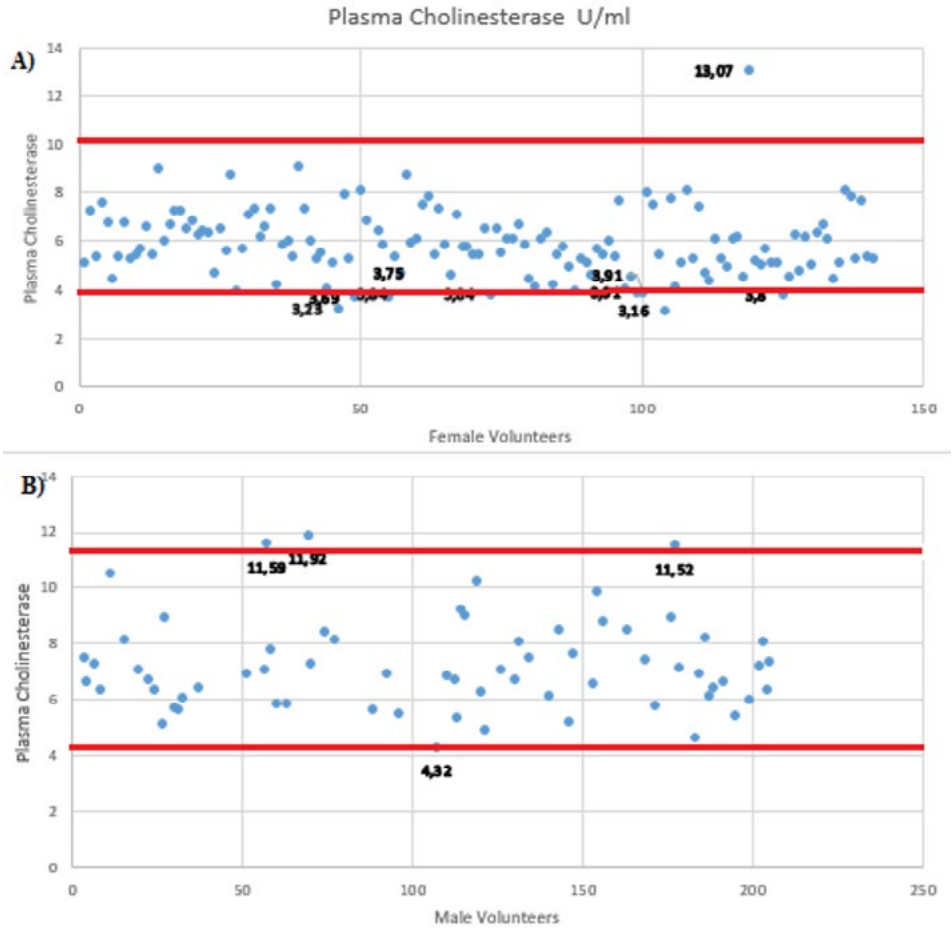


Figure 1. Plasmatic levels of cholinesterase in volunteers. The red lines delimitate reference values (3,93 – 10,80 U/mL female volunteers and 4,62 – 11,50 U/mL male volunteers)

detected pesticide waste in 42% of food sampled and 38.3% presented pesticide waste less than or equal to maximum allowed limit which is considered safe.[13] However, chlorpiryphos was present in 342 occurrences in non-approved crops and 1 occurrence with waste higher than maximum allowed limit,[13] evidencing irregularities in the use of chloriryphos in this country.

From 383 pesticides tested in 27 blood samples of Pakistani rural workers, only chlorpyrifos (0.009 mg/L) was found in 1 volunteer. This result suggests the possible degradation of the other residues during this period. It is important to consider that, in general, organophosphates are rapidly metabolized in the environment.[14] *In vivo*, their metabolism is relatively fast, and the majority suffers hepatic biotransformation before inhibit acetylcholinesterase. Symptoms of intoxication reach the peak 5 to 8 hours after contact depending on absorption pathway and exposure dose.[15] Little is known about abamectin degradation route. It is known that abamectin is rapidly absorbed and it is classified as non-persistent in soil and water, despite its leaching power.[16,17] Diuron is considered one of the most dangerous herbicides to the environment with half-life up to 30 days due to low solubility in water and high chemical stability.[18] Atrazine' half-life in soil is 50 days and from 105 to 200 days in water, being one of the pesticide most detected in water.[19] Despite pharmacokinetic particularities, human blood contamination by pesticides was already reported.[6]

Recently, our research group analyzed pesticide residues in organs from owls found dead to evaluate possible bioaccumulation. Although owls did not

present any blood residue, we found traces of chlorpiryphos-ethyl in liver from 2 samples (unpublished results). Thus, the absence of blood contamination does not exclude the possibility that pesticide residues are accumulating in another human organs.

Studies describing the possible contamination of humans with pesticide are important considering health effects in man from exposure to pesticides. This is also a subject of concern to the population considering the strong association of pesticide exposure to several types of cancer and neurotoxicity.[2]

Even the pesticides studied are widely employed in our region, for the first time it is shown that the resident population does not present residues in blood or enzymatic changes suggestive of acute intoxication related to this exposure. This is an important finding which can increase the sense of security related to agrarian practice.

References

1. Costa ET. Boletim epidemiológico. 48th ed., 2009; p.1-13.
2. Almeida MD, Cavendish TA, Bueno PC, et al. A flexibilização da legislação brasileira de agrotóxicos e os riscos à saúde humana: análise do projeto de lei nº 3.200/2015. Cad Saúde Pública. 2017;33(7):01-11
3. Hyland C, Bradman A, Gerona R, et al. Organic diet intervention significantly reduces urinary pesticide levels in U.S. children and adults. Environ Res. 2019;171(1):568-75.
4. Li AJ, Martinez-Moral M, Kannan K. Temporal variability in urinary pesticide concentrations in repeated-spot and first-morning-void samples and its association with oxidative stress in healthy individuals. Environ Intern. 2019;130:104904.
5. Sierra-Diaz E, Larosa AC, Lozano-kasten F, et al. Urinary Pesticide Levels in Children and Adolescents Residing in Two Agricultural Communities in Mexico. Int J Environ Res Public Health. 2019;16(4):562.
6. Latif Y, Sherazi STH, Bangher MI, et al. Evaluation of Pesticide Residues in Human Blood Samples of Agro Professionals and Non-Agro Professionals. AJAC. 2012;8(3).
7. Piccoli C, Cremonese C, Koifman R, et al. Occupational exposure to pesticides and hematological alterations: A survey of farm residents in the South of Brazil. Cien Saúde Colet [Internet]. 2017 Sep [Cited 2019]. Available from: http://www.cienciaesaudecoletiva.com.br/artigos/occupational-exposure-to-pesticides-and-hematological-alterations-a-survey-of-farm-residents-in-the-south-of-brazil/16406?id=16406&id=16406.
8. Friedrich MT, Martins M, Prestes O, et al. Use of Factorial Design in the Development of Multiresidue Method for Determination of Pesticide Residues in Wheat by Liquid Chromatography-Tandem Mass Spectrometry. Food Anal Methods. 2016;9(9):2541-51.
9. Romero-González R, Frenish AG, Vidal JI, et al. Simultaneous determination of pesticides, biopesticides and mycotoxins in organic products applying a quick, easy, cheap, effective, rugged and safe extraction procedure and ultra-high performance liquid chromatography–tandem mass spectrometry. J Chromat A. 2011; 1218(11):1477-85.
10. Chielle EO, Bergmann WCK, Pereira DL. Avaliação da Expressão Sérica da Enzima Colinesterase e de Marcadores Bioquímicos Hepáticos e Renais em Plantadores de Tabaco. Unoesc & Ciência [Internet]. 2015 Jun [Cited 2019];6(2). Available from: https://editora.unoesc.edu.br/index.php/acbs/article/viewFile/7802/5056.
11. Soares W, Almeida RM, Moro S. Trabalho rural e fatores de risco associados ao regime de uso de agrotóxicos em Minas Gerais, Brasil. Cad Saúde Pública. 2003;19(4):1117-27.
12. Ott DR, Silva LLM, Toscani NV, et al. Variação dos Níveis de Colinesterase Eritrocitária e Plasmática ao Longo do Ciclo Menstrual. Cien Saúde [Internet] 2018 Out [Cited 2019];16. Available from: https://www.lume.ufrgs.br/bitstream/handle/10183/73767/Resumo_20040655.pdf?sequence=1.
13. Gerência-Geral de Toxicologia. Programa de Análise de Resíduos de Agrotóxicos em Alimentos – PARA. [Internet]. Brasília (DF). Available from: http://portal.anvisa.gov.br/documents/219201/2782895/Relat%C3%B3rio+PARA+Vers%C3%A3o+Final/1230de7d-306d-4249-a62c-a68708fab153.
14. Nakagawa LE, Luchini LC, Musumeci MR, et al. Comportamento da atrazina em solos brasileiros em condições de laboratório. Pes Agrop Bras, 1995;30(4):471-76.
15. Marrs RH, Frost AJ, Plant RA, et al. Determination of buffer zones to protect seedlings of non-target plants from the effects of glyphosate spray drift. Agric Ecosys Environ. 1993;45:283-93.
16. Carvalho GA, Carvalho SM, Carvalho CF, et al. Toxicidade de acaricidas/inseticidas empregados na citricultura para a abelha africanizada *Apis melifera L*. Arq Inst Biol, 2009;76(4):597-606.
17. Silva GS, Junior ECA, Junior ACA, et al. Avaliação da Potencial Contaminação das Águas Superficiais e Subterrâneas por Agrotoxicos em Áreas de Produção de Uva para Exportação no Vale do São Francisco. Assoc Bras Eng Amb Sanit, 2014;12(1):1-7.
18. Mansano AS. Efeitos dos agrotóxicos diuron e carbofuran, isolados e em mistura, sobre organismos aquáticos e avaliação de risco ecológico. [Dissertation]. São Carlos- SP. Universidade Federal de São Carlos; 2016. 238p.
19. Dores EFGC, De-Lamonica-Freire EM. Contaminação do ambiente aquático por pesticidas. Estudo de caso: águas usadas para consumo humano em primavera do leste, mato grosso - análise preliminar. Quím. Nova. 2001;24(1):27-36.

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Review article

Keep your droplets to yourself: Universal use of face masks along with social distancing

Helena Carvalho,[1]* Daniel Contaifer Jr.,[2] Renata N. Aranha,[3] Juliana A. de Matos[4]

Abstract

Introduction: As the COVID-19 pandemic progresses around the world, the universal use of face masks imposes itself as a measure to mitigate the transmission of SARS-CoV-2 and is currently recommended by the World Health Organization. However, its effectiveness as a method of preventing COVID-19 is still controversial. Objective: To review the literature on the universal use of facial masks, including fabric ones, and their recommendations for use. Methods: Narrative review of published studies on the topic. Results: Face masks act predominantly as a source control mechanism, as they capture the droplets expelled by the user when speaking, coughing or sneezing, protecting other people and the environment from contamination by potentially infecting droplets. Evidence of the effectiveness of its universal use as a method of mitigating epidemics of viral respiratory infections is derived from experimental studies and mathematical models. Proper use of facial masks is essential to ensure their effectiveness and prevent damage, and includes covering the nose, mouth and chin, washing the fabric masks with soap and water after use and hand hygiene several times a day, especially when handling the mask. Conclusions: The universal use of facial masks in the context of the COVID-19 pandemic is justified, especially considering the occurrence of virus transmission in the pre-symptomatic period, and should be adopted in conjunction with other measures such as adequate social distance and hygiene from the hands, following the motto "I protect you and you protect me".

Keywords: Coronavirus infections; Masks; Prevention & control.

1. Department of Basic Sciences Education. Virginia Tech Carilion School of Medicine. Roanoke, VA, USA.
2. Department of Pharmacotherapy and Outcomes Sciences. School of Pharmacy, Virginia Commonwealth University, Richmond, VA, USA.
3. Department of Gynecology and Obstetrics, Faculty of Medical Sciences. State University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
4. Laboratory for Research on Immunization and Health Surveillance. National Institute of Infectious Diseases Evandro Chagas, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil.

***Correspondence address:**
Department of Basic Science Education
Virginia Tech Carilion School of Medicine
1 Riverside Circle, Suite 202. Roanoke, VA, USA. 24016
E-mail: helena@vt.edu
ORCID: https://orcid.org/0000-0001-9607-2452

BJHBS, Rio de Janeiro, 2020;19(2):114-123

Received on 26/06/2020. Approved on 06/10/2020.

Resumo

Mantenha suas gotículas para si mesmo: uso universal de máscaras faciais e distância social

Introdução: À medida que a pandemia de COVID-19 progride em todo o mundo, o uso universal de máscaras faciais se impõe como uma medida para mitigação da transmissão do SARS-CoV-2, sendo atualmente recomendado pela Organização Mundial de Saúde. No entanto, sua eficácia como método de prevenção da COVID-19 ainda é controversa. Objetivo: Revisar a literatura a respeito do uso universal de máscaras faciais, incluindo as de tecido e suas recomendações de uso. Métodos: Revisão narrativa de estudos publicados sobre o tema. Resultados: As máscaras faciais atuam predominantemente como um mecanismo de controle de fonte, pois capturam as gotículas expelidas pelo usuário ao falar, tossir ou espirrar, protegendo outras pessoas e o ambiente da contaminação por gotículas potencialmente infectantes. As evidências da eficácia do seu uso universal como método de mitigação de epidemias de infecções respiratórias virais derivam de estudos experimentais e modelos matemáticos. O uso adequado das máscaras faciais é fundamental para garantir sua eficácia e prevenir danos e inclui cobrir o nariz, boca e queixo, lavar as máscaras de tecido com água e sabão após o uso e higienizar as mãos várias vezes ao dia, especialmente ao manipular a máscara. Conclusões: O uso universal de máscaras faciais no contexto da pandemia de COVID-19 é justificado, especialmente considerando a ocorrência da transmissão do vírus no período pré-sintomático, e deve ser adotado em conjunto com outras medidas como o distanciamento social adequado e a higiene das mãos, seguindo a máxima "eu te protejo e você me protege".

Descritores: Infecções por Coronavírus; Máscaras; Prevenção & controle.

Resumen

Mantén tus gotas para ti: uso universal de mascarillas junto con distancia social

Introducción: A medida que avanza la pandemia de COVID-19 en todo el mundo, el uso universal de mascarillas se impone como una medida para mitigar la transmisión del SARS-CoV-2 y actualmente es recomendado por la Organización Mundial de la Salud. Su efectividad como método para prevenir COVID-19 aún es controvertida. Objetivo: Revisar la literatura sobre el uso universal de las máscaras faciales, incluidas las de tela, y sus recomendaciones de uso. Métodos: Revisión narrativa de estudios publicados sobre el tema. Resultados: Las mascarillas actúan predominantemente como un mecanismo de control de la fuente, ya que capturan las gotitas expulsadas por el usuario al hablar, toser o estornudar, protegiendo a otras personas y al medio ambiente de la contaminación por gotitas potencialmente infecciosas. La evidencia de la efectividad de su uso universal como método para mitigar epidemias de infecciones respiratorias virales se deriva de estudios experimentales y modelos matemáticos. El uso adecuado de las mascarillas faciales es fundamental para asegurar su eficacia y evitar daños, e incluye cubrirse la nariz, la boca y el mentón, lavar las mascarillas de tela con agua y jabón después de su uso e higiene de manos varias veces al día, especialmente al manipularlas. la máscara. Conclusiones: Se justifica el uso universal de mascarillas faciales en el contexto de la pandemia COVID-19, especialmente considerando la ocurrencia de transmisión del virus en el período presintomático, debiendo ser adoptado en conjunto con otras medidas como la adecuada distancia social e higiene de las manos, siguiendo la máxima "Yo te protejo y tú me proteges".

Palabras clave: Infecciones por Coronavirus; Mascarillas; Prevencion & control.

Introduction

The world is experiencing an emergency scenario in dealing with COVID-19. While there is not an effective treatment or vaccine, non-pharmaceutical prevention methods have been adopted as a means of mitigating the spread of its causative virus, SARS-CoV-2. These methods comprise different approaches to minimize social contact, from shelter-at-home policies to city lockdown; face mask ordinances; universal symptom survey; contact tracing and quarantine of all confirmed and potential cases and exposed individuals, among others. The effectiveness of these methods should be constantly assessed by monitoring infection rates and effective reproduction numbers, considering data continuously drawn from different sources, including surveillance data and results of serological surveys designed to estimate population immunity.[1] Many of these methods have been compromised due to limited availability of tests. Non-pharmaceutical methods applied to new viruses are also prone to variabilities in their efficacy due to the necessity of population adherence.

It is currently not possible to identify all carriers due to the lack of available universal testing, besides the limitations of performance of existing tests. In addition, it must be noted that evidence has shown that infected people can be contagious shortly before symptoms begin, the so-called pre-symptomatic period, i.e., the last 2 days of the incubation period, which can last on average 5-6 days, and up to 14 days.[2] Preliminary evidence suggests that transmission by truly asymptomatic individuals is also possible.[3] Therefore, it is advisable to adopt barrier measures, such as the consistent use of face masks by all individuals, along other non-pharmaceutical measures, to mitigate the effects of the pandemic.

In the context of the developing pandemic, the universal use of face masks is a low cost and simple measure that can be easily implemented. However, the recommendation of universal use of face masks by the general population has been delayed by the official health authorities in several countries, causing confusion and controversy about the correct application of the measure. Notwithstanding, the resistance to use face masks seems inconsistent with the knowledge of the virus' transmission, either by droplets from the respiratory tract or by contact with surfaces contaminated by respiratory secretions containing viable viral particles.

In many countries where using masks in public was considered a stigma, now its use has been introduced as a new paradigm of social behavior and health protection. Countries like Austria, Brazil, Czech Republic, China, Hong Kong, Israel, Italy, Japan, Mongolia, Singapore, South Korea, Taiwan, Turkey, and the United

States have taken varied steps to advocate universal masking as an additional measure to reduce community transmission of SARS-CoV-2.[4-6]

Our goal is to review the risks and benefits of universal use of face masks for the general population and recommendations for its use, while contributing to the awareness of the general population about its value.

Non-pharmaceutical Measures Recommended During Pandemic

Thus far, health authorities have struggled to implement effective measures of mitigation of COVID-19 pandemics. Regardless of the chosen strategy, the economic cost to society will be significant until the pandemic is under control.[7]

At the beginning of the COVID-19 outbreak, all cases of symptomatic patients, regardless of severity of the disease, were usually dealt with by an emergency method of containment, where isolation of all cases is the primary method to control the spread of the disease. This strategy requires the patient to be placed in airborne isolation rooms, under supervision of health care professionals using adequate personal protective and other disposable equipment until active transmission of the virus is ruled out. However, it is estimated that a high percentage of infected patients have minimal or mild symptoms, therefore, the virus would already be silently spreading through the population before detection and isolation occurs.[8] Evidence has shown that asymptomatic individuals can shed viral particles (defined as a positive PCR test for SARS-CoV-2 on nasopharyngeal swab) with a median duration of 19 days (interquartile range: 15-26 days), while the shortest duration detected is 6 days, and the longest, 45 days. In mild symptomatic patients the median duration of viral shedding was 14 days.[9]

In addition, limitation of availability and performance of molecular tests, cultural and economic challenges can compromise the ability of the containment strategy to control the dissemination of the virus, leading to the community transmission of SARS-CoV-2. In this scenario, the containment strategy must be substituted by a mitigation one, to prevent the increased number of hospitalizations that overwhelm the healthcare system with patients infected with SARS-CoV-2. Mitigation strategy is generally based on the recommendations of handwashing, closing of schools and businesses, travel limitations, social distancing, and home quarantine of mild symptomatic cases and groups of more susceptible individuals (e.g. elders and adults with chronic ailments such as diabetes and cardiovascular diseases.[10] Mitigation measures are aimed to decrease the burden on the health care system, allowing the health care system to be better prepared for treatment of moderate and severe cases. Therefore, it is suggested that a combination of case isolation, social distancing of the entire population and either household quarantine or school and university closure are required.[11] Nonetheless, although the mitigation strategy using non-pharmaceutical measures mentioned above were common sense among health agencies such as the World Health Organization (WHO), the Centers of Disease Control and Prevention of the United States (CDC), and the Brazilian Ministry of Health (MS), the recommendation for wearing masks by the general population was delayed.

The use of face masks is an attractive public health measure because of its low cost and speed of implementation: it is easier to execute than other more complicated strategies that have been successfully adopted in other countries to control the disease, such as mass testing, contact tracing, and hospitalization of positive patients even with mild forms of the disease. Currently, Brazil has adopted the universal use of face masks in public places. The use of face masks in Brazil by the general population has been increasing since April 1st, when the Minister of Health in Brazil published guidelines on how to make face masks and how to properly use them.[12]

Rational for use of Face Masks as a Preventive Meaasure Against COVID-19

Face masks, as other barrier prevention methods, can be used as a means to prevent individuals with confirmed or suspected infections from spreading respiratory contaminated droplets, i.e., as a source control measure. They can also be used to protect susceptible individuals from acquiring an infection, i.e., as an individual protective measure.[13]

There is considerable controversy in medical literature regarding nomenclature of respiratory particles of different sizes. WHO and CDC postulate that the particles of more than 5 μm as droplets, and those less than 5 μm as aerosols or droplet nuclei. Droplets tend to remain trapped in the upper respiratory tract (i.e., nose and throat), whereas aerosols or droplet nuclei have the potential to be inhaled into the lower respiratory tract (the bronchi and alveoli in the lungs).[14]

Respiratory droplets can be produced through breathing, talking, or coughing.[15] Droplets smaller than

100μm in diameter will dry out before falling approximately 2 meters to the ground, forming the basis for the theory of droplet nuclei transmission depending on the size of the infected droplet. Droplet nuclei can be carried by the movement of air into the surrounding air spaces during daily activities as result of walking, or the opening of a door.[16]. It is said that most viral charge is transmitted in larger droplets, when we cough, sneeze, or talk. Minimizing the viral discharge into the atmosphere (i.e., use as control of source), particularly in larger droplets, is believed to be highly advantageous, and therefore, mechanical blockage in relatively simple masks is efficient in this case.

Filtration in masks uses three mechanisms. The first one is mechanical blockage of droplets that are of a size (e.g. >5 μm) comparable to or larger than the mean space between the filaments that embody the mask as cellulose, cotton, etc. Moreover, large particles, and in this case, large virus-carrying droplets cannot penetrate the material. The second mechanism is filtration of very small particles or droplets (e.g., <200 nm) by direct collision with the mask filaments. Brownian motion causes very small droplets to move in a zig-zag motion and collide with the mask material. Filtration of very small particles is therefore relatively efficient. Respirators (e.g. N95) have the additional third filtration mechanism based on electrostatic attraction. Particles of intermediate size (e.g. 0.3-1 μm) are attracted to the mask filament due to a residual electrical charge that they have.[17]

It is believed that the transmission of the small coronavirus takes place primarily transported in larger water droplets. However, since the SARS-CoV-1 (predecessor of the SARS-CoV-2) was found spreading in the air during the 2003 epidemic, it has been speculated that SARS-CoV-2 be transmitted by the same mechanism.[18] The possibility that SARS-CoV-2 is not only transmitted by virus-containing droplets (5 to 10 μm of diameter) but also by aerosols (≤5 μm) has created a popular question if face masks can be efficient against this virus. Although it is not clear that airborne transmission through aerosols is occurring with SARS-CoV-2, as was proposed for SARS-CoV-1 outbreak in 2003,[19] more studies are necessary to ascertain the same for SARS-CoV-2. Nonetheless, the cautious approach assumes this possibility and reinforces the use of face masks as a critical barrier for reduction of transmission and infection.[20]

Transmission of SARS-CoV-2 by aerosol has long been recognized in the context of aerosol producing procedures in health care facilities by WHO, CDC, among other entities, but its role on community spread of disease was never admitted.[18] SARS-CoV-2 in aerosol (< 5μm) is viable for about 3 hours and can be found on any surface. However, the virus has been found to be more stable on plastic and stainless steel than on copper and cardboard. In this particular study, a viable virus was detected up to 72 hours on plastic and stainless steel, although with a greatly reduced viral titer.[21]

Covering the mouth and nose with a surgical or cloth face mask, instead of a respirator, can trap the large infectious droplets that are expelled when the wearer is speaking, coughing or sneezing, thereby protecting other people from the wearer (i.e. source control). However, it's value as an individual protective measure is questionable. Interesting, even though there is no direct evidence that a person wearing a face mask is protected from developing COVID-19, some studies have shown the effectiveness of surgical masks to protect against Influenza and other common seasonal coronaviruses.[22] Moreover, there is some evidence that masks protect the wearer by reducing the inoculum of virus, which results in milder disease.[23] The authors on this later study point out that the use of face masks might be in part responsible for asymptomatic and milder disease with lower mortality contrasting with the beginning of the pandemic, when face masks weren't being used by the general population.

Medical Versus Non-Medical Face Masks

A recent meta-analysis study found consistent evidence that in addition to other infection control measures, the use of medical masks (surgical masks and N95 respirators) by health professionals is effective at reducing the risk of contagion of respiratory diseases.[24] However, the WHO emphatically states that fabric masks (for example, cotton or gauze) are not justified under any circumstances for use by health professionals.[25] Evidence against the use of fabric masks by health professionals comes from a cluster randomized study in which health units were randomly assigned for one of three patterns of use of face masks: universal use of surgical masks, universal use of fabric masks (two layers of cotton) or use of masks according to the unit standard (control). The inclusion of a control arm without face masks was considered unethical and discarded. In this study, the number of respiratory infections and cases of flu-like syndrome was higher in the fabric mask group than in both the universal surgical mask group and the

standard use group. However, the professionals who were in the group "universal use of surgical mask" received two masks per 8-hour shift, whereas those in the group that used the fabric masks were instructed to wear a single mask per shift, which should be washed daily after use with soap and water and worn again the following day.[26] It is known that the prolonged use of face masks causes their saturation by the humidity of the breath, compromising their filtration capacity.[27] Therefore, there was no valid comparison between the arms "universal use of surgical mask" and "universal use of cloth mask". Neither could the impact of using the cloth mask be evaluated versus the absence of a mask. Based on the results of the study, the authors concluded that the use of cloth masks by health professionals during care of sick patients is not to be recommended, which undoubtedly represented an advance on safety for healthcare professionals. The validity of the universal use of cloth masks for the general population, under the circumstances of a pandemic of a deadly respiratory infectious disease, was not addressed by this study.

The use of cloth face masks by the general population was already supported by a few scientific publications when the world assumed that the next pandemic would be an emerging influenza virus.[28] These studies focused on the filtration capacity of cloth masks compared to surgical masks and respirators (N95, PFF-2 and similar).[26,29] The results indicated that cloth masks have a lower filtration capacity (from around 50% to 70%, depending on the material) than surgical and respirator masks (more than 95%), but also demonstrated that some filtration capacity exists depending on the type of fabric used in its manufacturing. These comparative studies considered that based on the risk to the overall population, although cloth masks are likely to reduce the exposure and infection spread at some level, they are not as efficient as surgical masks. For this reason, cloth masks are not recommended to health professionals, while it can be used by the general population.

Zangmeister et al tested the efficiency of 32 cloth materials used in face masks to filter nanometer-sized particles to micrometer-sized droplets calculating the filtration effectiveness of the fabric.[30] They found that woven 100% cotton with high to moderate yarn counts had the best performance, while synthetic fabrics yield the poorest performance. Also, in this regard, Verma et al found that face masks with multiple layers of cotton quilting fabric and well fitted to the wearer face was the most effective to reduce droplets dispersal. Otherwise, loosely folded face masks and bandana-style covering were the least effective.[31]

In a recent study Aydin et al used mechanical methods to evaluate common cloth masks efficiency by challenging the fabrics with high and low-velocity droplets with use of a metered-dose inhaler loaded with a suspension of 100 nm fluorescent beads in distilled water to create the droplets range from 0.1 mm to 1 mm. They found that effectiveness of fabric masks is dependable on four main factors. The breathability, the porosity, the hydro-affinity, and the fitness to the wearer face.[32] The fabric of choice should be breathable as well as impermeable to the impact from high and low-velocity droplets. It is important to notice the anti-correlation of porosity and breathability of a fabric. With low fabric porosity, and bad fit to the wearer face, the flow of air is directed to the sides and other points of leakage on the mask, decreasing its effectiveness. Interestingly, the authors suggest that the high hydro-affinity of fabric on two-layered t-shirt face masks contribute to blocking high volume droplets. Moreover, it has been reported in another study that, independently of the fabric of choice for homemade face masks, the performance of efficient block droplets is dependent on the fit of the mask on the wearer face.[33]

Universal Use of Face Masks for the General Population

The arguments supporting the universal use of face masks by the general population have been debated since the start of the pandemic. As the disease progresses around the world, the decision to adopt such a feasible and potentially effective measure can result in a significant number of lives spared. Studies using mathematical models, with or without implementing lockdown, indicates that if the population wears a face mask 100% of the time combined with lockdown, the desired impact in mitigating the spread of COVID-19 such as flattening the curve and preventing secondary and tertiary waves of infections can be achieved.[34, 35] Most importantly, the results apply even considering face masks would have only 50% effectiveness at capturing viruses from respiratory droplets, i.e., similar to the effectiveness of cloth face masks.[34] Also, these simulations indicate that use of face masks by the general public could potentially diminish community transmission and alleviate the burden of the pandemic.

The rationale for universal use of face masks comes from increasing evidence that viral transmission by

infected individuals who have very mild symptoms, or who are asymptomatic, can have a more relevant role in the spread of the disease than previously assessed.[36,37] Even more critical is the evidence that the immunity against SARS-CoV-2 from survivors of COVID-19 may only lasts 2 months. This means that previously infected individuals could potentially become re-infected and contagious. Therefore, carriers, when wearing the face mask, would avoid the contamination of susceptible people and the environment, as the face mask would create a barrier for the respiratory droplets eliminated during breathing.[38]

Respiratory etiquette has changed with time (Figure 1). In the past coughing/sneezing openly was accepted. Then with knowledge of airborne disease, covering a cough/sneeze with hands became the norm. Later, to prevent the spread of germs through contaminated hands or handkerchief, the use of the elbow to cover a cough/sneeze was recommended. Currently, the use of face masks is becoming socially acceptable to keep droplets to oneself, even in countries where it used to be a stigma (e.g. western countries).

Currently the recommendation for the general population is to wear a face mask all the time, except with people in the same quarantine pod or outside with good ventilation. Pods are a small self-containing network of people who limit their non-distance social interaction with one another. The implication is that even in someone's house if they receive a visitor from outside the pod, all people should wear a face mask while in the presence of a person from outside the pod. It is not recommended, however, for individuals with limited compliance and/or risk of suffocation with masks, such as those with mental health disorders, developmental disabilities, and children. For these groups, face shields may be considered as an alternative, even though they are inferior to face masks in preventing droplet transmission.[25]

However, the WHO has identified potential pitfalls from the use of face masks by the general population and indicated the following potential risks that should be carefully taken into consideration in any decision-making process: self-contamination by touching and reusing contaminated face masks; potential breathing difficulties depending on the type of face mask used; a false sense of security, potentially leading to lower adherence to other preventive measures such as physical distancing and hand hygiene; diversion of resources from effective public health measures, such as hand hygiene; and diversion of medical mask supplies and consequent shortage of proper masks for health-care workers.[39]

In a review study of the social behavior related to the use of face mask, the authors discussed that the adherence to proper use and disposal of masks would be difficult to implement in a short time, and the risk of improper use of it could end up facilitating the transmission of the virus, instead of decreasing

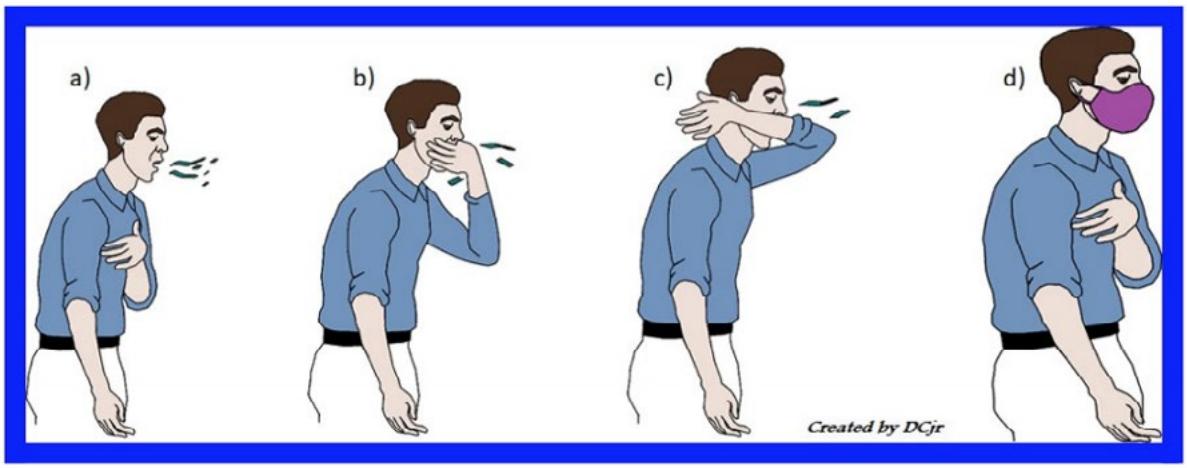


Figure 1. Respiratory etiquette evolution according to perceived social behavior. a) Openly coughing/sneezing without protection; b) cover cough/sneeze with hands; c) cough/sneeze into the elbow to prevent hands contamination; d) currently recommended use of face mask to keep drops to oneself

it, which may offset its potential benefit.[40] It points to the urgency to educate the general population on how to correctly use face masks, and why and when to quarantine asymptomatic and symptomatic patients. Therefore, with education, the use of face masks is an important tool for everyone, given their contribution to the well-being of the population.

Regarding the question of diversion of medical mask supplies, the use of cloth masks represents a cheap and feasible alternative for sparing those supplies while conferring protection for the population. Another advantage, especially relevant in low income countries, is the role of production and commercialization of cloth face masks as a source of income for families already abated by the economic crises. It is of paramount importance, however, to provide clear instructions not only regarding the adequate use of face masks by the population, but also the adequate confection and maintenance.

Cloth Face Masks and Proper Care Procedures

The necessity for clear guidelines on the use of cloth face masks has grown over time, and the benefits for wearing face masks by asymptomatic individuals became justifed by evidence that they possess some filtering capacity and are an alternative when surgical masks are in limited supply. It is clear that homemade masks are cheap, washable, easy to make, and can be used by the general population without imposing extra cost to local governments.

The recommendation for homemade face masks is to use 100% cotton fabric, such as cotton from T-shirts, antibacterial or normal pillow covers, or dish towels.[41] Despite the lack of conclusive evidence regarding the benefit of adopting the universal use of face masks, the spontaneous use of them by the population is already noted. Initiatives for "do it yourself" projects to alleviate the burden of mass production of personal protective equipment (PPE) have stirred the imagination and creativity of the people wanting to engage in helping at this stressful moment.[42] For example, concern regarding the effectiveness of homemade face masks in protecting the asymptomatic public has led to added treatments of starch to increase the pathogenic droplet absorption of the fabric, and salt to improve virus deactivation.[43] These initiatives highlight that it is necessary to provide guidance on the best way to make homemade face masks in order to avoid risks related to inappropriate use.

Based on the best practices for use and manipulation of face masks by health authorities and on scientific publications presented in our review, we suggest a simple and safe procedure for use of the face mask in public. Figure 2 displays the correct use and handling of the face mask. The procedure includes covering the nose, mouth and chin with the face mask. Avoid uncovering the nose or the mouth to speak when in presence of others. To remove the mask, use the mask handle and never touch the front of the used mask.

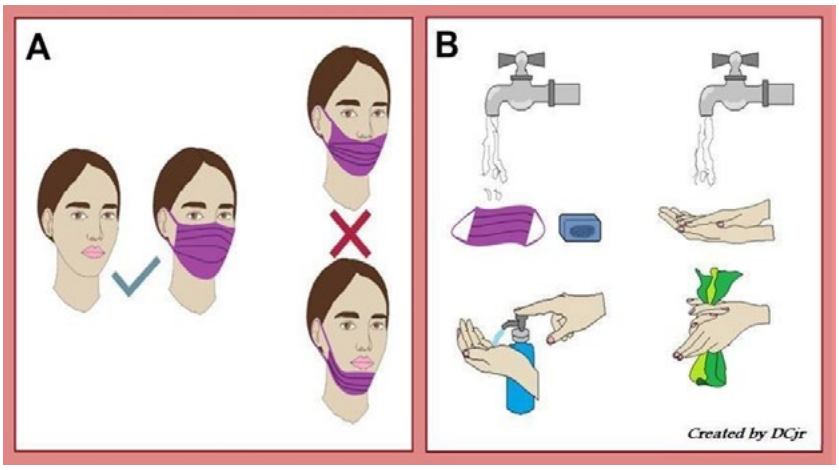


Figure 2. Recommendation of best practices on how to manipulate a mask as a non-pharmaceutical measure to combat COVID-19. A) Face masks must cover the nose, mouth and chin. Do not uncover your nose and mouth to speak nearby other people. To remove the mask, use the masks handle and never touch the front of used mask. B) After removing the mask, hands must be cleaned with hand-sanitizer with at least 60% ethanol and reusable masks must be washed with soap or laundry detergent

After their use, the mask must be washed with soap or laundry detergent. The hands also need to be cleaned with soap and water, or hand-sanitizer containing at least 60% ethanol. More detailed information on how to prepare/manipulate the face mask can be found on Table 1.

Conclusion

From this literature review, we recommend the universal use of face masks by the general population as an additional resource to already established non-pharmacological measures as maintaining social distance (Figure 3) and hand hygiene, providing an

Table 1. Guidance and practical considerations - Adapted from WHO and Brazilian Health Surveillance National Agency (ANVISA) guidelines[6, 25]

Fabric selection:
Choose materials that capture particles and droplets but remain easy to breathe through.
Avoid stretchy material for making masks as they provide lower filtration efficiency during use and are sensitive to washing at high temperatures.
Fabrics that can support high temperatures (60 °C or more) are preferable.
Construction:
A minimum of three layers is required, depending on the fabric used: an inner layer touching the mouth and an outer layer that is exposed to the environment.
Choose water-absorbing (hydrophilic) materials or fabrics for the internal layers, to readily absorb droplets, combined with an external synthetic material that does not easily absorb liquid (hydrophobic).
Mask management:
Masks should only be used by one person - do not share your mask, even if it is clean.
Avoid use of make up on face while using face masks.
All masks should be changed after 3h of continuous use or before, if soiled or wet; a soiled or wet mask should not be worn for an extended period of time.
Non-medical masks should be washed frequently and handled carefully, so as not to contaminate other items. Clothing fabrics used to make masks should be checked for the highest permitted washing temperature, which is indicated on the clothing label.
Non-woven polypropylene (PP) spunbonded may be washed at high temperature, up to 140 °C. The combination of non-woven PP spunbonded and cotton can tolerate high temperatures; masks made of these combinations may be steamed or boiled.
Where hot water is not available, wash mask with soap/detergent at room temperature water, followed by either i) boiling mask for one minute OR ii) soak mask in 0.1% chlorine for one minute then thoroughly rinse mask with room temperature water, to avoid any toxic residual of chlorine.
Discard your mask if visibly damaged (i.e., torn, with less adjustment, deformation, etc.) or after 30 washes.
Store clean masks in a clean and closed container.

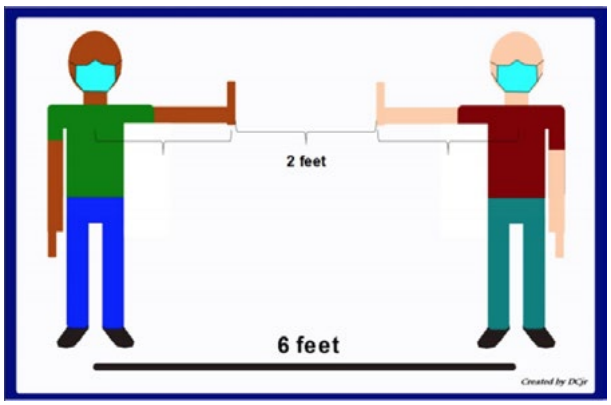


Figure 3. Use of face masks concomitant with social distance of at least 6 feet, or approximately 1.8 meters, between each person provide protection from respiratory droplets that are potentially contaminated with the virus. An approximation of the 6 feet distance can be achieved by the person estimating that from the center of their chest to the palm of your hand, with their arm stretched at a 90 degree' angle, is approximately 2 feet. By staying 3 times this length from another person, social distance is achieved

efficient way to minimize the spread of COVID-19. A word of caution: for the homemade face mask to be beneficial it is necessary to follow the proper recommendations related to the composition of the face masks and proper handling, including proper hand hygiene. The authors endorse the selfless principle "I protect you, and you protect me". In this context, keeping your droplets to yourself regardless of current or previous health status. Every responsible citizen should wear face masks not only for self-protection and others but also to contribute to the end of the pandemic and start reversing the economic impact of the pandemic.

Acknowledgment

To Walter Margulis for his fundamental participation in the initial phases to this manuscript and his intellectual contribution during the entire process. Also to Gilberto Azevedo for reviewing the English in the manuscript.

References

1. Hartley DM, Perencevich EN. Public Health Interventions for COVID-19: Emerging Evidence and Implications for an Evolving Public Health Crisis. JAMA. 2020 May 19;323(19):1908–9.
2. Liu Y, Centre for Mathematical Modelling of Infectious Diseases nCoV Working Group, Funk S, et al. The contribution of pre-symptomatic infection to the transmission dynamics of COVID-2019. Wellcome Open Res. 2020 Apr 1;5:58.
3. Chaw L, Koh WC, Jamaludin SA, et al. SARS-CoV-2 transmission in different settings: Analysis of cases and close contacts from the Tablighi cluster in Brunei Darussalam. medRxiv. 2020 Jul 10;2020.05.04.20090043.
4. Keshtkar-Jahromi M, Sulkowski M, Holakouie-Naieni K. Public Masking: An Urgent Need to Revise Global Policies to Protect against COVID-19. Am J Trop Med Hyg. 2020 Jun;102(6):1160–1.
5. Cheng KK, Lam TH, Leung CC. Wearing face masks in the community during the COVID-19 pandemic: altruism and solidarity. The Lancet [Internet]. 2020 Apr 16 [cited 2020 May 27];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30918-1/abstract
6. ORIENTAÇÕES GERAIS – Máscaras faciais de uso não profissional [Internet]. [cited 2020 Sep 9]. Available from: http://portal.anvisa.gov.br/documents/219201/4340788/NT+M%C3%A1scaras.pdf/bf430184-8550-42cb-a975-1d5e1c5a10f7
7. Atkeson A. What Will Be the Economic Impact of COVID-19 in the US? Rough Estimates of Disease Scenarios [Internet]. Cambridge, MA: National Bureau of Economic Research; 2020 Mar [cited 2020 Jun 7] p. w26867. Report No.: w26867. Available from: http://www.nber.org/papers/w26867.pdf
8. Parodi SM, Liu VX. From Containment to Mitigation of COVID-19 in the US. JAMA. 2020 Apr 21;323(15):1441–2.
9. Long Q-X, Tang X-J, Shi Q-L, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020 Jun 18;1–5.
10. Anderson RM, Heesterbeek H, Klinkenberg D, et al. How will country-based mitigation measures influence the course of the COVID-19 epidemic? The Lancet. 2020 Mar 21;395(10228):931–4.
11. Ferguson N, Laydon D, Nedjati Gilani G, et al. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand [Internet]. Imperial College London; 2020 Mar [cited 2020 Jun 5]. Available from: http://spiral.imperial.ac.uk/handle/10044/1/77482
12. Máscaras caseiras podem ajudar na prevenção contra o Coronavírus [Internet]. [cited 2020 Jun 7]. Available from: https://www.saude.gov.br/noticias/agencia-saude/46645-mascaras-caseiras-podvidasem-ajudar-na-prevencao-contra-o-coronavirus
13. MacIntyre CR, Chughtai AA. A rapid systematic review of the efficacy of face masks and respirators against coronaviruses and other respiratory transmissible viruses for the community, healthcare workers and sick patients. Int J Nurs Stud. 2020 Aug;108:103629.
14. Jayaweera M, Perera H, Gunawardana B, et al. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res. 2020 Sep;188:109819.
15. Anderson EL, Turnham P, Griffin JR, et al. Consideration of the Aerosol Transmission for COVID-19 and Public Health. Risk Anal. 2020;40(5):902–7.
16. Atkinson J, Chartier Y, Pessoa-Silva CL, et al. Respiratory droplets [Internet]. Natural Ventilation for Infection Control in Health-Care Settings. World Health Organization; 2009 [cited 2020 Jun 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK143281/
17. Tcharkhtchi A, Abbasnezhad N, Zarbini Seydani M, et al. An overview of filtration efficiency through the masks: Mechanisms of the aerosols penetration. Bioact Mater. 2020 Aug 11;6(1):106–22.
18. Morawska L, Cao J. Airborne transmission of SARS-CoV-2: The world should face the reality. Environ Int. 2020 Jun 1;139:105730.
19. Tellier R, Li Y, Cowling BJ, et al. Recognition of aerosol transmission of infectious agents: a commentary. BMC Infect Dis. 2019 Jan 31;19(1):101.
20. Prather KA, Wang CC, Schooley RT. Reducing transmission of SARS-CoV-2. Science. 2020 Jun 26;368(6498):1422–4.
21. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020 Apr 16;382(16):1564–7.
22. Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Nat Med. 2020 May;26(5):676–80.
23. Gandhi M, Beyrer C, Goosby E. Masks Do More Than Protect Others During COVID-19: Reducing the Inoculum of SARS-CoV-2 to Protect the Wearer. J Gen Intern Med. 2020 Jul 31;1–4.
24. Offeddu V, Yung CF, Low MSF, et al. Effectiveness of Masks and Respirators Against Respiratory Infections in Healthcare

Workers: A Systematic Review and Meta-Analysis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2017 Nov 13;65(11):1934–42.
25. WHO-2019-nCov-IPC_Masks-2020.4-eng.pdf [Internet]. [cited 2020 Jul 1]. Available from: https://apps.who.int/iris/bitstream/handle/10665/332293/WHO-2019-nCov-IPC_Masks-2020.4-eng.pdf?sequence=1&isAllowed=y
26. MacIntyre CR, Seale H, Dung TC, et al. A cluster randomised trial of cloth masks compared with medical masks in healthcare workers. BMJ Open. 2015 Apr 1;5(4):e006577.
27. van der Sande M, Teunis P, Sabel R. Professional and Home-Made Face Masks Reduce Exposure to Respiratory Infections among the General Population. PLoS ONE [Internet]. 2008 Jul 9 [cited 2020 May 27];3(7). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2440799/
28. Garrett L. The Next Pandemic? Foreign Aff. 2005;84(4):3–23.
29. Davies A, Thompson K-A, Giri K, et al. Testing the Efficacy of Homemade Masks: Would They Protect in an Influenza Pandemic? Disaster Med Public Health Prep. 2013 May 22;7(4):413–8.
30. Zangmeister CD, Radney JG, Vicenzi EP, et al. Filtration Efficiencies of Nanoscale Aerosol by Cloth Mask Materials Used to Slow the Spread of SARS-CoV-2. ACS Nano. 2020 Jul 28;14(7):9188–200.
31. Verma S, Dhanak M, Frankenfield J. Visualizing the effectiveness of face masks in obstructing respiratory jets. Phys Fluids. 2020 Jun 1;32(6):061708.
32. Aydin O, Emon MAB, Cheng S, et al. Performance of Fabrics for Home-Made Masks Against the Spread of Respiratory Infections Through Droplets: A Quantitative Mechanistic Study [Internet]. Epidemiology; 2020 Apr [cited 2020 Aug 19]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.19.20071779
33. Mueller AV, Eden MJ, Oakes JM, et al. Quantitative Method for Comparative Assessment of Particle Removal Efficiency of Fabric Masks as Alternatives to Standard Surgical Masks for PPE. Matter [Internet]. 2020 Jul 9 [cited 2020 Aug 19]; Available from: http://www.sciencedirect.com/science/article/pii/S2590238520303647
34. Stutt ROJH, Retkute R, Bradley M, et al. A modelling framework to assess the likely effectiveness of facemasks in combination with 'lock-down' in managing the COVID-19 pandemic. Proc R Soc Math Phys Eng Sci. 2020 Jun 24;476(2238):20200376.
35. Eikenberry SE, Mancuso M, Iboi E, et al. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. Infect Dis Model. 2020 Jan 1;5:293–308.
36. Wei WE. Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 [cited 2020 May 27];69. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e1.htm
37. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science. 2020 May 1;368(6490):489–93.
38. Howard J, Huang A, Li Z, et al. Face Masks Against COVID-19: An Evidence Review. 2020 Apr 12 [cited 2020 May 24]; Available from: https://www.preprints.org/manuscript/202004.0203/v1
39. WHO-2019-nCoV-IPCPPE_use-2020.2-eng.pdf [Internet]. [cited 2020 Jun 7]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331498/WHO-2019-nCoV-IPCPPE_use-2020.2-eng.pdf
40. Sim SW, Moey KSP, Tan NC. The use of facemasks to prevent respiratory infection: a literature review in the context of the Health Belief Model. Singapore Med J. 2014 Mar;55(3):160–7.
41. Mahase E. Covid-19: What is the evidence for cloth masks? BMJ [Internet]. 2020 Apr 7 [cited 2020 May 29];369. Available from: https://www.bmj.com/content/369/bmj.m1422
42. Chagas AM, Molloy JC, Prieto-Godino LL, et al. Leveraging open hardware to alleviate the burden of COVID-19 on global health systems. PLOS Biol. 2020 Apr 24;18(4):e3000730.
43. M. Mehedi R, Bhuyan MAH, Khan R, et al. A Simple Homemade Cloth Mask for Mass People in Covid-19: Salt-Starching Treatment on Fabric for Better Bioaerosol Filtration Efficiency. 2020 [cited 2020 May 24]; Available from: http://rgdoi.net/10.13140/RG.2.2.26003.91681

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Review article

Pulmonary and central nervous system infiltration of chronic lymphocytic leukemia with concomitant diffuse large B-cell lymphoma: Case report and review of literature

Saulo F. D. Batista,[1] Karina V. de Melo,[2] Patricia Horn,[2] Vinicius da C. Lisboa,[3] Ana Sheila Cypriano,[3] Andrea Pires,[4] Marilza de M. Ribeiro-Carvalho,[3] Fábio Santiago,[3]* Maria Helena F. O. de Souza[3, 5]

Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) and chronic lymphoid leukemia (CLL) are lymphoproliferative diseases of B lymphocytes. Objective: To describe the concomitance of diseases with pulmonary and CNS involvement. Clinical case: A 67-year-old patient with DLBCL and CLL obtained partial remission of the diseases after six cycles of standard combined chemotherapy. Relapse of CLL (del17p; TP53+) occurred after 22 months, becoming refractory to a new treatment. Monoclonal B lymphocyte infiltration was found in the cerebrospinal fluid and bronchoalveolar lavage, leading to death due to respiratory failure. Conclusion: The unfavorable outcome shows a rare and serious complication in the concomitance of these diseases.

Keywords: Chronic lymphoid leukemia (CLL), Diffuse large B-cell lymphoma (DLBCL), Central Nervous System infiltration; Pulmonary infiltration.

1. Medical Clinic Service, Pedro Ernesto University Hospital, Rio de Janeiro State University (UERJ). Rio de Janeiro, Brazil.
2. Hematology Service, Pedro Ernesto University Hospital, Rio de Janeiro State University (UERJ). Rio de Janeiro, Brazil.
3. Department of General Pathology, Faculty of Medical Sciences. Rio de Janeiro State University (UERJ), Rio de Janeiro, Brazil.
4. Fonte Medicina Diagnóstica Laboratory. Niterói, Brazil.
5. Postgraduate Program in Medical Sciences (PGCM), Rio de Janeiro State University (UERJ). Rio de Janeiro, Brazil.

***Correspondence address:**
Departamento de Patologia Geral e Laboratórios
Avenida Professor Manoel de Abreu, 444, 4º andar
Rio de Janeiro, RJ, Brasil.
CEP: 20550-170.
E-mail: dr.fabiosantiago@gmail.com

BJHBS, Rio de Janeiro, 2020;19(2):124-129

Received on 08/05/2020. Approved on 30/06/2020.

Resumo

Infiltração pulmonar e do sistema nervoso central da leucemia linfocítica crônica com Linfoma difuso de grandes células B concomitantes: relato de caso e revisão da literatura

Introdução: Linfoma difuso de grandes células B (LDGCB) e leucemia linfoide crônica (LLC) são doenças linfoproliferativas dos linfócitos B. Objetivo: Descrever concomitância das doenças com acometimento pulmonar e do Sistema Nervoso Central. Caso clínico: Paciente de 67 anos, com LDGCB e LLC, obteve remissão parcial das doenças após seis ciclos de quimioterapia combinada padrão. Evoluiu após 22 meses com recidiva da LLC (del 17p TP53+), tornando-se refratário a novo tratamento. Foi constatada infiltração de linfócitos B monoclonais no liquor e no lavado broncoalveolar, levando-o ao óbito por insuficiência respiratória. Conclusão: O desfecho desfavorável evidencia como uma rara e grave complicação na concomitância dessas doenças.

Descritores: Leucemia linfoide crônica (LLC); Linfoma difuso de grandes células B (LCGCB); Infiltração de Sistema Nervoso Central; Infiltração pulmonar.

Resumen

Infiltración pulmonar y del sistema nervioso central de leucemia linfocítica crónica con Linfoma difuso de células B grandes concomitante: reporte de un caso y revisión de la literatura

Introduction: El linfoma difuso de células B grandes (LDGCB) y la leucemia linfoide crónica (CLL) son enfermedades linfoproliferativas comunes. Objetivo: Describir la concomitancia de ambos con compromiso pulmonar y del líquido cefalorraquídeo. Caso clínico: El paciente con LDGCB y CLL fue tratado con 6 ciclos de RCHOP (ciclofosfamida, doxorrubicina, vincristina, prednisona y rituximab), obteniendo remisión. La recaída de la CLL refractaria al tratamiento ocurrió y FISH mostró del 17p TP53 +. El paciente desarrolló afectación extramedular de CLL y evolucionó a insuficiencia respiratoria y muerte. Conclusión: La concomitancia de estas dos neoplasias malignas con afectación pulmonar y del SNC es un evento raro.

Palabras clave: Linfoma difuso de células B grandes (LLC); Linfoma difuso de células B grandes (LCGCB); Infiltración del Sistema Nervioso Central; Infiltración pulmonar.

Introduction

Diffuse large B-cell lymphoma (DLBCL) and B-cell chronic lymphocytic leukemia (B-CLL) are the most common types of lymphoproliferative diseases in elderly people.[1] The DLBCL is the most common subtype of non-Hodgkin lymphoma (NHL) characterized by large or medium lymphoid cells with B-cell markers growing in a diffuse rather than nodular pattern. It corresponds to a biologically heterogeneous family of diseases and it is subdivided into morphological, biological, and clinical studies. The neoplastic cells express CD19, CD20, CD22, CD79a, and Ki-67 (with a high proliferation index, more than 40%).[1, 2] B-CLL is characterized by proliferation and accumulation of monoclonal B lymphocytes, expressing CD5, CD20, and CD23 molecules in the cells of blood, bone marrow, and lymphoid organs. The clinical presentation is insidious and frequently the diagnosis is made by an incidental finding of lymphocytosis in a complete blood count requested by another cause, followed by lymphadenomegaly, B symptoms (fever, night sweats, weight loss, and fatigue) and cytopenias such as anemia, thrombocytopenia, and neutropenia due to bone marrow infiltration.[3] Traditionally, CLL has been stratified by RAI and Binet staging systems that take into account symptoms, involvement of lymphoid tissues, physical examination, imaging, and laboratory results, the Lugano Modification of Ann Arbor staging system depending on the extension of nodal and extranodal disease, cytogentics, showing mutations on Bruton Tyrosine Kinase and phospholipase Cy2 genes, deletion of 17P and TP53 mutation, NOTCH1, SB3B1 and BIRC3 gene mutations, and, over flow cytometry, indicating the status of IGHV mutational, CD49d, CD38 and ZAP-70 available or not to indicate treatment.[4, 5]

Many complications can be found that interfere with the prognosis of CLL. Most common among them are infections, autoimmune cytopenias, and transformation into high-grade lymphoma – diffuse large B-cell lymphoma (Richter's syndrome).[3] Extramedullary manifestations are considered rarer and are defined as any presentation of CLL outside of the blood or bone marrow, occurring with or without the presence of systemic CLL. According to the Ratterman and colleagues study (2014), central nervous system, skin, gastrointestinal, and genitourinary/ gynecology infiltrations are more frequent, whereas lung, ocular, and other sites, as shown in Figure 1.[6] Here we describe a case of DLBCL and CLL concomitance in which there was relapse with refractory CLL after 22 months post-treatment and progression to simultaneous leptomeningeal and lung involvement.

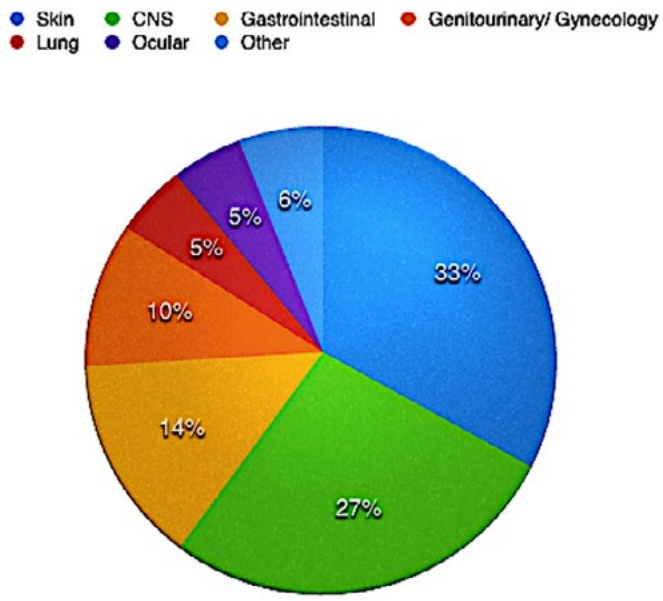


Figure 1. The most commonly reported extramedullary manifestations of chronic lymphocytic leukemia[6]

Case Report

A 67-year-old man was admitted to the HUPE/UERJ in December 2013, presenting generalized lymph node enlargement in cervical, axillary, and inguinal chains without symptoms. The admission blood exams revealed normal values (hematocrit 38%; hemoglobin 13.5 g/dL; WBC 5460 cell/mm^3; lymphocytes 2620 cell/mm^3; platelets 172,000/ mm^3 and negative serologies (HIV, HCV, HBV, and CMV).

A cervical ganglion biopsy was performed and the immunohistochemical analysis was compatible with DLBCL (CD20, Bcl2, CD10 positives; CD3 negative; and Ki-67 labelling index > 40% (Figure 2, a, b and c). In March 2014, a bone marrow biopsy (BMB) revealed infiltration of small B-cell CD20 positive (Figure 2 d). In July 2014, the remission was obtained after RCHOP treatment (6 cycles) and no more neoplastic cells were detected in the bone marrow analysis.

The patient maintained regular hematological follow-up until April 2016, when lymphocytosis and generalized lymph node enlargement were observed (WBC 44,900 cell/mm^3, with 70% lymphocytes). The immunophenotypic analysis revealed a monoclonal B lymphocyte infiltration (87%) in the bone marrow biopsy, compatible with LLC recurrence (Figure 3 a and b). Soon afterwards a new chemotherapy treatment was started with five cycles of fludarabine and cyclophosphamide, without clinical success. The treatment was suspended after the ninth month due to many complications, such as bleeding and febrile neutropenia (hematocrit 13%; hemoglobin 4.2 g/dL; WBC 945 cell/mm^3; platelets 172,000/mm^3).

Fluorescent in Situ Hybridization (FISH) analysis was performed with a poor prognostic result (del 17p; TP53+). The thorax tomography evidenced a lung nodule and pleural effusion with a positive galactomannan blood test, suggesting opportunistic infection by aspergillus. Despite antibiotic therapy (meropenem and voriconazole), the patient progressed with worsening of the general condition, maintenance of daily fever (with temperatures up to 39 °C), dyspnea, severe holocranial headache, and visual turbidity. Due to this clinical condition, bronchoscopy and lumbar puncture were performed for BAL and

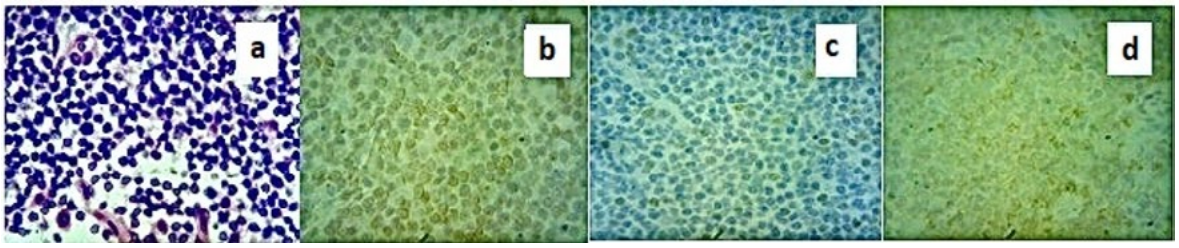


Figure 2. A cervical ganglion biopsy was performed and the immunohistochemical analysis was compatible with DLBCL (Figure 1 HE, CD 20, Bcl2; (Figure 1, a, b, and c). In March 2014, a bone marrow biopsy (BMB) revealed infiltration of small B cells (CD20 positive) (Figure 1, d)

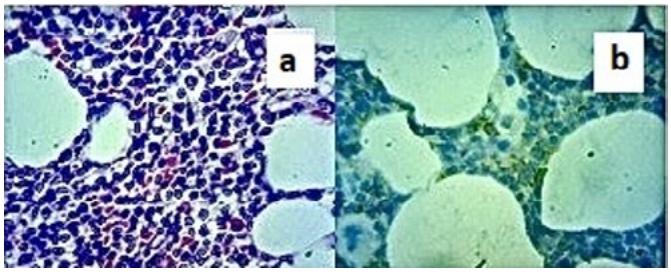


Figure 3. HE and the immunophenotypic (CD20) analysis revealed B lymphocyte infiltration (87%) in the bone marrow biopsy, compatible with LLC recurrence (Figure 2, a and b)

LCR investigation. Note that BAL and LLC cultures for microorganisms were negative; however, the immunophenotypic studies evidenced a massive monoclonal B-cell infiltration in both organs (Figure 4 a and b). Thus, the ibrutinib treatment was immediately started, but pulmonary and renal conditions worsened evolving to death.

Discussion

Two or more synchronous hematologic neoplasms in the same patient are often observed in clinical practice.[7] In our experience we have already described one case involving acute myeloid leukemia (AML) and chronic lymphoid leukemia (CLL).[8] Although DLBCL and CLL are the most common lymphoproliferative diseases in this age group, this concomitant or metachronous presentation is rare with few cases described.[9, 10] One possibility is that this patient had a previous CLL with evolution to Ritcher syndrome and transformation to DLBCL. This patient has presented DLBCL diagnosed in January 2014 and CLL diagnosed in March 2014, respectively. This short time between them suggests that both can be considered concomitant B-cell neoplasms.[11] The review of the ganglion sample at diagnosis was found to be CD5 positive. This reinforces the hypothesis of concomitance of DLBCL and CLL since the patient did not have significant lymphocytosis at this time (less than >5 109/L). In our case, DLBCL was firstly diagnosed by histopathological study while small cell lymphoma went unnoticed and was only diagnosed two months later in a bone marrow biopsy. At that time the hemogram revealed lymphocytes 2.6 x 109, so the possible diagnosis was monoclonal B lymphocytosis or CLL.[12] Richter's syndrome (RS) is considered a rare complication in patients with CLL.[13] Its prognosis is unfavorable because the disease transforms into diffuse large B-cell lymphoma (DLBCL). Approximately only 5 to 10% of CLL patients develop this complication during long-term follow-up. Half of these patients develop RS in the absence of any therapy for CLL, suggesting that there is an inherent biological risk for the development of RS in patients independent of CLL therapy.

In this case report there are some aspects that are worthy of note. The patient remained under careful observation for 28 months after being diagnosed as having DLBCL. Twenty-two months after completing R-CHOP-based chemotherapy, the CLL patient relapsed with hyperleukoctosis. According to Brazilian legislation, rituximab cannot be administered in relapsed patients.

Although CLL is classified as a low-grade B-cell malignancy, some patients, like our patient, experienced an aggressive form. This patient had treatment refractoriness characterized by high lymphocyte levels (>100,000 cells/mm3) and FISH evidenced del 17p TP53+. TP53 disruption in chronic lymphocytic leukemia (CLL) is a well-established prognostic marker and informs on the appropriate course of treatment for patients. TP53 status is commonly assessed by fluorescence in situ hybridization (FISH) for del (17 p) and Sanger sequencing for TP53 mutations.[15, 16]

In addition, our patient developed extra medullary manifestations characterized by neurological and pulmonary involvements. Neurological manifestations in CLL patients can vary from headache, mental confusion, and seizure to neurological deficits. Distinguishing whether neurological symptoms are

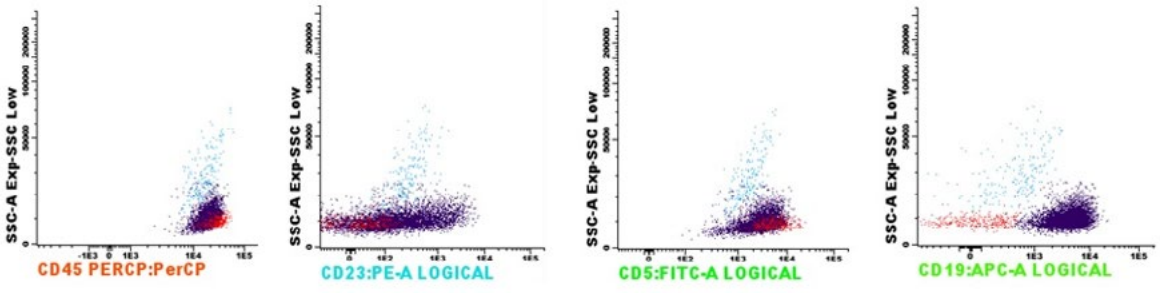


Figure 4. Analysis of CSF performed through immunophenotyping. The following results were found: monocytes (2.7%);T lymphocytes (4.83%); B lymphocytes (91.42% - CD5+/CD23+)

due to CLL or other etiologies can be challenging, requiring extensive research.[17-20] Although all symptomatic patients should be initially approached with imaging, magnetic resonance imaging, or cranial and/or spinal tomography depending on the complaint, the cerebrospinal is considered of great value. Cerebrospinal fluid (CSF) analysis is required and flow cytometry should be requested to distinguish normal from neoplastic lymphocytes. Other tests should also be requested to rule out different causes, such as direct fungal and gram screening, bacterial and fungal culture, and virus screening, especially for herpes and JC virus. Diagnosis is made when there is evidence of CNS involvement by CLL, with no other more likely cause. There is no clear relationship between the stage of the disease and CNS involvement, and all patients should be investigated, regardless of their staging.[17-20]

In the case discussed, the patient had recent and progressive neurological symptoms (headache and blurred vision), with no solid image on the tomography of the skull or spine. There were numerous cells with CLL-compatible cytometry and phenotyping, with no other causes that could better explain the symptoms. Ibrutinib was chosen, which has shown promising results in the treatment of CLL with CNS involvement.[21, 22] Unfortunately, due to bureaucratic barriers, the drug was started too late and only a single dose was given. During that time the patient developed a poor outcome, tumor lysis syndrome, respiratory failure, and death. Pulmonary complications in patients with leukemia are often due to pneumonia, hemorrhage, edema, and/or drug toxicity. However, there are several causes of pulmonary disease that are directly related to leukemia, including leukemic pulmonary infiltration, pulmonary leukostasis, leukemic cell lysis, and hyperleukocytic reaction. In the case of our patient, the first hypothesis suggested was aspergillus with positive serum galactomannan (GM) measurements. The treatment with antibiotics had no benefit.

Leukemic pulmonary infiltration occurs most commonly in the terminal stage of the disease. Autopsy studies have found leukemic pulmonary infiltration in more than 25% of patients with leukemia.[23]

In conclusion, CSF and BAL cytology examinations are considered the "gold standard" for diagnoses of EM involvement of CLL. Also, CLL lymphocytes cannot be distinguished from reactive lymphocytes by morphology alone. For this reason, flow cytometry is a useful tool for distinguishing the lymphocytes. Flow cytometry immunophenotyping (FCI) is an objective and rapid method of qualitative and quantitative analysis of cell suspensions. It can detect small populations of tumor cells with aberrant surface-marker expression through multicolor and multiparameter analysis. FCI is considered to be two to three times more sensitive than cytology in detecting CSF and lung malignant infiltration. There is little consolidated information on prognostic factors or guidelines for the CNS approach to pulmonary and CNS involvement. Multiple treatments with different mechanisms of action have been tested with varying response rates and response maintenance time. Among the few existing studies, ibrutinib monotherapy has been showing good results, being one of the drugs of choice for treatment. Unfortunately, in the present case, the treatment was started too late due to bureaucratic difficulties in acquiring the drug.

References

1. Chastain EC, Duncavage EJ. Clinical prognostic biomarkers biomarkers in chronic lymphocytic leukemia and diffuse large B-cell lymphoma.Arch Pathol Lab Med. 2015;139(5): 602–7.
2. Swerdlow SH, Campo E, Pileri SA, et al. Who Classification of tumours of Haematopoietic and lymphoid Tissues. IARC, Lyon 2017.
3. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. Lancet. 2018;391(10129):1524–1537.
4. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219–234.
5. NCCN Clinical Practice Guidelines in Oncology. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 4.2020. National Comprehensive Cancer Network website. Nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed April 22, 2020.
6. Ratterman M, Kruczek K, Sulo S, et al. Extramedullary chronic lymphocytic leukemia: systematic analysis of cases reported between 1975 and 2012. Leuk Res. 2014;(38):299–303.
7. Abuelgasim KA, Rehan H, Alsubaie M, et al. Coexistence of chronic myeloid leukemia and diffuse large B-cell lymphoma with antecedent chronic lymphocytic leukemia: a case report and review of the literature. J Med Case Rep. 2018;(12):641.
8. Ornellas MHF, Fernandez TS, Diamond HR, et al. Cytogenetic and immunophenotypic evidence of independent clonal origins of concomitant chronic lymphocytic leukaemia and acute myeloid leukaemia. European Journal of Haematology. 2001; (66):281–283.

9. Langer S, Dass J, Mittal S, et al. Concomitant Presence of CD5-Positive Diffuse Large B-Cell Lymphoma and Monoclonal B Cells with the “CLL Immunophenotype” - Is It Richter’s Transformation? Turk J Haematol. 2017;34(2):188–190.
10. Wei Q, Sebastian S, Papavassiliou P, et al. Metachronous/ concomitant B-cell neoplasms with discordant light-chain or heavy-chain isotype restrictions: evidence of distinct B-cell neoplasms rather than clonal evolutions. Hum Pathol. 2014;(45):2063–2076
11. Anderson JR, Armitage JO, Weisenburger D. Epidemiology of the non-Hodgkin’s lymphomas: Distributions of the major subtypes differ by geographic locations. Annals of Oncology 1998;(9):717–72.
12. Porcu P, Cripe LD, Ng EW, et al. Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation and management. Leuk Lymphoma. 2000;39(1-2):1–18.
13. Wąsik-Szczepanek E, Szymczyk A, Szczepanek D. et al. Richter syndrome: rare complication of chronic lymphocytic leukemia or small lymphocytic lymphoma. Adv Clin Exp Med. 2018;27(12):1683–1689.
14. Parikh AS, Shanafelt TD. Risk Factors for Richter Syndrome in Chronic Lymphocytic Leukemia. Curr Hematol Malig Rep. 2014;(9):294–299.
15. Catherwood MA, Gonzalez D, Donaldson D, et al. Relevance of TP53 for CLL diagnostics. J Clin Pathol. 2019;72(5):343–346.
16. Campo E, Cymbalista F, Ghia P, et al. TP53 aberrations in chronic lymphocytic leukemia: an overview of the clinical implications of improved diagnostics. Haematologica. 2018;103(12):1956–1968.
17. Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. Blood. 2015 Jul 23;126(4):454–62.
18. Strati P, Uhum HJ, Kaulfmann TJ, et al. Prevalence ad Characterisitics Of Central Nervous System Involvement by Chronic Lymphocytic Leukemia. Haematologica. 2016; 4.
19. Lopes da Silva R. Spectrum of neurologic complications in chronic lymphocytic leukemia. Clin Lymphoma Myeloma Leuk. 2012;(12):164–179.
20. Souza SL, Santiago F, Ribeiro-Carvalho M, et al. Leptomeningeal involvement in B-cell chronic lymphocytic leukemia: a case report and review of the literature. BMC Res Notes. 2014;(3)7:645.
21. Wanquet A, Birsen A, Choquet S, at al. Central Nervous System Involvement in Chronic Lymphocytic Leukemia: Diagnosis and Treatment in a Retrospective Cohort of Thirty Patients. American Society of Hematology, 2015; 12(3).
22. Wanquet A, Birsen R, Lemal R, et al. Ibrutinib responsive central nervous system involvement in chronic lymphocytic leukemia. Blood. 2016 May 12;127(19):2356-8.
23. Barcos M, Lane W, Gomez GA, et al. An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). Cancer. 1987 Aug 15;60(4):827-37.

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Review article

Legal and biological safety of legal reprocessing of medical-hospital materials

Paula Z. P. F. Pinto,[1]* Nelson Massini[2]

Abstract

Introduction: Procedures using disposable materials in the health area began to be performed, for example in cardiac catheterization, which has a high prevalence of morbidity and mortality. Objective: To justify and reaffirm the reuse of single-use catheters in surgeries, as it is justified by the economic benefit gained from replacing the purchase of new materials by reusing them. Materials and methods: A bibliographic and documentary narrative review was carried out using LILACS and NCBI as database, with previously defined filters and selection criteria. Resultados: Decontamination, disinfection, conditioning, sterilization, and quality control tests are critical stages and, therefore, require training. Each of these stages also has characteristic risks, which must be minimized. In order to ensure the quality of the catheter reuse process, after the cleaning and sterilization process, techniques beyond microscopic and visual evaluation of the device are required. A diversity of techniques is addressed so that the quality of the process is assured. Although legislation and supervision are divergent around the world, many countries choose to adopt reprocessing with economic justification in most cases. The reuse of hospital devices involves several physico-chemical processes, which must be performed with quality and safety. Conclusion: The need for greater rigor in the norms and guidelines that address this practice is clear and urgent, as well as the greater intensity and rigidity of the responsible inspection agencies. The use of luminol as an indicator of organic contaminants may generate a false positive result. Therefore, 3M™ Clean-Trace ™ is the best instrument found in the world market to ensure that the material that has been reused is free of organic waste, and thus fit for use in hospitals.

Keywords: Single use of catheters; Ablation catheter; Hospital infection; Catheter cleaning and sterilization; Quality control.

1. Master in Health, Laboratorial Medicine and Forensic Technology. Institute of Biology Roberto Alcântara Gomes, University of the State of Rio de Janeiro. Rio de Janeiro, RJ, Brazil.

2. Legal Medicine Department. University of the State of Rio de Janeiro. Rio de Janeiro, RJ, Brazil.

***Correspondence address:**
Rua Valeriana 132, apto 202
Rio de Janeiro, RJ, Brasil.
CEP: 21920-280.
E-mail: zdanowskypaula@hotmail.com
ORCID: https://orcid.org/0000-0002-2463-3932

BJHBS, Rio de Janeiro, 2020;19(2):130-141

Received on 13/02/2020. Approved on 03/08/2020.

Resumo

Introdução: Procedimentos com materiais descartáveis reutilizados na área da saúde passaram a ser realizados, a exemplo do cateterismo cardíaco, que apresenta elevada prevalência de morbimortalidade. Objetivo: Justificar e reafirmar a reutilização de cateteres descartáveis em cirurgias, visto que se justifica pelo benefício econômico obtido com a substituição da compra de novos materiais pelo reaproveitamento. Materiais e métodos: Foi realizada uma revisão narrativa bibliográfica e documental utilizando o LILACS e o NCBI como base de dados, com filtros e critérios de seleção previamente definidos. Resultados: Os testes de descontaminação, desinfecção, acondicionamento, esterilização e controle de qualidade são etapas críticas e, portanto, requerem treinamento. Cada uma dessas etapas também possui riscos característicos, que devem ser minimizados. Para garantir a qualidade do processo de reutilização do cateter, após o processo de limpeza e esterilização, são necessárias técnicas além da avaliação microscópica e visual do dispositivo. A diversidade de técnicas é abordada como forma de garantir a qualidade do processo. Embora a legislação e a supervisão sejam divergentes em todo o mundo, muitos países optam por adotar o reprocessamento com justificativa econômica na maioria dos casos. O reaproveitamento de dispositivos hospitalares envolve diversos processos físico-químicos, que devem ser realizados com qualidade e segurança. Conclusão: É clara e urgente a necessidade de maior rigor nas normas e diretrizes que tratam dessa prática, bem como a maior intensidade e rigidez dos órgãos fiscalizadores responsáveis. O uso do luminol como indicador de contaminantes orgânicos pode gerar um resultado falso positivo. Portanto, o 3M ™ Clean-Trace ™ é o melhor instrumento encontrado no mercado mundial para garantir que o material que foi reutilizado esteja livre de resíduos orgânicos e, portanto, adequado para uso em hospitais.

Descritores: Uso único de cateteres; Cateter de ablação; Infecção hospitalar; Limpeza e esterilização de cateteres; Controle de qualidade.

Resumen

Introduccíon: Los procedimientos utilizando materiales desechables en el área de la salud se comenzaron a realizar, por ejemplo en el cateterismo cardíaco, los cuales tienen una alta prevalencia de morbilidad y mortalidad. Objetivo: Justificar y reafirmar la reutilización de catéteres de uso único en cirugías, justificado por el beneficio económico que se obtiene al reemplazar la compra de nuevos materiales por su reutilización. Se llevó a cabo una revisión narrativa bibliográfica y documental utilizando las base de datos LILACS y NCBI, con filtros y criterios de selección previamente definidos. Materiales y métodos: Descontaminación, desinfección, acondicionamiento, esterilización y control de calidad son etapas críticas y, por tanto, requieren entrenamiento. Cada una de estas etapas tienen riesgos característicos, los cuales deben ser minimizados. Para asegurar la calidad del proceso de reutilización del catéter, después del proceso de limpieza y esterilización, se requieren técnicas más allá de la evaluación microscópica y visual del dispositivo. Se aborda una diversidad de técnicas como medio para garantizar la calidad del proceso. Aunque la legislación y la supervisión son diferentes en todo el mundo, muchos países optan por adoptar el reprocesamiento con justificación económica en la mayoría de los casos. La reutilización de dispositivos hospitalarios implica varios procesos físico-químicos, los cuales deben realizarse con calidad y seguridad. Conclusión: Es clara y urgente la necesidad de un mayor rigor en las normas y lineamientos que abordan esta práctica, así como una mayor intensidad y rigidez por parte de los organismos de inspección responsables. El uso de luminol como indicador de contaminantes orgánicos puede generar un falso positivo como resultado. Por lo tanto, 3M ™ Clean-Trace ™ es el mejor instrumento que se encuentra en el mercado mundial para garantizar que el material que se ha reutilizado esté libre de desechos orgánicos y, por lo tanto, apto para su uso en hospitales.

Palabras clave: Catéteres de uso único; Catéter de ablación; Infección hospitalaria; Limpieza y esterilización de cateteres; Control de calidad.

Introduction

More than one million coronary interventions occur annually worldwide. In Brazil, from January 2008 to June 2010, 286,343 diagnostic cardiac catheterizations were performed according to DataSus.[1,2] Over 80% of the vascular catheterizations (CATs) were performed on an outpatient basis in patients with stable coronary disease.

The advancement of technology is continuous and increasingly accelerated, which, in the health area, enables several alternatives and therapeutic improvements. During the 1960s, the start of the use of disposable materials in health could be noticed.[3] This practice has taken extensive and worldwide proportions. Thus, surgical procedures using those materials were positively impacted in favor of reduced disease transmission and improved performance of procedures in general.

CAT then began to be performed with disposable devices, which led to a growing increase in health care, especially in the medical area which has a higher prevalence of morbidity and mortality. As a result of this problem, many hospitals have adopted the practice of reusing single-use medical products.[3]

Countries such as Switzerland, Germany, the United States, and Canada already have this issue clarified and allow the reprocessing of some single use materials as long as each country's regulations are followed. In Africa, Asia, Eastern Europe, Central America, and South America this practice is permitted, but without specific regulation.[4]

As a method of economics, many hospitals around the world began to adopt the practice of reprocessing disposable materials from 1970.[5] Since then, studies have been emerging and answering several questions about the risks and effectiveness of such procedure.

In England, using the practice of reusing single-use medical devices, intermittent catheter costs increased from £13.5 million in 1999 to £88 million in 2013.[6] This scenario encourages England, Brazil and several other countries already mentioned to adhere to the practice of reuse.

The reprocessing of surgical materials can be performed inside the hospital, or, most often, this service can be outsourced to companies specialized in cleaning and sterilization. Both processes need to ensure the quality and safety of the devices, and for this they must follow cleaning protocols validated by the responsible health institutions, and under a rigorous process of control of all steps.[1]

The growing and imminent concern with the reuse of medical devices has led the Food and Drug Administration (FDA) to pronounce on the issue. The FDA is a federal agency of the United States Department of Health and Human Services, which in response to healthcare professionals, catheter producers and reprocessing companies, has created a guide document

on the reuse processes of single-use catheters. This guide, released in 2000, contains the process that should be used when reprocessing a catheter: cleaning, remodeling, integrity and functionality inspection, and sterilization. This document also includes a list of risks associated with the procedure, categorized as high, medium, or low risk.[7]

Currently, the process of reusing single use medical devices is provided by the United States Federal Food, Drug and Cosmetic Act (FDCA). Thus, all reprocessed material that meets the requirements of this law may be legally commercialized in the country.[7]

Current Brazilian legislation does not prescribe a specific protocol for catheter reuse, leaving it to the discretion of each hospital to create its own, and with the obligation to validate it by the competent body. On February 7, 1986, the National Health Surveillance Agency (ANVISA) classified single-use articles through Ordinance No. 3[8] and 4,[9] prohibiting their reprocessing. In 2006 ANVISA published Special Resolution (RE) No. 2605[10] and 2606,[11] which lists medical products considered difficult to reprocess, also the list of materials which must contain in their packaging the term "PROHIBITED TO REPROCESS" in order not to be reprocessed. On August 11 of the same year, RDC 156 was elaborated, which updates Ordinances No. 3 and 4, and Ordinance No. 822, of July 8, 1988, providing guidelines for the prohibition or permission to reprocess single use surgical materials. Later, in 2012, RDC 15[14] was published on March 15, which established good practice requirements for the processing of health products.

The Brazilian Society of Interventional Hemodynamics and Cardiology (SBHCI) does not oppose the reuse of hospital materials such as cardiac catheters, but recommends several procedures until ANVISA regulates all stages of the reprocessing of single use materials and also supervises this activity. In practice, SBHCI recommends that hospitals and companies reprocessing these materials follow the practices already established by ANVISA itself: validation of the technique, training of professionals involved, surveillance of possible adverse effects on patients who used such materials, and quality control of all steps.[15]

Hospital-acquired infection is a major cause of morbidity, mortality, prolongation of hospitalization, and represents an increase in patient treatment costs.[16] According to Humphreys,[17] there has been an increasing importance of blood-focused infections, which represent the highest cause of mortality, and also infection at the surgical incision site, which remains one of the most routine acute complications in hospitals.

Infectious disease is the main criticism of reprocessing single use materials, and often the reason why such practice should not be performed.[18] Although few studies show data proving the increased risk for the patient using such materials, this subject is still regulated by several researchers. The risk is imminent and potential when devices have contact with blood and body fluids, so they must be thoroughly reprocessed. Even with proper disinfection and sterilization processes, infectious agents may pose a risk to the patient, although the most frequent data found in the literature do not show significant differences between infectious occurrences using new and reused devices.[19]

This situation, besides being a worldwide problem in public health, still impacts the economy. Health care expenditures for patients who acquire infections in hospitals are estimated to reach $ 5.7 million each year.[20] Thus nosocomial infections, which are the most common adverse events in the hospital setting, become the focus of many public health research studies.

Reprocessing catheters is justified by the economic benefit gained from replacing the purchase of new materials with their reuse. However, this practice has negative factors, which weigh on the decision making by hospitals.

The reuse of hospital devices involves several physical and chemical processes, which must be performed with quality and safety. Decontamination, disinfection, packaging, sterilization, and quality control testing are critical steps and therefore require training. Each of these steps also has characteristic risks that should be minimized.[21]

The initial lavage of a catheter already used is either performed inside the hospital, at the Sterilization Center (CME) or at the External Sterilization Center (CEE), depending on the hospital in question. This activity is intended to keep the material "minimally" clean, free of coarse and apparent dirt, to continue to the sterilization process.[20]

Sterilization can take place at the CME itself or from the EEC to outsourced companies, which will proceed with the material reprocessing procedure. At this stage, various techniques or a combination of these are used to eliminate viable microorganisms such as viruses and bacteria, and the toxic and virulent substances released by them, as well as remnants of blood cells that may have "deposited" in the catheter.[20]

Finally, after reprocessing, the catheters should be tested for quality and process effectiveness. These tests, here in Brazil, mostly boil down to visual and mechanical inspections, to certify that they are, in fact, fit for use again.[1]

Chemical residues and biological agents are the major concern regarding the source of contamination due to the use of reprocessed catheters. Blood is one of the biological agents possibly found in materials used multiple times. Remnants of blood cells and proteins, in particular, are able to adhere to catheter material and can be a potential source of contamination.[22]

Optical microscopy, scanning electron and transmission techniques are used to detect these biological residues. Because the indicators are rarely used in Brazil, due to their high cost, the process of cleaning and sterilization of catheters becomes a determining factor for the elimination of such dirt.[23]

However, there are more advanced and specific methods for determining the effectiveness of the catheter cleaning process that will be reused. And while simple visual inspection is still widely used as a final quality control method of the process, specific testing for the presence of particles and blood cells is now available worldwide. Tests such as TEST SOIL and TOSI® are used to monitor the quality of electronic cleaners used during the catheter cleaning process. However, end-of-process methods can be equally effective in quality control of reused medical and surgical devices. Chemiluminescent techniques such as luminol and bioluminescence techniques such as 3M ™ Clean-Trace ™ ATP Surface devices, 3M ™ Clean-Trace ™ ATP Water and Clean Trace Protein HS are viable options for analytical markers for detecting blood cells and their remnants in these devices.[24]

Methods

The present work used as methodology a bibliographic and documentary narrative review. From the article selection, explained below, this article was written using the most important and pertinent references.

The databases used were the Latin American and Caribbean Health Sciences Database (LILACS) and the National Center for Biotechnology Information (NCBI). Data were collected from April 1 to 4, 2018. In this research, the descriptors used were divided into stages, since the diversity of subjects is extensive, and many of them were not found in related articles. A total of 348 articles were searched through advanced searches.

In the initial research, the descriptors used were divided into four stages, since the diversity of subjects is extensive, and many of them were not found in related articles. The keywords used were: "Catheter AND Reuse", "Hospital AND (infection control OR infection)", "Luminol And Blood", "Blood And Contamination And Infection".

In addition, filters were used in order to preserve the relevance of the researched literature. They were: human species, literary revision as article type, title and abstract. The language was not filtered, but the input only contained articles in English, Portuguese or Spanish.

At first it was also defined as exclusion criterion the publication time of up to 5 years, however, initial surveys indicated the precariousness of articles related to the theme. Thus, the criterion "date of publication" was excluded and the search redone.

The exclusion criteria for articles found from descriptors were the title and the abstract. Thus, the content should be in accordance with the research theme for the article to be used. Thus, 271 articles were excluded for not having relevant content for the current work. The rest was completely read and the relevance to the current work was evaluated.

Other searches in the same databases were conducted for specific issues, such as the concept of nosocomial infection, blood cells and red blood cell cycle. Such articles were chosen for the content relevant to the theme, and found both in the databases cited and in the references of articles already selected as pertinent to the theme. In total, 46 papers were used through this differentiated selection, since the scarcity of material was affecting the development of this research.

Of all the articles read and used, some of their references that had relevance to the subject were included. After the initial selection and exclusion phase of the articles based on the pre-defined criteria, the exploratory and analytical reading of the remaining articles began, followed by data analysis and writing.

Results

The economic issue is the main reason for the reuse of single use hospital supplies. And it also explains the cost-benefit of possible infections with the practice. Malanoski and collegues,[25] in a study of the complications of unusual infections due to

catheterizations performed in the United States in 1995, said that this year the country spent $4.5 billion on treating infectious complications, contributing to over 88,000 deaths.

In developing or underdeveloped countries, the reuse of single-use surgical materials has a poor regulation and almost no supervision, as it can be seen in table 1 below. As is the case in South America, where Brazil[26, 27] and Chile[28] are the only ones with legislation, however, there are still many controversies about the practice, in which lists are available in both countries, containing the devices whose reuse is permitted. In Brazil, ANVISA[8-14] is responsible for such regulations and leaves the adopted method to the establishment, requiring only that it be duly validated and approved. In contrast, there are no regulations or recommendations in Ecuador.[28]

In Europe, the reuse of single-use surgical items is very common in hospitals in countries as Denmark,[29] Madrid[30] and Germany,[31] and in Spain, where this practice occurs in approximately 37%, 80% and 40% of hospitals,[31] respectively. However, each European country may differ in the practices adopted for reprocessing, depending on their current laws. According to the European Association for the Reprocessing of Medical Devices, this practice can be performed in almost all European countries, and especially without requiring quality standards.[32-34]

However, high quality standards are required by regulations in Germany, the Netherlands, Denmark, Sweden, Belgium, Slovakia and Finland. Austria, Luxembourg, the Czech Republic and Slovenia are still undergoing evaluations of the procedure, where

Table 1. Current conditions of each continent, and in some cases specific countries, regarding the procedure for reuse of single-use surgical materials and their legal implications, as well as supervisory bodies, where relevant

Continent	Country	Inspection	Regulation	Procedure
North America	United States	FDA	Yes	Permitted according to materials manufacturers.
	Canada	CCOHTA	Yes	Each region defines its own legislation.
Latin and South America	Brazil	ANVISA	Yes (poor)	Allowed but with little regulation.
	Chile	ANAMED		
	Ecuador	-	No	With the help of the Pan American Health Organization (PAHO) and the US Society of Hospital Epidemiologists (SHEA), they have hospital infection control programs.[50]
Asia	Japan	-	No	There are no regulations, although there is 86.2% of hospitals reuse disposable products by inconsistent methods without protocols and standards.[30]
	India	-	No	Each hospital has its own committee of doctors, microbiologists, nurses, administrators who, together with the CCIH staff, create protocols (mirrored in the FDA) and supervises reprocessing.[51]
Africa	Sub-Saharan Africa	-	No	Poor practice due to lack of supervision.
	South Africa	CAP	Yes	Allowed from WHO Good Manufacturing and Management Practice Guidelines.
Europe	Spain	EU Medical Device Regulation	No	Forbidden.
	Germany		Yes (high standard)	Allowed and required high quality standards.
	France	-	Yes	Forbidden.
	United Kingdom	MHRA	Yes	Recommendations against practice.
Middle East	Arabian countries	-	No	The hospital is responsible for developing the protocol and performing reprocessing locally, but there is no regulatory system.[30]
	Egypt	-	Yes	MS has set guidelines, but poor working conditions prevent compliance.
Oceania	Australia	TGA e AHMAC	Yes	It is up to the manufacturers to determine if the material can be reprocessed.

standards, methods and legislation are not yet conclusive and practice is still poorly regulated. There is no legislation available in Estonia, Latvia, Lithuania, Malta, Cyprus, Greece and Poland. And yet, Ireland, Portugal, Spain, Italy and Hungary do not yet have recommendations for reprocessing to occur in hospitals.[30-34]

In France, reprocessing is prohibited and in the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHRA), which is a union of The Medicines Control Agency, and The Medical Devices Agency issued a statement in 2003 against the practice, claiming that the practice may compromise the safety, performance and effectiveness of the devices, and that the risk to patients outweighs any benefit.[28]

One of the countries with the highest quality control of the catheter reuse process is the United States, which has a disposable medical device reuse rate in about 25% of hospitals. The FDA has created a list of 70 products that can be legally reprocessed within hospitals themselves, or even by third parties (which account for 40-50% of reprocessing practice), and still requires that original manufacturer's regulations must be met.[35-38]

In Canada each province has its own jurisdiction, and that is why the practice of catheter reuse still happens with poor or none regulation in some territories. Competent federal agencies argue that single use devices should not be reused unless the institution wishing to do so has adequate facilities and quality service. Thus, given this issue of provincial jurisdiction and national determination, most hospitals do not adopt catheter reprocessing (72%). However, among those which reuse surgical materials, 85% do so through in-hospital procedures, most of them without even having a written policy on the subject (approximately 40%).[39]

Koh and Kawahara[40] conducted a survey in 2005 in Japan in which hospitals were asked about the reuse of single-use surgical materials. The response rate was 30%, and 80 to 90% of the hospitals that responded said they performed such practice.

The most available literature data on reprocessing single-use materials in Asia is about syringes and needles. WHO[41] estimates that around 300,000 people die each year in India from the use of unsterile or reused syringes, and this practice is often repeated also in countries south of the continent, the Eastern Mediterranean and the Western Pacific.[42]

In the 1980s in Australia, 50% of hospitals reprocessed single use devices. Even before regulations were introduced in the country in 2005, the number of reprocessing had already been reduced in 2001.[43] Currently, the country only permits the reuse of disposable materials by meeting all requirements regulated by the device manufacturer.[44] A Guide to Disposal Control Infection[45] was created in 2003 with the support of the Australian Regulatory Agency (Therapeutic Goods Administration – TGA) and the Advisory Council of Health Ministers of Australia (AHMAC) to prevent contamination among patients who have reused single use equipment. Accordingly, such materials labeled "SINGLE USE" cannot be reprocessed in the country.[46]

WHO estimates sub-Saharan Africa to be slightly better off than Asia, where approximately 18% of reused syringes and needles do not undergo any sterilization process.[41,47] Some of these countries have no structure for the production of surgical materials, as distribution centers, do not even have national logistics for such an area. This fact requires many hospitals to reprocess single-use materials so that health care delivery in Africa occurs minimally.[28] South Africa is one of the countries that has regulation on the WHO Good Practice Reprocessing Regulation Manufacturing and Management and also guidelines for infection control in hospital units.[48]

Limited health resources extend to Arab countries, which justifies the need for reuse of catheters and some other materials, such as masks and mist tubes, in some hospitals in the region. Reprocessing is done locally at the hospital level, and there are no defined regulations for such practice, and each institution is responsible to formulate its own protocol.[41] In Egypt, the Ministry of Health has formulated National Infection Control Guidelines outlining appropriate procedures for reuse single use materials. However, poor working conditions, such as overtime and lack of human resources, compromise the correct application of such practices.[49]

In the current context of Brazilian health, the predominance of diagnostic and therapeutic procedures encourages legislation to adapt to the reality of the country. The high cost of surgical materials, such as ablation catheters, also justifies the practice of reuse in hospitals. And while Brazilian law does not determine a specific protocol for reprocessing, some requirements are mandatory to ensure the safety, effectiveness and quality of the process. Decisions and

Resolutions of the Collegiate Board (RDC) competent to the activity are described in table 2.

ANVISA acts by directing and supervising the re-sterilization activity of surgical materials. Special Resolutions (RE) have established product lists and parameters that are prohibited from being reused, as explained in table 2.

Surgical site infections (SSI) account for 38% of all hospital infections. In Brazil, they rank third among Health Care-Related Infections (HAI). Not unlike in the United States, SSI is the second leading cause of HAI in postoperative patients. In numbers, more than 500,000 cases of infections from the surgical incision site are detected every year.[52]

The high cost provided by the increased length of hospitalization, associated with the expense of antimicrobial therapy, laboratory tests and diagnosis has led to further studies in this area. A US health data survey showed that the number of extra hospitalization days added for all patients diagnosed with SSI was $3.7 million, representing an extra $1.6 billion in the nation's health budget.[52]

Several researchers have come to the conclusion that the practice of reusing catheters rather than buying new ones would economically benefit the healthcare industry without complicating the patient. Veras and collegues,[54] in their cost-effectiveness analysis of catheter reuse in the city of Rio de Janeiro, emphasizes that this strategy can cost 2.5 times less than the purchase of new medical devices. In the same vein, Dunn (cited Bomfim and collegues), in 2002, stated that savings can reach 50% when cardiac procedures are performed with catheters reused by third parties.

Within hospitals, reprocessing single use devices is routinely performed by the Sterile Material Center (SME) worldwide.[20] According to Resolution RDC no. 307 of November 14, 2002, CME is considered a technical support industry, which has the function of providing properly cleaned and sterile materials, providing care to patients within the health facility.[53]

The SME is an intrahospital unit of high complexity and importance, and must have trained professionals to operate the actions performed in the sector. It is the process of receiving materials considered dirty and contaminated from the entire hospital, for subsequent decontamination and sterilization.[20]

As provided by ANVISA,[54] it is the responsibility of each institution to determine a protocol for the material cleaning and sterilization practices, provided that it is validated and within the Good Practice recommendations determined by the health surveillance agency itself. Given this, the most diverse types of practices are

Table 2. Legislation pertaining to the reuse of medical-hospital materials said to be of single use in Brazil

Legislation	Publication date	Guideline
Ordinances No. 3 and 4	February 7, 1986	Standardization of the use and reuse of disposable medical and hospital materials. Forbidden to reprocess needles with plastic components (including fistula cannulas), scalps; disposable scalpels and blades; venous puncture catheters; equipment for administration of intravenous solutions, blood, plasma and parenteral nutrition, blood bags; plastic syringes; simple urethral aspiration and gastric tubes; open drainage urine collectors; Penrose and Kehr drain; peritoneal dialysis catheters.
Ordinances No. 8	July 8, 1988	Authorizes the execution of re-sterilization service and processing of medical-hospital articles
RE 2605	August 11, 2006	Establishes the list of single-use medical products forbidden from being reprocessed, a total of 63 items.
RE 2606	August 11, 2006	Establishes parameters that guide the elaboration, validation and implementation of medical device reprocessing protocols by health services and reprocessing companies in order to guarantee the safety and efficacy of the products.
RDC 156	August 11, 2006	Provides for the registration, labeling and reprocessing of medical products, and makes other arrangements.
RDC 15	March 15, 2012	Establishes the best practice requirements for the operation of services that perform the processing of health products aiming at the safety of the patient and the professionals involved.

Legend: RE: Especial Resolution in Portuguese.
Authorship: The authors.

performed in different hospitals in the country. The combination of these techniques is also very common in Brazil and around the world.

When this procedure is performed externally, the External Sterilization Center (ESC) is the sector responsible for the steps of pre-washing and packaging of materials until they are sent to third parties that will actually perform the washing and sterilization procedure, which follows same protocols as the SME.

Cleaning and disinfection are responsible for eliminating most contaminants from surgical devices. However, some microorganisms in their vegetative or sporulated form are able to survive the most extreme conditions. The sterilization process is effective and indispensable for catheter reuse in order to eliminate even those forms of microorganisms.[1]

After the cleaning step, the catheter is normally subjected to enzymatic disinfection preparations to eliminate organic materials such as blood by breaking it. It is of utmost importance to take into consideration the instructions of the manufacturers of each material at all times. Characteristics such as product residence time in diluents, dilution pH and appropriate procedure environment are uniquely relevant for steps involving device washing. Equally important, having a skilled professional and validated techniques throughout the reuse process is of utmost necessity.[1]

The FDA, as the world's leading regulator, sets maximum plasma concentrations of ethylene oxide and various other substances, which are followed by many hospitals across the globe. Nevertheless, observations of ethylene oxide residue levels in re-sealed electrophysiology catheters up to 8 times above allow attention to concern about imminent toxicity risks during reprocessing. Therefore, the 14 days rest time after reprocessing is essential to detoxify the material after exposure with ethylene oxide.[22]

The Hospital Infection Control Program (PCIH) was created in 1988 and regulated by Ordinance No. 2616/1998[11] of the Ministry of Health, which determined the actions that should be taken by each hospital to reduce the incidence of nosocomial infections and its severity. Thus, the PCIH guides Hospital Infection Control Commission (HICC) professionals in setting objectives and priorities for each institution. There is also the Inspection Roadmap for the Hospital Infection Control Program, established by RDC No. 48/2000,[55] which, together with the PCIH, can be used as a basis to guide the elaboration of CCIH standards in hospitals.

For the final catheter evaluation, after all cleaning and sterilization steps, most hospitals and third parties still use simple visual inspection as the final process quality control. As its name implies, this assessment basically consists of the naked eye examination of the catheter that is ready to be reused in its final packaging.[1]

Visual inspection, although the most commonly used, is the least effective. Currently, it is already recommended that microscopic techniques that guarantee the visualization of possible microscopic changes, as well as determine the presence of particles and blood cells, should be used for this purpose in surgical materials to be reused, being one of the most reliable and safe. Tessarolo and colleagues also emphasizes the importance of using scanning electron microscopy to observe possible macro and micro residues of coagulated blood in catheters.[1, 23]

In addition to microscopy equipment, other methods can be employed for the same purpose, such as TEST SOIL and TOSI®,[1] which are useful for monitoring the control of cleaning efficiency in relation to blood and blood components after the cleaning process of surgical materials.[24]

In just 30 seconds, any of the three Clean-Trace Systems can quantify the cleanliness level using ATP as an indicator. ATP is found in most cells and is a source of energy for metabolic processes such as respiration and cell reproduction, as well as muscle contraction.[56] The presence of ATP in all life forms favors its excellent use as an indicator of the presence of cell viability, since it is only present in living cells.[57] Thus, it can be used to identify the existence of microorganisms as bacteria and fungi, but also human cells. Hence, ATP measurement represents the measurement of the presence of viable cells, which represent contamination levels of the studied sample, whether catheters, surfaces or water, being a conclusive factor for determining the effectiveness of quality control of the reprocess of surgical devices.

The 3M ™ Clean-Trace ™ ATP Surface device is based on ATP quantification to assist the cleanliness of medical devices and environmental surfaces. The higher the presence of ATP on a surface, the higher the level of organic contamination present on it. This system has suggested applications in the hospital environment, especially with regard to terminal room cleaning, transplantation center, hemodialysis, isolated environments, staff hand cleaning, and surgical instruments that have been reused, and CME stands.[24]

The 3M ™ Clean-Trace ™ ATP Water System,[24] as its name implies, quickly assesses the level of contamination of a water sample. The assessment of water contamination used throughout the cleaning and sterilization process is of utmost importance as it may be the source of toxins causing pyrogenic reactions, as previously discussed. Thus, this system is used as a quality control of the process, not of the final product control itself. However, it is equally relevant and effective in ensuring catheter non-contamination.

Lastly, 3M ™ Clean Trace ™ Protein HS[24] has high sensitivity in detecting protein residues from around 3 μg, a value considered safe for minimal measurement that should be considered as a sign of contamination. The mechanism of action of this device is through the semi-quantitative evaluation of proteins present in blood and other body tissues in surgical materials and also on surfaces. The Association for the Advancement of Medical Instrumentation (AAMI),[58] an organization for the advancement of the safe and effective development and use of medical technology, has developed a guide to health care sterilization, which has been quoted as indicating that protein is the most common marker used to evaluate cleaning efficiency by determining the presence or absence of organic matter in hospital settings.

Discussion

The reuse of single use medical supplies is a problem worldwide. In general, developed countries already have legal regulations that support the reprocessing of such devices. In addition, they have strict enforcement agencies, such as the FDA in the United States.

Concerns about SSIs increases when surgery is performed with reused catheters. The additional risk of contamination by infectious agents, toxic substances and other harmful substances has been the target of scholars. The monetary incentive is of great value to hospital institutions wishing to reuse such surgical materials. However, it is extremely important to determine the safety of the process, thus ensuring the improvement of patients' health, without exposing them to greater risks.

The reuse of catheters has several justifications, especially the economic one. However, the budget benefit cannot be above health security. To be reused, the catheters must be free of any particles with a potential risk of infection. Viruses, bacteria and fungi are examples of microorganisms that can cause harm to the patient and must be eradicated from reused surgical materials. Blood cell debris, pyrogenic agents and toxic residues also need to be disposed of before reuse.

Pre-cleaning and cleaning are in fact key steps in continuing the entire process, and while all steps are critical, these are the most important and key when looking at the macro process. In these phases there should be the extinction of wastes that favor the emergence of infections.[1]

The time between catheter use and the first step of catheter reprocessing, pre-cleaning, should not be too long. Decontamination of possible infectious causes should occur as soon as possible, as they may adhere to the catheter material and pass intact through the cleaning agents, thereby compromising the entire procedure and consequently, the reuse of the material.[1]

After all the cleaning and sterilization steps previously discussed, it is noted that problems related to nosocomial infections deserve continuous attention from all relevant sectors of the hospital. In this context of awareness of the risks of infection transmission through the use of reused catheters in surgical procedures, the HICC plays an essential role, especially in the disinfection and sterilization processes of such materials. The CCHI then has the responsibility to standardize the procedures of each hospital, and through these rules, establish rules to be followed by health professionals, aiming to minimize the occurrences and risks of hospital infections. Equally important is the installation of educational actions that disseminate the fundamental knowledge for the implementation of preventive activities, through lectures, courses or posters, for example.

Thus, the HICC acts in the control of nosocomial infections, and it is therefore responsible for the quality assurance of the reprocessed surgical materials. In order to minimize and avoid the imminent risks of infection associated with the reuse of single use medical devices, control methods should be adopted in addition to naked eye examination or visual inspection with microscopes.

The criticality of eliminating organic waste such as blood, tissues and bones, as well as microorganisms such as fungi and bacteria, is due to the need to minimize health risks such as postoperative infections, for example. Thus, the standardization, monitoring and quality control of this process are fundamental for the quality of life of patients undergoing surgical procedures using reprocessed materials.

Although luminol is widely used in the detection of blood in criminal environments, its use in hospital settings can be considered limited, since, according to Bergervoet and colleagues,[59] luminol is not only

specific for hemoglobin, but other substances are also responsible for the reaction of luminescence of luminol as environmental, domestic and industrial substances. This compound has a positive reaction (luminescence emission) with others who have peroxidase activity, and therefore, the most commonly found false positive results are related to peroxidases of plant origin, copper, cupric sulfate, ferric sulfate and iron.

The luminescence produced by the reaction of luminol with reused hospital material may result in a false positive result due to interference from various other substances, which then function as reaction catalysts, thus generating luminescence emission in the same way as with iron present in his own blood.[60,61]

The 3M ™ Clean-Trace ™ ATP[24] Cleaning Monitoring System is one of the tools used to evaluate medical device contamination through a bioluminescence reaction. Thereby, catheters, surfaces and the water used for cleaning and sterilizing these materials can be evaluated for the effectiveness of the entire reuse process. The results provided by the luminometer are two possible, "Pass", ensuring that the collected sample is clean, or "Fail", suggesting that the test be performed again to ensure a safe result.

There are standards for the use of biological indicators worldwide. In Brazil, the Brazilian Association of Technical Standards (ABNT)[62] has published the standard ABNT NBR ISO 11138-1: 2016 - Sterilization of Health Products - Biological Indicators - Part 1: General Requirements, prepared by the Brazilian Dental-Medical-Hospital Committee (ABNT / CB-026), an addendum to ISO 11138 which establishes "the general requirements for production, labeling, test methods and performance characteristics of biological indicators, including inoculated carriers and suspensions, and their components, to be used in the validation and routine monitoring of sterilization processes". In this sense, international standards are also followed by Brazilian hospital institutions and in several countries. AAMI itself issued the ANSI / AAMI ST79 standard, regarding the use of biological indicators, standardizing the frequency of organic load monitoring in hospital devices and environments, in favor of a high-quality standard offered by these health institutions, always ensuring improving patient health care.[63]

Conclusion

Despite the numerous possible risks, studies indicate that there is no impact on the number of cases of infections with reused catheters, as there is assurance that the entire reuse process is carried out by validated and quality-controlled procedures. The need for greater rigor in the norms and guidelines that embody such practice is clear and urgent, as well as the greater intensity and rigidity of the responsible supervisory bodies. Also, the presence of competent professionals and the guarantee of the quality of the final product infer in a beneficial result to the patient's health, regarding care practice.

Despite the use of indicators in chemiluminescence reactions are more specific for detecting possible organic contaminants, luminol has the huge disadvantage that it may generate a false positive result. Finally, it is concluded that 3M ™ Clean-Trace ™ is, in fact, the best instrument found in the world market to ensure that the material that has been reused is free of organic waste, and thus fit for use in hospitals.

References

1. Bomfim FM, Lima SG, Guimarães V. Análise do reprocessamento de cateteres de hemodinâmica em uma capital brasileira. Rev Bras Cardiol. 2013;26(1):33-39.
2. Ministério da Saúde (Brazil). DATASUS. Informações de Saúde. Sistema de Informações Hospitalares do SUS [accessed in 21 aug 2018]. Available at: www.datasus.gov.br
3. Crawford TC, Eagle KA. Reuse of catheters and devices labelled for single use: evidence, recommendations and oversight. Heart Asia. 2018;10(2).
4. Mansur AP. Favarato D. Mortalidade por doenças cardiovasculares no Brasil e na região metropolitana de São Paulo. Arq. Bras. Cardiol. 2012;99(2):755-761.
5. Costa EA. Gerenciando risco em reprocessamento de produtos para Saúde: Uma metodologia para serviços hospitalares. Revista SOBECC 2013;18(2):33-44.
6. Buckley BS, Fader M, Macauley MS. Giving intermittent catheter users more choice. Br J Gen Pract. 2015;65(637):419
7. Kapoor A, Vora AM, Natarai G, et al. Guidance on reuse of cardio-vascular catheters and devices in India: A consensus document. Indian Heart J. 2017;69:357-63.
8. Agência Nacional de Vigilância Sanitária (Brasil). Portaria nº 3 de 7 de fevereiro de 1986.
9. Agência Nacional de Vigilância Sanitária (Brasil). Portaria nº 4 de 7 de fevereiro de 1986.
10. Agência Nacional de Vigilância Sanitária (Brasil). RE nº 2605 de 11 de agosto de 2006.
11. Agência Nacional de Vigilância Sanitária (Brasil). RE nº 2606 de 11 de agosto de 2006.
12. Agência Nacional de Vigilância Sanitária (Brasil). RDC nº 156 de 11 de agosto de 2006.

13. Agência Nacional de Vigilância Sanitária (Brasil). Portaria nº 8 de 8 de julho de 1988.
14. Agência Nacional de Vigilância Sanitária (Brasil). RDC nº 15 de 15 de março de 2012.
15. Baffi, SH. Reprocessamento e reutilização de cateteres em hemodinâmica: a busca de qualidade nesta prática. [Dissertação de doutorado em Enfermagen] – Universidade de São Paulo; 2001.
16. Meijs AP, Ferreira JA, DE Greeff SC, et al. Incidence of surgical site infections cannot be derived reliably from point prevalence survey data in Dutch hospitals. Epidemiol Infect. 2017;145(5):970-980.
17. Humphreys, H. Preventing surgical site infection. Where now? J Hosp Infect. 2009;73:316-22.
18. Ribeiro SM. Reprocessamento de cateteres de angiografia cardiovascular após uso clínico e contaminados artificialmente: avaliação da eficácia da limpeza e da esterilização. [Tese de doutorado em Enfermagem] – Universidade de São Paulo;2006.
19. Smith JJ, Henderson JA, Baim DS. The Food and Drug Administration and reprocessing of single-use medical devices: a revised policy and new questions. J Vasc Interv Radiol 2002;13(12):1179-1182.
20. Costa EA, Costa EA, Graziano KU, et al. Reprocessamento de produtos médicos: uma proposta de modelo regulatório para hospitais brasileiros. Rev Esc Enferm USP. 2011:45(6):1459-1465.
21. Duffy RE, Couto B, Pessoa JM, et al. Improving water quality can reduce pyrogenic reactions associated with reuse of cardiac catheters. Infect. Control Hosp. Epidemiol. 2013;24(12):955-960.
22. Kuniyoshi RR, Sternick EB, Nadalin E, et al. Reprocessing of Medical Products in Electrophysiology. Arq Bras Cardiol. 2017;108(2):169-172.
23. Mender RR, Albuquerque GS, Silva MN, et al. Reutilização de cateteres cardíacos de eletrofisiologia. RELAMPA, Rev. Lat.-Am. Marcapasso Arritm. 2011;24(3):151-160.
24. 3M. 3M Surface Test para Mercado Hospitalar [accessed in 21 aug 2018]. Available at: https://www.3m.com.br/3M/pt_BR/3m-do-brasil/todos-os-produtos-3m-do-brasil/~/Todos-os-Produtos-3M/Limpeza-e-Monitoramento-da-Esteriliza%C3%A7%C3%A3o/Sa%C3%BAde/Mercado-Hospitalar/Surface-Test/?N=5002385+8707795+8707798+8711017+8711099+8717846+3294857441&rt=r3>.
25. Sato A, Nakamura I, Fujita H, et al. Peripheral venous catheter-related bloodstream infection is associated with severe complications and potential death: a retrospective observational study. BMC Infect Dis. 2017;17(1):434.
26. Amaranta JM, Toscano CM, Pearson ML, et al. Reprocessing and reuse of single-usemedical devices used during hemodynamic procedures in Brazil: a widespread and largely overlooked problem. Infect. Control Hosp. Epidemiol. 2008;29:854–858.
27. Silva MV, Martinez MB, Andreoli J. Microbiological evaluation of reused catheter guides in a Brazilian hospital. PDA J. Pharm. Sci. Technol. 2006;60:356–365.
28. Popp W, Rasslan O, Unahalekhaka A, et al. What is the use? An international look at reuse of single-use medical devices. Int J Hyg Environ Health. 2010;213:302–7.
29. Wang D, Wu J. Reprocessing and reuse of single-use medical devices in China: a pilot survey. BMC Public Health. 2019;19(1):461.
30. Costa EA. Panorama internacional do reprocessamento de produtos médicos de uso único. Revista SOBECC. 2016;21:203.
31. Ischinger TA, Neubauer G, Ujaky R, et al. Wiederverwendung von medizinischen Einwegprodukten nach qualitätsgesicherter Wiederaufbereitung: ein Modell zur Kostendämpfung? Z. Kardiol, 2002;91:889–898.
32. European Commision. European Commission: synthesis document – Outcome of the first public consultation on the reprocessing of medical devices. May 2008; EAMDR (European Association for Medical Device Reprocessing; SUPROMED 200.7
33. European Comission. European Commission: synthesis document. Outcome of the first public consultation on the reprocessing of medical devices. Brussels, 2008b.
34. Tessarolo F. Reuse of single-use medical devices for interventional cardiology. Appl Surf Sci. 2004;238:341- 46.
35. Quirck M. Most US hospitals avoid reuse of single-use devices. Lancet Infect. Dis. 2002;2:714.
36. United States Government Accontability Office (United States of America) 2008. Report to the Committee on Oversight and Government Reform, House of Representatives. Reprocessed single-use medical devices. FDA Oversight Has Increased, and Available Information Does Not Indicate That Use Presents an Elevated Health Risk. GAO-08-147.
37. Alfa MJ, Castillo J. Impact of FDA policy change on the reuse of single-use medical devices in Michigan hospitals. Am. J. Infect. Control. 2014;32:337–341.
38. The Association of Perioperative registered nurses. AORN guidance statement: reuse of single-use devices. AORN J. 2006;84:876–884.
39. Jacobs PD, Polisena J, Hailey D, et al. Economic analysis of reprocessing single-use medical devices: A systematic literature review. Infect. Control Hosp. Epidemiol. 2008;29(4):297-301.
40. Koh AL, Kawahara K. Current practices and problems in the reuse of single-use devices in Japan. J. Med. Dent. Sci. 2005;52:81–89.
41. World Health Organization. The Joint Commission, Joint Commission International: Single use of Injection Devices. WHO: Geneva; 2007.
42. Hutin YJ, Hauri AM, Armstrong GL. Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. BMJ. 2003;327:1075–1078.
43. Collignon PJ, Dreimanis DE. Beckinha WD. Reuse of single-use medical devices in sterile sites: how often does this still occur in Australia? MJA. 2003;179:115–116
44. Hailey D, Jacobs PD, Ries NM, et al. Reuse of single use medical devices in Canada: clinical and economic outcomes, legal and ethical issues, and current hospital practice. Int. J. Technol. Assess. Health Care. 2008;24:430–436.
45. Department of Health (Australia). Infection control guidelines for the prevention of transmission of infectious diseases in the health care setting. [accessed in 21 aug 2018]. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/DEF2A0D0C4D47A69CA257BF0001B0827/$File/icg-rescinded.pdf
46. Therapeutic Goods Administration (Australia). Australian regulatory guidelines for medical devices. Version 1.1, May 2011. [accessed in 21 aug 2018]. Available at: https://www.tga.gov.au/sites/default/files/devices-argmd-01.pdf
47. Schmid GP, Buvé A, Mugyenyi P, et al Transmission of HIV-1 infection in sub-Saharan Africa and effect of elimination of unsafe injections. Lancet. 2004;363:482–488.

48. Jama ZV, Chin A, Badri M, et al. Performance of re-used pacemakers and implantable cardioverter defibrillators compared with new devices at Groote Schuur Hospital in Cape Town, South Africa. Cardiovasc J Afr. 2015;26(4):181-7.
49. World Health Organization. Regional. Infection prevention and control in health care: time for collaborative action. WHO: Committee for the Eastern Mediterranean; 2010.
50. Raposo M. CME - O coração do hospital: Uma investigação ergonômica em centrais de materiais esterelizados em unidades públicas de saúde. [Dissertação de mestrado em Design] - PUC-Rio de Janeiro: 2007.
51. Kapoor A, Vora A, Nataraj G, et al. Guidance on reuse of cardio-vascular catheters and devices in India: A consensus document. Indian Heart J. 2017; 69:357-63.
52. Oliveira AC, Gama CS. Avaliação da adesão às medidas para a prevenção de infecções do sítio cirúrgico pela equipe cirúrgica. Belo Horizonte: Rev Esc Enferm USP. 2015;49(5):767-74.
53. Veras BM, Senna KM, Correia MG, et al. Análise de custo-efetividade do reuso de cateteres de cinecoronariografia sob a perspectiva de uma instituição pública no Município do Rio de Janeiro, Brasil. Cad. Saúde Pública, Rio de Janeiro. 2013;29:S110-S120.
54. Leite FB. Central de material esterilizado: projeto de reestruturação e ampliação do hospital regional de Francisco Sá. Brasília (DF): Ministério da Saúde; 2008.
55. Lucas CT, Barbosa MP, Oliveira AC. Validação do reprocessamento de cateteres cardíacos angiográficos: uma avaliação da funcionalidade e da integridade. Rev Esc Enferm USP. 2010; 44(4):947-955.
56. Patel G, Hopwood AJ. An evaluation of luminol formulations and their effect on DNA profiling. J. Legal Med. 2013;127(4):723-729.
57. Mathews KC, Holde KE. Bioquímica. 2 ed. Madrid: McGraw-Hill/ Interamericana de España; 2000.
58. Ferreira AM, Andrade D, Rigotti MA, et al. Avaliação da desinfecção de superfícies hospitalares por diferentes métodos de monitoramento. Rev. Latino-Am. Enfermagem. 2015;23(3):466-474.
59. Agência Nacional de Vigilância Sanitária (Brazil). Resolução – ANVISA/DC nº 48, de 2 de junho de 2000.
60. Bergervoet PW, Riessen NV, Zwet WC. Application of the forensic Luminol for blood in infection control. J Hosp Infect. 2008;68(4):329-333.
61. Dilbeck, L. Use of Bluestar forensic in lieu of luminol at crime scenes. Journal of Forensic Identification 2006;56(5):706.
62. Association for the Advancement of Medical Instrumentation (United States of America). Comprehensive guide to steam sterilization and sterility assurance in health care facilities 2017.
63. Associação Brasileira de Normas Técnicas (Brazil). Esterilização de produtos para saúde - Indicadores biológicos - Parte 1: Requisitos gerais. [accessed in 21 aug 2018]. Available at: http://www.abnt.org.br/noticias>

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Review article

Benefícios motores da Realidade Virtual na Encefalopatia Crônica da Infância: uma revisão narrativa

Rebeca C. L. de Oliveira,[1] Priscila S. Cardoso,[1] Ingridi M. B. Almeida,[1] Francisco J. S. da Silva,[2] Leissa da S. Melo-Figueiredo,[2] Bruno B. M. de Oliveira,[2, 3] Danúbia da C. de Sá-Caputo,[2, 3] Laisa L. Paineiras-Domingos[2, 3]*

Resumo

Introdução: A encefalopatia crônica da infância (ECI), ainda mundialmente chamada de paralisia cerebral, é definida como um conjunto de desordens motoras causadas por afecções não progressivas do sistema nervoso central, resultando em alterações do tônus muscular e da postura. Estas alterações são estabelecidas no período pré, peri ou pós-natal e inúmeras modalidades fisioterapêuticas vêm sendo sugeridas para o manejo dessas alterações. A realidade virtual (RV) tem sido usada como uma ferramenta terapêutica inovadora, com uma abordagem motora que envolve o indivíduo e um campo de interação computadorizado, com a simulação de exercícios capazes de estimular os movimentos em tempo real, a motivação e o feedback sensorial. Objetivo: Descrever os benefícios motores da RV como modalidade terapêutica em crianças com ECI. Materiais e métodos: Foi desenvolvida uma revisão narrativa, selecionando artigos nas bases de dados Bireme (BVS) e na biblioteca virtual Scientific Eletronic Library Online (SciELO). Os descritores utilizados foram: fisioterapia, realidade virtual, criança e ECI. Resultados: Apenas cinco artigos foram selecionados. Conclusão: Os artigos consultados sugerem que o uso do a RV influencia na melhora principalmente do equilíbrio da criança, auxiliando no tratamento cinesioterapêutico. Entretanto, com um pequeno número de publicações relacionadas à abordagem fisioterapêutica pediátrica por meio da RV, são necessários mais estudos para uma melhor comprovação científica desta ferramenta.

Descritores: Paralisia cerebral; Realidade virtual; Fisioterapia..

1. Faculdade Bezerra de Araújo (FABA). Rio de Janeiro, RJ, Brasil.
2. Departamento de Fisioterapia. Faculdade Bezerra de Araújo (FABA), Rio de Janeiro, RJ, Brasil.
3. Laboratório de Vibrações Mecânicas e Práticas Integrativas, Departamento de Biofísica e Biometria e Policlínica Américo Piquet Carneiro. Universidade de Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brasil.

***Endereço para correspondência:**
Rua Carius, 179, Rio de Janeiro, RJ, Brasil.
CEP: 23052-180.
E-mail: laisanit@gmail.com
ORCID: https://orcid.org/0000-0003-3451-5056

BJHBS, Rio de Janeiro, 2020;19(2):142-150

Recebido em 18/04/2020. Aprovado em 29/06/2020.

Abstract

Driving Benefits of Virtual Reality in Cerebral Palsy: a narrative review

Introduction: Chronic childhood encephalopathy (CCE), still called cerebral palsy worldwide, is defined as a set of motor disorders caused by non-progressive disorders of the central nervous system, resulting in changes in muscle tone and posture. These changes are established in the pre, peri or postnatal period and numerous physical therapy modalities have been suggested for the management of these changes. Virtual reality (VR) has been used as an innovative therapeutic tool, with a motor approach that involves the individual and a computerized interaction field, with the simulation of exercises capable of stimulating movements in real time, motivation and sensory feedback. Objective: To evaluate the motor benefits of VR as a therapeutic modality in children with CCE. Materials and methods: A narrative review was carried out, with articles found in the Bireme database (BVS) and in the virtual library Scientific Eletronic Library Online (SciELO). The descriptors used were: physiotherapy, virtual reality, children and CCE. Results: Only five articles were selected. Conclusion: The articles consulted suggest that the use of VR influences the improvement mainly of the child's balance, helping kinesiotherapeutic treatment. However, with a small number of publications focused on the pediatric physiotherapeutic approach through VR, further studies are needed for better scientific proof of this tool.

Keywords: Cerebral palsy; Virtual reality; Physical therapy specialty.

Resumen

Beneficios de conducción de la realidad virtual en la parálisis cerebral: una revisión narrativa

Introducción: la encefalopatía infantil crónica (EIC), todavía llamada parálisis cerebral en todo el mundo, se define como un conjunto de trastornos motores causados por trastornos no progresivos del sistema nervioso central, que resultan en cambios en el tono muscular y la postura. Estos cambios se establecen en el período pre, peri o postnatal y se han sugerido numerosas modalidades de fisioterapia para el manejo de estos cambios. La realidad virtual (RV) se ha utilizado como una herramienta terapéutica innovadora, con un enfoque motor que involucra

al individuo y un campo de interacción computarizado, con la simulación de ejercicios capaces de estimular movimientos en tiempo real, motivación y retroalimentación sensorial. Objetivo: Evaluar los beneficios motores de la RV como modalidad terapéutica en niños con EIC. Materiales y métodos: Se realizó una revisión narrativa, con artículos encontrados en la base de datos Bireme (BVS) y en la biblioteca virtual científica electrónica electrónica en línea (SciELO). Los descriptores utilizados fueron: fisioterapia, realidad virtual, niños y EIC. Resultados: Solo se seleccionaron cinco artículos. Conclusion: Los artículos consultados sugieren que el uso de RV influye en la mejora principalmente del equilibrio del niño, ayudando al tratamiento kinesioterapéutico. Sin embargo, con un pequeño número de publicaciones centradas en el enfoque fisioterapéutico pediátrico a través de la realidad virtual, se necesitan más estudios para una mejor prueba científica de esta herramienta.

Palabras clave: Parálisis cerebral; Realidad virtual; Fisioterapia.

Introdução

A encefalopatia crônica da infância (ECI) não progressiva,[1, 2] também conhecida mundialmente como paralisia cerebral,[3] é caracterizada por alterações neurológicas permanentes que afetam o desenvolvimento motor e cognitivo, causando limitações nas atividades cotidianas. A ECI é um distúrbio não progressivo que acontece durante o desenvolvimento do cérebro fetal ou infantil, considerado o distúrbio mais comum na infância[4]. A principal alteração presente nas crianças com ECI é o comprometimento motor, que ocasiona várias modificações decorrentes desta enfermidade, com consequentes alterações na biomecânica corporal. Além disso, a criança pode apresentar distúrbios cognitivos, sensitivos, visuais e auditivos que, somados às alterações motoras, restrições da tarefa e do ambiente,repercutem de diferentes formas no seu desempenho funcional.[5, 6]

Abordagens fisioterapêuticas psicomotoras visam facilitar a interação entre a motricidade, a afetividade e a mente.[7] Em geral, os pacientes da terapia psicomotora são estimulados a interferir em cada exercício proposto para obter experiências significativas. A fisioterapia vem, pouco a pouco, utilizando-se de ferramentas dinâmicas capazes de desenvolver os aspectos: motor, intelectual e, de forma integral, o aspecto afetivo.[7]

Ribeiro[8] atentou que cerca de 17 milhões de pessoas desenvolvem a ECI. Segundo ele, 1 em cada quatro crianças com esse diagnóstico não fala; uma em cada três não anda; uma em cada duas tem deficiência intelectual e uma em cada quatro tem também epilepsia. Do Nascimento e colaboradores[2] consideram que a ECI ocorre durante o desenvolvimento do feto ou, mais raramente, resultado de uma lesão cerebral após o parto e, embora esteja presente no nascimento, pode não ser detectada após meses de vida.

As principais causas da ECI descritas na literatura são: a hipóxia, as anomalias da placenta ou cordão umbilical, o trauma craniano durante o trabalho de parto, as infecções durante a gravidez que podem danificar o desenvolvimento fetal, a icterícia grave, o Fator Rh incompatível entre mãe e bebê, o diabetes mellitus, a hipertensão materna durante a gestação (eclâmpsia), a desnutrição fetal, o uso de drogas e álcool pela mãe durante a gestação, a hemorragia intracraniana, a hipoglicemia fetal, problemas genéticos e a e prematuridade, com consequente fragilidade vascular.[9, 10]

Também é preciso atentar para outras classificações da ECI visando uma definição precisa das alterações decorrentes desta enfermidade.[11] Quanto à gravidade, a ECI pode ser também classificada como leve, moderada ou grave.[8] Quanto ao tipo de comprometimento do sistema nervoso central (SNC), a ECI pode se manifestar por meio de distúrbios motores, incluindo problemas na marcha e equilíbrio, limitações funcionais, alterações do tônus muscular, distonia e alteração na postura;[12, 13] cognitivos, envolvendo distúrbios na fala, no comportamento e raciocínio, dificuldade de interação social; ou mistos (quando ambos são afetados).

Outra demanda necessária na abordagem da enfermidade é identificar os diferentes quadros clínicos da ECI. Considerando o tipo e a localização da alteração motora,[14] a ECI pode se manisfestar nas formas: espástica, discinética ou atáxica.

Adicionalmente, testes e classificações funcionais são cada vez mais aderidos ao programa de reabilitação proposto pelo fisioterapeuta e a equipe interdisciplinar no qual ele deve estar inserido. Estes possibilitam uma melhor abordagem terapêutica, a escolha de ferramentas mais eficazes e adequadas ao padrão motor/cognitivo/afetivo de cada criança, individualmente. Dentre os principais testes e classificações funcionais, podemos citar o Manual Abilities Classification System (MACS);[15] o teste Gross Motor Function Measure (GMFM-66)[16] e o teste Pediatric Evolution of Disability Inventrory (PEDI), que se preocupa com as habilidades funcionais e assistência do cuidado em autocuidado e mobilidade. Os três testes citados são padronizados e validados, comumente utilizados para avaliar a função motora grossa e o desempenho funcional de crianças com ECI.[17]

Outra classificação muito recomendada na abordagem fisioterapêutica em crianças com ECI, é a Classificação Internacional de Funcionalidade, incapacidade e saúde (CIF).[18] Esta classificação permite avaliar as necessidades funcionais das pessoas e pode ser considerada uma importante ferramenta estatística, na coleta e registro de dados; de pesquisa, para medir resultados, qualidade de vida ou fatores ambientais; clínica, na avaliação de necessidades, compatibilidade dos tratamentos com as condições específicas, avaliação vocacional, reabilitação e avaliação dos resultados; de política social, no planejamento dos sistemas de previdência social, sistemas de compensação e projetos e implantação de políticas públicas e pedagógicas, como instrumento usado na elaboração de programas educativos para aumentar a conscientização e realizar ações sociais.

De forma geral, autores[9] reforçam há anos, a importância da classificação da ECI, valorizando alguns aspectos como: agrupar os indivíduos com características clínicas semelhantes; uma linguagem comum para comunicação entre os profissionais; uniformizar os estudos e condutas quanto ao diagnóstico e tratamento, e melhor entendimento do prognóstico.

Considerando a importância no cuidado no diagnóstico e na definição das (in)capacidades e necessidades de cada criança com ECI, surge a necessidade de definição de melhores estratégias terapêuticas para a manejo das complicações decorrentes da ECI. Uma das tecnologias que vem sendo utilizada para a intervenção fisioterapêutica em crianças com ECI é a realidade virtual (RV).[2]

A RV surgiu com os simuladores de vôo para testes na Força Aérea dos Estados Unidos, construídos após a Segunda Guerra Mundial, em 1950. A partir daí, houve um aumento tecnológico, chegando na indústria do entretenimento. O termo RV foi criado na década de 1980 por Jaron Lanier, um artista e cientista da computação que conseguiu convergir dois conceitos contrários em um novo e vibrante conceito, capaz de captar a essência dessa tecnologia: a busca pela fusão do real com o virtual. O aumento tecnológico na área de comunicação e informação alargou a utilização da RV, possibilitando que outras áreas do conhecimento também se desenvolvessem e beneficiassem de sua utilização. Por admitir uma interação homem e computador em ambiente tridimensional (3D) e possibilitar a reprodução de situações reais, passou a ser considerado um recurso de amplo potencial para a área da saúde, tema que nos interessa.[2]

A RV já está sendo aplicada em muitas situações de interação e terapia. Com os sistemas de simulação acabam criando ambientes que buscam criar experiências da vida real e contribuindo para que ocorram as simulações, como por exemplo: (a) no entretenimento, utilizada em games e viagens virtuais; (b) nos negócios, como em maquetes virtuais, edificações, interiores; (c) no treinamento profissional, como em simuladores de vôo, motocicletas, teste de qualidade de veículos; (d) na educação; (e) em viagens no espaço; e na saúde, como nas salas de cirurgias e nos programas de tratamento e reabilitação[19].

Monteiro,[20] reforçou que o uso da RV vem sendo recomendadas como uma opção para o tratamento de crianças com ECI por se tratar de uma modalidade lúdica, bem mais atrativa, possibilitando a melhoria da aprendizagem motora, gradativamente. Além de favorecer a melhora do desenvolvimento físico, os jogos em RV podem contribuir para o desenvolvimento cognitivo por meio de funções básicas, como, memória, concentração, entre outras atividades que tem relação com as realizadas diariamente.

Autores vêm sugerindo o uso terapêutico desta ferramenta, diante de resposta terapêuticas que possibilitam a interação do indivíduo em um ambiente multidimensional e multissensorial, contribuindo para superação de desafios para conseguir melhores resultados com expedientes lúdicos. A RV é utilizada em vários setores, tanto no entretenimento, na educação, na medicina, Engenharia, Artes e inúmeros outros. Na verdade, com o aumento crescente de investimento em tecnologia, a RV promete um grande salto em várias áreas do conhecimento.

Esta é uma tecnologia de interface, ou seja, precisa de um usuário e uma máquina na tentativa de envolver este mesmo usuário em outra realidade, ou seja, uma realidade ficcional. Para que a interação aconteça, há a necessidade do uso de técnicas e de equipamentos computacionais. Em geral, a RV refere-se a uma experiência imersiva e interativa baseada em imagens gráficas 3D geradas em tempo real por computador, ou seja, é uma simulação gerada por computador, de um mundo real ou apenas imaginário.[21]

Existem várias plataformas possíveis para um jogo eletrônico, tais como os computadores, os consoles (popularmente conhecidos como video-games), os miniconsoles (handhelds) e os dispositivos móveis (aparelhos celulares, Palms, etc.). Existe uma gama de plataformas possíveis para um jogo eletrônico. Cada qual com a sua característica de poder de processamento principal e de vídeo.[21]

Neste contexto, este trabalho objetivou descrever, por meio de uma revisão narrativa, potenciais benefícios motores da RV como adjuvante na intervenção fisioterapêutica de crianças com ECI.

Materiais e métodos

Trata-se de uma revisão narrativa envolvendo a ECI e RV como ferramenta de intervenção fisioterapêutica. A busca bibliográfica foi realizada no dia 26 de novembro de 2018, por três revisores independentes, na base de dados Bireme (BVS) (https:/bvsald.org) e na biblioteca virtual SciELO (*Scientific Eletronic Library Online*), com o suporte da professora da disciplina de Trabalho de Conclusão de Curso (TCC) da Faculdade Bezerra de Araújo, Rio de Janeiro, RJ, Brasil. Conforme os Descritores em Ciências da Saúde (DeCS), foram utilizados os termos: paralisia cerebral, fisioterapia, realidade virtual, criança, no idioma português. Estabelecidos os critérios de inclusão, foram incluídos nesta revisão bibliográfica apenas: (1) artigo científico disponibilizado na íntegra; (2) escritos na língua portuguesa; e (3) publicados entre os anos de 2013 e 2018. Foram excluídos: dissertações ou teses, artigos que apresentavam apenas o resumo, estudos preliminares, revisões narrativas ou sistemáticas e estudos que não apresentavam aderência ao tema ECI e RV.

Resultados

A figura 1 mostra um diagrama representando a busca e seleção dos artigos utilizados com base teórica desta revisão narrativa. Foram encontradas 46 referências, sendo 43 textos completos. Ao considerar os critérios de inclusão desta pesquisa, foram excluídos 35 artigos originais, 1 revisão de literatura, 1 tese e 1 estudo preliminar. Ao final da seleção, foram considerados para esta revisão, 3 artigos de intervenção (Mucelin e colaboradores, 2015;[22] Rossi e colaboradores, 2015;[23] do Nascimentoe colaboradores, 2018[2]) e 2 estudos de caso (Silva e colaboradores, 2014[1] e Pavão e colaboradores, 2014[24]), totalizando 5 artigos.

Na tabela 1, são apresentadas as principais descrições dos artigos selecionados, que utilizaram a RV como tecnologia auxiliar na intervenção fisioterapêutica de crianças com ECI. Silva e colaboradores, 2014[1] realizaram o estudo de caso com 1 criança com ECI, utilizando a RV durante 40 sessões, por 30 minutos no período da manhã, 3 vezes por semana, durante 4 meses, observando efeitos sobre a marcha, equilíbrio e coordenação motora. Pavão e colaboradores 2014,[24] consideraram que a RV pode ser uma ferramenta promissora a ser incorporada no processo de reabilitação de paciente com disfunções neuromotoras, após avaliarem o desenvolvimento motor e o equilíbrio de uma criança de 7 anos, após abordagem fisioterapêutica através da RV (XBOX®360 Kinect®).

Estudos com um número maior de crianças também avaliaram o efeito da RV. De acordo com Mucelin e colaboradores, 2015,[22] pacientes com ECI apresentaram melhora em seu desempenho neuromotor associado com o ensino de ciências, demonstrando ser possível a potencialização do aprendizado motor com a aproximação do aprendizado científico. O protocolo com RV investigado por Rossi e colaboradores, 2015[23] propiciou melhoras clínicas (sem significância estatística), com um aperfeiçoamento na função motora ampla e no equilíbrio de crianças entre 7 e 12 anos, durante 24 sessões de RV. Do Nascimento e colaboradores, 2018,[2] avaliaram o uso da RV comparando o tratamento com o treino convencional em 3 crianças com ECI. Foram realizados três dias de procedimento: as crianças participaram de

Figura 1. Diagrama de fluxo da seleção dos artigos

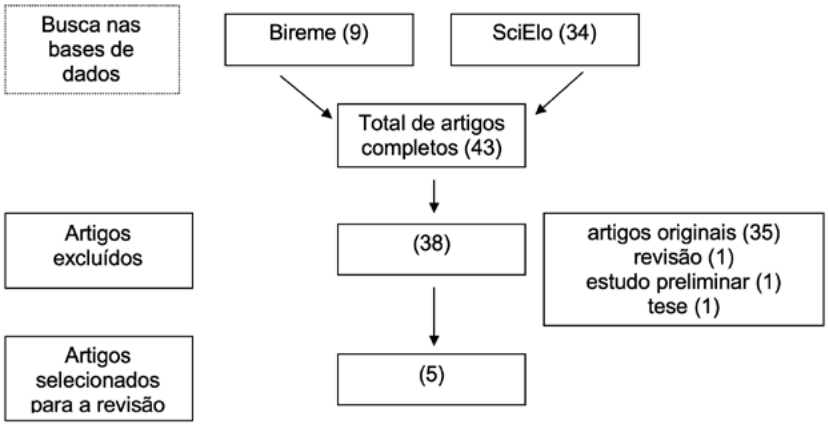


Tabela 1. Estudos selecionados que utilizaram a RV como tecnologia auxiliar na intervenção fisioterapêutica em crianças com ECI

Estudos	Amostra	Objetivo	Método utilizado com a RV	Investigação motora	Resultados
Silva et al., 2014[1]	Estudo de caso com uma criança, gênero masculino, 12 anos, com ECI, sem antecedentes de doenças respiratórias, cardíacas ou ortopédicas prévias, marcha independente e capacidade cognitiva preservada.	Avaliação inicial segundo a EEB para análise do equilíbrio estático; o protocolo da Kay Cerny para análse cinemática da marcha; e a escala de GMFM-66, analisando a motricidade global grossa.	Durante as sessões com o RV, foram utilizados 12 jogos da seguinte maneira: nos dias impares foram jogados *Hula Hoop*, *Seg Way(r) Circuit*, *Basic Step*, *Obstacle Course*, *Soccer Heading* e *Balance Bubble*. Nos dias pares, *Skateboard Arena*, *Table Tilt*, T*orso Twist*, *Tight Rope Walk*, *Penguin Slide* e *Basic Run res*.	Escala de Berg, Protocolo de Kay Cerny, e GMFM-66. 2.RV 3x por semana em sessões de até 30 minutos, por meio dos jogos Wii Fit Plus, plataforma Balance Board e controle Wii Remote durante 4 meses, totalizando 40 sessões.	O uso da RV influencia na melhora principalmente do equilíbrio da criança quando usada em complemento com o tratamento cinesioterapêutico, porém, é necessária a realização de estudos com populações maiores para comprovação de sua eficácia.
Pavão et al., 2014[24]	Uma criança com PC hemiplégica espástica de 7 anos, nível de GMFCS I.	Verificar o efeito de um protocolo terapêutico baseado em RV sobre o desempenho motor e o equilíbrio funcional de uma criança com ECI.	Protocolo de intervenção fisioterapêutica de 12 sessões de 45 minutos, 2x por semana, com RV (XBOX®360 Kinect®) capaz de rastrear a movimentação corporal, reproduzindo-a em uma tela.	Anteriormente à intervenção, foram realizadas avaliações do desenvolvimento motor pela EDM e do equilíbrio pela PBS.	Depois do protocolo de intervenção, o paciente aumentou o escore do instrumento PBS em três pontos, atingindo o teto da escala e, no instrumento EDM, passou de um desempenho motor "muito inferior" para apenas "inferior".
Mucelin et al., 2015[22]	Quatro sujeitos, entre 11 e 18 anos, sendo um pré-adolescente e outros três já adolescentes, portadores de disfunções neuromotoras, devidamente matriculados no ensino fundamental da rede de ensino do município de Teresópolis, Rio de Janeiro, Brasil.	Analisar ações de uma prática clínica em fisioterapia que vise à aprendizagem motora, entender como podem ser estabelecidos vínculos com a aprendizagem científica, em sua interface com as ciências tecnológicas, no favorecimento do processo de aprendizagem motora via RV.	Intervenção fisioterapêutica 2x por semana, durante quatro meses, com duração de 1 mês ou 8 sessões durante 1 hora de intervenção para cada oficina, visando à construção do conhecimento sobre aprendizado motor de forma gradual, utilizando recursos da realidade virtual, por meio do XBOX®360 Kinect.	Escala GMFM antes e após a intervenção composta por 88 itens, subdivididos em cinco grupos (1: deitar e rolar; 2: sentar; 3: engatinhar e ajoelhar; 4: em pé; 5: andar, correr e pular), que foram avaliados separadamente, cada um com um escore máximo de pontuação equivalente à capacidade que o indivíduo teve de realizar as atividades propostas pela escala.	Os pacientes apresentaram melhora em seu desempenho neuromotor associado com o ensino de ciências, demonstrando ser possível a potencialização do aprendizado motor com a aproximação do aprendizado científico. Em relação à escala GMFM, notou-se aumento de 4% na média geral, confirmando o avanço motor dos participantes.

Tabela 1. Estudos selecionados que utilizaram a RV como tecnologia auxiliar na intervenção fisioterapêutica em crianças com ECI (cont.)

Estudos	Amostra	Objetivo	Método utilizado com a RV	Investigação motora	Resultados
Rossi et al., 2015[23]	Pacientes entre 7 e 14 anos, selecionados pelo GMFM *Classification System*, nível I, II ou III, com capacidade de cognição verificada pelo miniexame do estado mental.	Investigar o efeito da RV, na função motora ampla e no equilíbrio na ECI.	24 sessões, sendo 12 semanas, em 2 sessões semanais, de aproximadamente 40 minutos; 4 jogos, repetidos 3x, totalizando 12 partidas em cada sessão (3 jogos voltados aos objetivos do estudo: o controle de grupos musculares importantes para a estabilidade postural, como quadríceps e paravertebrais; o aperfeiçoamento do equilíbrio com deslocamentos laterolateral e anteroposterior; e o deslocamento do centro de gravidade e treino de marcha), e um quarto jogo a critério do participante.	Avaliados pré- e pós-intervenção, a medida do GMFM (função motora grossa) e escala de equilíbrio de Berg.	Todos apresentaram melhora na função motora ampla e no equilíbrio, com mediana pré- e pós-intervenção de 90,41% e 93,63%; 51,5% e 53,5%, respectivamente.
Do Nascimento et al., 2018[2]	Três crianças, de ambos os sexos, com idades de 9 a 12 anos.	Avaliar os efeitos do treino com RV no movimento de alcance manual em crianças com ECI, do tipo hemiparesia espástica.	2 sessões de treinos A (RV) e B (convencional), com intervalo de uma semana entre os treinos. Assim, o primeiro treino foi iniciado no dia da avaliação, o segundo treino ocorreu após uma semana, a cinemática foi realizada antes e após os treinos e depois de uma semana do treino.	3 dias de procedimentos, (uma avaliação inicial de tônus muscular, amplitude de movimento, força de preensão manual, incapacidades e análise cinemática dos membros superiores, realizada pelo Qualisys Motion Capture System.	As crianças apresentaram alterações nas variáveis analisadas do membro superior parético, após ambos os treinos, sobretudo depois do treino com RV. Os treinos utilizando jogos do software Nintendo Wii e convencional foram capazes de alterar as variáveis angulares e espaço temporais, o que sugere uma melhora do movimento de alcance manual das 3 crianças.

Legenda: RV: realidade virtual; ECI: encefalopatia crônica da infância não-progressiva; EEB: Escala de Equilibrio de Berg; GMFM: *Gross Motor Function Classification System*; EDM: Escala de Desenvolvimento Motor; PBS: *Pediatric Balance Scale*.

Fonte: Os autores.

duas sessões de treino de RV e convencional, que ocorreu com intervalo de uma semana entre os treinos. Assim, o primeiro treino foi iniciado no dia da avaliação, o segundo treino ocorreu após uma semana, cinemática foi realizada antes e após o treino e. depois de uma semana de treino, observaram o movimento de alcance manual. Foram analisadas as variáveis angulares, observando as possíveis alterações do arco de movimento.

Discussão

Considerando que a melhora da capacidade de manutenção do equilíbrio é essencial para quem apresenta algum comprometimento motor, como a ECI, autores descritos nesta revisão concordam que a RV vem sendo utilizada na reabilitação fisioterapêutica, através dos videogames. Para esses autores, por meio do ambiente interativo proporcionado pela RV, é possível desenvolver a aprendizagem, diversão e aquisição de novas habilidades. Seus jogos demandam uma rica variedade de movimentos ao jogador, auxiliando no desenvolvimento da força muscular de membros superiores e inferiores.

Os cinco estudos selecionados sugerem a RV na reabilitação de crianças com ECI, pois ela favorece uma melhora na motivação para realização do tratamento, contribui para o armazenamento das atividades, estimula a orientação espaço-temporal e promove uma grande interatividade das crianças. Os estudos também concluíram que a RV foi capaz de auxiliar na aquisição de respostas funcionais, beneficiando o ganho do arco de movimento, a melhora do equilíbrio e a adequação da marcha.

Benefícios motores da RV também foram encontrados em estudos com crianças com outros tipos de distúrbios motores. Mello e Ramalho, 2015,[25] investigaram o uso da RV em crianças com Síndrome de Down. Eles observaram que, utilizando como interface usuário-sistema do Nintendo Wii, foi gerado nos pacientes um alto nível de interesse. E concluíram que a partir de respostas visuais e auditivas, este método oferece ao paciente a informação sobre seu desempenho e os resultados de seus movimentos, simultaneamente à realização da tarefa, fornecendo feedback sobre o sucesso da ação e sobre os erros de descolamento, estimulando o cérebro e o cerebelo para que façam as correções necessárias ao bom desempenho. Assim, afirmam que a RV pode ser uma ferramenta importante. Revisões sistemáticas também reforçam o uso da RV na abordagem fisioterapêutica em crianças com condições clínicas que envolvem distúrbios neuromotores. Massetti e colaboradores, 2016,[26] investigaram estudos que envolviam a esclerose múltipla e a RV como método de reabilitação. Ao analisarem 10 estudos, concluíram que a RV tem sido proposta como útil para a forma de avaliação e reabilitação, representando um fator motivacional e eficaz para a reabilitação motora. Massetti e colaboradores, 2018,[27] ao considerarem que as experiências de RV, por meio de jogos e ambientes virtuais estão sendo cada vez mais usadas em aspectos físicos, cognitivos e intervenções psicológicas, investiga o uso da RV na neuroreabilitação. Considerando pacientes pós-AVC, pacientes com ECI, lesões na medula espinhal e outros distúrbios neurológicos, eles afirmaram que uma variedade de benefícios foi associada a intervenções de RV, incluindo melhora nas funções motoras, psicológica e cognitiva, além de maior participação da comunidade.

Coadjuvante no tratamento fisioterapêutico, a RV pode promover melhoras significativas nas alterações sensório-motoras e no combate à resistência de execução de uma atividade física. Silva e colaboradores, 2014,[1] e do Nascimento e colaboradores, 2018,[2] pontuaram que as crianças, mesmo estando claramente cansadas, não se queixaram e se mantiveram motivados para executar cada movimento proposto pelo uso da RV. Mucelin e colaboradores, 2015,[22] apontou em sua investigação que o termo "aprender praticando" se fez presente, pois o sujeito participante passou a entender conceitos necessários para seu desenvolvimento motor e o porquê deve realizá-los, tendo nova visão sobre a importância da qualidade de cada movimento. Dessa forma, a constituição do sujeito do conhecimento se efetiva, podendo gerar autonomia, e a tão devida e almejada independência plena.

Apesar de Silva e colaboradores, 2014,[1] e do Nascimento e colaboradores, 2018[2] optarem por utilizar o sistema Nintendo Wii, os Softwares Eye-Toe e PlayStation 2, também vêm trazendo benefícios motores, como a melhora da postura, da força muscular, do equilíbrio estático e dinâmico, dos estímulos cognitivos, da percepção visual e da motivação.[28, 29] Esse sistema permite a interação com o jogador por meio de sistema de detecção de movimento da representação do seu avatar (representação gráfica de um utilizador de RV) no vídeo, possui um controle remoto com o sistema wireless, responsável em detectar velocidade, direção, aceleração e desaceleração do movimento. Os movimentos realizados pelo jogador são capturados e reproduzidos em uma tela via sensor de luz infravermelha posicionado acima da televisão. O *feedback* dado pela tela da televisão proporciona

oportunidade de observação do próprio movimento em tempo real, gerando esforço positivo e facilitado o treino e melhora da tarefa.[30]

Embora os estudos tenham demonstrando os benefícios da utilização da RV como adjuvante na abordagem fisioterapêutica, as evidências encontradas ainda são limitadas, especialmente de sua utilização em crianças de baixo comprometimento funcional. De Campos e colaboradores, 2011,[31] pontuaram que quanto menor o comprometimento motor observado em crianças com ECI, mais difícil a obtenção de ganhos terapêuticos no processo de reabilitação. Para eles, a progressão da terapia nestas crianças muitas vezes fica comprometida pela dificuldade em encontrar tarefas que as motivem e ao mesmo tempo apresentem eficácia terapêutica.

Conclusão

Com os avanços mundiais relacionados aos cuidados da saúde e promoção de qualidade de vida, é cada vez mais necessário o desenvolvimento de tecnologias que possam ser utilizada nos âmbitos da educação e da saúde da nossa sociedade, sobretudo na reabilitação física e cognitiva de indivíduos com distúrbios crônicos, como a ECI, no qual comprometem a independência funcional e contribuem para o aparecimento de complicações motoras.

Os estudos apresentados nesta revisão consideraram a RV como uma ferramenta de grande potencial reabilitador. Porém, esta inovação tecnológica requer mais estudos, com melhor rigor científico na aplicação da sua ferramenta, em amostras mais expressivas que seja capaz de destacar seus reais benefícios.

Este trabalho, porém, torna-se relevante para a população que necessita de intervenções terapêuticas, pois discute a ação da RV e a sugere como mais um recurso disponível, de fácil execução e acessível. Tornando, assim, a intervenção fisioterapêutica, uma modalidade adequada, lúdica e dinâmica.

Referências

1. Silva RR da, Iwabe-Marchese C. Uso da realidade virtual na reabilitação motora de uma criança com Paralisia Cerebral Atáxica: estudo de caso. Fisioter. Pesqui. [online]. 2015;22:97-102.
2. Do Nascimento NF, Marques JS, Lucena LC, et al. Treino com realidade virtual no alcance manual de crianças com paralisia cerebral: estudo de três casos. Fisioter Bras. 2018;19:223-30.
3. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Diretrizes de atenção à pessoa com paralisia cerebral / Ministério da Saúde, Secretaria de Atenção à Saúde, Departamento de Ações Programáticas Estratégicas. – Brasília: Ministério da Saúde, 2014. 72 p. : il.
4. Silva LM da, Monteiro ES, Paiva SSC de, et al. Efeitos da Equoterapia na função motora grossa de pacientes com encefalopatia crônica não progressiva. Rev Neurociênc. 2019;23:16-22.
5. Schwartzman JS. Paralisia cerebral. Arquivos Brasileiros de Paralisia Cerebral. 2004;1:4-17.
6. Mancini MC, Alves ACM, Schaper C, et al. Gravidade da paralisia cerebral e desempenho funcional. Rev Bras Fisioter. 2004;8:253-60.
7. Castilho-Weinert LV, Santos EL dos, Bueno MR. Intervenção fisioterapêutica psicomotora em crianças com atraso no desenvolvimento. Rev Bras Ter Saúde. 2011;1:75-81.
8. Ribeiro M. Paralisia Cerebral Pode Afetar o Desenvolvimento Motor e Cognitivo. 2018. Portal Drauzio Varela. Disponível em: https://drauziovarella.uol.com.br/neurologia/paralisia-cerebral-afeta-desenvolvimento-motor-e-cognitivo/ Acesso em: 19 set. 2019.
9. Diament A. Encefalopatia Crônica na Infância (Paralisia Cerebral). In: Diament A. & Cypel A, editores. Neurologia Infantil 3ª ed. SP: Atheneu; 1996. p.781-98.
10. Rottan T. Paralisia Cerebral, Novas Perspectivas Terapêuticas. J Pediatr. 2002;78:S48-S54.
11. Leite JMRS, Prado GF do. Paralisia cerebral Aspectos Fisioterapêuticos e Clínicos. Rev Neurociênc. 2019;12:41-5.
12. Assis-Madeira EA, Carvalho SG. Paralisia cerebral e fatores de risco ao desenvolvimento motor: uma revisão teórica. Cad Pós-Grad Distúrb Desenvolv. 2009;9:142-63.
13. Souza NT de. Qualidade de vida e funcionalidade de crianças com paralisia cerebral. Juiz de Fora, 2011. Trabalho de Conclusão de Curso (Fisioterapia) - Universidade Federal de Juiz de Fora, 2011;1.
14. Monteiro CBM, Abreu LC, Valenti VE. Paralisia Cerebral - Teoria e Prática. São Paulo: Ed. Plêiade, 2015; 25-43.
15. Eliasson A, Krumlinde-Sundholm L, Rösblad B, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: Scale development and evidence of validity and reliability. Dev Med Child Neurol. 2006;48:549-54.
16. Harvey AR. The Gross Motor Function Measure (GMFM). J Physiother. 2017;63:187.
17. Chagas PSC, Defilipo EC, Lemos RA, et al. Classificação da função motora e do desempenho funcional de crianças com paralisia cerebral. Braz J Phys Ther. 2008;12:409-16.
18. CIF Organização Mundial da Saúde. CIF - CJ: Classificação Internacional de Funcionalidade, Incapacidade e Saúde para Crianças e Jovens. São Paulo: EDUSP, 2011.
19. Almeida L, Correa C. Percepções sobre os jogos de simulação de voo na formação de pilotos privados de avião. Novas Tecnologias na Educação. RENOTE. 2017;15:1.

20. Monteiro CBM. Realidade virtual na paralisia cerebral. São Paulo: Plêiade, 2011; 220p.
21. Braga M. Realidade Virtual na Educação. Rev Biol Ciênc Terra. 2001. Volume 1.
22. Mucelin M, Carrapatoso BC, Souza PCS, et al. Virtual reality as a therapeutic possibility for teenagers with chronic not-progressive encephalopathy of childhood. Rev Bras Neurol. 2015; 51:37-44.
23. Rossi JD, Oliveira GC, Böck THO, et al. Rehabilitation in cerebral palsy with Nintendo™ Wii® associated with Wii Fit®. ConS Saúde. 2015;14:277-82.
24. Pavão SL, Arnoni JLB, Oliveira AKC, et al. Impacto de intervenção baseada em realidade virtual sobre o desempenho motor e equilíbrio de uma criança com paralisia cerebral: estudo de caso. Rev Paul Pediatr. 2014;32:389–94.
25. Mello BCC, Ramalho TF. Uso da realidadd virtual no tratamento fisioterapêutico de indivíduos com síndrome de Down. Rev Neurocienc. 2015;23:143-14.
26. Massetti T, Trevizan IL, Arab C, et al. Virtual reality in multiple sclerosis – A systematic review. Mult Scler Relat Dis. 2016; 8:107-12.
27. Massetti T, Silva TD, Crocetta TB, et al. The clinical utility of virtual reality in neurorehabilitation: a systematic review. J Cent Nerv Syst Dis. 2018;10:1–18.
28. Machado LS, Souza DFL, Souza LC, et al. Desenvolvimento Rápido de Aplicações de Realidade Virtual e Aumentada Utilizando Software Livre. Realidade Virtual e Aumentada na Prática. 2008;5-33. Minicursos do SVR2008.
29. Machado LC, Morais RM, Nunes FLS. Serious Games Para Saúde e Treinamentos Imersivos. 2015;2:254-62.
30. Nunes FLS, Costa RMEM, Machado LS, et al. Realidade Virtual para saúde no Brasil: conceitos, desafios e oportunidades. Braz J Biom Eng. 2011;27:243-58.
31. De Campos AC, da Costa CS, Rocha NA. Measuring changes in functional mobility in children with mild cerebral palsy. Devel Neurorehabil. 2011;14:140-4.

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Clinical Case

Basilar dolichoectasia with otorhinolaryngological symptoms: A case report

Tuani A. Stroke,[1]* Ana Cristina C. Martins,[1, 2] Lucas A. L. T. Silva,[1] Henrique José C. Artigoza,[1] Annelise O. A. B. Figueira,[1] Fernando José M. Mendes,[1] Rafael Hollanda[3]

Abstract

Introduction: Basilar dolicoectasis is an uncommon change, which makes the vessel tortuous and dilated, which can lead to ischemic, hemorrhagic or compressive changes. Objective: The present study is case report of a patient with basilar artery dolicoectasis and otorhinolaryngological symptoms. Clinical Case: Patient, 53 years old, male, smoker, hypertensive, atrial fibrillation and gout, who after hospitalization due to stroke suffered a complaint of hearing loss, facial paralysis and dizziness. During hospitalization, he was diagnosed with basilar artery dolichoectasia. Conclusion: Basilar artery dolichoectasia is rare, the otorhinolaryngologist should be aware of vascular causes when evaluating a patient with otoneurological symptoms. The treatment of basilar artery dolichoectasis remains controversial.

Keywords: Stroke; Basilar dolicoectasis; Basilar megadolism; Hearing loss; Peripheral facial paralysis; Dizziness.

1. Posgraduate studies in Otorhinolaryngology, Specialized Service in Otorhinolaaryngological Prevention and Treatment (SEPTO). Pontifical Catholic University of Rio de Janeiro, RJ, Brazil.
2. Otorhinolaryngology Departament. Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, RJ, Brazil.
3. Radiology Departament. Casa de Portugal Hospital, Rio de Janeiro, RJ, Brasil.

***Correspondence address:**
240, Andrade Neves st. 404
Rio de Janeiro, RJ, Brazil.
Zip Code: 20510230
E-mail: tuanistroke@hotmail.com
ORCID: https://orcid.org/0000-0001-8421-8557

BJHBS, Rio de Janeiro, 2020;19(2):151-155

Received on 26/08/2020. Approved on 17/09/2020.

Resumo

Dolicoectasia Basilar com alterações otorrinolaringológicas: Um relato de caso

Introdução: A dolicoectasia basilar é uma alteração incomum, que torna o vaso tortuoso e dilatado que pode levar a alterações isquêmicas, hemorrágicas ou compressivas. Objetivo: Relatar um caso de dolicoectasia da artéria basilar com sintomas otorrinolaringológicos. Caso Clínico: Homem, 53 anos, tabagista, hipertenso, fibrilação atrial e gota, o qual após internação hospitalar por acidente vascular encefálico evoluiu com hipoacusia, paralisia facial e tontura, quando, neste período, foi diagnosticado com dolicoectasia da artéria basilar. Conclusão: A dolicoectasia da artéria basilar é uma entidade rara. O otorrinolaringologista deve estar atento às causas vasculares quando avaliar um paciente com sintomas otoneurológicos. O tratamento permanece controverso.

Descritores: Acidente vascular encefálico; Dolicoectasia basilar; Megadolico basilar; Perda auditiva; Paralisia facial periférica; Tontura.

Resumen

Dolicoectasia basilar com alteraciones otorrinolaringológicas: Reporte de un caso

Introducción: La dolicoectasia basilar es una alteración infrecuente, que torna el vaso tortuoso y dilatado, pudiendo ocasionar cambios isquémicos, hemorrágicos o compresivos. Objetivo: El presente estudio tiene como objetivo reportar el caso de un paciente con cuadro de dolicoectasia de arteria basilar con sintomatología otorrinolaringológica. Caso clínico: Paciente de 53 años, varón, fumador, hipertenso, con fibrilación auricular y gota, que tras ser hospitalizado por ictus sufrió un cuadro de hipoacusia, parálisis facial y mareos. Durante la hospitalización se le diagnosticó un cuadro de dolicoectasia de la arteria basilar. Conclusión: La dolicoectasia de la arteria basilar es una entidad poco frecuente. El otorrinolaringólogo debe conocer las causas vasculares al evaluar a un paciente con síntomas otoneurológicos. Su tratamiento sigue siendo controvertido.

Palabras clave: Ictus; Dolicoectasia basilar; Megadolismo basilar; Hipoacusia; Parálisis facial periférica; Mareos.

Introduction

Basilar artery dolichoectasia is rare vasculopathy with unknown etiology. It occurs due to anatomical modifications that makes the basilar artery elongated, tortuos and sometimes aneurysmatic. When symptomatic, it is presented with hemodynamic disorders or compressive effects.[1] Also, it can affect the emerge site of the cranial nerves. The most affected cranial nerves are V and VII pairs, which leads to trigeminal neuralgia and hemifacial paralysis, respectively. The compressive effect of the VIII pair leads to a clinical condition called vestibular paroxysm.

The magnetic resonance imaging (MRI) is the most common exam, in which is possible to observe the caliber of the vessel, its aberrant shape, and possible affected structures.

Treatment can be conservative or intervencional, and it is necessary a multidisciplinary approach, with na otorhinolaryngologist, neurologista and neurosurgeon.[2]

Case Report

C.P, 53 years old, male, smoker, engeneer professional, came to the specialized service of otorhinolaryngology after hospitalization due to acute ischemic event, complaning of hearing loss, facial paralisys and dizziness.

He had a past pathological history of a long term hearing lost in the right ear, with no defined ethiology (before the ischemic event), and was treated for systemic arterial hypertension, arterial fibrillation and gout.

The otorhinolaringological physical exam revealed intact bilateral tympanic membranes, rhinoscopy and oroscopy with no alterations, peripheral facial paralisys on the left side House-Brackmann classification level IV, Romberg test falling to the right side, Fukuda test with ataxic gait, spontaneous nistagmus to the right, head impulse test with corrective saccades to the right.

The paciente brought the MRI and agioresonance performed during the hopitalization time, which showed acute ischemic lesion in the pons and in the base of the left cerebelar hemisphere. Dolichoectasia of the basilar artery, with tortuos path through almost all of its extension, with fusiform aneurysmatic dilatation in the adjacent segment to the transition beteween the bulb and the pons on the right, which determined extrinsec compression on the pons.

The audiometry performed during hospitalization had moderate to severe sensorioneural loss in the right ear and moderate to profound sensorioneural loss in the left ear. Immitance testing showed type A curves and absent contralateral acoustic reflexes.

On the day of the medical appointment, a second audiometry was performed to evaluate the current situation. The right ear presented moderated to severe sensorioneural loss and the left ear presented mild to moderate sensorioneural loss. There was no discrimination in the right ear. Immitance testing showed type A curves in both ears.

After discussing the case, it was decided, at first, to iniciate treatment with thiamine nitrate compound (B1 vitamin) with pyridoxine hydrocloride (B6 vitamin) 5000 IU, 1 tablet once a day for 60 days, E vitamin 400 IU, 1 tablet every 12 hours for 30 days, A vitamin 50000 IU 1 tablet every 12 hours for 30 days and D vitamin 1 tablet every 12 hours for 30 days, flunarizine dihydrochloride with dihydroergocrisine mesylate 1 tablet every 12 hours for 5 days gradually decreasing 1 tablet once a day for another 10 days, and finally, dexamethasone 4mg, 2 tablets in the mornign for 7 days, followed by its reduction to 1 tablet once a day for 5 days and later half tablet for 2 more days.

The following complementary exams were requested: brainstem evoked response audiometry (BERA), eletrocochleography (ECochG), and vectoelectronystamography. In addition, the need for neurological and physical therapy monitoring was reforced. After the end of the treatment, serial audiometries were performed for follow-up, and maintenence treatment was started with betahistine 24 mg 1 tablet every 12 hours.

The third audiometry (performed after the treatment) showed an improvement with moderate sensorioneural loss in the right ear and mild sensorioneural loss in the left ear.

The ECochG exam showed endolinphatic hydrops in the right ear.

BERA, on the other hand, showed suggestive signs of retrocochlear disfunction for both ears (more evidently for the right ear). The exam suggested psycoacoustic threshold of 75 Db Nhl (approx. 65 – 70 dB NA) for the tested frequency range (2000 – 4000 Hz) for the right ear, and psycoacoustic threshold of 60 Db Nhl (approx. 55 – 60 dB NA) for the tested frequency range (2000 – 4000 Hz) for the left ear.

The vectoeletronistagmography exam showed spontaneous nystagmus to the right and semi-spontaneous nystagmus to the right with positive Dix-Hallpike to the right and caloric test without dizziness with the predominance of the labyrinth to the left.

With the results of complementary exams and the patient's clinical history, it was decided for the use of hearing aids.

After the fourth audiometry, already in use of hearing aids, the result showed mild to moderate sensorioneural loss to the right ear and mild to moderate sensorioneural loss to the left ear. Discrimitation was absent in the right ear. A free field audiometry was performed with the use of hearing aids to verify the auditory gain.

On the following routine appointments the patient still complained of ocasional mild dizziness. It was indicated vestibular rehabilitation therapy. However, the patient did not return to follow-up.

Discussion

Basilar dolichoectasia is a clinical entity defined as vascular dilation and tortuosity. The incidence of intracranial dolichoectatic vassels varies between 0.06 – 5.8%. Vertebral and basilar arteries are the most affected.[3] In about 40% of the cases, this alterations is asymptomatic and it's a radiological finding.[4] Its prevalence increases with age and it is associated with cardiovascular risk factors and the male gender.[5]

Genetic, infectious, inflammatory, immunological, and degenerative factors may play an importante role in children.[6]

Definitions for basilar artery dolichoectsia vary according to studies. The mean diameter of the basilar artery at the level the pons is 3.17 mm.[6] The vessel is considered elongetad when it's lateral to the clivus of the dorsum sellae, and dilated if its diameter exceeds 4.5mm.[4, 6, 7] Patients with normal basilar artery caliber, but with tortuosity, are more likely to have cranial nerve involvment alone, while those with vascular dilation without tortuosity generally develop compressive symptoms or neurological deficits due to ischemia.[3]

Studies have shown that ischemic stroke is the most common clinical manifestation of vertebro-basilar dolichoectasia and the most important cause of death in patients with this desease. The main subtype of ischemic stroke is posterior circulation ischemia, and vertebro-basilar dolichoectasia alone is already an independent risk fator for ischemia in this area.[8] The seccond most frequent manifestation is the compression of cranial nerves. V and VII cranial pairs are the most affected and it results in trigeminal neuralgia and hemifacial paralisys. However, there may also be compression of the abducent, trochlear and oculomotor nerve. Compression of the brain stem in its lower portion can lead to nystagmus, tinnitus, dysphagia and dysphonia.[4] When compressively affected, the VIII pair can also cause vestibular paroxysm, a pathology initially discribed in 1984 by Jannetta as at least 10 spontaneous or semi-spontaneous rotatory vertigo attacks, lasting less than 1 minute, stereotyped phenomenology, positive response to treatment with carbamazepine or oxacarbamazepine with no other diagnostic hypotesis to better explain the patient's clinic.[9]

Intracranial hemorrhagy is also an equally frequent manifestation when compared to nerve compression in cases of basilar artery dolichoectasia. However, it must be noted that this vasculopathy can present itself with numerous other symptoms as well as being asymptomatic.[4]

Involvment cases of III, IV, VII, IX an X cranial pairs by compression are rare.[10]

Therefore, we bring to discussion a basilar dolichoectasia case report discovered after ischemic event that evolved with hypoacusis and left peripheral facial paralysis associeted with dizziness and previous history of hearing loss in the right ear without defined ethiology.

The reported patient had VIII and VII cranial pairs affection after the stroke. As a result of this, he presented hearing loss and hemifacial paralysis both on the left side. This situation is justified once the path and anatomy of the nerves are analyzed together with the result of the acute ischemic injury located at the pons and base of left cerebellar hemisphere. However it has to be questioned whether the origin of contralateral hearing loss could be related to the vascular alteration. The result obtained in the patient's ECochG and the fluctuating character of the hearing loss found in the audiometries on the right side is compatible with endolymphatic hydrops, however in the MRI the aberrant basilar artery is in close contact with the VIII pair, which could generate a compressive effect on this nerve.

The labyrinthine artery can be highly variable in its origin. It can be a branch of the basilar artery or, as in most of the cases, it can be a branch from the anterior cerebellar artery.[11, 12]

However, there are studies that show that the prduction of endolymph by the vascular stria, does not present any changes from abnormal arterial flow of the vertebro-basilar system. When discussing Meniére's disease, Lopes-Escamez et al.[13] mentions cerebral vascular diseases as a possible diferencial diagnosis (stroke/transient ischemic attack on vertebro-basilar system). Audiological and vestibular symptoms, when presented together, are quite charcteristic of cerebral vascular disease, since the blood suply of the inner

ear derives from the vertebro-basilar circulation. Still on the diferencial diagnoses of Meniére's disease, the author exposes in his article the possibility of the compressive effect being generated by masses that may arise in the pontocerebellar angle in addition to the neurovascular compression syndrome (vestibular paroxysm).[13] However it does not mention whether an alteration such as dolichoectasia basilar itself could simulte endolinphatic hydrops, either by vascular hypoflow or by mass effect.

Angiography is considered the gold standard for diagnosing vertebro-basilar dolichoectasia, on the other hand, MRI was cited as the exam of choice in most services, due to the possibility of better assessing the relationship between vascular structures and brains tissues.[14] BERA can also be considered for investigation of asymetric hearing loss associeted with basilar dolichoectasia.[2]

Adequate treatmente for the condition under discussion remains a dilema. Patients who have already presented ischemia or are carriers of intravascular thrombus, can be treated with anticoagulants and atiplatelets agentes, however the mechanical distortion of the vessel contributes to ischemic strokes and therefore it is questionable whether the treatment with these medications in fact gets the desired effetc.[4] We can still highlight that this therapy increases the risk for hemorrhagic episodes.[15, 16]

Patients with compressive neurological manifestations should probably have a surgical evaluation. Surgical decompression of the cranial nerve can be achived by repositioning the artery. For patients with cerebrovascular complications, tratment should be based on care practice for patients with hemorrhagic or ischemic stroke.[16]

Among individuals with newly diagnosed vertebro-basilar dolichoectasia, it is recomended to screen for other potentially fatal arterial disorders. In young individuals with no vascular risk factors, primary predisposisng conditions such as Marfan, Fabry and Pompe's disease beginning in adulthood, should be considered. Serial imaging exams are recomended every six months and therafter, annual follow-up to monitor vessel enlargement.[16]

Conclusion

Basilar artery dolichoectasia is still a rare entity and very little explored both in clinical and therapeutic settings. Its presentation, associated with otorhinolaryngological signs and symptoms, is even less common.

It is very importante that the otorhinolaryngologist is awere of the ethyological possibility of this pathology during his anamnesis and physical examination, as it may be responsable for a range of conditions within otoneurology (tinnitus, dizziness, hearing loss, among others). A situation like that, in the eyes of a less experienced specialist, may go unnoticed and result in a more severe and possibly fatal condition.

The protocol tratment for these patients still remains very uncertain, each case has its specificities, and patient must be treated according to them. In conclusion, we emphasize the importance of a multidisciplinary approach in all cases.

References

1. Najafi MR, Toghianifar N, Esfahani MA, et al. Dolichoectasia in Vertebrobasilar Arteries Presented as Transient Ischemic Attacks: A Case Report. ARYA Atheroslcer (Isfahan). 2016; 12(1):55–58.
2. Melo AA. Dolicomega da artéria vértebro-basilar como causa de perda auditiva neurossensorial assimétrica: relato de caso. Braz J Otorhinolayngol. (São Paulo).2011;15(3):385-387.
3. Mohammed K, Iqbal J, Kamel H, et al. Obstructive hydrocephalus and facial nerve palsy secondary to vertebrobasilar dolichoectasia: Case Report. Surg. Neurol. Int. (Doha). 2018;9:60.
4. Alabri H, Lewis WD, Manjila S, et al. Acute Bilateral Ophthalmoplegia Due to Vertebrobasilar Dolichoectasia: A Report of Two Cases. Am. J. Case Rep. 2017;18:1302-1308.
5. Ortak H, Tas U, Aksoy DB, et al. Isolated Upgaze Palsy in a Patient with Vertebrobasilar Artery Dolichoectasia: a Case Report. J Ophthalmic Vis Res (Totak). 2014;9(1):109–112.
6. Tuzcu EA, Bayarogullari H, Coskun M, et al. Bilateral Abducens Paralysis Secondary to Compression of Abducens Nerve Roots by Vertebrobasilar Dolichoectasia. Neuroophthalmology (Hatay). 2013;37(6):254–256.
7. Yuan Y, Xu K, Luo Q, et al. Research Progress on Vertebrobasilar Dolichoectasia. Int J Med Sci (Changchun). 2014;11(10):1039–1048.
8. Wang F, Hu XY, Wang T. Clinical and imaging features of vertebrobasilar dolichoectasia combined with posterior circulation infarction: A retrospective case series study. Medicine (Baltimore). 2018;97(48):e13166.
9. Jannetta PJ, Moller MB, Moller AR. Disabling Positional Vertigo. N Engl J Med (Pittsburgh). 1984;310:1700–1705.
10. Pham T, Wesolowski J, Trobe JD. Sixth cranial nerve palsy and ipsilateral trigeminal neuralgia caused by vertebrobasilar dolichoectasia. Am J Ophthalmol Case Rep (Michigan). 2018;10:229–232.
11. Zemlin WR. Princípios de anatomia e fisiologia em fonoaudiolo-

gia. Artes Médicas (Porto Alegre).2000;4(5):338-44.
12. Hain TC, Ramaswamy TS, Hillman MA. Anatomia e fisiologia do sistema vestibular normal. In: HERDMAN, S.J. Reabilitação vestibular. Manole (São Paulo). 2002;1(1):3-23.
13. Lopes-Escamez JA, Carey J, Chung W, et al. Diagnostic criteria for Menière disease. J Vestib Res. (Granada). 2015;25:1-7.
14. Han J, Wang T, Xie Y, et al. Successive occurrence of vertebrobasilar dolichectasia induced trigeminal neuralgia, vestibular paroxysmia and hemifacial spasm: A case report. Medicine (Baltimore). 2018;97(25):e11192.
15. Yuan F, Lin J, Ding L, et al. Hemifacial spasm and recurrent stroke due to vertebrobasilar dolichoectasia coexisting with saccular aneurysm of the basilar artery: a case report. Turk Neurosurg. (Cheng Du). 2013;23(2):282-284.
16. Del Brutto VJ, Ortiz JG, Biller J. Intracranial Arterial Dolichoectasia. Front Neurol. (Chicago). 2017;8:344.

Normas para publicação

Submissão de artigos – Brazilian Journal of Health and Biomedical Sciences

O ***Brazilian Journal of Health and Biomedical Sciences*** **(BJHBS)**, inicialmente denominado Revista HUPE, publica artigos inéditos sobre temas diversos em todas as áreas relacionadas às ciências da saúde e biomédicas, e que não estejam simultaneamente em avaliação em nenhum outro periódico. Este jornal rejeita prontamente as práticas de plágio e autoplágio. É composto de seções dedicadas a estudos originais, revisões, estudos de caso e cartas ao editor. Os textos são aceitos em um dos três idiomas: português, inglês e espanhol. O processo de submissão de manuscritos deve considerar as seguintes orientações:

Avaliação por pares: os manuscritos são revisados por pelo menos dois especialistas no assunto. Aqueles que forem aceitos serão editados de acordo com o padrão editorial do **BJHBS**, com o objetivo de melhorar a clareza e eliminar possíveis redundâncias, sem, contudo, alterar o sentido original. A versão final editada será submetida aos autores para aprovação.

Termo de transferência de direitos autorais/conflitos de interesses: após o aceite final do artigo para publicação, os autores deverão enviar o termo de transferência dos direitos assinados pelo autor principal representando cada um dos autores. Neste termo deverão ser declarados quaisquer conflitos de interesses.

Carta de apresentação: uma carta que deverá acompanhar obrigatoriamente o artigo submetido, contendo, pelo menos, as seguintes informações:

- uma declaração de que o manuscrito não foi submetido para publicação em outro periódico;
- recomendação de dois consultores qualificados que sejam especialistas na área científica do artigo submetido (informando *e-mail* e afiliação). O Conselho Editorial poderá escolher algum destes consultores ou não;
- declaração sobre conflitos de interesse: informar se os autores possuem ou não algum conflito de interesse. Conflitos de interesse são aqueles com potencial de influenciar o conteúdo da publicação de forma a impedir a objetividade, integridade ou percepção do valor da publicação;
- declaração sobre autoria: fornecer o nome completo e as afiliações de todos os autores e o endereço de contato do autor para correspondência (endereço, endereço de *e-mail*). Os autores são ainda solicitados a declarar objetivamente que o manuscrito submetido representa um material original, além de informar que ele não foi publicado anteriormente e que não está sendo avaliado para publicação em nenhum outro lugar.

  Se os autores receberam ajuda de escritores técnicos ou revisores de idiomas quando prepararam o manuscrito, isto deve ser explicitado na carta de apresentação, junto com a declaração de que os autores são totalmente responsáveis pelo conteúdo científico do manuscrito.

  Informação da autoria: o mérito da autoria científica deve ser limitado aos participantes que contribuíram intelectualmente no trabalho, além de uma colaboração efetiva para a realização da pesquisa. Portanto, para ser considerado um autor, cada colaborador deve, no mínimo, preencher as seguintes condições: (a) ter contribuído significativamente na concepção e desenho do estudo, ou na análise e interpretação dos dados; (b) ter contribuído substancialmente na elaboração do artigo, ou revisado criticamente o seu conteúdo intelectual e (c) ter aprovado sua versão final a ser publicada. A supervisão/coordenação geral do grupo de pesquisa por si só não justifica a autoria. A contribuição somente na aquisição de verbas provenientes de fontes financiadoras ou na coleta de dados também não é suficiente para justificar autoria. A fim de garantir a transparência dessas informações, os autores são solicitados a incluir uma declaração a respeito da autoria, descrevendo o papel dos autores no estudo e na preparação do manuscrito. A falta desta declaração sobre autoria na carta de apresentação implicará na desconsideração do artigo para avaliação.

  A carta deverá ser assinada pelo autor principal, que representará os demais autores neste documento.

  Página de título: esta página deverá conter as informações de título, autores, conforme segue:

- título (em português, inglês e espanhol) com até 100 caracteres com espaço;
- título abreviado (em português, inglês e espanhol) com até 50 caracteres com espaço;
- nome de cada autor com a respectiva afiliação, nesta ordem: prenome, nomes intermediários abreviados, último sobrenome. Departamento (ou serviço). Faculdade. Universidade (ou instituição). Cidade, UF, país.
- dados de contato do autor correspondente: prenome, nomes intermediários abreviados, último sobrenome, endereço de correspondência, *e-mail*.

Tipos de artigos

1. Artigos originais:

Artigos que resultam de pesquisas originais. São limitados a 5.000 palavras (excluindo resumo e referências) e um máximo de cinco figuras ou tabelas. A lista de referências é limitada a 40 itens. Devem ser apresentados no seguinte formato:

- **resumo:** deve ser apresentado em português, inglês e espanhol, limitado a 250 palavras. Deve seguir o modelo de resumo estruturado, contendo, obrigatoriamente: introdução, objetivos, materiais e métodos, resultados e conclusões. Sabe-se que o resumo alcança maior visibilidade e distribuição do que o artigo em si, por isto deve conter as informações essenciais do artigo, mas não deve ser uma simples composição de frases copiadas do texto integral.

  Deve ser sucinto e objetivo, destacando o que há de mais importante no texto, com o objetivo de atrair o leitor para a leitura integral. Ao final, a conclusão deve constar a relação dos resultados obtidos com os objetivos estabelecidos para o estudo. Adicionalmente, faz-se necessário apontar as contribuições desses resultados para o conhecimento acerca do tema pesquisado.
- **descritores**: devem ser apresentados três a seis termos referentes ao tema apresentado, separados por ponto e vírgula, conforme os Descritores em Ciências da Saúde (DeCS), para os idiomas português e espanhol, ou o Medical Subject Headings (MeSh) para o idioma inglês.

Texto do artigo:

- **introdução**: deve ser curta e conter o propósito (contexto e justificativa) do estudo, incluindo um breve resumo dos estudos relevantes sobre o assunto em questão, citando seus avanços mais recentes, citando apenas as referências pertinentes.
- **materiais e métodos**: esta seção deve constar, resumidamente, as informações que permitam que o estudo seja replicado por outros pesquisadores. Os procedimentos adotados devem ser descritos claramente, bem como as variáveis analisadas, com as respectivas definições sempre que necessário, além da descrição da hipótese a ser testada. Devem ser descritas a população e a amostra, instrumentos de medida, com a apresentação, se possível, de medidas de validade, e conter também informações sobre a coleta e processamento de dados. Deve ser incluída a devida referência para os métodos e técnicas empregados, inclusive os métodos estatísticos. Métodos novos ou substancialmente modificados devem ser descritos, justificando as razões para seu uso e mencionando suas limitações. Os critérios éticos da pesquisa devem ser respeitados. Os autores devem explicitar que a pesquisa foi conduzida dentro dos padrões éticos e aprovada por comitê de ética.
- **resultados**: essa seção deve ser um relato conciso da nova informação descoberta, com o mínimo de julgamento pessoal. Devem ser apresentados numa sequência lógica, iniciando pela descrição dos dados mais importantes. Não se deve repetir nos textos os dados de tabelas e ilustrações, mas apresentá-los resumidamente.

Normas para publicação

- **conclusões**: deve relatar a significância da nova informação e a relevância das novas descobertas em comparação com a literatura científica e as teorias existentes. Nesta seção devem ser mencionadas as limitações do trabalho e também suas implicações para pesquisas futuras. Por fim, as conclusões devem fazer parte da finalização, relacionando com os objetivos apontados na introdução.
- **agradecimentos**: devem ser registrados de forma concisa e limitados àquelas pessoas e/ou instituições que contribuíram para a pesquisa de alguma forma, mas não puderam ser incluídos como coautores.
- **citações no texto**: o **BJHBS** adota o estilo Vancouver, seguindo as normas gerais dos Requisitos Uniformes para Manuscritos Apresentados a Periódicos Biomédicos (www.ncbi.nlm.nih.gov/books/NBK7256/). Para citações no texto, use numerais arábicos sobrescritos,[1] sem espaço, logo após a palavra e após pontuação se houver: "A descrição da doença de Parkinson[1] remete aos idos de 1950,[2] quando...". Em alguns casos, os nomes dos autores podem aparecer no texto: "Phillips[12] avaliou diversos quadros de...", e devem ser citados no texto até dois autores: "Handel e Matias[15] fizeram um estudo sobre...". Porém, quando o número de autores for três ou mais, deve-se citar o primeiro autor acrescido da expressão "e colaboradores": "Silveira e colaboradores[13] propuseram uma nova metodologia...".
- **referências**: todas as referências citadas no texto deverão compor a lista de referências. As referências devem ser restritas a material publicado, artigos ou resumos. Os autores são responsáveis por preencher as referências de modo preciso e completo. Para referências com mais de um autor, deve-se listar até três autores por extenso, acima disso, deve-se listar os três primeiros autores seguidos de ", et al.". O total de referências não deve exceder 40.
- **tabelas e/ou figuras**: deverão somar no máximo cinco.
- **tabela**: deve ser elaborada com programas apropriados, tais como o Excel, podem ter a largura proporcional à largura de uma página diagramada, considerando fonte Arial de tamanho 9, espaçamento simples. Devem ser submetidas em arquivo de texto: DOC (Microsoft Word), RTF (Rich Text Format) ou ODT (Open Document Text). Numeradas em ordem crescente e acompanhadas de título e/ou legenda explicativa, com uma referência objetiva no texto. Em nenhuma situação o conteúdo de uma tabela deverá replicar o de uma figura ou vice-versa. Devem ser numeradas em ordem crescente com números arábicos, em conforme o aparecimento no texto.
- **figuras**: podem ser fotos, ilustrações, gráficos, desenhos etc. Devem ser enviadas em arquivos separados (formato *tiff ou JPEG). Devem ser numeradas em ordem crescente com números arábicos, conforme o aparecimento no texto.

2. Casos clínicos:

a. **Relato de caso**: normalmente descrevem de um a três pacientes ou uma família. O texto deve ter até 2.000 palavras, um total de três tabelas e/ou figuras e até 25 referências. O resumo deve ter até 100 palavras.

b. **Solução de caso clínico**: esse texto deve conter o passo a passo do processo decisório de casos clínicos. As informações do paciente devem ser apresentadas para um ou mais clínico(s) especialista(s) em etapas (texto com fonte em negrito) para simular o modo como a informação aparece na prática clínica. O clínico deve responder (texto com fonte regular) conforme as novas informações são adicionadas, compartilhando suas justificativas/argumentos com o leitor. O texto deve ter até 2.500 palavras e até 15 referências.

3. Artigos de revisão:

Devem versar sobre temas relevantes para a prática médica. Estes artigos comporão a seção que versará sobre o tema comum daquela edição, na área de saúde. São limitados a 5.000 palavras (excluindo resumo e referências) e um máximo de cinco figuras e/ou tabelas. A lista de referências é limitada a 40 itens. Os trabalhos serão submetidos à avaliação do conselho de editores via convite ao editor que organizará esta seção, conforme regras que seguem:

Página de título: esta página deverá conter as informações de título, autores, conforme segue:

- título (em português, inglês e espanhol) com até 100 caracteres com espaço;
- título abreviado (em português, inglês e espanhol) com até 50 caracteres com espaço;
- nome de cada autor com a respectiva afiliação, nesta ordem: prenome, nomes intermediários abreviados, último sobrenome. Departamento (ou serviço). Faculdade. Universidade (ou instituição). Cidade, UF, país.
- dados de contato do autor correspondente: prenome, nomes intermediários abreviados, último sobrenome, endereço de correspondência, *e-mail*.

Texto do artigo:

- **resumo**: deve ser apresentado em português, inglês e espanhol, limitado a 250 palavras. Deve seguir o modelo de resumo estruturado, com introdução, materiais e métodos, resultados e discussão. Sabe-se que o resumo alcança maior visibilidade e distribuição do que o artigo em si, por isto deve conter as informações essenciais do artigo, mas não deve ser uma simples composição de frases copiadas do texto integral. Deve ser sucinto e objetivo, destacando o que há de mais importante no texto, com o objetivo de atrair o leitor para a leitura integral. Ao final, a conclusão deve constar a relação dos resultados obtidos com os objetivos estabelecidos para o estudo. Adicionalmente, faz-se necessário apontar as contribuições desses resultados para o conhecimento acerca do tema pesquisado.
- **descritores**: devem ser apresentados três a seis termos referentes ao tema apresentado conforme lista dos Descritores em Ciências da Saúde (DeCS), para os idiomas português e espanhol ou do Medical Subject Headings (MeSh) para o idioma inglês. Devem ser separados por ponto e vírgula.

Os artigos de revisão poderão ser de dois tipos:

a. **Revisão sistemática e meta-análise** – Por meio da síntese de resultados de estudos originais, quantitativos ou qualitativos, o artigo deverá responder à pergunta específica e de relevância para os artigos sobre o tema da edição, no contexto da área de saúde (ver foco do **BJHBS**). Descreverá de modo detalhado o processo de busca dos estudos originais, os critérios utilizados para seleção daqueles que foram incluídos na revisão e os procedimentos empregados na síntese dos resultados obtidos pelos estudos revisados (que poderão ou não ser procedimentos de meta-análise).

b. **Revisão narrativa/crítica** – A revisão narrativa ou revisão crítica possui caráter descritivo-discursivo, e visa à apresentação abrangente e à discussão de temas de interesse científico na área de saúde. Deve apresentar formulação clara de um objeto científico de interesse, argumentação lógica, crítica teórico-metodológica dos trabalhos consultados e síntese conclusiva. Deve ser elaborada por pesquisadores com experiência no campo em questão ou por especialistas de reconhecido saber.

- Agradecimentos: devem ser registrados de forma concisa e limitados àquelas pessoas e/ou instituições que contribuíram para a pesquisa de alguma forma, mas não se encaixam nos critérios estabelecidos para os coautores.
- Citações no texto: o **BJHBS** adota o estilo Vancouver, seguindo as normas gerais dos Requisitos Uniformes para Manuscritos Apresentados a Periódicos Biomédicos (www.ncbi.nlm.nih.gov/books/NBK7256/). Para citações no texto, use numerais arábicos sobrescritos,[1] sem espaço, logo após a palavra e após pontuação se houver: "A descrição da doença de Parkinson[1] remete aos idos de 1950,[2] quando...". Em alguns casos, os nomes dos autores podem aparecer no texto: "Phillips[12] avaliou diversos quadros de...", e devem ser citados no texto até dois autores: "Handel e Matias[15] fizeram um estudo sobre...". Porém, quando

o número de autores for três ou mais, deve-se citar o primeiro autor acrescido da expressão "e colaboradores": "Silveira e colaboradores[13] propuseram uma nova metodologia...".

- Referências: todas as referências citadas no texto deverão compor a lista de referências. As referências devem ser restritas a material publicado, artigos ou resumos. Os autores são responsáveis por preencher as referências de modo preciso e completo. Para referências com mais de um autor, deve-se listar até três autores por extenso, acima disso, deve-se listar os três primeiros autores seguidos de ", et al.". O total de referências não deve exceder 40.
- Tabelas e/ou figuras: deverão somar no máximo cinco.
- Tabela: deve ser elaborada com programas apropriados, tais como o Excel, podem ter a largura proporcional à largura de uma página diagramada, considerando fonte Arial de tamanho 9, espaçamento simples. Devem ser submetidas em arquivo de texto: DOC (Microsoft Word), RTF (Rich Text Format) ou ODT (Open Document Text). Numeradas em ordem crescente e acompanhadas de título e/ou legenda explicativa, com uma referência objetiva no texto. Em nenhuma situação o conteúdo de uma tabela deverá replicar o de uma figura ou vice-versa. Devem ser numeradas em ordem crescente com números arábicos, em conforme o aparecimento no texto.
- Figuras: podem ser fotos, ilustrações, gráficos, desenhos etc. Devem ser enviadas em arquivos separados (formato *tiff ou JPEG). Devem ser numeradas em ordem crescente com números arábicos, conforme o aparecimento no texto.

4. Outras submissões:

Editorial: trata-se de um comentário e análise relativa a um artigo na edição em questão. Pode incluir uma figura ou tabela e limita-se a 750 palavras, com até cinco referências. Será elaborado pelo editor e/ou algum colaborador convidado por ele.

Cartas ao editor: espaço para comunicação dos leitores a respeito de artigos recém-publicados, limitados a até 200 palavras (excluindo referências), até cinco referências e uma figura ou tabela, devendo ser submetida em até seis meses após a publicação do artigo. Para cartas com assuntos não relacionados aos artigos do **BJHBS** devem ser limitadas a até 500 palavras (excluindo as referências), com até cinco referências e uma figura e/ou tabela. São solicitados os dados dos autores, bem como endereço de correspondência e/ou declarações de possíveis conflitos de interesses. A decisão de publicar o conteúdo da carta é de responsabilidade do editor.

5. Submissão *on-line*:

Os artigos e demais tipos de colaborações devem ser enviados para o *e-mail* submission.bjhbs@gmail.com, juntamente com a carta de apresentação. O assunto do *e-mail* deve ser: "Tipo de manuscrito [artigo original, relato de caso, artigo de revisão ou carta ao editor] – título do manuscrito" + último sobrenome do autor principal em letras MAIÚSCULAS.

Todas as comunicações subsequentes deverão ser feitas através da opção "responder" deste *e-mail* original.

O comitê editorial fará a avaliação do manuscrito de acordo com a linha editorial da revista e retornará a respeito do aceite para avaliação por pares no menor prazo possível. Caso ele seja considerado adequado para publicação, de acordo com a política editorial do **BJHBS**, entrará no fluxo editorial e passará pelas etapas de revisão textual e diagramação.

Após o aceite do artigo deverá ser enviado o termo de transferência dos direitos autorais e declaração de conflitos de interesses.

A prova de prelo será encaminhada para avaliação final em formato .pdf antes da efetiva publicação do texto e deverá retornar no prazo estabelecido pela equipe editorial.

Os textos e artigos que não atenderem às especificações descritas nestas normas serão devolvidos sem prévia avaliação pelo conselho de editores do **BJHBS**. Esses textos deverão ser resubmetidos ao processo de avaliação.

Paper submission – Brazilian Journal of Health and Biomedical Sciences

Brazilian Journal of Health and Biomedical Sciences (BJHBS), formely titled **Revista HUPE**, publishes new articles about several themes all related to health and biomedical sciences, provided they're not in simultaneous analysis for publication in any other journal. It rejects promptly any plagiarism and selfplagiarism practices. It features dedicated sections to original research, literature reviews, case studies, and letters to the editor. Papers must be submitted in one of three languages: Portuguese, Spanish, and English. The submission process comprises the following steps:

Peer review: papers are reviewed by at lest two specialists. Accepted papers will be edited according to the publishing standards of **BJHBS**, to improve readability and minimize redundancy, without loss of original meaning. The final edited version will be sent to authors for approval.

Copyright/conflicts of interest agreement: after the final approval, authors must send the copyright transfer agreement signed by the first author representing each additional author. In this agreement must be stated any conflicts of interest.

Introduction letter: a letter that must come with the submitted paper and contains at least the following information:

- a statement that the paper has not been submitted for publication in another journal;
- recommendation of two specialists for consulting in the scientific field of the submitted paper. The Editorial Board may or may not choose any of these consultants;
- conflicts of interest statement: state if the authors have any conflicts of interest. Conflicts of interest are those with potential influence over the published content, compromising the objectivity, integrity, or perceived value of the paper;
- author information: to provide full name and institutional affiliations of every author and a mailing address of the main author (postal and e-mail). Authors will be required to objectively state that the submitted paper consists of original content, informing it has not been previously published nor is it being analysed with this intent elsewhere.

  If the authors had assistance from technical writers or language reviewers, it must be explicitly stated in the introduction letter, along with the assurance that the authors are fully responsible for the scientific content of the paper.

  Authorship information: scientific authorship must be limited to those who contributed with intellectual work, with actual collaboration in the research. Therefore, to be considered an author, each contributor must meet the following conditions: (a) significant contribution to the creation and design of the study or to the analysis and interpretation of its results; (b) substantial contribution to the production of the paper, or critical review of its intellectual content, and (c) approval of the final version for publication. Leading or supervising a research lab/group does not in itself qualify as authorship. Sole contributions to fund raising or to data gathering also do not qualify as authorship. To ensure transparency in this aspect authors are expected to include a statement of authorship detailing the role of each author in the study and in the production of the paper. In

the absence of this authorship statement within the introduction letter, the paper will be disqualified for analysis.

The letter must be signed by the main author, who will represent all other authors in this document.

Title page: this page must contain title and author information as follows:

- title (in Portuguese, English, and Spanish) 100 characters maximum, counting spaces;
- short title (in Portuguese, English, and Spanish) 50 characters maximum, counting spaces;
- the name of each author with their affiliation in this particular order: first name, abbreviated middle names, last name. Department (or service). Course. University (or institution). City, state/province/territory, country.
- contact information for an author: first name, abbreviated middle names, last name, mailing address, e-mail.

Types of papers

1. **Original papers**:

Papers resulting of original research. Maximum of 5,000 words (excluding abstract and references) and five images or tables. Maximum of 40 listed references. They must be submitted in the following format:

- **abstract**: must be written in Portuguese, English, and Spanish, with a maximum of 250 words. Must follow the structured abstract model, with mandatory introduction, methodology and resources, results and discussion. It is well known that the abstract gets more visibility and distribution than the full text of the paper. Therefore, it must contain the essential information in the paper, but cannot be just a patchwork of sentences from it. It must be succinct and direct, highlighting what is most important in the full text in order to encourage a full reading. In the conclusion, all results must be related to the objectives of the study. The discussion must assert the contribution of the results to the body of knowledge about the subject of research.
- **keywords**: three to six terms related to the subject must be given, separated by semicolons, according to DeCS (Descritores em Ciências da Saúde) for Portuguese and Spanish, and also MeSh (Medical Subjects Headings) for English.

Full text

- **introduction**: it must be short and present the purpose (context and justification) of the study, including a short review of relevant studies about the subject, mentioning any recent progress, and referencing just what is appropriate.
- **methodology and resources**: this section must briefly present all the information needed for other researchers to replicate the study. Adopted procedures must be clearly described, as must the analysed variables and tested hypotheses. Definitions must be given whenever necessary. Population, sample, and measurement instruments must be described and information about data gathering and processing must be given. If possible, validity scores must be included. Methods an techniques used must be duly detailed, including statistic methods. New or substantially modified methods must be described, with a justification for its use and mention of its limitations. Research ethics must be observed. Authors must explicitly state that the research was done within ethical standards and with the approval of an ethics committee.
- **results**: this section must be a concise report of all new information found, with minimum personal bias and judgment. The data must be presented in a logical sequence, starting with the most important information. Data from tables and images must not be repeated, but briefly referred to. It must state the significance of the new data and the relevance of the new findings in relation to established theories and to scientific literature. In this section must also be mentioned the limitations of the present work, as well as its implications for future research. Finally, conclusions must be included in this section, always related to the initially stated objectives.
- **acknowledgments**: must be concise and limited to people and institutions that contributed to the research in some degree, but could not be included as authors.
- **in-text citations**: **BJHBS** follows the Vancouver style, according to the general rules of The NLM Style Guide for Authors, Editors, and Publishers, second edition (www.ncbi.nlm.nih.gov/books/NBK7256/). For in-text citations, use Arabic numerals superscript,[1] without spaces, right after a word or punctuation: "Parkinson's Disease[1] description began in the 1950s,[2] when..." In some cases, the names of the authors may figure in the text: "Phillips[12] analysed several conditions of..."; and up to two authors can be named: "Handel and Matias[15] conducted a study about..." However, when the number of authors is three or more, the first author must be named along with the expression "et al": "Silveira et al[13] have proposed a new methodology..."
- **references**: all referenced cited in-text must be in the reference list. References are limited to published material, papers, and abstracts. Authors are responsible for providing precise and complete references. In references with more than one author, authors up to three must be named. From there on, an "et al" must follow the first three authors. There must be no more than 40 references.
- **tables and/or images**: up to a maximum of five.
- **tables**: must be created in dedicated software, such as Excel. The width must be proportional to one page in the current layout. The font must be Arial, size 9, single space. Tables must be imported to and submitted in a text file: .doc/.docx (Microsoft Word), .rtf (Rich Text Format), or .odt (Open Document Text). They must be assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text. The content of a table must not replicate that of an image nor vice versa. Their numbers must be assigned according to the order in which they are referenced in-text.
- **images**: can be photos, illustrations, graphics, drawings, etc. Images must be submitted as separate files (.tiff or .jpeg). They must be assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text

2. **Clinical cases**:

a. **Case report**: usually describes one to three patients or a family case. The text must be up to 2,000 words long, with up to three tables or images and up to 25 references. The abstract must be no more than 100 words long.

b. **Clinical case solution**: must contain a step by step description of the decision process of clinical cases. Patient information must be presented to one or more clinical experts in stages (text in bold) to simulate the way information is made available in clinical practice. The expert must answer (text in regular font) as new information is added, sharing their reasoning/arguments with the reader. The text must be up to 2.500 words long, and must have up to 15 references.

3. **Literature review**:

Must be about subjects relevant to medical practice. These will form a section about the common theme of each issue. These are limited to 5,000 words (excluding abstract and references) and a maximum of five images and/or tables. Maximum of 40 listed references. Literature reviews will be submitted for the editorial board analysis under invitation by the guest editor of this section, and must conform to the following standards:

Title page: this page must contain title and author information as follows:

- title (in Portuguese, English, and Spanish) 100 characters maximum, counting spaces;

- short title (in Portuguese, English, and Spanish) 50 characters maximum, counting spaces;
- the name of each author with their affiliation in this particular order: first name, abbreviated middle names, last name. Department (or service). Course. University (or institution). City, state/province/territory, country.
- contact information for an author: first name, abbreviated middle names, last name, mailing address, e-mail.

Full text:

- **abstract**: must be written in Portuguese, English, and Spanish, with a maximum of 250 words for each language. Must follow the structured abstract model, with mandatory introduction, methodology and resources, results and discussion. It is well known that the abstract gets more visibility and distribution than the full text of the paper. Therefore, it must contain the essential information in the paper, but cannot be just a patchwork of sentences from it. It must be succinct and direct, highlighting what is most important in the full text in order to encourage a full reading. In the conclusion, all results must be related to the objectives of the study. The discussion must assert the contribution of the results to the body of knowledge about the subject of research.
- **keywords**: three to six terms related to the subject must be given according to DeCS (Descritores em Ciências da Saúde) for Portuguese and Spanish, and also MeSh (Medical Subjects Headings) for English. Keywords must be separated by semicolons.

Literature reviews may fall into two types:

a. **Systematic review and meta-analysis** – Through a synthesis of original studies' results, the paper must answer specific relevant health sciences questions about the theme of its issue (see **BJHBS'** focus). It must detail the search process to find the original studies, selection criteria, and synthesis procedures for the results of the reviewed studies (which may or may not be meta-analysis procedures).

b. **Narrative/critic review** – Narrative or critic review has a descriptivediscoursive character, and aims to offer a broad presentation and to discuss themes of scientific interest within the health field. It must have a clear formulation of the scientific subject of interest, a theoretical-methological critic of the reviewed works, and a conclusive synthesis. It must be elaborated by experienced researchers in the field in question or by renowned experts of notorious knowledge.

- **Acknowledgments:** must be concise and limited to people and institutions that contributed to the research in some degree, but could not be included as authors.
- **In-text citations: BJHBS** follows the Vancouver style, according to the general rules of The NLM Style Guide for Authors, Editors, and Publishers, second edition (www.ncbi.nlm.nih.gov/books/NBK7256/). For in-text citations, use Arabic numerals superscript,[1] without spaces, right after a word or punctuation: "Parkinson's Disease[1] description began in the 1950s,[2] when..." In some cases, the names of the authors may figure in the text: "Phillips[12] analysed several conditions of..."; and up to two authors can be named: "Handel and Matias[15] conducted a study about..." However, when the number of authors is three or more, the first author must be named along with the expression "et al": "Silveira et al[13] have proposed a new methodology..."
- **References:** all referenced cited in-text must be in the reference list. References are limited to published material, papers, and abstracts. Authors are responsible for providing precise and complete references. In references with more than one author, authors up to three must be named. From there on, an "et al" must follow the first three authors. There must be no more than 40 references.
- **Tables and/or images:** up to a maximum of five.
- **Tables:** must be created in dedicated software, such as Excel. The width must be proportional to one page in the current layout. The font must be Arial, size 9, single space. Tables must be imported to and submitted in a text file: .doc/.docx (Microsoft Word), .rtf (Rich Text Format), or .odt (Open Document Text). They must be assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text. The content of a table must not replicate that of an image nor vice versa. Their numbers must be assigned according to the order in which they are referenced in-text.
- **Images:** can be photos, illustrations, graphics, drawings, etc. Images must be submitted as separate files (.tiff or .jpeg). They must be assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text

4. Other submissions:

Editorial: it's a commentary on or analysis of papers in a given issue. It may include an image or table and be no more than 750 words long, containing up to five references. It will be written by the editor in chief or by an invited contributor at their request.

Letters to the editor: space for reader's to talk about recently published papers. Each letter must have up to 200 words (excluding references), five references and one image or table. It must be submitted no later than six months after the publication of the relevant paper. Letters non-related to papers published by **BJHBS** are limited to 500 words (excluding references), five references, and one image or table. Authors of letters will be required to provide their details, as well as contact information and possible conflicts of interest. The decision about the publication of a letter is made by the editor in chief.

5. On-line submission:

Papers and other types of material must be sent to submission.bjhbs@gmail.com, along with the introduction letter. The subject of the e-mail must be: "Type of paper [original paper, case report, literature review]" or "Letter to the editor" -- title" + last name of its main author in UPPER CASE.

All subsequent communication must happen through responses to the original e-mail.

The editorial committee will analyse the material according to the editorial policies of **BJHBS** and will answer regarding acceptance for peer review as soon as possible. If it's considered fit for publication, it will be processed and proceed to editing, proofreading and layout.

After a paper's acceptance, the term of copyright transfer and the statement of conflicts of interest must be sent as soon as possible.

The final layout will be forwarded to the authors for final approval in .pdf format. This approval must be given according to a deadline defined by the editorial team.

Papers and other texts that do not conform to the specifications of these guidelines will be returned without any analysis by the editorial board of **BJHBS**. Such material must be re-submitted for new analysis once specifications are followed.

Normas para publicação

Sumisión de artículos - Brazilian Journal of Health and Biomedical Sciences

El ***Brazilian Journal of Health and Biomedical Sciences*** **(BJHBS)**, anteriomente titulado **Revista HUPE**, publica artículos inéditos sobre diversos temas relacionados con el área de ciencias de la salud y biomédicas que no estén siendo considerados simultáneamente en ninguna otra revista. Rechaza prontamente cualquieres práctica de plagio y/o de auto plagio. Está compuesta por secciones dedicadas a estudios originales, revisiones, estudios de caso y cartas al editor. Los textos son aceptados en uno de los tres idiomas: portugués, inglés y español. El proceso de sumisión de manuscritos debe considerar las siguientes pautas:

Evaluación por pares: los manuscritos son revisados por lo menos por dos especialistas en la materia. Aquellos que fuesen aceptados serán editados de acuerdo con la norma editorial del **BJHBS**, con el objetivo de dar más claridad y eliminar posibles redundancias, sin que eso quiera decir alterar el significado original. La versión final editada será sometida a los autores para aprobación.

Declaración de transferencia de los derechos de autor/conflictos de interés: después de la aceptación final del artículo para la publicación, los autores deberán enviar la declaración de transferencia de los derechos, firmada por el autor principal en representación de cada uno de los autores. En esta declaración deberán ser mencionados cualesquiera conflictos de interés.

Carta de presentación: una carta que deberá acompañar obligatoriamente el artículo sometido, conteniendo, por lo menos, las siguientes informaciones:

- una declaración de que el manuscrito no fue sometido para publicación en otra revista;
- recomendación de dos consultores calificados que sean especialistas en el área científica del artículo sometido (informando correo electrónico y entidad). El Consejo Editorial podrá escoger cualquiera de estos consultores o no;
- declaración de conflictos de interés: informar si los autores poseen o no algún conflicto de interés. Los conflictos de interés tienen el poder de influenciar el contenido de la publicación evitando la objetividad, integridad o percepción del valor de la publicación;
- declaración de autoria: proporcionar el nombre completo y las entidades de todos los autores y la dirección de contacto del autor para correspondencia (dirección, dirección de correo electrónico). También se solicita a los autores declarar objetivamente que el manuscrito sometido es material original, además de informar que no fue publicado anteriormente y que no está siendo valorado para publicación en ningún otro lugar.

  Si los autores recibieron ayuda de escritores técnicos o revisores de idiomas cuando prepararon el manuscrito, esto debe ser explicitado en la carta de presentación, junto con la declaración de que los autores son totalmente responsables por el contenido científico del manuscrito.

Información de la autoria: el mérito de la autoria científica debe limitarse a los participantes que contribuyeron intelectualmente en el trabajo, mas allá de una colaboración efectiva para la realización de la investigación. Por lo tanto para ser considerado un autor, cada colaboradordebe como mínimo cumplir con las siguientes condiciones: (a) haber contribuido de manera significativa en la concepción y diseño del estudio, o en el análisis e interpretación de los datos; (b) haber contribuido sustancialmente en la elaboración del articulo o revisado críticamente el contenido intelectual y (c) haber aprobado la versión final a ser publicada. La supervisión/coordinación general del grupo de investigación por si sola no justifica la autoria. Solo la contribución en la adquisición de sumas de dinero provenientes de fuentes financiadoras o en la recogida de datos tampoco es suficiente para justificar la autoria. Con el fin de garantizar la transparencia de esas informaciones, se solicita a los autores incluir una declaración al respecto de la autoria, describiendo el papel de los autores en el estudio y en la preparación del manuscrito. La falta de esta declaración sobre autoria en la carta de presentación implicará la desconsideración del artículo para valoración.

La carta deberá ser firmada por el autor principal, que representará a los demás autores en este documento.

Página del título: esta página deberá contener las informaciones del título, autores, de la siguiente manera:

- título (en portugués, inglés y español) de hasta 100 caracteres con espacio;
- título abreviado (en portugués, inglés y español) de hasta 50 caracteres con espacio;
- nombre de cada autor con su respectiva afiliación, en este orden: nombre, segundos nombres abreviados, último apellido. Departamento (o servicio). Facultad. Universidad (o institución). Ciudad, Unidad de la Federación (UF), país.
- datos de contacto del autor correspondiente: nombre, segundos nombres abreviados, último apellido, dirección de correspondencia, correo electrónico.

Tipos de artículos

1. **Artículos originales:**

Los artículos resultantes de investigaciones originales. Se limitan a 5.000 palabras (excluyendo resumen y referencias) y a un máximo de cinco figuras o tablas. La lista de referencias se limita a 40 ítems. Deben presentarse en el siguiente formato:

- **resumen:** debe presentarse en portugués, inglés y español, limitado a 250 palabras. Debe seguir el modelo de resumen estructurado, incluyendo, obligatoriamente: introducción, materiales y métodos, resultados y discusión. Se considera que el resumen alcanza una mayor visibilidad y distribución que el articulo en si, por esto debe contener las informaciones esenciales del artículo, pero no debe ser una simple composición de frases copiadas del texto integral.

  Debe ser sucinto y objetivo, destacando lo que es más importante en el texto, con el objetivo de atraer al lector a leerlo íntegramente. Al final, la conclusión debe comentar la relación de los resultados obtenidos con los objetivos establecidos para el estudio. Adicionalmente, es necesario hacer alusión a las contribuciones de esos resultados en el conocimiento acerca del tema investigado.
- **palabras clave:** deben presentarse de tres a seis términos concernientes al tema presentado, separados por punto y coma, conforme con las palabras clave en Ciencias de la Salud (DeCS), para los idiomas portugués y español, o el Medical subject Headings (MeSh) para el idioma inglés.

Texto del artículo

- **introducción:** debe ser corta y contener el objetivo (contexto y justificación) del estudio, incluyendo un breve resumen de los estudios relevantes sobre el tema en cuestión, citando los avances más recientes, citando apenas las referencias pertinentes.
- **materiales y métodos:** esta sección debe constar de, brevemente, las informaciones que permitan que el estudio sea replicado por otros investigadores. Los procedimientos adoptados deben ser descritos claramente, así como las variables analizadas, con las respectivas definiciones siempre que sea necesario, más allá de la descripción de la hipótesis a prueba. Deben describirse la población y la muestra, los instrumentos de medida, con la representación, si es posible, de las medidas de validez, y contener también informaciones sobre la recogida y procesamiento de datos. Debe incluirse la debida referencia para los métodos y técnicas empleados, inclusive los métodos estadísticos. Los métodos nuevos o sustancialmente modificados deben ser descritos, justificando las razones para su uso y mencionando sus limitaciones. Los criterios éticos de la investigación deben ser respetados. Los autores deben aclarar que

la investigación se llevó a cabo dentro de los patrones éticos y aprobada por el comité de ética.

- **resultados:** esa sección debe tener una descripción concisa de la nueva información descubierta, con el mínimo juicio personal. Deben presentarse en una secuencia lógica, a partir de la descripción de los datos más importantes. No debe repetirse en los textos los datos de tablas e ilustraciones, sino presentarlos resumidamente.
- **conclusiones:** debe mencionar el significado de la nueva información y la relevancia de los nuevos hallazgos en comparación con la literatura científica y las teorías existentes. En este apartado deben mencionarse las limitaciones del trabajo y también las implicaciones para las investigaciones futuras. Por último, las conclusiones deben ser parte del final, relacionandola con los objetivos citados en la introducción.
- **agradecimientos:** deben registrarse de forma concisa y limitarse a aquellas personas y/o instituciones que contribuyeron en la investigación de alguna forma, pero que no pudieron ser incluidos como coautores.
- **citaciones en el texto:** el **BJHBS** adopta el estilo Vancouver, siguiendo las normas generales de los Requisitos Uniformes para los Manuscritos presentados a Periódicos Biomédicos (www.ncbi.nlm.nih.gov/books/NBK7256/). Para citaciones en el texto, use números arábigos sobrescritos,[1] sin espacio, después la palabra y después la puntuación si hubiera: "La descripción de la enfermedad de Parkinson[1] ataca a los años de 1950,[2] cuando...". En algunos casos, los nombres de los autores pueden aparecer en el texto: "Phillips[12] valoró diversos cuadros de...", y deben citarse en el texto hasta dos autores: "Handel y Matias[15] hicieron un estudio sobre...". Sin embargo, cuando el número de autores es de seis o más, se debe citar al primer autor añadiendo la expresión "y colaboradores": "Silveira y colaboradores[13] propusieron una nueva metodología...".
- **referencias:** todas las referencias citadas en el texto deberán constar en la lista de referencias. Las referencias deben restringirse a material publicado, artículos o resumes. Los autores son responsables de llenar las referencias de modo preciso y completo. Para referencias con más de un autor, debe enumerarse los nombres por completo de hasta seis autores, por encima de esto, se debe enumerar los seis primeros autores seguidos de ", et al.". El total de referencias no debe exceder 40.
- **tablas y/o figuras:** deberán sumar como máximo cinco.
- **tabla:** debe elaborarse con programas apropiados, tales como Excel, pueden tener el ancho proporcional al ancho de una página diagramada, teniendo en cuenta el tamaño de fuente Arial 9, espacipo simple. Se deben entregar en archivo de texto: DOC (Microsoft Word), RTF (Rich Text Format) ou ODT (Open Document Text). Numeradas en orden ascendente y acompañadas por título y/o subtítulo explicativo, con una referencia objetiva en el texto. En ningún caso el contenido de una tabla deberá copiar el de una figura o vice-versa. Deben numerarse en orden creciente con números arábigos, conforme aparezcan en el texto.
- **figuras:** pueden ser fotos, ilustraciones, gráficos, diseños etc. Deben enviarse en archivos separados (formato *tiff ou JPEG). Se deben numerar en orden creciente con números arábigos, conforme su aparición en el texto.

2. **Casos clínicos:**

a. **Reporte de casos:** suele describir de uno a tres pacientes o una familia. El texto se limita a 2.000 palabras, un total de tres tablas y/o figuras y hasta 25 referencias. El resumen debe ser de 100 palabras.

b. **Solución de caso clínico:** ese texto debe contener los pasos del proceso decisorio de casos clínicos. Las informaciones del paciente deben presentarse a uno o más experto (s) clínico (s) por etapas (texto en negrita) para imitar el modo en el que la información se presenta en la practica clínica. El clínico debe hacer lo mismo (texto en fuente normal) conforme con las recientes informaciones adicionadas, compartiendo las justificaciones/argumentos con el lector. El texto debe tener hasta 2.500 palabras y 15 referencias.

3. **Artículos de revisión:**

Deben tratar temas de interés para la practica médica. Estos artículos comprenden la sección que abordará el tema común de aquella edición, en el área de salud. Se limitan a 5.000 palabras (excluyendo resumen y referencias) y a un máximo de cinco figuras y/o tablas. La lista de referencias se limita a 40 ítems. Los trabajos serán sometidos a la valoración del consejo de editores por medio de invitación al editor que organizará esta sección, conforme con las reglas que siguen:

Página del título: esta página deberá contener las informaciones del título, autores, de la siguiente manera:

- título (en portugués, inglés y español) de hasta 100 caracteres con espacio;
- título abreviado (en portugués, inglés y español) de hasta 50 caracteres con espacio;
- nombre de cada autor con su respectiva afiliación, en este orden: nombre, segundos nombres abreviados, último apellido. Departamento (o servicio). Facultad. Universidad (o institución). Ciudad, Unidad de la Federación (UF), país.
- datos de contacto del autor correspondiente: nombre, segundos nombres abreviados, último apellido, dirección de correspondencia, correo electrónico.

Texto del artículo:

- **resumen:** debe presentarse en portugués, inglés y español, limitado a 250 palabras. Debe seguir el modelo de resumen estructurado, con introducción, materiales y métodos, resultados y discusión. Se considera que el resumen alcanza una mayor visibilidad y distribución que el artículo en si, por esto debe contener las informaciones esenciales del artículo, pero no debe ser una simple composición de frases copiadas del texto integral. Debe ser sucinto y objetivo, destacando lo que es más importante en el texto, con el objetivo de atraer al lector a leerlo íntegramente. Al final, la conclusión debe incluir la relación de los resultados obtenidos con los objetivos establecidos para el estudio. Adicionalmente, es necesario hacer alusión a las contribuciones de esos resultados en el conocimiento acerca del tema investigado
- **palabras clave:** deben presentarse de tres a seis términos concernientes al tema presentado conforme con la lista de las palabras clave en Ciencias de la Salud (DeCS), para los idiomas portugués y español, o del Medical subject Headings (MeSh) para el idioma inglés. Se deben separar por punto y coma.

Los artículos de revisión podrán ser de dos tipos:

a. **Revisión sistemática y meta-análisis** - A través de la síntesis de resultados de los estudios originales, cuantitativos o cualitativos, el artículo deberá responder a la pregunta específica y de relevancia para los artículos sobre el tema de la edición, en el contexto del área de salud (véase el enfoque del **BJHBS**). Describe en detalle el proceso de búsqueda de los estudios originales, los criterios utilizados para la selección de los que se incluyeron en la revisión y los procedimientos empleados en la síntesis de los resultados obtenidos de los estudios revisados (que pueden ser o no procedimientos de meta-análisis).

b. **Revisión narrativa/crítica** - La revisión narrativa o revisión critica posee carácter descriptivo-discursivo, y se destina a la presentación exhaustiva y a la discusión de temas de interés científico en el área de salud. Debe presentar la formulación clara de un objeto científico de interés, argumentación lógica, crítica teórica y metodológica de los trabajos consultados y síntesis final. Debe ser elaborado por investigadores con experiencia en el campo en cuestión o por especialistas de conocimientos reconocidos.

- **Agradecimientos:** deben registrarse de forma concisa y limitarse a aquellas personas y/o instituciones que contribuyeron en la investigación de alguna forma, pero que no corresponden con los criterios establecidos para los coautores.

- **Citaciones en el texto:** el **BJHBS** adopta el estilo Vancouver, siguiendo las normas generales de los Requisitos Uniformes para los Manuscritos presentados a Periódicos Biomédicos (www.ncbi.nlm.nih.gov/books/NBK7256/). Para citaciones en el texto, use números arábigos en sobrescrito,[1] sin espacio, después la palabra y después la puntuación si hubiera: "La descripción de la enfermedad de Parkinson[1] ataca a los idus de 1950,[2] cuando...". En algunos casos, los nombres de los autores pueden aparecer en el texto: "Phillips[12] evaluó diversos cuadros (marcos) de...", y deben citarse en el texto hasta dos autores: "Handel y Matias[15] hicieron un estudio sobre...". Sin embargo, cuando el número de autores es de seis o más, se debe citar el primer autor añadiendo la expresión "y colaboradores": "Silveira y colaboradores[13] propusieron una nueva metodología...".
- **Referencias:** todas las referencias citadas en el texto deberán constar en la lista de referencias. Las referencias deben restringirse a material publicado, artículos o resumes. Los autores son responsables de llenar las referencias de modo preciso y completo. Para referencias con más de un autor, debe enumerarse los nombres por completo de hasta seis autores, por encima de esto, se debe enumerar los seis primeros autores seguidos de ", et al.". El total de referencias no debe exceder 40.
- **Tablas y/o figuras:** deberán sumar como máximo cinco.
- **Tabla:** debe elaborarse con programas apropiados, tales como Excel, pueden tener el ancho proporcional al ancho de una página diagramada, teniendo en cuenta el tamaño de fuente Arial 9, espacipo simple. Se deben entregar en archivo de texto: DOC (Microsoft Word), RTF (Rich Text Format) ou ODT (Open Document Text). Numeradas en orden ascendente y acompañadas por título y/o subtítulo explicativo, con una referencia objetiva en el texto. En ningún caso el contenido de una tabla deberá copiar el de una figura o vice-versa. Deben numerarse en orden creciente con números arábigos, conforme aparezcan en el texto.
- **Figuras:** pueden ser fotos, ilustraciones, gráficos, diseños etc. Deben enviarse en archivos separados (formato *tiff ou JPEG). Se deben numerar en orden creciente con números arábigos, conforme su aparición en el texto.

4. Otras sumisiones:

Editorial: Se trata de un comentario y análisis concerniente a un artículo en la edición en cuestión. Puede incluir una figura o tabla y se limita a 750 palabras, de hasta cinco referencias. Será elaborado por el editor y/o algún colaborador invitado por él.

Cartas al editor: espacio de comunicación para los lectores con relación a los artículos recién publicados, limitados a 200 palabras (excluyendo referencias), hasta cinco referencias y 1 figura o tabla, debiendo ser sometida en hasta seis meses después de la publicación del artículo. Para cartas con temas no relacionados con los artículos del **BJHBS** deben limitarse a 500 palabras (excluyendo las referencias), con un máximo de cinco referencias y una figura y/o tabla. Se solicitan los datos de los autores, así como la dirección de correspondencia y/o declaraciones de posibles conflictos de intereses. La decisión de publicar el contenido de la carta es la responsabilidad del editor.

5. Sumisión on-line:

Los artículos y otros tipos de colaboraciones deben ser enviados al correo electrónico submission.bjhbs@gmail.com, junto con la carta de presentación. El asunto del correo electrónico debe ser: "Tipo de manuscrito [articulo original, reporte de caso, artículo de revisión o carta al editor] – título del manuscrito" + el último apellido del autor principal en MAYÚSCULAS.

Todas las comunicaciones posteriores se llevarán a cabo a través de la opción "responder" de este primer correo electrónico.

El comité editorial valorará el manuscrito de acuerdo con la línea editorial de la revista y responderá con respecto a la aceptación para la valoración por pares en el menor plazo posible. En caso de que sea considerado adecuado para publicación, de acuerdo con la política editorial del **BJHBS**, entrará en el flujo editorial y pasará por las etapas de revisión textual y diagramación.

Después de la aceptación del artículo deberá enviarse la declaración de transferencia de los derechos de autor y declaración de conflictos de interés.

Una prueba de imprenta sera enviada para la valoración final en formato pdf antes de la publicación definitiva del texto y deberá devolverse en el plazo establecido por el equipo editorial.

Los textos y artículos que no cumplan con las especificaciones descritas en estas normas serán devueltos sin previa valoración del consejo de 'editores del **BJHBS**. Esos textos deberán volverse a someter al proceso de valoración.

bjhbs.hupe.uerj.br