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Review article

Action of painkillers with caffeine and pain crises

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Abstract

Pain is considered to be one of the main consequences of trauma and migraines, and is characterized by moderate to severe headache attacks that affect more than one billion people worldwide. Its treatment is mainly done by over-the-counter drugs, most of which are combined with caffeine. Objective – To analyze whether analgesics combined with caffeine are more effective for the treatment of acute and/or chronic pain than analgesics not combined with caffeine. Methods – A systematic review was carried out based on scientific articles published in the following databases: SCIELO, PubMed and Science Direct. We analyzed 15 original articles with clinical trials and controlled trials that evaluated the efficacy of analgesics combined with caffeine and were published between 2010 and 2020. Results – The 15 studies under analysis evaluated a total of 5,030 patients. Of these studies, ten concluded that analgesics associated with caffeine are more effective for the treatment of acute and/or chronic pain; four concluded that the two types of analgesics are equally effective; and one study concluded that the non-combined analgesic is more effective. Conclusion – analgesics combined with caffeine are more effective for the treatment of acute and/or chronic pain crises, since they promote faster pain relief and achieve a complete cessation of pain. Caffeine is believed to act by inhibiting cyclooxygenase at some sites and by blocking central and peripheral adenosine receptors.

Keywords: Migraine; Caffeine; Combined pain relievers.

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Introduction

Pain is considered to be one of the main consequences of trauma and migraines, and potentially harmful to the body. It is seen as an alert that something in the body is not right, and may be related to traumatic conditions, burns, infections, inflammatory processes, sensitivity light and sounds, among others[1], with intensities ranging from moderate to intense.[2-4]

In the case of migraine attacks, pain can generally be divided into four distinct phases: prodrome, aura, headache and post drome, with (a) the first phase presenting symptoms such as yawning, fatigue, cravings and mood swings; (b) the second phase being characterized by cortical spreading depression, with depression of the electrical activity of the cortical tissue, due to a depolarizing wave that acts on the neuronal and glial membranes;[5-6] (c) the third phase being characterized by the propagation of pain perception information from the meninges to the central areas of the brain; and (d) the fourth phase, characterized by cognitive difficulties, tiredness, gastrointestinal discomfort and weakness.[2]

In contrast, in the case of acute pain triggered by injuries and/or traumatic conditions, a synthesis and release of algogenic substances occurs at the injury site, stimulating nerve endings (nociceptors) of thin myelinated or unmyelinated fibers, which transmit impulses to the posterior horn of the spinal cord or to the sensory nuclei. At these sites, modulation (amplification or suppression) of the signal may occur, before it is projected to specific areas of the brainstem, thalamus, hypothalamus, and cerebral cortex, where it is interpreted. Along these pain conduction pathways, reflexes are triggered that involve neuroendocrine changes.[7]

Studies on the prevalence of pain in Brazil show a frequency that is significantly higher than the world average, with approximately 41% of the population suffering from this type of pain.[8] This disease ranks as the second most disabling condition present in

the world population, second only to chronic pain. Both types of pain are associated with other medical comorbidities, such as sleep disorders, cardiovascular diseases and psychiatric diseases, and affect a variety of areas of the patient's life, from the welfare of individuals and their families, to the academic, occupational and social spheres.[9-10]

Pain crises can last from 4 to 72 hours when untreated and, since it is a very complex disease, can be triggered by several causes, the most common of which are stress, fasting, sleep disorders, auditory stimuli and scents, as well as dietary constituents, such as alcohol, dairy products, monosodium glutamate, aspartame, nitrites, chocolate, among others.[11-12]

The main drugs used to treat pain are over-the-counter medications, chosen according to the intensity of the pain,[13] such as non-steroidal anti-inflammatory drugs and combined analgesics containing aspirin, paracetamol and caffeine, which are considered first-line treatments for mild to severe migraines,[14] as well as triptans, which are indicated for the first-line treatment of moderate to severe cases, since evidence shows that the combination of analgesics increases the effectiveness of the treatment.[15]

Caffeine is a substance used as an adjuvant to analgesics, since it increases the impact of the primary constituent, in addition to having an antinociceptive effect.[16] Studies report that the addition of caffeine to other actives substances improve the quality of the treatment, because its presence provides a faster analgesic effect and greater pain relief when compared to the use of the same active substances without the addition of this stimulant.[17]

Some population-based studies have reported a higher prevalence of chronic pain in caffeine consumers when daily intake exceeds 400 mg/day. However, moderate daily intake (up to about 300 mg/day) do not result in harmful effects[18] and has beneficial effects, such as reducing depression and improving mood.

The main negative association found between caffeine and pain is related to the abrupt withdrawal of caffeine from the routine of regular consumers. This can trigger withdrawal crises with the presence of headaches, similar to migraines, but which disappear after a new intake of caffeine.[19]

Caffeine is the most consumed psychostimulant drug in the world; because it is a trimethylxanthine, which after being consumed orally, approaches 100% bioavailability, reaching peak plasma concentration 30 to 45 minutes after ingestion, and presenting a half-life of 2.5 to 4.5 hours, with positive effects on cognitive functions and increased alertness.[20]

Data shows that around 80% of the world's population consume caffeine-containing products every day, making it the most widely used and popular active food ingredient. In addition to coffee, caffeine is found in teas, chocolates, guarana, cocoa, among other foods.[9]

Because their structure is similar to that of adenosine, caffeine molecules act as competitive inhibitors, canceling the action of adenosine, which is responsible for inhibiting excitatory neurotransmitters, and generating a drop in cortical excitability.[21] In addition, adenosine is one of the neuromodulators that favor the pathophysiology of acute pain.[9]

Another mechanism of action of caffeine in the body relates to gastric performance. During an acute pain crisis, gastric motility falls and, consequently, drug absorption is delayed. Meanwhile, caffeine is capable of increasing gastric motility, by enhancing drug absorption and improving the effectiveness of pain treatment.[22] These results suggest that the greater pain relief achieved following use of analgesics that contain caffeine is a consequence of these mechanisms of action of this stimulant.[23]

Therefore, the objective of this study is to analyze whether analgesics that are combined with caffeine are more effective in the treatment of acute and/or chronic pain and in pain relief than analgesics that are not combined with caffeine.

Objective

To analyze whether analgesics combined with caffeine are more effective for treating and relieving pain than analgesics not combined with caffeine.

Methods

This is a systematic literature review, based on articles published between 2010 and 2020 in the SCIELO, PubMed and Science Direct databases. The English search terms used were "acute pain", "chronic pain", "migraine", "caffeine", "adjuvant analgesic". Based on these descriptors, the following combinations of words were investigated: "caffeine and migraine", "caffeine and pain" "caffeine benefits in pain", "ratio of caffeine in pain", "caffeine action in pain" and "analgesics combined with caffeine".

A total of 4,847 articles were found, but it was impossible to identify how many were repeated in the research sites. Inclusion criteria were original articles with clinical trials and controlled trials, published between 2010 and 2020, that evaluated and compared the effectiveness of analgesics combined with caffeine in the treatment of acute and chronic pain crises, in comparison with analgesics not combined with caffeine.

In order to pre-screen the articles, their titles and abstracts were read; a full reading of the 15 selected articles was then carried out. Review articles published after the date defined for inclusion were excluded.

After choosing the articles, the following information was extracted: year of publication, author, number of participants, age of participants, number of pain episodes studied, number of pain episodes treated with each type of analgesic and most efficient analgesic (whether combined or not with caffeine).

Results

In the selected articles, 8,454 migraine episodes were studied. One of the 15 articles did not provide the number of participants, only the number of episodes studied. Two of the studies did not specify the number of episodes treated with each type of analgesic. Of those that did specify the type of analgesic, a total of 2,797 episodes were treated with analgesics combined with caffeine and 2,910 cases were treated without the presence of caffeine in the composition. In total, more than 5,030 people participated in the studies.

Both men and women participated in the tests, but most volunteers were women, totaling 3,278 female participants (65.2% of the population) among the sum of the 13 articles that provided this information. The mean age was 35 years, ranging from 16 to 72; and only Palmer[24] did not inform the age of the participants.

All studies used the Visual Analogue and Verbal Assessment Scales to analyze pain intensity before and after the use of the tested medication, at predetermined times, by the volunteers. Ten of the 15 articles concluded that analgesics associated with caffeine were more effective in the treatment of pain crises, that is, they achieved a greater reduction in pain intensity. Four of the 15 articles concluded that, regardless of the presence of caffeine in the analgesic composition, both treatments were equally effective in treating crises, while only one article concluded that the medication without caffeine was slightly more effective for treatment. (Table 1).

Borel[25] clarified that he considered both types of analgesics to be equally effective because, at the end of the 6 hours following the use of the medication, the difference between the intensity of pain between both treatments was not very significant. However, the analgesics combined with caffeine needed a very short time (about 45 minutes) to provide considerable relief from pain intensity – almost 50% reduction –, while the other method required 5 hours to reach levels of pain reduction. similar to those of the first type.

A study by Diener[26] found that the pain intensity was reduced by half after 1 hour and 24 minutes of using the medication containing caffeine. Achieving the same reduction using the medication without the psychostimulant took 2 hours and 19 minutes. Goldstein[27] also provided time information in his work and revealed that, in the case of the analgesic combined with caffeine, the time required to halve the pain was 1 hour, while 1 hour and 30 minutes was needed to achieve the same reduction in the absence of caffeine.

The article by Carvalho[28] found that the combined therapy was statistically significantly superior to the non-combined treatment, because after 120 minutes of medication use, a 75.2% reduction in pain intensity was observed with treatment containing caffeine, compared to a reduction of only 54.5% in pain intensity in the case of treatment without this combination.

The time required to reduce the intensity of pain by 50% was not reported in the study by Palmer,[24] but of the 1,518 episodes of pain analyzed in this study, 833 episodes were treated with a combined therapy and achieved a reduction in pain intensity by half, while the other 685 episodes treated without combination with the stimulant substance did not achieve this reduction and rescue medication needed to be used (which the volunteers were accustomed to using on a daily basis) to achieve the cessation of pain.

Graph 1 shows the authors' conclusion regarding the effectiveness of each type of treatment, comparing the use of analgesics combined with caffeine and non-combined analgesics.

Discussion

In this work, we analyzed articles that studied and compared the effectiveness of treating an acute

Table 1. Main data presented in the work

Author, Year	N	Ages	Episodes Studied	Type of treatment		Most effective treatment	
				Analgesics with Caffeine	Analgesics without Caffeine	Analgesics with Caffeine	Analgesics without Caffeine
Palmer H[24], 2010	NR	NR	1.518	802	716	More effective	Less effective
Borel JF[25], 2010	232	16 to 60	232	114	118	Equally effective	Equally effective
Diener HC[26], 2011	606	18 to 65	1.695	482	128	More effective	Less effective
Goldstein J[27], 2014	660	18 to 58	660	286	374	More effective	Less effective
Carvalho DS[28], 2012	81	18 to 65	243	NR	NR	More effective	Less effective
Pini LA[29], 2012	108	18 to 62	264	131	133	Equally effective	Equally effective
Derosier F[30], 2011	442	18 to 65	941	304	637	Slightly less effective	Slightly more effective
Bjørkedal E[31], 2011	20	17 to 25	20	12	8	More effective	Less effective
Weiser T[32], 2019	18	18 to 55	18	10	8	More effective	Less effective
Fox AW[33], 2012	206	18 to 62	206	101	105	Equally effective	Equally effective
Weiser T[34], 2019	72	28 to 49	72	38	34	More effective	Less effective
Erol DD[35], 2010	42	30 to 62	42	21	21	Equally effective	Equally effective
Aicher B[36], 2011	1419	16 to 72	1.419	NR	NR	More effective	Less effective
Forderreuther S[37], 2020	562	18 to 27	562	213	349	More effective	Less effective
Weiser T[38], 2017	562	18 to 55	562	283	279	More effective	Less effective

Legend: NR – Not reported.

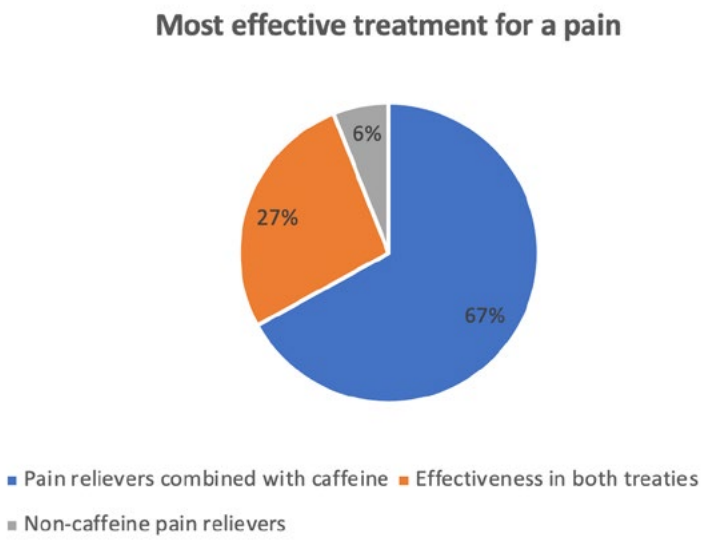

Figure 1. Authors conclusion regarding the most effective treatment

and/or chronic pain crisis by use of two types of pain-treatment medication: analgesics combined with caffeine and analgesics not combined with caffeine.

All articles used the Visual Analogue Scale (VAS) and Verbal Assessment Scales (VRS) to measure the intensity of pain in patients. The VAS consists of a horizontal line that represents the absence of pain at one end and, at the opposite end, the worst possible pain. This line is graded from 0 to 10, where 0 means no pain at all and 10 the maximum level of pain that one can take. Patients scored the intensity of their pain experience on this scale, and the distance from the "absence of pain" end to the marked point is its classification. The VRS, on the other hand, uses subjective phrases of pain intensity to classify each patient's experience; these phrases range from "no pain" to "worst possible pain".[36]

Considering the scales used to measure pain, it was observed that the number of volunteers in the analyzed studies was composed mostly of women, who represented 65.2% of the total population. This data is in line with findings in the literature, which state that the prevalence of acute and/or chronic pain is higher among women than men.[39]

It is known that sex hormones play an important role in the epidemiology of pain, so girls are affected by this disease in approximately the same proportions as boys before puberty is reached. However, this proportion changes in adulthood, when women are three times more affected than men[39].

In the case of the incidence of migraine, this increase is linked to hormonal differences, especially in relation to estrogen, since women have more intense, longer lasting and more frequent headaches than men. However, other factors, such as central processing, prostaglandins and serotonin, are also very important in the pathophysiology of pain.[39]

Regarding the prevalence of migraine according to the age of the carriers, the American Migraine Prevalence and Prevention study found a higher incidence of migraine among adults aged 30 to 39 years.[39] In line with these results, in this analysis, the mean age of the volunteers studied with a migraine attack was 35 years old.

In the case of acute and/or chronic pain, according to Barros e cols.,[8] the prevalence found in the Brazilian population (45.7%) lies in between those found in American and English population studies, of 64% and 38%, respectively. The maximum pain score in the previous 24 hours was considered to be moderate, with 48.4% of women presenting chronic pain over the last six months, compared to a prevalence of 32.8% among men.[8]

Studies available in the literature confirm that caffeine is capable of improving the performance of analgesics, thus increasing pain relief when combined with medications.[9] The findings of this study corroborate this statement, since 10 of the 15 articles analyzed reached the same conclusion.

The exact mechanism of action by which caffeine achieves these results has not yet been discovered. However, it is believed that this stimulant causes pain relief by inhibiting cyclooxygenase in some places, in addition to blocking central and peripheral adenosine receptors.[30-33] In addition, caffeine is capable of increasing gastric motility, thus favoring drug absorption and helping to improve pain management.[22]

On the other hand, the literature also mentions that caffeine plays an ambiguous role in migraines, because it can also trigger withdrawal migraine attacks and excessive consumption of caffeine can convert episodic cases of the disease into a chronic condition. Studies claim that the ingestion of doses higher than 200mg/day of caffeine is a risk factor for chronic episodic migraine. That is, sporadic episodes of headache may persist for at least 15 days a month, over more than 3 months.[9]

Despite this, it has been reported that an abrupt cessation of caffeine consumption, can cause withdrawal headaches in individuals who consume this substance in doses greater than 200mg/day for at least two weeks. These headaches appear 24 hours after the last instance of caffeine consumption. The pain stops one hour after taking the substance again (at least 100mg) or disappears one week after the stimulant is withdrawn. The higher the intake, the greater the likelihood of withdrawal migraines.[9]

The exact mechanism by which caffeine triggers attacks of pain and migraines in these conditions is also unknown, but as caffeine consumption stimulates the loss of magnesium through the urine and probably reduces its reabsorption, it is believed that the decrease of this mineral triggers the onset of pain, since caffeine is related to nerve transmission and neuromuscular conduction.[9]

Another hypothesis is related to dehydration, which is a possible trigger of pain and migraines. A high caffeine consumption has an acute diuretic effect, which can lead the body to become dehydrated, thus inducing the onset of a pain episode.[9]

Conclusion

In conclusion, analgesics combined with caffeine are more effective for the treatment of pain and migraine attacks than analgesics that are not combined with the stimulant, since the first type of medication is able to decrease the intensity of pain more rapidly and eventually manages to completely eliminate the pain.

The exact mechanism of action by which caffeine achieves these results is not yet known, but pain relief is believed to be provided by the inhibition of cyclooxygenase at some sites and by the blocking of central and peripheral adenosine receptors.

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Review article

Editorial Comment: Action of painkillers with caffeine and pain crises

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Caffeine is the most widely used psychoactive drug in the world. Studies show that 80% of the population uses caffeine daily, this use varies between countries and in the United States of America it reaches 90%.[1] Drinks containing caffeine such as tea and coffee became widespread in the 15th and 16th centuries in Arabian countries and in the 18th and 19th centuries in Europe.[1]

Caffeine affects innumerous physiological structures including: physical resistance, humor, sleep and pain. When it is used in moderation is safe for most healthy, non-pregnant individuals. It boosts alertness, energy, response speed, wakefulness, and the capacity to concentrate and focus attention while also reducing weariness. It also improves short-term memory, and cognitive abilities.[2]

It seems that caffeine's medical effects had been known long before it became a part of regular daily drinks.[4] Several analgesic drugs, mainly for headaches, contain caffeine associated with paracetamol or with non-hormonal anti-inflammatory drugs.[2]

An adjuvant component is something that is added to a medicine to enhance its effectiveness. Low doses of caffeine are present as an adjuvant in combination with acetaminophen and non-steroidal anti-inflammatory drugs in many over the counter analgesics. Clinical studies have tested and demonstrated its adjuvant analgesic effects since at least in the 80's decade. The mechanism of action of caffeine as adjuvant in pain treatment remains unclear. Caffeine's actions on adenosine receptors may help people feel less discomfort, as well as inhibition of cyclooxygenase activity, have been raised to explain these effects. Among patients with headache conditions, caffeine is used as an analgesic adjuvant.[2]

The most common illnesses studied were headaches, postoperative dental pain, and postpartum discomfort. There were no major side effects recorded in these investigations, and the authors indicated that adding 100 milligrams or more of caffeine to an analgesic might be beneficial.[3]

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There are several studies, mainly in patients with migraine, which suggest that the efficacy is superior to medications without caffeine association. In other types of pain, the results of studies are conflicting and it does not seem to be such a clear benefit.[3]

During the migraine attack there is a gastroparesis that hinders the absorption and effectiveness of oral medications and, by all indications, the acceleration of gastric emptying and consequent improvement in medication absorption could be a mechanism of action of caffeine as an adjuvant to the treatment.[4]

Analgesics associated with caffeine are widely sold over the counter in pharmacies both in Brazil and in the rest of the world. This facilitates self-medication and the abuse of analgesics.

Most people with migraine or tension type headache treat their acute headache episodes with medications. Worldwide, more than half of the patients with migraine (57%) or tension type headache (>80%) choose over-the-counter medications to manage their condition, rather than prescription treatments.[4] The search for a prophylactic treatment is probably much lower that it should be.

The relationship between caffeine and headache is complex, paradoxical, and often misunderstood. Used appropriately, caffeine significantly enhances the effectiveness of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of patients with migraine and tension type headache.

Used in excess, caffeine-containing analgesics can place patients at risk of medication overuse headache and the progressive development of chronic tension type headache or chronic migraine. At the same time, results from an uncontrolled, clinic-based study suggest that discontinuing caffeine consumption can improve the efficacy of acute migraine treatment.[4]

In the case of sporadic migraine, treatment with medications associated with caffeine may be a good option due to better efficacy, easy assessment and low cost.

However, if the patient has frequent or chronic headache, this frequent dose of analgesics may be enough to reach a dose daily intake of caffeine that generates dependence and abstinence upon withdrawal, generating greater use of medication and greater pain chronification.

Therefore, the indiscriminate use of medications associated with caffeine can, in many cases, end up making pain crises more frequent and difficult to treat.[5]

Although analgesics associated with caffeine apparently have a greater effect on the treatment of migraine attacks, there are no studies in the literature comparing these medications to triptans and association of triptans with analgesics or anti-inflammatories.

Due to the possibility of the indiscriminate use of over-the-counter analgesics and caffeine withdrawal being a cause of headache, the recommendation of this type of medication should be made with caution, especially for those who have frequent headaches.

In conclusion, caffeine is widely consumed around the world in both food, supplements and beverages and in medical applications. The action of caffeine in controlling pain may be multifactorial, and it is much more evident as an adjunct in the treatment of primary headaches than in isolation or in other types of pain.

In patients with headache disorders, its principal role is as an adjuvant in combinations with analgesic medications for acute treatment of tension type headache and migraine. Evidence from clinical trials in these patient populations indicates that combining caffeine with over the count analgesic medications improves efficacy over the analgesic alone and tolerability is good for the vast majority of patients.

However, when used in larger doses or even abstinence when used chronically, they can be precipitating factors for pain. Despite its proven efficacy and good tolerance, care should be taken with the abuse of over-the-counter medications and the risk of pain chronification.

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