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REVIEW ARTICLE

Efficacy and safety of acetaminophen and caffeine for the management of acute dental pain: A systematic review

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KEYWORDS

Acetaminophen;
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Opioids;
Systematic review

Abstract *Aim:* Because the use of non-steroidal anti-inflammatory drugs and opioids has several restrictions, this review evaluates the efficacy and safety of acetaminophen and caffeine for the management of dental pain.

Methods: A search of the literature was carried out looking for randomized controlled trials on the use of acetaminophen and caffeine for the management of dental pain, performed on humans and written in English, Italian, French or Arabic languages. The following databases were searched: PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Medline and Scopus.

Results: Three controlled clinical trials were retrieved and evaluated by using the Study Quality Assessment Tool of the National Institute for Health and Clinical Excellence.

Conclusion: The use of acetaminophen and caffeine appears to be effective in achieving good control of acute dental pain compared to placebo and other analgesic medications, but clinical recommendations cannot be made for the limited number of studies assessed.

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Contents

1. Introduction

A common drug recommended for the management of dental pain is acetaminophen. This is due to the fact that it is a very safe medication in therapeutic doses, with a favorable risk/benefit balance both in adults and children (Haas, 2002a). However, it is recommended in cases of mild to moderate pain, and, whenever more analgesia is required (for example in cases of severe pain), non-steroidal anti-inflammatory drugs (NSAIDs) or opioids analgesics are suggested, either in combination with acetaminophen or as a separate dose (Haas, 2002a).

NSAIDs include different medications with analgesic, anti-inflammatory and antipyretic actions, which are indicated for mild, moderate and severe dental pain. Unfortunately, many side effects are associated with the use of such drugs: including dyspepsia, gastric mucosal damage, possible renal impairment, anaphylactoid reactions (Haas, 2002a; Haas, 2002b; Wolfe et al., 1999; Davis and Robson, 2016). Furthermore, several contraindications limit their use, for example: gastric ulcers or gastrointestinal inflammatory disease, acetylsalicylic acid (ASA) or other NSAID induced hypersensitivity, ASA induced asthma and nasal polyps, bleeding concerns, third-trimester pregnancy, significant renal disease, concurrent use of antihypertensives, lithium, anticoagulants, antineoplastic dose of methotrexate, alcohol, digoxin (if patient is old or has renal disease), other NSAIDs or acetaminophen (for long term therapies) (Haas, 2002a; Haas, 2002b; Wolfe et al., 1999; Davis and Robson, 2016).

When NSAIDS are contraindicated, opioids are a valid alternative for the management of dental pain.

In the United States there has been an escalation of the use and abuse of opioids for pain management and also for non-medical use; this is probably due to the increased prevalence of chronic pain (Manchikanti et al., 2012; Denisco et al., 2011). Retail sale of Hydrocodone, the most prescribed opioid medication in the United States, has increased by 280% from 1997 to 2007 (Manchikanti et al., 2012). However, major side effects and contraindications limit the use of such medications. Reported side effects include sedation, nausea, vomiting, constipation, miosis, mood alteration (euphoria/dysphoria), respiratory depression, tolerance and physical dependence with long term use, and potential addiction (Haas, 2002a). Contraindications include severe chronic respiratory disease, severe inflammatory bowel disease, concurrent use of alcohol (Haas, 2002a). A significant relationship has been shown between sales of opioid analgesics and deaths, including overdose deaths and drug-related suicides. Opioid analgesics may lead to fatalities due to opioid abuse, increasing the dose, and doctor shopping, with patients seeing multiple doctors (Manchikanti et al., 2012; Denisco et al., 2011). Opioid abuse is a major issue, affecting both adults and adolescents, males more than females, and also including pregnant women (Manchikanti et al., 2012).

Because of the limitations on the use of NSAIDs and opioids, other effective and safe alternatives are preferred for the management of mild, moderate, and severe dental pain. A recent review that was published in the Chocrane Database of Systematic Reviews, assessed the efficacy of caffeine as an analgesic adjuvant for acute pain in adults. Caffeine was also associated with other analgesic medications such as acetaminophen, ibuprofen, aspirin, diclofenac sodium, tolfenamic acid. The results of the Chocrane review indicated that caffeine provided additive analgesia with an increased number of patients who experience a good level of pain relief (Derry et al., 2014).

Based on these results, the aim of the present study was to conduct a systematic review of randomized controlled trials (RCTs) to evaluate the efficacy and safety of acetaminophen and caffeine for the management of dental pain.

2. Material and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was followed while writing this review (Moher et al., 2009).

2.1. Literature search

A systematic review of the literature was performed looking for all articles published on the use of acetaminophen with caffeine for the treatment of dental pain.

Inclusion criteria were the following: RCTs on the use of acetaminophen and caffeine compared to placebo or compared to other medications; pain of dental origin, periodontal origin, post-surgical pain after dental extraction or dental implant positioning.

Exclusion criteria were the following: review articles, case control and case series studies, non-randomized controlled studies, studies describing the use of acetaminophen combined with opioids or NSAIDs.

On the 4th of April 2019, the literature search was performed by the use of the following key words: dental pain,

Table 1 Literature search.

	PubMed	CENTRAL	Ovid Medline	Scopus
1	Acetaminophen OR Paracetamol **#26,510**	Acetaminophen OR Paracetamol **#7,913**	Acetaminophen OR Paracetamol **#26,526**	Acetaminophen OR Paracetamol **#79,379**
2	Caffeine **#32,881**	Caffeine **#3,472**	Caffeine **#32,558**	Caffeine **#47,838**
3	Combine 1 AND 2 **#932**	Combine 1 AND 2 **#231**	Combine 1 AND 2 **#930**	Combine 1 AND 2 **#3,866**
4	Dental pain OR Odontogenic pain OR Pulpitis OR Periodontitis OR Dental surgery OR Tooth extraction OR Third molar extraction OR Dental implant surgery OR Wisdom teeth extraction **#16,0757**	Dental pain OR Odontogenic pain OR Pulpitis OR Periodontitis OR Dental surgery OR Tooth extraction OR Third molar extraction OR Dental implant surgery OR Wisdom teeth extraction **#12,324**	Dental pain OR Odontogenic pain OR Pulpitis OR Periodontitis OR Dental surgery OR Tooth extraction OR Third molar extraction OR Dental implant surgery OR Wisdom teeth extraction **#57,497**	Dental pain OR Odontogenic pain OR Pulpitis OR Periodontitis OR Dental surgery OR Tooth extraction OR Third molar extraction OR Dental implant surgery OR Wisdom teeth extraction **#116,484**
5	Combine 3 AND 4 **#25**	Combine 3 AND 4 **#40**	Combine 3 AND 4 **#15**	Combine 3 AND 4 **#36**
6	Limit 5 to Clinical trials, English, Italian, French, Arabic languages, Humans **#12**	Limit 5 to Trials **#20**	Limit 5 to Clinical trials, English, Italian, French, Arabic languages, Humans **#5**	Limit 5 to English, Italian, French, Arabic languages, Humans **#22**
7	Excluded (Examining different medications: #6; Not controlled trials: #1; Unrelated to the topic: #2) **#9**	Excluded (Examining different medications: #12; Unrelated to the topic: #3; Duplicate: #2) **#17**	Excluded (Examining different medications: #3; Not controlled trials: #1) **#4**	Excluded (Examining different medications: #7; Not controlled trials: #6; Unrelated to the topic: #5; No convenient language: #1) **#19**
8	Selected **#3**	Selected **#3**	Selected **#1**	Selected **#3**
9	From references, Registers of clinical trials **#0**	From references, Registers of clinical trials **#0**	From references, Registers of clinical trials **#0**	From references, Registers of clinical trials **#0**
10	Selected **#3**			

odontogenic pain, pulpitis, periodontitis, dental surgery, tooth extraction, third molar extraction, dental implant surgery, wisdom teeth extraction (for the identification of the pathology); combined with the following key words: acetaminophen or paracetamol, and caffeine (for the identification of the therapy). The following databases were searched: PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Medline, Scopus. The register of clinical trials ClinicalTrials.gov of the U.S. National Library of Medicine, the Health Canada's Clinical Trials Database, the EU Clinical Trials Register, and the International Clinical Trials Registry Platform of the World Health Organization were also searched. Hand search of the cited references of the selected articles was performed to look for additional articles.

A detailed diagram of the systematic literature searches is shown in Table 1 and Fig. 1.

Two authors (Y. A., M. M.) independently screened the titles and the abstracts of the articles for relevance. In case of disagreement a decision was made after a consensus was reached. Cited references of the articles included were also searched to look for additional studies.

2.2. Assessment of the studies

The studies included in the review were evaluated to assess the risk of bias in each study by using the Study Quality Assessment Tool of the National Institute for Health and Clinical Excellence, specifically, the Quality Assessment of Controlled Intervention Studies was used (National Heart, Lung, and Blood Institute. Study quality assessment tools). The tool consists of 14 criteria that need to be verified, to evaluate randomization (1–3), blinding (4,5), baseline characteristics (6), dropouts (7,8), adherence to the intervention (9), other interventions (10), outcome assessment (11,13), sample size (12), and intention-to-treat analysis (14). Each criterion needs to be assessed with one of the following answers: yes, no, cannot determine (CD) not reported (NR), not applicable (NA). Assessment was carried out by two authors (Y. A., M. M.) independently, and, in case of disagreement, the final decision was made after a consensus was reached (National Heart, Lung, and Blood Institute. Study quality assessment tools).

3. Results

After combining the two groups of key words, a total of 25 selections were identified in PubMed, 40 in CENTRAL, 15 in Medline, 36 in Scopus; after limiting the search, 12 papers remained in PubMed, 20 in CENTRAL, 5 in Medline, 22 in Scopus. After screening the titles and the abstracts of the articles, most of these were excluded because either they reported cases examining different medications, or were not controlled trials, or were not related to the topic in question, or were

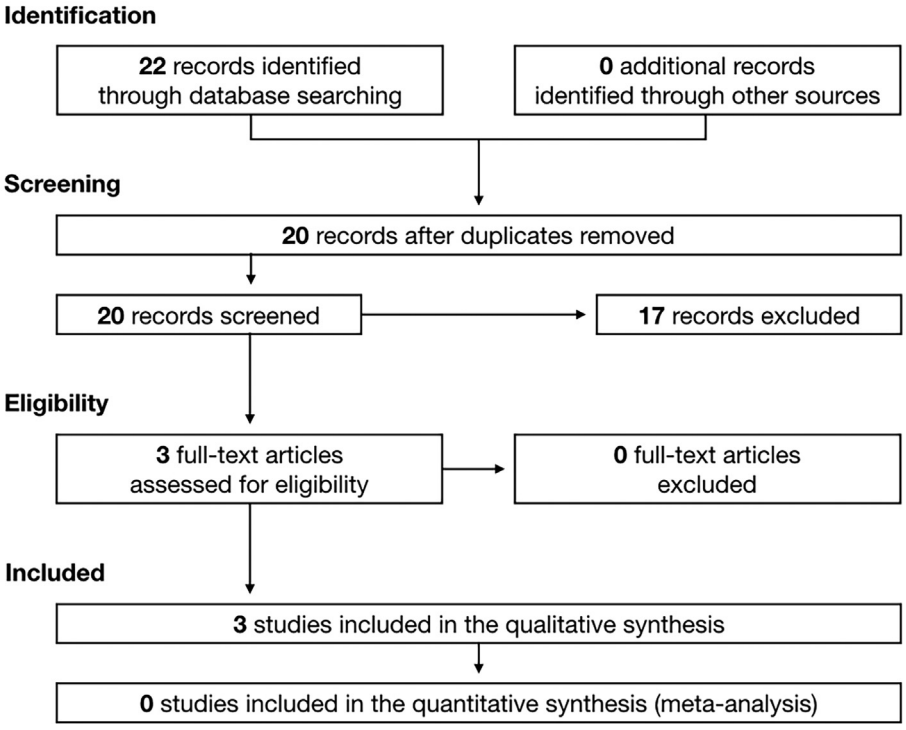

Fig. 1 PRISMA Chart.

Table 2 Assessment of the risk of bias for each study.

Criteria		Laska	Rashwan	Samierad
1	Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Y	Y	Y
2	Was the method of randomization adequate (i.e., use of randomly generated assignment)?	NR	NR	Y
3	Was the treatment allocation concealed (so that assignments could not be predicted)?	Y	NR	Y
4	Were study participants and providers blinded to treatment group assignment?	Y	Y	Y
5	Were the people assessing the outcomes blinded to the participants' group assignments?	Y	NR	Y
6	Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	NR	CD	Y
7	Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Y	Y	Y
8	Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	NR	Y	Y
9	Was there high adherence to the intervention protocols for each treatment group?	Y	Y	Y
10	Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Y	Y	Y
11	Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Y	Y	Y
12	Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	N	N	N
13	Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Y	Y	Y
14	Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	N	Y	Y

Y: yes; N: no; CD: cannot determine; NA: not applicable; NR: not reported.

not written in English, Italian, French or Arabic languages, or were duplicates. The final selection included only 3 articles (Laska et al., 1983; Rashwan, 2009; Samierad et al., 2017). No further papers were identified after searching the register of clinical trials ClinicalTrials.gov of the U.S. National Library of Medicine, the Health Canada's Clinical Trials Database, the EU Clinical Trials Register, and the International Clinical Trials Registry Platform of the World Health Organization, and after examining the cited references of the articles included. All details of the systematic literature search and the results are presented in Table 1.

The three articles were assessed for the risk of bias by using the Study Quality Assessment Tool of the National Institute for Health and Clinical Excellence, specifically, the Quality

Assessment of Controlled Intervention Studies was used. All 3 studies were considered double-blind RCTs, although 2 of them did not specify it in the title and abstract, only one described the method of randomization, one did not report the concealment of the treatment allocation and blinding of the subjects assessing the outcome. Only one study described baseline characteristics of the patients in the two groups and none of them described a calculation of the power of the study in relation to the number of subjects enrolled. Intention-to-treat analysis was not carried out in one study because of drop-outs (Table 2).

Since the outcome of the studies was evaluated differently in the trials, a meta-analysis of the results was not conducted.

The RCT by Laska et al. (1983) evaluated the efficacy of acetaminophen (500 mg) associated with caffeine (65 mg) compared to acetaminophen (500 mg) alone or placebo for the management of postpartum pain or pain after surgical removal of impacted third molars. Hence, only the study regarding the dental procedure was considered, where the use of acetaminophen and caffeine was compared to acetaminophen alone. No placebo was used.

A total of 200 patients were enrolled in the study, but only 173 were used for statistical calculations after 27 were dropped out for protocol violations and caffeine use during the study. Each subject was interviewed when medication was administered, 1/2 h later, and then hourly for 4 h for pain rating and relief. Intensity of the pain was scored as 0 = none, 1 = slight, 2 = moderate, 3 = severe; while percentage of pain relief was scored as 0 = none, 1 = 25%, 2 = 50%, 3 = 75%, 4 = 100%.

The results showed that the mean response for the combination of acetaminophen and caffeine was superior to the mean response of acetaminophen alone. No side effects from the medications were reported by the subjects.

The RCT by Rashwan (2009) evaluated the efficacy of acetaminophen (500 mg) associated with caffeine (30 mg) compared to ibuprofen (400 mg) for the management of postoperative pain after periodontal surgery. No placebo was used.

Fifteen patients were enrolled and completed the study. Each subject received one dose of medication immediately after surgery, and 8 h later. They rated their pain every hour for 8 h after the procedure, and three times (morning, afternoon, night) the following day by using a numeric rating scale (0–100) (NRS-101) and a verbal rating scale (0–4) (VRS-4).

When comparing the pain scores of the two groups using NRS-101, mean pain scores after 1 and 2 h were significantly lower in the acetaminophen and caffeine group, but mean pain scores after 6, 7, and 8 h were significantly lower in the ibuprofen group. On the second day, no significant difference was found between the groups. Furthermore, no significant difference was found between the groups at any time when comparing the pain scores using VRS-4. No side effects from the medications were reported by the subjects.

Samierad et al. (2017) evaluated the efficacy of acetaminophen (300 mg) associated with caffeine (20 mg) compared to acetaminophen (300 mg) associated with codeine (30 mg) for the management of postoperative pain after implant surgery. No placebo was used.

From the 80 patients that were enrolled, only 76 completed the study after 4 dropped out for either self medicating or because they refused to deliver the answer sheets. However, randomization was performed for the remaining 76 patients. Each subject received one dose of medication 30 min before and after surgery. They rated their pain before surgery, and then at 30 min, 3 h, 6 h, 12 h, 1 day, 2 days, 3 days, and 7 days after surgery by using a visual analog scale (VAS) 0 to 10. Swelling was also evaluated, but it is not reported here because it is not the topic of this review.

At 3 h, 6 h, and 12 h after surgery pain intensity was lower for the acetaminophen and codeine group. No difference between the groups was found for all the other intervals. The greater difference was registered at 6 h after surgery and was of 1.67 points (6.06 in the acetaminophen and caffeine group, 4.39 in the acetaminophen and codeine group).

The occurrence of side effects from the medications was not mentioned in the study.

A summary of the characteristics and outcome of the three studies is displayed in Table 3.

4. Discussion

The results of the studies included in this review suggest that the combination of acetaminophen and caffeine is efficacious for the management of dental pain. It is superior to acetaminophen alone, similar to ibuprofen, and slightly inferior to acetaminophen and codeine. These results seem to confirm that adding caffeine to analgesic medications provides a synergetic analgesic effect. Other studies report similar results although using different drugs. Forbes et al. evaluated the effect of caffeine in postoperative oral surgery pain in two different studies. In the first study, the analgesic effect of aspirin 650 mg was compared with the analgesic effect of aspirin 650 mg and caffeine 65 mg. Analgesic efficacy was increased in the group that used the combination of the drugs (Forbes et al., 1990). In the second study, different dosage of ibuprofen (50, 100, 200 mg) was compared with the same dosage of ibuprofen and caffeine 100 mg. The results showed that the combination of the drugs was 2.4–2.8 times more potent than ibuprofen alone, with more rapid onset and longer duration of analgesia (Forbes et al., 1991).

Table 3 Characteristics and outcome of the selected studies.

Studies	Number	Procedure	Comparison	Dosage	Outcome
Laska	200	Third molar extraction	Acetaminophen	500 mg + 65 mg	Acetaminophen + caffeine > acetaminophen
Rashwan	15	Periodontal surgery	Ibuprofen	500 mg + 30 mg	Acetaminophen + caffeine = ibuprofen
Samierad	80	Implant surgery	Acetaminophen + codeine	300 mg + 20 mg	Acetaminophen + caffeine < acetaminophen + codeine

Comparable results were achieved by McQuay et al., who reported that combining caffeine to ibuprofen 200 mg increased analgesic effect of ibuprofen through an earlier onset of analgesic effect after third molar surgery (McQuay et al., 1996).

Similar outcome was also demonstrated in the management of different pain conditions, such as dysmenorrhea (acetaminophen 1000 mg compared to acetaminophen 1000 mg and caffeine 130 mg) (Ali et al., 2007), tonsillopharyngitis (aspirin 800 mg compared to aspirin 800 mg and caffeine 64 mg) (Schachtel et al., 1991), orthopedic postoperative pain and idiopathic headache (acetaminophen 500 mg compared to acetaminophen 500 mg and caffeine 50 mg) (Wojcicki et al., 1977), tension-type headache (ibuprofen 400 mg compared to ibuprofen 400 mg and caffeine 200 mg) (Diamond et al., 2000), migraine (diclofenac 100 mg compared to diclofenac 100 mg and caffeine 100 mg) (Peroutka et al., 2004).

The mechanism through which caffeine enhances the analgesic activity of pain medications is not well understood (Derry et al., 2014). Self reported dietary caffeine consumption is associated with higher pain sensitivity, especially in subjects with caffeine plasma concentration higher than 300 ng/ml, therefore it does not seem to have an analgesic effect when administered alone (Karunathilake et al., 2012). Caffeine is a competitive antagonist of adenosine A_1 and A_2 receptors, therefore many presumed mechanisms of action are attributed to dysregulation of normal adenosine signaling. Caffeine might improve analgesia by improving drug absorption through lower gastric pH and increased gastric blood flow, by reducing metabolic clearance of drugs through reduced hepatic blood flow, by blocking peripheral pro-nociceptive adenosine signaling, and activation of the central noradenosine pathway, by producing transcriptional down-regulation of cyclo-oxygenase-2 via blockade of the adenosine A_{2a} receptor, by relieving inhibitor adenosine actions on central cholinergic nerve terminals, by changing mood and emotional state contributing to changes in the perception of pain (Derry et al., 2014; Renner et al., 2007; Sawynok and Yaksh, 1993; Zhang, 2001).

Thus, the combination of acetaminophen and caffeine can be an important alternative for patients for whom the use of NSAIDs and opioids are contraindicated. In fact, in therapeutic doses such as 500–1000 mg in adults and 10–15 mg/Kg in children every six hours, acetaminophen is considered a safe medication (Haas, 2002a). The recommended maximum daily dose of acetaminophen is 4000 mg for adults and 65 mg/Kg for children, although the Food and Drug Administration (FDA) suggested, but did not mandate, the maximum daily dose for adults not to exceed 3000 mg (Haas, 2002a). The major concern is the occurrence of liver toxicity, therefore, it must be used with caution in patients with history of liver disease or alcoholism. Also, long term use should be avoided because it might cause renal toxicity (Haas, 2002a).

Furthermore, the potential toxicity of caffeine in the therapeutic doses used for pain control needs to be evaluated. A recent systematic review of the literature assessed the potential adverse effects of caffeine in adults, pregnant women, adolescents and children (Wikoff et al., 2017). The potential adverse effects considered were bone damage due to excessive urinary calcium excretion (risk of fractures, bone mineral density, osteoporosis), cardiovascular effects (cardiovascular mortality and morbidity, blood pressure, heart rate, serum cholesterol, heart rate variability), mood states (anxiety, anger and confusion, depression), headache, effect on sleep, risk-taking behavior, effects on reproduction and development (fecundability, fertility, reproductive measures, spontaneous abortion, recurrent miscarriage, stillbirth, preterm birth and gestational age, fetal growth, birth defects, childhood cancers), acute toxicity (Wikoff et al., 2017).

A dose of 400 mg/day of caffeine intake was considered acceptable to prevent any adverse effect on calcium balance in conditions of adequate calcium intake, as well as any possible adverse cardiovascular effects in healthy adults. Regarding mood, the reference dose of 400 mg/day was also considered an acceptable intake that is not associated with mood changes, except for a small increase of anxiety, and the same dose was also considered an acceptable intake that is not associated with headaches and sleep disturbances in adults. There was a higher risk of risk-taking behavior, although small, with a caffeine dose greater than 570 mg/day. A dose of 300 mg/day for pregnant women and 400 mg/day for healthy adults was generally considered an acceptable intake that is not associated with adverse effects on reproduction and development. However, a higher risk was possible for effects on fetal growth, childhood cancers, and isolated congenital malformations. The reference dose of 400 mg/day was also considered an acceptable intake that is not associated with acute toxicity in adults and adolescents, insufficient data precluded conclusions on children and pregnant women. Based on these data, the maximum dose consumption of 400 mg/day for adults, 300 mg/day for pregnant women and 2.5 mg/Kg/day for children and adolescents was recommended (Wikoff et al., 2017; Turnbull et al., 2017; Temple, 2019).

The dosage of caffeine in the medications assessed in this study was of 65 mg, 30 mg, and 20 mg, associated with acetaminophen 500 mg, 500 mg, and 300 mg respectively (Laska et al., 1983; Rashwan, 2009; Samierad et al., 2017). Thus, when administering the medication every 6 h, 4 times a day, the maximum dosage reached would be of 260 mg/day, with 2 g/day of acetaminophen. This amount is clearly below the recommended doses both for adults, pregnant women and adolescents. Obviously, attention should be paid in case of caffeine intake from other sources (coffee, tea, chocolate, sodas) (Temple et al., 2017). If a higher dose of medication is needed, for example the use of 1000 mg of acetaminophen instead of 500 mg, every 6 h, the amount of caffeine needs to be considered, and the use of medications with lower doses is advised.

The main limitation of this review is due to the limited number of studies retrieved, examining a limited population of patients. This restricts the generalization of the results. In addition, the three studies examined reported the effect of acetaminophen associated with different dosage of caffeine compared to other analgesic medications, but the associations of acetaminophen with different dosages of caffeine were not compared to each other. This does not allow a quantification of the minimal and optimal dose of caffeine needed to obtain the enhancement of the analgesic activity of acetaminophen.

Other limitations are the short follow-up of the patients included in these studies (4 h to 1 week), which restricts the results to the management of acute dental pain, and the limited varieties of dental pain evaluated (third molar extraction, periodontal surgery, implant surgery), which makers uncertain its efficacy in managing other types of odontogenic pain, such as pulpitis, periodontitis, dental abscess.

5. Conclusion

Because of the limitations mentioned in the previous section, although the use of acetaminophen and caffeine seems to be effective to achieve a good control of acute dental pain compared to placebo and other analgesic medications, a strong recommendation for its use in clinical practice cannot be made. Further well designed RCTs are still needed to confirm the results of the few studies described in this review. However, because of its safety, both in adults and children, and also in pregnant women, it can be considered an efficacious alternative to NSAIDs and opioids, with minimal contraindications and side effects in the therapeutic dosage.

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Ethical statement

The study does not involve trials involving experiments in humans.

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