

Safety and efficacy of the combination Acetaminophen-Codeine in the treatment of pain of different origin

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Abstract. – BACKGROUND: Pain is the most common reason people see doctors in developed Countries and a very common cause of access in Emergency Department (ED). The combination acetaminophen/codeine represents the standard medication in the second step of the WHO analgesic scale and codeine is one of the most commonly used opioid analgesic for a variety of pain conditions. However, many aspects related to safety and efficacy are still undefined.

AIM: To summarize and review the results of the most relevant studies on the efficacy and safety profile of acetaminophen/codeine combination in the treatment of pain of different origin.

MATERIALS AND METHODS: We performed a literature search to identify and evaluate all relevant english-language randomized controlled trials (RCTs), meta-analyses and reviews about the codeine plus paracetamol combination in the treatment of pain from any source.

RESULTS: Acetaminophen/codeine combination is effective in the treatment of moderate to severe pain in all setting analyzed in this study, which include headache, postoperative, osteoarticular and post-traumatic. The best results in terms of safety and efficacy have been obtained in postoperative pain. Efficacy of acetaminophen/codeine combination is not inferior to NSAIDs.

CONCLUSIONS: Acetaminophen/codeine combination is effective in the treatment of pain, through a synergistic action of the two molecules, and is not inferior to NSAIDs. Side effects of acetaminophen/codeine are usually minor, differently from NSAIDs, which may induce some potentially lifethreatening conditions.

Key Words:

Fungal peritonitis, Peritoneal dialysis, Bacterial peritonitis.

Introduction

Everyone is likely to experience pain at least once in a life, either acute or chronic. Indeed, pain is the most common reason patients see their doc-

tor or access to an Emergency Department (ED)¹⁻⁴. Pain is a very complex phenomenon that simultaneously involves different spheres, including sensorial, emotional and spiritual one⁵⁻⁸. The complexity of the algogenic stimuli explains why so many different molecules may be effective in the treatment of different kind of pain. The World Health Organization (WHO) promotes and supports optimal pain relief as a fundamental human right⁹. An analgesic ladder with a stepwise approach was developed by WHO in 1986, as a guideline to assist physicians in managing pain treatment among patients with cancer¹⁰. This stepwise approach is today applied not only to manage cancer pain, but also to approach each type of pain requiring relief¹¹.

There are different methods to assess pain; most of the studies published on pain treatment evaluate the efficacy of a specific analgesic by means of the visual analogue scale (VAS)¹². This scale can be used to easily evaluate pain severity and relief^{13,14}, as well as the effect of different drugs on pain¹⁵. The VAS scale is a 10 cm line where no pain is at one extremity and severe pain at the other. Patients are asked to indicate the level of pain experienced at the time of evaluation by drawing a line along the scale¹³⁻¹⁵.

Acetaminophen/codeine combination represents the standard medication in the second step of the WHO analgesic ladder and is the most commonly used opioid analgesic for a variety of pain conditions¹⁶⁻¹⁹. The combination of two different drugs acting centrally and peripherally has been specifically ideated in order to potentiate both efficacy and tolerability²⁰⁻²².

The mechanism of action of acetaminophen is not completely understood yet, but there are some evidences supporting a central analgesic effect^{23,24}. To date, acetaminophen seems to be involved in five different action pathways: (1) Inhibition of cyclooxygenase (COX) isoenzymes in

CNS without any interaction with the binding site²⁵; (2) Activation of the serotonergic bulbospinal pathway^{26,27}; (3) Activation of the nitric oxide (NO) pathway²⁸; (4) Activation or modulation of the endogenous opioids pathway²⁹; (5) Increase in cannabinoid tone^{30,31}. Acetaminophen is widely prescribed and has a low appearance of adverse effects, except from those related to hepatotoxicity but at very high doses^{32,33}.

Codeine is a selective μ opioid receptor agonist that is converted to the more active compound morphine after a hepatic O-demethylation. However, this conversion is not equal in all patients due to genetic polymorphism among different ethnic groups³⁴⁻³⁶. Adverse effects of opioids include nausea, constipation, abdominal pain, respiratory depression, urinary retention, sedation, pruritus and dependence^{35,37}.

Acetaminophen/codeine combination is recommended for pain not controlled by acetaminophen alone. Despite the results of studies published so far, there are still some aspects to be clarified, ranging from the efficacy and safety profile of the association acetaminophen/codeine to the comparison to other drugs, especially NSAIDs, among different kind of pain. Therefore, the purpose of this paper is to summarize and review, among relevant studies, the efficacy and safety of acetaminophen/codeine among different pain conditions and sources, in comparison with other drugs.

Materials and Methods

We performed a literature search using PubMed/MEDLINE (1975-2012) to identify and evaluate all relevant English-language randomized controlled trials (RCTs), meta-analyses and reviews about the acetaminophen/codeine combination in the treatment of pain from any source. The search strategy was conducted following the principles previously published^{38,39}. We used the following key words: acetaminophen; paracetamol; codeine; pain; relief; efficacy; safety. Articles were also identified by a manual search of bibliographies from retrieved articles. The literature search was conducted by two reviewers, independently of one another, and any discrepancy was resolved by consensus with a third author. We used the GRADE system to evaluate the overall quality of the evidence and the strength of the recommendations⁴⁰.

Results

Postoperative Pain

De Craen et al³⁵ conducted a systematic review to evaluate the efficacy and safety of acetaminophen/codeine in different settings, but mostly in postsurgical pain management and to verify whether the combination was better than acetaminophen alone. Results from this study clearly showed that acetaminophen/codeine provided a 5% increase in analgesia on the sum pain intensity difference, and that acetaminophen/codeine combination was significantly superior than acetaminophen alone. In most studies the treatment was taken when pain was moderate or severe. Concerning adverse effects, the cumulative occurrence with each medication was similar in the single dose trials, whereas a significantly higher proportion of side effects occurred with acetaminophen/codeine combination in the multidose studies, mostly consisting with nausea, vomiting, dizziness, drowsiness and constipation³⁵.

Moore et al¹⁷ conducted a systematic review to assess the efficacy of single oral doses of acetaminophen alone and in combination with codeine in postoperative pain relief. They analyzed three different arms of treatment: acetaminophen vs placebo, acetaminophen/codeine vs placebo and acetaminophen/codeine vs acetaminophen alone at the same dosage. The result was that acetaminophen/codeine combination had the better number-needed-to-treat (NNT), compared to placebo and acetaminophen alone, producing a better pain relief even in single oral doses.

Another meta-analysis⁴¹ of randomised controlled trials conducted on the use of acetaminophen/codeine for acute postoperative pain reached similar conclusion. In fact, acetaminophen 1000 mg plus codeine 60 mg combination resulted to be an effective analgesic drug with a low NNT, compared to placebo and either acetaminophen 1000 mg or codeine 60 mg alone. Furthermore, this combination demonstrated a similar efficacy to that reported for nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diflusal, ketorolac and flurbiprofen, tested in the same trials.

Nauta et al²¹ conducted a systematic review to compare the efficacy and safety profile of codeine plus acetaminophen combination and NSAIDs in the management of post-laparotomy pain. The conclusion was that the effect of acetaminophen/codeine was similar to that shown by NSAIDs. Moreover, the majority of the studies

included in the review did not show a significant difference in the number of patients with adverse effects between the two treatment arms.

A recent Cochrane review¹⁸ of randomised controlled trials comparing acetaminophen/codeine combination with placebo or acetaminophen alone at the same dosage, for the relief of acute postoperative pain in adults, confirmed previous findings. Acetaminophen/codeine was significantly better than placebo and acetaminophen alone, with also a longer duration of the analgesic action. Regarding the adverse events, there was a significant difference between acetaminophen/codeine and placebo for the numbers of patients experiencing any adverse event, but no significant difference was found between acetaminophen/codeine and acetaminophen alone.

Several trials⁴²⁻⁴⁸ have been published regarding the comparison between acetaminophen/codeine combination and different NSAIDs in the treatment of postoperative pain, but the differences among different study designs (placebo-controlled or not, effective randomization), patients' clinical condition (different baseline pain levels) and analgesic administration (different doses, timings and medications), makes difficult to summarize and quantify the evidence from those trials. Overall, acetaminophen/codeine showed similar analgesic priorities than NSAIDs, without significant differences in terms of side effects, except for nausea⁴⁴⁻⁴⁶.

Concerning the treatment with other opioids, Crighton et al⁴⁹ found no significant differences in terms of efficacy between tramadol and acetaminophen/codeine for pain relief during the first twenty-four hours after day case laparoscopic sterilization. Nevertheless, they found a lower accuracy of central nervous system adverse effects (drowsiness, dizziness and headache) in the acetaminophen/codeine group, compared with the tramadol group. Similarly, Smith et al⁵⁰ reported an analogous efficacy between acetaminophen/tramadol and acetaminophen/codeine in the treatment of abdominal postoperative pain. The frequencies of adverse side effects were also similar between the two groups, except for constipation and vomiting, which were slightly increased in patients receiving acetaminophen/codeine. Other studies^{51,52} have compared tramadol and hydrocodone to acetaminophen/codeine in postoperative pain but the results are still inconclusive; further studies are needed to assess the efficacy and safety of different opioid combinations in postoperative pain relief.

Cancer Pain

Acetaminophen/codeine represents the standard treatment in the second step of the WHO analgesic ladder for cancer pain relief¹⁰. However, in the last years several authors proposed tramadol, hydrocodone or oxycodone as alternative drugs for the treatment of patients categorized within this step⁵³⁻⁵⁵. Rodriguez et al⁵³ found no significant differences in terms of analgesic efficacy and tolerability between hydrocodone/acetaminophen and acetaminophen/codeine for the management of moderate to severe, chronic cancer pain in adults. A recent systematic review⁵⁶ performed to verify whether tramadol is superior to acetaminophen/codeine combination for the treatment of mild to moderate cancer pain showed that evidences are inconclusive to recommend the routine use of tramadol as an alternative to acetaminophen/codeine.

Osteoarthritis-Related Pain

In this field, acetaminophen and NSAIDs still represent the recommended first-line therapy, based on WHO recommendation. Nevertheless, the occurrence of potentially severe side effects related to the use of NSAIDs, especially in older patients, should be taken into account when choosing the most appropriate drug⁵⁷. Results from meta-analyses showed that there is a role for opioids in the treatment of pain in osteoarthritis^{58,59}. Corsinovi et al⁶⁰ found a significantly higher efficacy of acetaminophen/codeine combination compared to NSAIDs or acetaminophen alone, in patients with moderate to severe osteoarthritis-related pain. Regarding safety, this study showed similar rates of adverse events between the different treatment groups, even between acetaminophen/codeine and oxycodone/acetaminophen. Colini Baldeschi et al⁶¹ compared the efficacy and tolerability of two different combinations, such as acetaminophen/tramadol and acetaminophen/codeine, for the treatment of patients with moderate to severe low-back pain caused by osteoarthritis. The study showed that acetaminophen/codeine had a better efficacy than acetaminophen/tramadol, and there was also a better tolerability of acetaminophen/codeine in terms of adverse events and drop out.

Other Kinds of Pain

Gatoulis et al⁴⁵ conducted a randomized, double-blind, placebo controlled, single-dose trial to evaluate the efficacy and safety of aspirin and ac-

etaminophen/codeine in the treatment of tension-type headache. The study showed that acetaminophen/codeine had the same efficacy with aspirin, without any statistically significant differences between the two groups concerning the occurrence of adverse events.

Innes et al⁶² carried out a trial to evaluate the analgesic efficacy and adverse effects of ketorolac and acetaminophen/codeine in ED patients with acute musculoskeletal low back pain. They found no significant differences in analgesic efficacy between the two treatment groups.

Mullican et al⁶³ compared the efficacy and safety of two different combinations, such as acetaminophen/tramadol and acetaminophen/codeine, for the treatment of chronic nonmalignant low back pain in adults. The results showed a similar analgesic efficacy between the two treatment groups with an analogous overall incidence of adverse events.

Finally, there is only one study regarding the efficacy of acetaminophen/codeine in patients with polytrauma, performed by our group⁶⁴. Sixty polytrauma patients were enrolled for this study. 30 patients were treated with acetaminophen 1000 mg plus codeine 60 mg tid for 24 hours, while the remaining 30 with ketorolac 10 mg qid for 24 hours. Interestingly, all those drugs determined a significant reduction of pain intensity during the course of therapy, without occurrence of severe side effects. We then concluded that acetaminophen/codeine is effective in pain control in polytrauma patients and that it may represent a valid alternative to NSAIDs, especially in patients with a documented hemorrhage or with a high hemorrhagic risk.

Discussion

The acetaminophen/codeine combination is effective in the treatment of mild to moderate pain in all the setting analyzed by different studies published in general literature. Postoperative pain is the most complete field in terms of evidence, whereas in other kind of pain studies are still incomplete. Nevertheless, the acetaminophen/codeine combination appears to be effective in the treatment of pain from any source, compared to placebo and acetaminophen alone.

Concerning the studies aimed at comparing the efficacy of acetaminophen/codeine and NSAIDs in pain from different sources, there are some points needing to be clarified. First of all, the lack-

ing of international guidelines concerning clear indications and doses of NSAIDs determined a proliferation of studies comparing the efficacy of a standard dosage of acetaminophen/codeine with different kind and dosage of NSAIDs. This makes difficult to produce a worthwhile meta-analysis that would be able to determine if there is any statistically significant difference between the two treatment profiles. For that reason we believe that it would be useful to have internationally accepted doses of these substances, in order to standardize trials and allow us, within few years, to achieve further evidence. Secondly, the comparison of side effects of acetaminophen/codeine and NSAIDs has not been really highlighted by studies included in this review. In fact, side effects of acetaminophen/codeine, usually consisting of nausea, vomiting, and constipation, may be considered minor when compared to those of NSAIDs. Indeed, side effects of NSAIDs may become even fatal, with an increased risk in older patients⁶⁵. The most common side effect is bleeding, especially from the upper gastrointestinal tract, that is very common particularly among patients with a history of either gastritis or peptic ulcer and surgery^{66,67}. In addition, recent studies have shown an active role of NSAIDs, especially when used in high doses and for a long period of time, in the precipitation of acute coronary syndromes including acute myocardial infarction, as some of the molecules categorized among NSAIDs may act as a COX-2 inhibitor⁶⁸⁻⁷⁰. Furthermore, they could be dangerous in patients with cardiovascular diseases as chronic heart failure, by impairing renal function, and in patients under treatment with aspirin for secondary prevention of coronary or neurological events⁷¹.

Concerning the comparison with other opioids, most studies found no significant differences in terms of tolerability between acetaminophen/codeine and minor opioids⁵⁰⁻⁵³. However, some studies showed a better tolerability profile of acetaminophen/codeine vs other minor opioids^{49,72}.

Acetaminophen/codeine has been effective in the treatment of cancer pain, especially in the second step of the WHO analgesic ladder, as well as in orthopedic pain, where it has shown a non-inferiority in terms of efficacy compared to NSAIDs. Finally, more recently, the combination acetaminophen/codeine has also been tested in different settings, such as in polytrauma patients, in subjects with headache, or in children with very promising results.

Conclusions

Acetaminophen/codeine combination is effective in the treatment of pain, through a synergistic action of the two molecules. Scientific evidence, although not yet conclusive due to heterogeneity of studies published so far, supports a non-inferiority of the acetaminophen/codeine combination compared to NSAIDs in the treatment of different kind of pain. Concerning side effects, NSAIDs may induce some potentially lifethreatening conditions differently from acetaminophen/codeine. This may allow us to suggest the use of acetaminophen/codeine in the management of mild to moderate pain, especially in older patients and in those with chronic pain requiring long-term treatment when the primary cause can not be otherwise resolved. Furthermore, it may also represent the treatment of choice in patients with an increased risk of cardiovascular events or in subjects undergoing primary or secondary prevention treatment of stroke and acute coronary syndromes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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