

## Systematic review with meta analysis

## The effectiveness of a single dose of oral ibuprofen plus caffeine in acute postoperative pain in adults

10.1136/ebmed-2015-110278

Sergio Bergese, Karina Castellon-Larios

Department of Anesthesiology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Correspondence to: Dr Sergio Bergese, Department of Anesthesiology, The Ohio State University Wexner Medical Center, 410 West 10th Ave, Columbus, OH 43210, USA; sergio.bergese@osumc.edu

Commentary on: Derry S, Wiffen PJ, Moore RA. Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2015;7:CD011509.

## Context

A number of studies have been performed regarding non-steroidal anti-inflammatory drugs (NSAIDs) and the combination with caffeine for the control of postoperative pain; most of them involving molar surgeries and tension headaches; none of them have been developed in the past 10 years. This study presented by Derry and colleagues assessed the analgesic efficacy of a single dose of ibuprofen plus caffeine when compared to placebo for moderate to severe postoperative pain.

## Methods

Up to February 2015, the authors searched the Cochrane Central Register of Control Trials, MEDLINE, EMBASE and the Oxford Pain Relief Database. Two independent authors assessed the search results and agreed which studies should be included in the analysis.

Double-blind, randomised, placebo-controlled studies were included in this review. The studies selected included patients aged 15 years or older, with moderate to severe postoperative pain (pain intensity >30 mm in the visual analogue scale) following dental surgery and episiotomy. In order to limit the risk of bias, studies that did not provide how blinding was achieved, the randomisation process or with <50 participants were excluded. A total of 5 studies and 1501 participants were included in the analysis (from 1988 to 1996).

The different treatment administered in these studies included: ibuprofen 200 mg+caffeine 100 mg; ibuprofen 100 mg+caffeine 100 mg; ibuprofen 200 mg+caffeine 50 mg; ibuprofen 200 mg+caffeine 200 mg. From all these possible combinations, only the first two were analysed. When compared to placebo, the use of 200 mg of ibuprofen plus 100 mg of caffeine showed a 59% of at least 50% of the pain relief; a dose of 100 mg of each showed a pain relief in 43% of the participants. From the 200/100 group 26% needed re-medication and 34% of the 100/100 group needed re-medication.

## Findings

The combination of ibuprofen plus caffeine was effective in a single dose for the treatment of moderate to severe postoperative pain, giving some of the lowest values of analgesics in pain models (number needed to treat

(NNT) 2.1 for the ibuprofen 200 mg+caffeine 100 mg group; NNT 2.4 for the ibuprofen 100 mg+caffeine 100 mg group) and a low percentage of re-medication. It was also shown that the combination of these two drugs was more beneficial than when administered separately.

## Commentary

The authors acknowledge certain limitations of the review, the most important one being the small number of studies they presented, as well as the small number of participants. Even though this paper focused on ibuprofen plus caffeine versus placebo, a study by Diamond and colleagues have also made comparison of its combination, or each one use separately and placebo for tension headaches. The combination of ibuprofen plus caffeine provided a greater pain relief than ibuprofen alone, caffeine alone or placebo.<sup>1</sup>

Just as explained by the authors, several studies for postoperative oral surgery pain compared the combination of ibuprofen and caffeine at different doses versus placebo in molar procedures, the combination of both analgesics showed an earlier onset of analgesic effect, 2.4–2.8 times as potent as ibuprofen alone.<sup>2 3 4</sup> Even though other studies were not taken into consideration in this analysis, Mehlisch *et al*<sup>5</sup> also showed the efficacy of ibuprofen alone, when used to treat pain compared to other NSAIDs. However, a very small study conducted by Raisian *et al* (N=80) reported no difference in pain relief (p=0.073) with ibuprofen alone when compared to a combination of ibuprofen, acetaminophen and caffeine.<sup>6</sup>

## Implications for practice

Even though there have been very few national and international studies comparing the efficacy of the combination of ibuprofen plus caffeine, there have not been major trials that show their superiority over ibuprofen alone. This needs to be taken into consideration especially in countries where this combination is not approved, thus the implementation of this combination remains a challenge.

**Contributors** SB and KC-L had substantial contributions to the conception and interpretation of the data. KC-L drafted the work and revised critically for important intellectual content. SB approved the final version of the manuscript.

**Competing interests** None declared.

**Provenance and peer review** Commissioned; internally peer reviewed.

## References

1. Diamond S, Balm TK, Freitag FG. Ibuprofen plus caffeine in the treatment of tension-type headache. *Clin Pharmacol Ther* 2000;68:312–19.
2. Forbes JA, Beaver WT, Jones KF, *et al*. Effect of caffeine on ibuprofen analgesia in postoperative oral surgery pain. *Clin Pharmacol Ther* 1991;49:674–84.
3. McQuay HJ, Angell K, Carroll D, *et al*. Ibuprofen compared with ibuprofen plus caffeine after third molar surgery. *Pain* 1996;66:247–51.
4. Sunshine A, Zigelboim I, Bartizek RD, *et al*. A double-blind, placebo-controlled, single-dose comparison study of ibuprofen, and ibuprofen in combination with caffeine, in the treatment of postepisiotomy pain. *Royal Society of Medicine International Congress and Symposium Series 218* 1996;218:105–88.
5. Mehlisch DR, Sollecito WA, Heffrick JF, *et al*. Multicenter clinical trial of ibuprofen and acetaminophen in the treatment of postoperative dental pain. *J Am Dent Assoc* 1990;121:257–63.
6. Raisian S, Fallahi HR, Badakhshan L, Zandian D. A randomized double blind controlled trial comparing ibuprofen versus ibuprofen plus acetaminophen plus caffeine for pain control after impacted third molar surgery. *Open J Stomatol* 2012;2:110–15.