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Analgesic efficacy and safety of Acetaminophen -Codeine combination versus acetaminophen for post operative analgesia in third molar surgery

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Abstract

Background: Post operative dental pain is frequently treated with codeine added to paracetamol; Studies have shown effectiveness in relief of post-operative pain at high doses but at the expense of central nervous and gastrointestinal side effects. This trial was to compare the efficacy and safety of paracetamol 1000mg with paracetamol 1000mg combined with codeine 30mg in treatment of post operative pain after third molar surgery.
Method: A randomized, double-blind prospective trial was performed to compare paracetamol 1000mg with paracetamol 1000mg with codeine 30mg for the relief of pain following surgical removal of impacted third molars, and analysed using a VAS scale. Forty patients were assigned randomly to receive either drug for a maximum of three doses. Patients recorded their pain intensity one hour after surgery and hourly thereafter for 6 hours.
Results: The average increase in pain intensity over 6 hours was significantly less in patients receiving paracetamol plus codeine than in those receiving paracetamol alone (p=0.03) -1.81cm/h compared with 0.45cm/h – a difference of 1.13cm/h (95 per cent Cl: 0.18 to 2.08). Of the patients who received Acetaminophen codeine combination, 62 per cent used rescue analgesics compared with 75 per cent of those on acetaminophen (p=0.20). There was no significant difference between the two groups in the proportion of patients experiencing adverse events (p=0.5).
Conclusion: A combination of 1000mg acetaminophen and 30mg codeine was effective in controlling pain for 6 hours following third molar removal, with no significant difference of side effects during the 6 hour period studied.
Keywords: Codeine, combination analgesics, paracetamol, post-operative pain, third molar removal.

1. Introduction

Pain is the most common complication after surgical removal of third molar which needs to be attended to with pharmacological measures. Dentists are able to choose from a number of medications to provide patients with post operative analgesia. Of these, paracetamol is among the most widely used agents for the relief of mild to moderate pain. After decades of use, its efficacy and excellent safety profile have established it as the standard analgesic recommended as the first-line choice of pain relief for a wide variety of patients and conditions.[1-4] Paracetamol is well tolerated and has an outstanding safety record when used in the prescribed dose and is devoid of the side effects associated with aspirin or non-steroidal anti-inflammatory drugs (NSAIDs).

Where stronger pain relief is required, there is a sound pharmacological basis for combining two drugs with differing modes of action and side-effect profiles. An additive or synergistic analgesic effect can result which avoids the need to use larger doses of single drugs and reduces the likelihood of side effects. [5]

The analgesic effect of codeine results from its conversion to morphine via hepatic O-demethylation.[6] Despite this, paracetamol-codeine preparations are widely recommended for the relief of pain that is not controlled by paracetamol alone.[7-12]

Though the combination has been shown to effectively relieve pain that lasts longer than one or two days,18-24 studies show a tendency for more side effects to develop with longer-term use of combinations that contain higher doses of codeine, for example 30mg codeine per tablet.[25]

However, pain can be difficult to quantify and its experience is always subjective. The methods of assessment used most frequently is the Visual Analogue Scale (VAS), a graded horizontal scale with endpoints labelled as 'no pain at all' and 'worst pain '. The VAS e and was chosen as the primary measure of efficacy in this study.

2. Methods

2.1 Inclusion and exclusion criteria:

Subjects eligible for inclusion in the trial were elective day-case patients undergoing surgical removal of impacted third molars under local anaesthesia.

Criteria for exclusion included age less than 17 years, breast-feeding, and pregnancy or suspected pregnancy. Additionally, people with a history of hepatic or renal insufficiency, respiratory depression, aspirin or NSAID- sensitive asthma, current active peptic ulceration or a history of recurrent peptic ulceration, active gastrointestinal bleeding, narcotic or alcohol addiction, known intolerance to any of the trial medications, or concur- rent administration of other analgesics were excluded from the study.

Group A (paracetamol 1000mg plus codeine 30mg) n=20 and Group B (paracetamol 1000mg) n=20. The randomization was done using a sealed envelope to ensure balanced patient numbers in both treatment arms over time and the randomization details were concealed from the patient and operator.

Surgery was performed under local anaesthesia using 2 per cent lignocaine with 1:80,000 adrenaline. After initial recording of post-operative pain at one hour, patients took the first dose (two tablets) of study medication under the supervision of the study co- ordinator. They were instructed to take two further doses of the study drug at four-hourly intervals, with the final dose to be taken eight hours after the initial dose.

2.2 Pain measurement

The evaluation was carried out over a 12-hour period. All patients were instructed to record their pain intensity on a 10cm VAS, on which the end points were defined as 0cm='no pain' and 10cm='worst pain'. Pain intensity was recorded prior to consuming the initial dose of study medication and then at hourly intervals for the following 12 hours.

All study patients were asked to record hourly pain intensity, use of study drug, adverse events and use of rescue analgesia in a proforma.

2.3 Statistical analysis

All analyses were performed on an intention-to-treat (ITT) basis, with the primary outcome measure being the average change in VAS pain intensity from baseline. That is, for each patient the VAS pain scores for hours one to 12 were averaged and then the baseline score was subtracted to give an hourly change in pain intensity, measured in cm/hour. For any patient who failed to complete the pain intensity questionnaire at any time during the 12-hour period, including those who fell asleep, their recorded score for the previous time-point was used.

3. Results

Patients receiving the paracetamol-codeine combination had a median increase in pain of 0.45cm/h, while in those receiving paracetamol alone the median increase in pain was 1.81cm/h. The median difference of 1.13cm/h (95 per cent CI 0.18 to 2.08cm/h) between the two treatment groups was statistically significant (P=0.03).

Escape analgesia (ibuprofen 200mg) was used by 12 (62 per cent) patients receiving the paracetamol- codeine combination and 15 (75 per cent) of those receiving paracetamol alone, a difference that was not statistically significant (p=0.20). The median number of tablets taken was two in both groups (Mann-Whitney p=0.14).

3.1 Adverse events

A comparison of the adverse event profiles of the two medications showed that only three (18 per cent) patients receiving paracetamol-codeine and two (13 percent) patients receiving paracetamol experienced an adverse event. This difference was not statistically significant (p=0.50) and none was deemed directly related to the study medication

In order to have 80 per cent power to detect a difference of 1cm/h on the VAS between the means of the two treatment groups at a two-sided 5 per cent significance level, 40 patients were recruited.

Due to the lack of normality of the primary outcome variable, the Mann-Whitney test was used to test the difference between the two treatment groups. This test was also used to compare the number of tablets of escape medication used. The proportions of patients requiring escape analgesia in the two groups were compared using a chi-square test, as were the proportions experiencing an adverse event. In addition, data from the VRS were analysed to determine a descriptive word equivalent to the various points on the VAS. All statistical analyses were conducted using Minitab.

4. Discussion

In this study the combination of paracetamol 1000mg and codeine 30mg resulted in significantly better analgesic than 1000mg of paracetamol alone. There was no significant difference in the proportion of patients needing escape analgesia, and no statistically significant increase in adverse effects with the combination preparation.

Paracetamol enjoys a long history of clinical use; its efficacy and good tolerability profile have contributed to its popularity such that it is now regarded as the first-line choice of analgesic for a wide variety of mild to moderate pain states. The combination of paracetamol and codeine is based on the rationale that together these two compounds will provide enhanced analgesic efficacy.

However, the lowest dose of codeine required to produce significant improved analgesia is not well defined. [4] Despite this, fixed-dose combinations of paracetamol and codeine are used frequently for the symptomatic relief of pain.

5. Conclusion

The present study demonstrates that there is a significant improvement in post- operative pain relief following this combination, and that the commonly prescribed preparation using 60mg codeine with its attendant high side effect profile, may be unnecessary. There was no significant difference in the side effects over the 12 hours, which we were only able to study for logistical reasons. This may not be the case should the medication be used for the full post- operative period.

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