Analgesia and side effects of codeine phosphate associated with paracetamol vs. paracetamol after the extraction of mandibular third molars: a randomized double-blind clinical trial using the split-mouth model

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Abstract

Purpose To assess the analgesia and side effects of codeine phosphate associated with paracetamol (test medication) as compared to paracetamol (control medication) after the extraction of impacted mandibular third molars.

Materials and methods Forty-seven patients removed the right and left impacted mandibular third molars. After one surgery, patients took the test medication and after the other surgery, they took the control medication. Patients with exacerbated pain were prescribed to use the rescue medication instead of the medication initially administered and were included in the rescue group. They were evaluated for 7 days postoperatively, and the mean score of the visual analogue scale (VAS) of pain between test and control medications was assessed by the Poisson distribution. The side effects of these medications were assessed by the patient's complaints. A *P* value of $< .05$ was considered to be statistically significant.

Results The mean score of the VAS of pain was not statistically different between test and control medications in the non-rescue group, but it was significantly greater in patients previously using paracetamol in the rescue group. The most common side effects reported in both groups, predominantly in patients using the test medication, were drowsiness, dizziness, and nausea.

Conclusion The use of codeine phosphate associated with paracetamol after the extraction of impacted mandibular third molars is a better choice to control the postoperative pain rather than paracetamol, but with more side effects, which are clinically acceptable.

Keywords Codeine phosphate · Paracetamol · Molar, third · Tooth extraction · Pain, postoperative

Introduction

The extraction of impacted mandibular third molars is the most common procedure performed by oral and maxillofacial

surgeons. The number of dentists performing this procedure has increased, but they may not be familiarized to treat the exacerbated postoperative pain [1] caused by the surgical trauma to the bone and oral mucosa. The psychological, social, and cultural aspects of patients may also influence the degree of pain, and their complaint must never be neglected [2].

The multimodal analgesia consists of the concomitant administration of two or more medications, and this regimen is very useful in the control of moderate postoperative pain with fewer side effects because of the smaller given dose of each medication [3–8]. In this context, the use of 30 mg of codeine phosphate (weak opioid) associated with 500 mg of paracetamol (acetaminophen) after a tooth extraction will act against the pain stimulus in the central nervous system and peripheral receptors, respectively. However, the lack of studies regarding the side effects of this association may make the establishment of the most effective dose difficult to be implemented [9].

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Additionally, many professionals in dentistry fear to use codeine, considering it as powerful as morphine.

The present study aims to assess the analgesia and side effects of codeine phosphate (30 mg) associated with paracetamol (500 mg) as compared to paracetamol (500 mg) after the extraction of the impacted mandibular third molars.

Materials and methods

Forty-seven healthy patients aged 21 years on average (30 women and 17 men), with clinical indications to remove the right and left impacted mandibular third molars, were randomly selected. The positions of these teeth were classified according to Pell and Gregory [10] and Winter [11]. Surgeries were performed under local anesthesia (3.6 ml of 2% mepivacaine/1:20.000 corbadrine) by the same professional. Patients received a preoperative dose of 8 mg of dexamethasone 1 h before the procedures to prevent swelling/trismus and waited 21 days between the surgeries.

Immediately after the extraction of one mandibular third molar, they took one capsule of codeine phosphate (30 mg) associated with paracetamol (500 mg), named “test medication.” After the extraction of the remaining mandibular third molar, they took one capsule of paracetamol (500 mg), named “control medication.” Neither researchers nor patients knew what medication has been prescribed after each procedure (Fig. 1). They were oriented to use the same medication with an interval of 6 h until pain improvement, and those patients with exacerbated or uncontrolled pain were prescribed to use codeine phosphate (30 mg) associated with paracetamol (500 mg), named “rescue medication,” instead of the medication initially administered. These cases were included in the

rescue group. On the other hand, patients that did not take the rescue medication were included in the “non-rescue group.”

Patients were examined immediately, 2 h, 1 day (24 h), 2 days (48 h), 3 days (72 h), 4 days (96 h), 5 days (120 h), 6 days (144 h), and 7 days (168 h) after the surgery. The efficacy of analgesia was evaluated through the visual analog scale (VAS) of pain, but we did not consider the data immediately after the surgery due to the residual effect of the local anesthesia. After all surgical procedures, patients were oriented to have a cold and soft diet for 24 h and to perform normal oral hygiene without the use of antiseptic solutions during all postoperative period. Also, they were requested to place an ice pack for 3 min on the mandibular angle in intervals of 6 h during the first day postoperatively and to sleep with the head elevated over 72 h to decrease the soft tissue swelling. The occurrence of postoperative side effects by medications was assessed by the patient’s complaints.

After the collection of all data, the medication used in each procedure was revealed.

Statistical analysis

The mean score from the VAS of pain during the postoperative period was compared between patients taking the test medication and the control medication by the Poisson distribution [12], corrected by the Bonferroni method [13] to check for differences in the postoperative periods. The number of capsules of test, control, and rescue medications consumed in the non-rescue group and rescue group was compared by the Poisson distribution [12]. The frequency of the positions of mandibular third molars [10, 11] was assessed by McNemar’s test [14]. A P value of $< .05$ was considered to be statistically significant.

Fig. 1 Capsules of codeine phosphate (30 mg) associated with paracetamol (500 mg) and capsules of paracetamol (500 mg). The letter “A” or “B” was attributed to these medications because neither researchers nor patients knew what medication has been prescribed after each procedure

Table 1 Mean score of the VAS of pain in patients using the test medication and the control medication as well as paracetamol + rescue medication

Postoperative period (in h)	Non-rescue group		Rescue group	
	Mean score of the VAS of pain ± SD			
	Codeine phosphate + paracetamol	Paracetamol	Codeine phosphate + paracetamol	Initially paracetamol, changed by the rescue medication ^a
2	1.73 ± 2.24	2.58 ± 2.44	2.29 ± 2.63	2.05 ± 2.22
24	2.38 ± 1.92	2.00 ± 1.60	2.95 ± 2.09	3.90 ± 2.86
48	2.19 ± 1.92	2.35 ± 1.60	3.52 ± 2.46	4.33 ± 2.24
72	1.27 ± 1.99	1.50 ± 1.18	3.00 ± 1.95	4.14 ± 2.27
96	1.08 ± 2.02	0.62 ± 0.90	2.14 ± 2.27	3.62 ± 2.54
120	0.46 ± 1.03	0.46 ± 0.71	0.76 ± 1.34	2.62 ± 2.64
144	0.15 ± 0.61	0.38 ± 0.98	0.29 ± 0.90	1.48 ± 2.64
167	0.00 ± 0.00	0.08 ± 0.39	0.00 ± 0.00	0.81 ± 2.18

SD standard deviation

^a Codeine phosphate (30 mg) + paracetamol (500 mg)

Results

All surgeries required osteotomy and tooth sectioning [15] and were concluded in 17 min on average. No complications occurred during surgeries, but two cases of mild alveolar infection in the non-rescue group and two cases of mild alveolar infection in the rescue group were observed, all of them occurring 7 days after the procedure and in different patients, with no need for further treatment. Considering the patients individually and according to the classification of Pell and Gregory [10] in 100% of the cases, both mandibular third molars showed the same type of inclusion, while in 93.6% of the cases, these

teeth showed the same type of inclination. According to Winter [11], in 85.1% of the cases, these teeth presented the same position.

Twenty-six patients were included in the non-rescue group. The mean score of the VAS of pain was not statistically different between patients using the test medication and the control medication in all postoperative periods ($P = .42$). They reported an increased pain between the first and second days after the surgery (Table 1; Fig. 2) and consumed a significantly higher number of paracetamol (18 capsules on average) than codeine phosphate associated with paracetamol (14 capsules on average) ($P = .001$). The most common side effects reported in this group, occurring between the first and second days after the surgery, were drowsiness and dizziness, which was predominantly reported in patients using codeine phosphate associated with paracetamol (Table 2).

Twenty-one patients were included in the rescue group, and only those taking paracetamol needed to use the rescue medication. The mean score of the VAS of pain in patients previously using paracetamol was significantly greater in all postoperative periods than in patients using only codeine phosphate associated with paracetamol ($P < .001$). They reported an increased pain between the first and third days after the surgery ($P < .05$) (Table 1; Fig. 3) and consumed a significantly higher number of the rescue medication (22 capsules on average) than patients that did not use the rescue medication (17 capsules of codeine phosphate associated with paracetamol on average) ($P = .001$). Regarding the four cases that developed a mild alveolar infection, observed in the seventh postoperative day, they did not report more pain nor consumed more capsules of medication than the other patients.

The most common side effects reported in this group were drowsiness, occurring between the first and third days after surgeries, and dizziness and nausea, occurring between the third and fourth days after surgeries (Table 2).

Fig. 2 In the non-rescue group, the mean score of the VAS of pain was not statistically different between patients using the test medication and the control medication in all postoperative periods

Table 2 Side effects in patients using the test medication and the control medication as well as paracetamol + rescue medication

Side effect	Non-rescue group Number of patients (%)		Rescue group Number of patients (%)	
	Codeine phosphate + paracetamol	Paracetamol	Codeine phosphate + paracetamol	Initially paracetamol, changed by the rescue medication ^a
Drowsiness	10 (38.5)	7 (26.9)	6 (28.6)	6 (28.6)
Dizziness	8 (30.8)	1 (3.8)	7 (33.3)	5 (23.8)
Nausea	4 (15.4)	0 (0.0)	4 (19.0)	7 (33.3)
Vomit	2 (7.7)	0 (0.0)	3 (14.3)	2 (9.5)
Hypotension	1 (3.8)	1 (3.8)	1 (4.8)	2 (9.5)
Muscle weakness	2 (7.7)	2 (7.7)	4 (19.0)	3 (14.3)
Respiratory depression	1 (3.8)	0 (0.0)	0 (0.0)	1 (4.8)
Arrhythmia	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)
Euphoria	2 (7.7)	0 (0.0)	1 (4.8)	1 (4.8)
Constipation	1 (3.8)	1 (3.8)	1 (4.8)	2 (9.5)
Pruritus	0 (0.0)	0 (0.0)	1 (4.8)	1 (4.8)
No side effect	13 (50)	9 (34.6)	13 (61.8)	13 (61.8)
Total	26 (100)	26 (100)	21 (100)	21 (100)

^a Codeine phosphate (30 mg) + paracetamol (500 mg)

Discussion

The extraction of impacted mandibular third molars is a well-established study design to evaluate drug therapies for the control of postoperative pain. One of the main advantages of such design is the possibility to conduct researches where the same patient is submitted to test and control treatments, i.e., self-controlled, using the split-mouth technique. However, the skills of the surgeon may interfere in the incidence of postoperative complications, and a surgical time of more than 25 min

will increase the risk of exacerbated postoperative pain [16–18]. In the present study, surgeries lasted 17 min on average and were technically challenging [15].

The analgesic effects of codeine phosphate associated with paracetamol after the extraction of impacted mandibular third molars seemed to be better than paracetamol alone because 21 patients, which were included in the rescue group, had to abandon the use of paracetamol to use the rescue medication. On the other hand, there was no difference in the mean score of the VAS of pain between patients using the test and control medication in the non-rescue group. Thus, patients from this group were considered to be more resistant to surgical trauma, confirming the theory that psychological, social, and cultural aspects may influence the degree of pain.

Patients consumed a higher number of capsules of paracetamol and rescue medication. In this respect, we can assume that once triggered, the pain stimulus is more difficult to control, and the use of 8 mg of dexamethasone 1 h before the surgery will also aid in the control of postoperative pain [19]. The authors also observed that patient's recovery was strictly related to the improvement of the swelling, controlled by the use of the corticosteroid [20–22].

According to the mean score of the VAS of pain, the most intense pain occurred between 24 and 48 h after surgeries in both groups (Table 1; Figs. 2 and 3). The evaluation of the analgesic effects of test and control medications over 7 days is, therefore, of utmost importance to assess the complete postoperative course of the treatment [5–8].

Considering all side effects evaluated, codeine phosphate (30 mg) associated with paracetamol (500 mg) caused more problems than paracetamol (500 mg) in the non-rescue group. Furthermore, the incidence of side effects between test and rescue medications was quite similar in the rescue group. Undoubtedly, codeine phosphate associated with paracetamol will be more problematic to patients in the postoperative period (Table 1), but not enough to discontinue this medication. On the contrary, patients reported that they were more satisfied using the codeine phosphate associated with paracetamol,

Fig. 3 In the rescue group, the mean score of the VAS of pain in patients previously using paracetamol was significantly greater in all postoperative periods than in patients using only codeine phosphate associated with paracetamol

indicating that the pain control is more important than the occurrence of side effects.

The effects of opioids in the central nervous system are not fully understood, but they have been increasingly used to treat cancer patients [23], suggesting the efficacy of this class of medication in the treatment of exacerbated pain. In turn, codeine phosphate is the most common weak opioid associated with other drugs worldwide. In dentistry, codeine phosphate (30 mg) associated with paracetamol (500 mg) will act in synergism with minimal side effects and drug interactions [24].

Conclusion

Although the analgesia between patients using codeine phosphate (30 mg) associated with paracetamol (500 mg) and paracetamol alone (500 mg) was not different in 26 patients, 21 out of 47 patients had to abandon the use of paracetamol to use the rescue medication. Furthermore, patients consumed more paracetamol and rescue medication. Therefore, the use of codeine phosphate associated with paracetamol after the extraction of impacted mandibular third molars is a better choice to control the postoperative pain rather than paracetamol, but with more side effects, which are clinically acceptable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The present study was approved by the ethics committee of the Faculty of Dentistry of the University of São Paulo (number 317.632/2013) and was conducted according to the principles of the Declaration of Helsinki.

Informed consent Written informed consent was obtained from all participants.

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