Oral and Maxillofacial Surgery (2018) 22:71–75
https://doi.org/10.1007/s10006-018-0669-y

ORIGINAL ARTICLE

Is dipyrone effective as a preemptive analgesic in third molar surgery? A pilot study

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Received: 29 April 2017 / Accepted: 28 December 2017 / Published online: 20 January 2018

Abstract

Purpose Studies on preemptive analgesia in maxillofacial surgery have shown several controversial clinical results, mainly due to the absence of a methodological standard, besides a wide variety of studied drugs. This study intended to answer the following hypothesis: Is the administration of dipyrone preemptively capable of decreasing trans- and postoperative pain in the third molar surgical extraction?

Methods A pilot prospective double-blind placebo-controlled study was carried out with 25 patients submitted to the third molar surgical extraction at two moments, one side in each intervention. Dipyrone (1 g) was preemptively administered (study group) for the extraction of two third molars on the same side and, in a second surgical procedure, dipyrone (1 g) was administered in the immediate postoperative period (control group). Evaluated variables were the amount of anesthetic, pain perceived through the visual analogue scale (VAS) in transoperative and immediate postoperative periods, and over 12-h investigation period, analgesic consumption, duration of surgery, and time to rescue analgesia.

Results The results were submitted to Student's *t* test and statistical differences were observed in transoperative ($p < 0.05$) and immediate postoperative ($p < 0.01$) periods, while the other studied variables did not present statistical differences.

Conclusion The preemptive administration of dipyrone decreased the perception of transoperative and immediate postoperative pain when compared to its use after surgery only.

Keywords Third molar surgery · Preemptive analgesia · Dipyrone

Introduction

The concept of preemptive analgesia, reported classically by Patrick Wall in 1988, consists of the reduction of postoperative pain through drug administration prior to surgical trauma. According to some studies, when painful peripheral stimuli are transmitted to the central nervous system (CNS), the process of central sensitization, named neural plasticity, occurs and contributes to hyperalgesia and postoperative allodynia [1–3].

Since the generation and the maintenance of pain are complex and multicentric processes, this chain can be interfered with at three different levels through the pharmaceutical groups: anesthetics, anti-inflammatory drugs, and analgesics.

Local anesthetics are effective in preventing the spread of impulses from the peripheral nervous system to the CNS. However, tissue injury locally promotes the release of inflammatory chemical mediators through a cascade, mainly that of prostaglandins. Anti-inflammatory drugs act in this level, inhibiting the formation of prostaglandins, either by inhibiting the enzyme cyclooxygenase by the nonsteroidal anti-inflammatory drugs (NSAIDs) or by inhibiting phospholipases A2 (corticosteroids) [2, 4, 5].

Studies involving animals have been quite favorable to the applicability of this concept. However, clinical studies in humans have shown controversial results due to (1) a wide variety of evaluated drugs and (2) the lack of methodological

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standard (surgical size, type of anesthesia, and mode of drug administration). Thus, the clinical applicability of preemptive analgesia in the third molar surgical extraction requires further studies [1–7].

Dipyrone acts on the CNS mainly through N-methyl-D-aspartate (NMDA) glutamate receptor antagonism and peripheral action, by the blockade of calcium influx into the nociceptor [8]. This mechanism of action is interesting to the use in preemptive analgesia, so that preoperative dipyrone administration leads to an increase in pain threshold in the transoperative period. Dipyrone would be able to decrease the pain sensitization in the transoperative period, providing less discomfort during surgery, as well as in the postoperative period through the blockade of central sensitization, with lower consumption of anesthetics in the transoperative period and analgesics in the postoperative one. Despite this bivalent mechanism of action, studies on the preemptive analgesia of dipyrone in oral and maxillofacial surgeries have not been carried out.

Thus, the present study intended to answer the following hypothesis: Is the administration of dipyrone preemptively capable of decreasing trans- and postoperative pain in the third molar surgical extraction, as well as the use of anesthetic drugs postoperatively?

Material and method

A pilot prospective double-blind placebo-controlled study was carried out. A total of 36 patients who sought the service of oral and maxillofacial surgery of the General Hospital "Dr. José Pangella de Vila Penteado," São Paulo, SP, Brazil, for the extraction of the four third molars were selected. Among inclusion criteria, teeth should be totally inside the bone and symmetrically between both sides; patients could not report a prior allergy to the drugs used in this study and should be classified according to the American Society of Anesthesiologists (ASA) at ASA I or II. Patients with coagulopathy and pregnant and breastfeeding women were excluded. In addition, the patient could not have an inflammation or infection in the local of the surgery, since they would sensitize the CNS and interfere with preemptive analgesia.

Patients were submitted to the third molar surgical extraction at two moments, with two teeth on the same side (superior and inferior) removed in each intervention. An interval of at least 2 months was given between surgeries in order to ensure that the healing process would not interfere with the preemptive analgesia of the second operated side. All surgeries were performed by the same surgeon (VTF).

Thus, on one operated side (study side), dipyrone was administered preoperatively, and in the other side (control side), dipyrone was administered in the immediate postoperative period, so that all patients were treated with both groups. The choice of the first side to be operated (study or control) was made in a random and double-blind manner, where neither the surgeon nor the patient had access to this information.

Subsequently, the results were grouped according to the use of dipyrone pre- or postoperatively, which consisted of the study group and the control group, respectively.

The drug protocol was identical in both surgical times, only with change in dipyrone administration (preoperatively or immediate postoperatively). Thus, 1 g cefazolin (intravenous, IV) and 8 mg dexamethasone (IV) were administered in all patients. In the study side, 1 g dipyrone diluted in 10 ml saline solution (IV) was administered, while only 10 ml saline solution (IV) was administered in the control side. In immediate postoperatively administration, 10 ml saline solution (IV) was administered in the study side, while 1 g dipyrone diluted in 10 ml saline solution (IV) was administered in the control side.

After surgery, all patients were treated with 50 mg diclofenac sodium for 3 days and 0.12% chlorhexidine digluconate for 7 days. They were advised to use 1 g dipyrone in case of pain (rescue drug). The use of dipyrone was recorded during the postoperative period, consisting of an indirect indicator of the amount of postoperative pain.

In order to evaluate the pain during surgery, the anesthetic technique and the number of used tubes were standardized as follows. For upper third molar extraction, posterior superior alveolar and palatine nerves were blocked through one anesthetic tube, each one containing 1.8 ml prilocaine 3% with 0.03 IU felipressine. For the extraction of inferior third molars, the pterygomandibular anesthetic technique was used to anesthetize inferior alveolar, lingual, and buccal nerves, with a total of two anesthetic tubes (3.6 ml). The need for anesthetic complementation was a quantitative variable of transoperative pain, in which the amount (total or fractional) of tubes required for effective anesthesia was recorded.

The technique was standardized in all surgeries: pterygomandibular access, peripheral ostectomy, odontosection (when necessary), luxation, avulsion, curettage, abundant irrigation with 0.9% saline solution, and suture.

At the end of surgery, patients received the respective medications and were submitted to a questionnaire containing the visual analogue scale (VAS), in which they were instructed to fill in with a score that best expressed the amount of pain felt at a certain time. Pain was recorded through VAS at eight periods: transoperative, immediately after surgery, and at 1, 2, 4, 6, 8, and 12 h after surgery.

In addition, patients received a table in which they were advised to record the day and the time when they needed to be medicated with dipyrone for analgesic control in the postoperative period.

The last studied variable consisted of the period between the end of surgery and the beginning of pain that required the use of dipyrone, named rescue drug time.

Table 1 Demographic details of patient's sample with results expressed as mean ± SD

Variable	
Number of subjects	36
Number of dropouts	11
Male:female	09:16
Age (years)	22.1 ± 4.4
Weight (kg)	61.4 ± 11.7

Moreover, surgical duration was recorded and compared between study and control groups.

The protocol of this study was approved by the local research ethics committee under number 44982115.2.0000.5446 and informed consent forms were obtained from all participating patients.

Results

From a total of 36 patients included in the study, 9 of them were excluded due to incomplete data at any study period, 1 of them was excluded due to a postoperative complication (alveolitis) and another one was excluded due to inconsistent data. The data of 25 patients were submitted to descriptive statistics and then to Student's *t* test (Table 1).

Demographic variables such as gender, age, and weight are described in Table 1. The results of both groups regarding the administered amount of local anesthetic, surgical duration, postoperative analgesic consumption, and the pain perceived by VAS from the transoperative period to 12 h after surgery are shown in Fig. 1 and Table 2 (95% confidence level, $p < 0.05$).

When comparing the use of dipyrone preemptively and postoperatively, statistically significant differences ($p < 0.05$) were observed only in pain represented by VAS in transoperative and immediate postoperative periods.

No differences were found when evaluating the administered amount of local anesthetic and surgical duration (Table 2).

Furthermore, results regarding rescue drug time are shown in Fig. 2. No differences ($p = 0.58$) were found in rescue drug time of dipyrone administered before and after surgery.

Discussion

This study indicated that the administration of dipyrone preemptively was more effective than its postsurgical use regarding pain perception in transoperative and immediate postoperative periods, with no impacts on the use of anesthetics in the surgical procedure, as well as the use of analgesics in the postoperative period.

Studies on preemptive analgesia have been methodologically performed in order to administer only the drug to be studied [9, 10]. A criticism on this work can be made with regard to the coadministration of dexamethasone and dipyrone, probably reducing the analgesic effect of dipyrone compared with its use singly. Several studies have reported the benefit of preemptive dexamethasone in reducing edema and postoperative trismus. The authors stated that the benefits already established by other studies cannot be ignored in the search for better therapeutic options. In this way, preemptive dexamethasone has been chosen for both groups, despite the bias of possible synergistic effect of both drugs [3, 11, 12].

In the literature, studies have evaluated preemptive analgesia in third molar surgery, with several drugs and protocols. Ong et al. [11] compared the administration of 30 mg ketorolac (IV) preemptively and postoperatively and observed that the preemptive use provided up to 2 h of a better analgesia than that of the postoperative one.

On the other hand, some works such as Jung et al. [5] evaluated the oral administration of a NSAID drug (370 mg

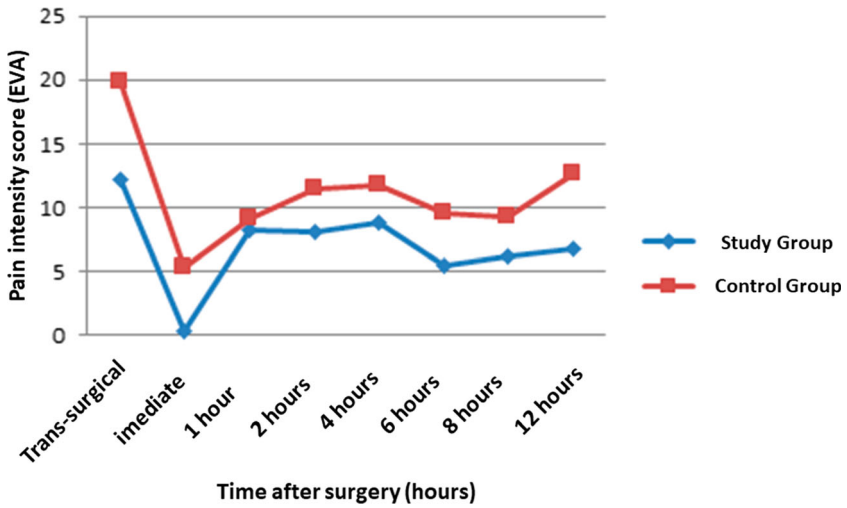

Fig. 1 Mean pain intensity scores (mm) recorded on VAS throughout the 12-h investigation period for the sides pretreatment and posttreatment with dipyrone sodium

Table 2 Operation details and efficacy parameters recorded in the investigation. Results are expressed as a mean ± SD and 95% confidence intervals for the mean

Variable	Pretreated sides	Posttreated sides	*p* value
Amount of local anesthetic used (ml)	5.90 ± 0.9	6.01 ± 0.9	0.5
Total analgesic consumption (dose)	1.2 ± 1.3	1.4 ± 1.9	0.4
VAS transsurgical (mm)	12.2 ± 14.3	19.9 ± 21.1	0.05 a
VAS postsurgical immediate (mm)	0.3 ± 1.0	5.3 ± 9.4	0.01 a
VAS postsurgical 1 h (mm)	8.2 ± 13.2	9.1 ± 15.2	0.7
VAS postsurgical 2 h (mm)	8.0 ± 12.4	11.4 ± 16.2	0.3
VAS postsurgical 4 h (mm)	8.8 ± 13.6	11.8 ± 17.6	0.1
VAS postsurgical 6 h (mm)	5.4 ± 8.9	9.5 ± 3.1	0.2
VAS postsurgical 8 h (mm)	6.1 ± 11.0	9.2 ± 19.2	0.4
VAS postsurgical 12 h (mm)	6.8 ± 11.1	12.6 ± 24.4	0.2
Duration of surgery (min)	41.8 ± 14.9	43.9 ± 17.3	0.3

[a] Significant difference between pretreated and posttreated sides

talniflumate) 1 h before the third molar extraction and observed no differences in the effectiveness of pain control when compared to its postoperative use.

Other studies including that of Kaczmarzyk et al. [13] compared the effect of oral administration of ketoprofen (100 mg) on three groups, i.e., 60 min before surgery, 60 min after surgery, and the placebo group, and observed that the use after surgery was the only group taking longer to present painful symptomatology, so that pain intensity was also lower.

Ong and Tan [12] compared the preemptive use of ketorolac (30 mg) and tramadol (50 mg) intravenously and observed that the former was more effective in controlling postoperative pain.

Bauer et al. [3] evaluated the effect of preemptive analgesia on Ibuprofen administration and did not observe differences when compared to the placebo group. The coadministration with dexamethasone preemptively was more effective in pain control than the placebo group. This same synergistic interaction between dexamethasone and Ibuprofen may have occurred in the present study.

Several studies have shown controversial results regarding preemptive analgesia involving the administration of NSAIDs [14]. The effect of talniflumate, diclofenac, aspirin, acetaminophen, ibuprofen, and rofecoxib were studied with no standardization, e.g., the administration of the same drug before and after surgery, the evaluation of pain perception, and the use of analgesic after surgery [2, 4, 5, 9]. In this way, the results cannot be compared with each other.

Pain perception (VAS) was lower in transoperative and immediate postoperative periods in patients who had used dipyrone preemptively. Theoretically, preoperative administration directly decreased the pain sensitization in such patients. Although both groups of patients have been equally anesthetized at these two moments, the results indicated that pain perception is not only related to anesthetic blockade, but also is influenced by decreased

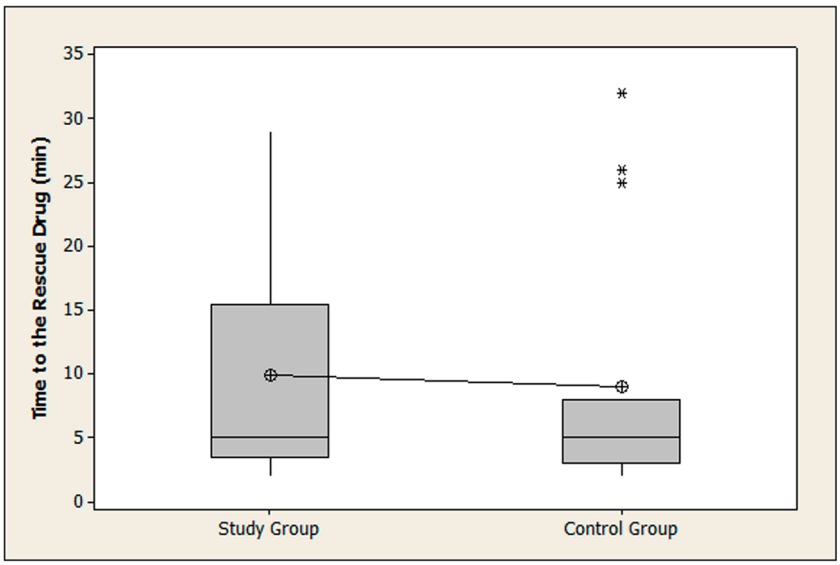

Fig. 2 Time of the rescue drug between pre- and postoperative. DS administered in preoperative (study group) and postoperative (control group), respectively

central sensitization, which reduces the perception of painful stimuli.

No differences were observed regarding rescue drug time in the comparison between groups. This fact is due to the analgesic needs to be used continuously after its half-life regardless of its preemptive or non-preemptive administration. Furthermore, dexamethasone has a longer half-life than dipyrone, which may have influenced the results of such a variable.

A low amount of anesthetic complementation was observed. The technique recommends 5.4 ml per side and the complementation was 0.5 and 0.6 ml on average for study and control groups, respectively (Table 2). This data reinforces the idea that the used drug protocol was efficient and did not interfere with preemptive analgesia.

Conclusion

The preemptive administration of dipyrone in the third molar surgical extraction was more effective when compared to its postoperative use in the reduction of pain perception in transoperative and immediate postoperative periods. Furthermore, such a drug has advantages including wide availability, low cost, and less side effects than those of analgesic drugs such as ketamine, tramadol, and codeine. We recommend its use prior to the beginning of the surgical procedure instead of only in the postoperative period, when surgical trauma already sensitized the central neurons. Thus, more comfort can be provided to patients during surgery and shortly after its end.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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