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Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction

OZGUL BAYGIN[1], TAMER TUZUNER[1], BERRIN ISIK[2], ADEM KUSGOZ[1] & MEHMET TANRIVER[1]

[1]Faculty of Dentistry, Department of Pediatric Dentistry, Karadeniz Technical University, Trabzon, and [2]Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Gazi University, Ankara, Turkey

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Background. This study investigates preliminary investigations that a pre-emptive analgesia administration may reduce post-extraction pain.

Aim. This prospective, placebo-controlled, randomized, double-blind trial was planned to compare the efficacy of the pre-emptive administration of ibuprofen, paracetamol, and placebo in reducing post-extraction pain in children.

Design. Forty-five children, ages 6–12, who needed primary mandibular molar tooth extraction were treated in paediatric dental clinics, with treatment preceded by local anaesthesia and analgesic drugs during the preoperative period. A five-face scale was used to evaluate pain reaction during the injection, extraction, and post-operative period. Self-report scores were recorded when the local anaesthesia had been administered in soft tissues and both before and after the extraction was completed. The Kruskal–Wallis and Mann–Whitney *U* tests (with Bonferroni correction paired *t*-test as the *post hoc* test) were used at a confidence level of 95%.

Results. The use of pre-emptive analgesics showed lower scores compared to the placebo, irrespective of the age, weight, gender of the child, and the number of teeth extracted during the study period. Additionally, ibuprofen exhibited lower pain scores ($P < 0.05$) compared to paracetamol at the 15-min ($P < 0.001$) and 4-h ($P < 0.009$) periods.

Conclusions. Preoperative use of ibuprofen and paracetamol may provide a pre-emptive analgesic effect in paediatric patients who receive adequate analgesia during mandibular primary tooth extraction.

Introduction

Pain experienced following dental extraction in children may cause distress for both the children and their parents.[1] Although in most cases, local anaesthesia will not wear off for several hours, it has been demonstrated in the literature that pain might be a problem for patients, particularly within the first few hours after dental extraction, because of the trauma to the hard and soft tissues during the tooth extraction period.[2]

In previous studies, analgesic use after tooth extraction in children was reported to be helpful.[3] In such studies, it was demonstrated that the preoperative oral usage of analgesics had beneficial post-operative pain relief properties over a placebo.[1,4] The dental literature identifies that preoperative usage of analgesics may decrease the post-extraction pain scores in adults.[5–7] Controversial reports, however, are found in the literature about the efficacy of preoperative induced analgesics on post-extraction pain relief in paediatric populations.[8,9]

Nonetheless, only a few studies have evaluated the use of preoperative analgesics on post-extraction pain relief in children. Primosch *et al.*[8] reported that there is no significant decrease in post-extraction pain scores between the placebo and paracetamol groups in children. Primosch *et al.*[9] also conducted a study of the efficacy of the preoperative usage of ibuprofen and paracetamol, compared with a placebo for pain relief after primary tooth

Correspondence to:
Dr. Ozgul Baygin, Faculty of Dentistry, Department of Pediatric Dentistry, Karadeniz Technical University, Trabzon, Turkey. E-mail: dtozgul@yahoo.com

extractions, and found that the preoperative administration of neither analgesic is superior to the placebo administration. McGaw *et al.*[10] found ibuprofen to be more efficacious than either paracetamol or a placebo for post-operative pain in children undergoing permanent tooth extraction. As stated in this article, preoperative analgesia may lessen post-operative pain in children.

To minimize the post-operative pain symptoms, the concept of administering analgesics before the painful stimulus begins – a practice known as pre-emptive analgesia – has attracted much interest.[11] It is also defined as an antinociceptive treatment that prevents altered central processing of afferent input sites from injury, which reduces the subsequent pain after the tissue injury occurs.[5,11] This procedure also allows post-operative pain management using local anaesthetics, NSAIDs, and opioids, as reported in previously published dental studies.[5] Ibuprofen, a propionic acid derivative analgesic that provides anti-inflammatory action, has been used in adult studies to evaluate its preoperative effect on post-extraction pain relief following dental procedures.[6,12–15] It was found to be a safe and effective analgesic as an anti-inflammatory agent in dosages ranging from 10 mg/kg/day to a maximum of 40 mg/kg/day.[9] It reached the peak plasma concentration 30 min after administration.[12–15] Paracetamol is also a traditional antipyretic and analgesic drug, as characterized in textbooks. Several investigations have reported its efficacy in post-operative pain relief after third molar surgery.[6] It was also found safe and effective analgesic as an antipyretic agent in dosages ranging from 15–20 mg/kg/day to a maximum of 60 mg/kg/day. It is rapidly absorbed following oral administration and reached the peak plasma concentration between the 1- and 2-h periods.[16]

Pain assessment is individual and subjective. The exact assessment of pain in children can be difficult. However, pain assessment can be performed via self-reporting measures.[1,9] Visual analogue pain scales, known as the easiest for children to use, have been employed successfully when determining the effects of analgesia.[17] Several visual analogue pain scales exist, but the five-face scale was chosen as the most appropriate one for younger children. Moreover, its extensive use and accuracy when measuring pain in children have been documented in the literature.[18] The five-face scale is easy to use, giving consistent scores from 0 to 4. It can be used for the subjective evaluation of feelings after the performance of painful dental procedures.[1]

Dental literature indicates that preoperative administration of analgesics may lessen post-extraction pain. Whereas many studies have evaluated the efficiency of analgesics before extraction in adults, little data have been published in children. The aim of this study was to assess whether pre-emptive analgesic medications have a beneficial effect in alleviating post-operative pain following tooth extraction in children.

Materials and methods

Forty-five children (25 boys, 20 girls), ages 6–12 (mean age 9.07 ± 1.76), who needed primary molar tooth extraction were treated in paediatric dental clinics, with treatment preceded by local anaesthesia. All patients were treated at the Karadeniz Technical University Pediatric Dental Clinic. This study was conducted after obtaining the approval of the Ethical Committee of Karadeniz Technical University, Faculty of Medicine, and informed consent obtained from the parents.

The tooth selection criteria included abscess with infection exceeding 1/3 of the interradicular area and teeth in which at least 2/3 of the roots were formed. Additionally, the children who had acute pain were excluded from the study. Patients taking analgesics within 5 h prior to the dental extraction and patients with a history of prolonged bleeding, platelet disorders, hypersensitivity, or allergic reactions to analgesics or any of the drugs tested were also excluded from the study.

Those having a parent able to understand and cooperate with the requirements of the protocol and able and willing to exercise an appropriate written informed consent were enrolled in the study. Patients without a home telephone or without parental supervision for the post-operative period were

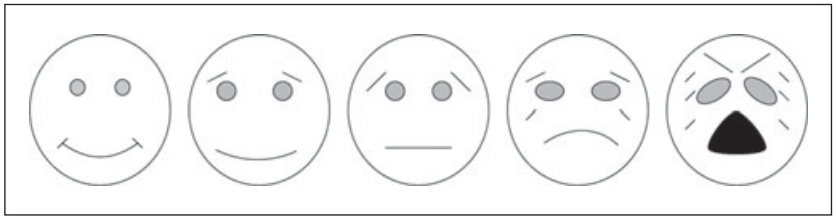

Fig. 1. Five-face scale for pain intensity measurement.

excluded from the study. The children and parents who agreed to wait after the extraction period were included.

Those subjects meeting the selection criteria were given one of the following three solutions: Group 1: Ibuprofen suspension (Ibufen®, 100 mg/5 mL; fruit flavoured, orange colour, Abbott, Istanbul, Turkey);

Group 2: Paracetamol elixir (Calpol™, 250 mg/5 mL; fruit flavoured, orange colour, GlaxoSmithKline, Istanbul, Turkey);

Group 3: A fruit-flavoured placebo solution.

The drugs in all of the groups were prepared in a fruit-flavoured solution of the same colour and scent. Patients were assigned in a blind, parallel, random fashion to one of the three pre-treatment drug groups. Fifteen containers of each solution were prepared and number-coded with the slips of paper by a secretary who was not associated with the study. The numbers were chosen by the patient. Thus, this allowed the subjects to be assigned into groups in a random fashion. Each patient received an age-dosed volume of the assigned solution from a number-coded lightproof plastic container containing a premeasured volume (20 mL). Both the researcher and the child/parent were blind to the content of the container. The assigned solution was taken by the patient at various times – 30 min (Ibufen®), 60 min (Calpol™), and 60 min (placebo solution) – before administration of the local anaesthetic agent. The time of the preoperative solution administration was recorded on the data sheet. All children were given 2% lidocaine with a 1 : 100,000 epinephrine (Maxicaine fort®, VEM Ilac San., Ankara, Turkey) injection for local anaesthesia sufficient for obtaining adequate anaesthesia. Topical anaesthesia in the form of benzocaine gel 20% was applied to the dried mucosa. Lidocaine 2% with 1 : 100,000 adrenaline was then given in a standardized manner to each quadrant for mandibular block just before dental treatment. All primary teeth were extracted intact with a minimum of surgical trauma in an uncomplicated fashion.

Pain scores were recorded in the Pediatric Dental Clinic using a five-face scale[1,19] that had been previously validated in children. This scale has shown good construct validity as a self-report pain measure. It measures the unpleasantness or affective dimension of a child's pain experience after injection and tooth extraction and is used in children aged 6–12 years. The child is shown a set of five cartoon faces with varying facial expressions ranging from a smile/laughter to tears. The scores given are (0) no sign of pain; (1) mild pain; (2) moderate pain; (3) severe pain; or (4) very severe pain (Fig. 1). In this study, each child was observed identifying the signs of their distress and pain when the sensation of numbness started. Additionally, five-face scores were recorded as a self-report measurement during the study periods. This ensured that both the patients and investigator were blind to the study group assignment. Blind investigators recorded the pain scores. After receiving verbal instructions about using the five-face scale, the children were asked to select the face that ''expresses your feelings that you feel deep down inside, in a real situation''. The children were asked to rank their sensations at the end of 5 min following local anaesthesia, and the score was evaluated. Extraction was performed in 15 min following local anaesthesia, and the score was evaluated again. Further, the pain scores were evaluated subsequently at 1, 2, 3 h, and 4-h time periods.

Patients were discharged when considered fit shortly after the 4 h measurements. The

self-report pain scores of the children and the need for analgesics after the 5, 6 h-, and 24-h post-operative periods were elicited from their parents by telephone. The telephone conversation followed a standardized format in which the parent was first asked whether the child had experienced pain. All parents answered without hesitation and seemed comfortable in their assessment. The parents were asked to explain the self-report measurements of their children. Parents were advised to observe their children for lip or cheek biting injuries or bleeding and to encourage them to stop should this be observed. They were also asked whether any lip or cheek biting injury or bleeding had occurred; if it had, they were offered an outpatient appointment for review.

Sample size was predetermined by power analysis using a five-face scale scores ($\alpha = 0.05$ and $\beta = 0.2$, SD: 0.87, mean difference 1.0, normal two-sided test). The analysis showed that 15 patients per group would be sufficient. Results were recorded and analysed using the statistical package SPSS 14.0.0 for Windows (SPSS Inc., Chicago, IL, USA). The age and weight results of the groups were cited as mean ± SD and analysed statistically using ANOVA. The gender and number of teeth extracted between the groups were evaluated using chi-square analysis. The Kruskal–Wallis test was used for statistical analysis of the pain scores. If there was a distinction, the Mann–Whitney *U* test (with Bonferroni correction paired *t*-test as the *post hoc* test) was used. A value of $P \leq 0.05$ was considered significant.

Results

All 45 patients enrolled in the study were evaluated. The research was designed so that 15 subjects were assigned randomly to each of the three solution groups. There was no significant difference between the groups at baseline with respect to gender (25 boys, 20 girls), age (mean ± sd, 9.0 ± 1.7 years), body weight (mean ± SD, 28.8 ± 7.1 per kg), and the number of teeth extracted ($P > 0.492$) (Table 1).

Figure 2 illustrates the pain scores (median, min/max values) of the groups including time periods. The usage of pre-emptive analgesics (Groups 1 and 2) showed significantly different and lower pain scores compared to placebo (Group 3) ($P < 0.05$) at 15 min, 1, 2, 3, 4, 5, 6 h, and 24 h. Additionally, ibuprofen exhibited lower pain scores ($P < 0.05$) compared to paracetamol at the 15-min ($P < 0.001$) and 4-h ($P < 0.009$) periods. The pre-emptive analgesic administration was provided sufficiently because of their longer preoperative waiting periods (30 and 60 min) reaching the adequate blood level, which resulted in a painless situation compared to the placebo group.

Three patients were reported by their parents to have a lip/cheek biting injury at 24 h after the extraction. Two of these patients

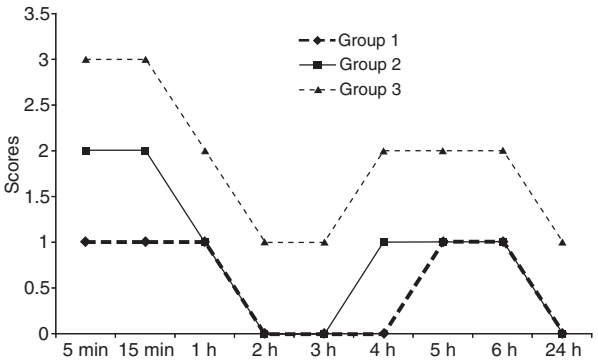

Fig. 2. Five-face scale pain scores (median, min/max values) of the groups including time periods.

Table 1. Demographic variables (*n*) and number of the teeth extracted according to groups.

Variables	Group 1	Group 2	Group 3
Gender (male/female)	10/5	8/7	7/8
Age (year) (mean ± sd)	8.53 ± 1.598	9.33 ± 1.397	9.33 ± 2.193
Weight (per kg) (mean ± SD)	26.20 ± 5.672	29.33 ± 7.423	30.93 ± 7.778
Number of the teeth extracted (Totally)	27	25	24
Mean ± sd, min/max	1.80 ± 0.414 (1/2)	1.67 ± 0.488 (1/2)	1.60 ± 0.507 (1/2)
$P > 0.05$	$P > 0.492$	$P > 0.492$	$P > 0.492$

were in Group 1, and the other was in Group 3. All three patients were followed up by review at an outpatient clinic, and all lesions healed spontaneously within a few days. One patient in Group 1 was reported by his parents to have post-operative bleeding, which subsequently stopped within 6 h.

Discussion

This study supports the idea that using pre-emptive analgesia could decrease the post-operative pain scores after primary tooth extraction in children. In paediatric dentistry, simple primary tooth extraction is known as a painful stimulation that may cause disruptive behaviours.[9] Moreover, the multifactorial and subjective nature of pain perception could exhibit varied outcomes for children in tooth extraction with the local anaesthesia.[8,9] However, despite the numbness observed, investigators reported such reaction-based pain problems after receiving the mandibular block anaesthesia in children irrespective of the age, gender, or the type of the extracted teeth.[20,21] Thus, an appropriate analgesic procedure should be an integral part of any dental service.[2] In general, in addition to orofacial pain, various side effects may occur in children that vary in intensity, such as lip or cheek biting.[1]

After tooth extraction procedures, pain problems can be reduced by using preoperative analgesia.[22] Investigators have found the preoperative usage of ibuprofen or acetaminophen to be effective in reducing post-operative pain in adult populations.[7,14,23,24] Both single-dose ibuprofen (4–10 mg/kg) and paracetamol (7–15 mg/kg) were shown to have similar efficacy and safety.[7] Ibuprofen was also found to be a safe and effective analgesic as an anti-inflammatory agent in dosages ranging from 10 mg/kg/day to a maximum of 40 mg/kg/day.[9] Paracetamol was also found to be safe and effective analgesic as an antipyretic agent in dosages ranging from 15–20 mg/kg/day to a maximum of 60 mg/kg/day.[16] According to this study method, we administered ibuprofen 100 mg/5 mL and paracetamol 250 mg/5 mL, which were tested for safety.

Ibuprofen has been evaluated extensively in post-operative dental pain, and several studies support its efficacy.[14,25] All these studies confirmed that using ibuprofen has potential advantages over acetaminophen and placebo because of its anti-inflammatory properties.[3,23,24] Ibuprofen has been also shown to be more effective than aspirin; paracetamol; the compound analgesic of aspirin, paracetamol, and codeine phosphate; and propoxyphene hydrochloride.[25] Gazal *et al.*[1] also support the oral administration of ibuprofen alone or in combination with paracetamol for post-operative analgesia in children having their teeth extracted under general anaesthesia. However, conflicting results were available in the literature, showing that ibuprofen did not have any clinical advantages compared to the placebo and paracetamol regimens with respect to alleviation of acute post-operative swelling and pain after third molar surgery.[6] Additionally, controversial reports can also be found in the literature about the efficacy of preoperative induced analgesics on post-extraction pain relief in paediatric populations.[8–10]

This study confirmed the results reported by Hill *et al.*,[14] Jackson *et al.*,[23] and Dionne *et al.*,[24] that were obtained by implementing pre-emptive analgesia.[7] This technique provides more comfort to the patient by giving analgesics before the painful stimulus begins. The clinical interest is in their potential for improving post-operative pain management.[5] It was found that ibuprofen and paracetamol can decrease the pain scores significantly compared to a placebo. Ibuprofen seems to be the most effective agent for relieving post-extraction pain, as mentioned earlier.[3,10] Additionally, ibuprofen exhibits lower pain scores ($P < 0.05$) compared to paracetamol at the 15-min ($P < 0.001$) and 4-h ($P < 0.009$) periods. This may be because of the anti-inflammatory properties of ibuprofen, which results in lower pain scores with regard to the painful stimulus of the local anaesthesia procedure at 15 min (before the extraction). At the 4 h post-operative time, when the effects of the local anaesthesia had faded, a prolonged analgesic effect occurred in the ibuprofen group compared to those receiving paracetamol. The results of this study show that both of these analgesics, but especially

ibuprofen when given pre-emptively, extend the onset of significant post-operative pain, as was described briefly.[1]

Moreover, previous investigators reported that when preoperative analgesics were given, 52–67% of children required post-operative analgesics after the extraction period.[8] In this study, no patient in either drug treatment group required analgesics. The pre-emptive technique also decreases the need for post-operative analgesic requirements and is an advantage in reducing the adverse effects of the analgesics.[26] Thus, particularly after the 4-h period, when the effect of local anaesthesia around the soft tissues has virtually disappeared, there was no need for analgesics. These results, in contrast with those form previous reports,[3,9] are likely related to a longer waiting periods before local anaesthesia was administered in the ibuprofen (30 min) and paracetamol (60 min) groups. With this technique, the drug effect could precede the inflammatory response and subsequent pain.[23] All data encourage the idea of using pre-emptive analgesics before the extraction of mandibular primary teeth in children.

Nevertheless, it is difficult to assess the real results of the role of analgesics on post-operative pain relief in paediatric dentistry.[1,27] Characteristically, parental observation for reporting pain has its limitations.[9] Quantifiable pain scales do exist that can be administered to children by trained personnel, but these are best given, for practical reasons, in close proximity to the pain stimulus.[28]

Furthermore, self-report visual analogue scales are known as the easiest to use in children and have been shown to be employed successfully when testing for the effects of analgesia.[17] In this way, misconception of the underestimation of a child's pain reaction might be minimized.[9]

In this study, the five-point pain scale with pictures of faces was used to obtain a pain measurement from the child during the study periods. This scale can be easily adapted to these age groups as previously reported (9.0 ± 1.7).[1] Moreover, Primosch *et al.*[9] conducted a study of 60 children (ages 2–10 years) to evaluate the efficacy of the preoperative administration of ibuprofen and paracetamol compared with a placebo for pain relief after tooth extractions. Moore *et al.*[3] studied child patients, ages 5–12 years, comparing ibuprofen, acetaminophen, and acetaminophen plus codeine with placebo. Considering these studies above, the age range tested in this study can be considered as an acceptable way to explain pain stress in these age groups. However, children younger than 7 years exhibited higher scores compared to older children because of their distress problems.[1] Pain response in young children undergoing similar surgical procedures may vary because of individual differences in temperament.[29] Although age characteristics may influence the reports of pain,[1,9] no differences were found in pain scores according to age in this study. Furthermore, in this study group, children could express their feelings in a real situation rather than relying on the opinion of observers. These factors may also help to better elucidate the efficacy of pre-emptive analgesic administrations in populations of these age groups.

Chi-square analysis also showed no significant differences in gender among the groups. The results of this study supported that gender and the number of teeth extracted had no effect on the results of pain scores. These findings were in accordance with other studies.[9,27] The difference in response to painful conditions with respect to gender is important because there is debate on this issue in the literature. It has been generally accepted that boys and girls respond differently to painful conditions. With few exceptions, according to the published literature, girls demonstrate a lower pain threshold and a lower tolerance of painful stimuli.[29] The fact that both of the pre-empted analgesics tested in this study, and particularly the ibuprofen group, resulted in lower pain scores when compared to the placebo could be related to the usage of self-report pain scores instead of the parental/trained personnel observation and their age characteristics.

Three patients were reported by their parents to have a lip/cheek biting injury at 24 h after extraction. Although one patient in Group 1 was reported by his parents to have post-operative bleeding, it subsequently stopped within 6 h. However, these events

were not serious and were spontaneously resolved. The ibuprofen may have caused a platelet dysfunction.[30] Overall, these side effects were not considered as serious complications in this study group.

This study demonstrates that pre-emptive analgesic administration can be considered as a routine and rational pain management strategy in mandibular primary tooth extraction procedures in children. Moreover, ibuprofen seems to result in lower pain scores compared to paracetamol.

What this paper or case report adds

- Pre-emptive analgesic medications have a beneficial effect in alleviating post-operative pain following tooth extraction in children.

Why this paper or case report is important to paediatric dentists

- Paediatric dentists may consider pre-emptive analgesics in children before extractions.

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