Preemptive Analgesia by Paracetamol, Ibuprofen or Placebo in Pediatric Dental Care: A Randomized Controlled Study

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Objective: *To compare postoperative pain among children who received an oral dose of paracetamol, ibuprofen or a placebo, prior to tooth extractions.* ***Study design:*** *Thirty minutes prior to dental treatment, children received a liquid dosage, fruit flavored and orange colored, of paracetamol, ibuprofen, or a placebo. Data accessed included children's dental history, their behavior, and their feeling of pain or anxiety according to Wong-Baker FACES: before treatment, following local anesthesia, and following treatment. Parents were interviewed by telephone regarding their children's need for a postoperative analgesia (paracetamol or ibuprofen), and their feeling of pain at four and 24 hours posttreatment.* ***Results:*** *Parents reported administering paracetamol or nurofen following the dental procedure to 9/43 (21%), 2/33 (6%) and 12/29 (41%) of the children in the preemptive paracetamol, ibuprofen, and placebo groups, respectively. For the 3 groups, mean pain assessment were similar: around the middle of the Wong-Baker FACES scale at baseline, slightly higher following local anesthesia, and low (pain-free) at four and 24 hours postoperative.* ***Conclusion:*** *Children who received paracetamol or ibuprofen prior to tooth extractions were less likely to need an analgesic following treatment, compared to children who received a placebo.*

Keywords: *preemptive analgesia, postoperative pain, ibuprofen, paracetamol*

INTRODUCTION

The establishment of a calm setting with minimal perioperative and postoperative pain is particularly important in pediatric dental treatment. Beyond the aspect of comfort, such atmosphere may contribute to a positive attitude towards the dental visit, which can facilitate future treatments. Conversely, postoperative pain may lead to reluctance to return to the dentist for future appointments[1].The benefit of preemptive analgesia in reducing postoperative pain has received clinical and research attention. Already in 1983, Woolf [2] provided evidence for a central component of post injury pain hypersensitivity. Several subsequent studies demonstrated the effectiveness of various anti-nociceptive analgesic techniques applied before injury in reducing postoperative pain.[3,4] However, two systematic reviews concluded that pain intensity was not reduced when the same analgesia was administered pre- rather than post-operatively[5,6]. None of the studies included in these reviews involved dental procedures and most were on adult populations. Among children who underwent adenotonsillectomy, those who received acetaminophen 30 minutes prior to the procedure reported less pain than did those who received either preemptive ibuprofen or a placebo.[7]

Investigations of the benefit of preemptive analgesia in the adult dental setting have shown conflicting results [8,9.] In the pediatric dental setting, literature regarding the benefit of preemptive analgesia is particularly sparse, and was assessed to be not of high

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quality[10] .A recent study showed lower pain scores and reduced use of postoperative analgesia among children who received 15 mg/kg intravenous paracetamol prior to undergoing dental rehabilitation under general anesthesia, compared to children who received 15 mg/kg of paracetamol at the end of treatment.[11]

The current study compared postoperative pain, as assessed by the need for analgesics, among children who received one of the three treatments procedures[2] prior to tooth extractions performed with the use of nitrous-oxide and oxygen .an oral dose of paracetamol; an oral dose of ibuprofen, a non-steroidal anti-inflammatory drug (NSAID); or a placebo. We hypothesized that children who received preoperative oral paracetamol or ibuprofen would be less likely to need a postoperative analgesic than would children who received a placebo.

Patients and Methods

105 children aged 5-12 years, who were scheduled to undergo at least one extraction of a primary tooth, at one of two pediatric dental clinics, after evaluation by a senior pediatric dentist. American Society of Anesthesiologists (ASA) I or II was an inclusion criterion. An allergy to paracetamol or ibuprofen, or any other contraindication to these drugs, and renal or hepatic insufficiency were study exclusion criteria. The study was approved by the Institutional Ethics Committees of Tel Aviv University, and informed consent was attained from the parents of all participating children.

Parents of participating children were requested to fill a questionnaire that accessed the age, gender and body weight of the children, the number of children in the family, the child's place in the family (first child, second child, etc.), past dental experience (yes / no), past experience with N2O (yes / no), previous tooth extractions (yes / no), the parents' assessment of their children's sensitivity to pain in a numerical method (1=high, 2=average, 3=low), their expectations of their children's cooperation in the treatment on a Likert scale ranging from 1 (full cooperation) to 4 (resistance to treatment), and the children's assessment of their pain, according to Wong-Baker FACES[12] (Figure 1). According to the latter, children were asked to choose one of 6 faces that expressed their feeling (0, 2, 4, 6, 8, 10; with 0 showing a happy face and 10 a distressed face). Pain scores were recorded at six time-points: before receiving the pre-operative syrup, before treatment, after local anesthesia, after extraction, 4 hours and 24 hours after the dental treatment.

Thirty minutes prior to their dental treatment, the children received one of three oral liquid solutions: 15 mg /kg of paracetamol (ACAMOL, Teva pharmaceutical Industries LTD, ISRAEL.) fruit flavored, orange color; 15 mg/kg ibuprofen (Nurofen, Ltd Reckitt Benckiser Healthcare UK.), fruit flavored, orange color; or a fruit flavored liquid, orange color placebo. The containers of the solutions were prepared and number-coded with slips of paper by an assistant who was not associated with the study. She arbitrarily handed one container to each parent of a participating child. The researcher, as well as the patients and their parents, were blind to the contents of the containers. All treatments were carried out under N_2O-O_2 sedation. Before the start of the dental treatment, all the children were administered 2% lidocaine with 1: 100,000 epinephrine, using a computerized delivery system (Wand; Milestone Scientific, Inc., Deerfield, IL, USA) via infiltration anesthesia after topical application of 20% benzocaine.

Written and verbal instructions for post-treatment were provided to parents. They were instructed to record their children's report of pain intensity at four and 24 hours following the procedure; and to administer pain medication as needed. The children's self-reported pain-score (Wong–Baker FACES scale) and the need for analgesics at four hours and 24 hours postoperative were elicited from the parents by telephone.

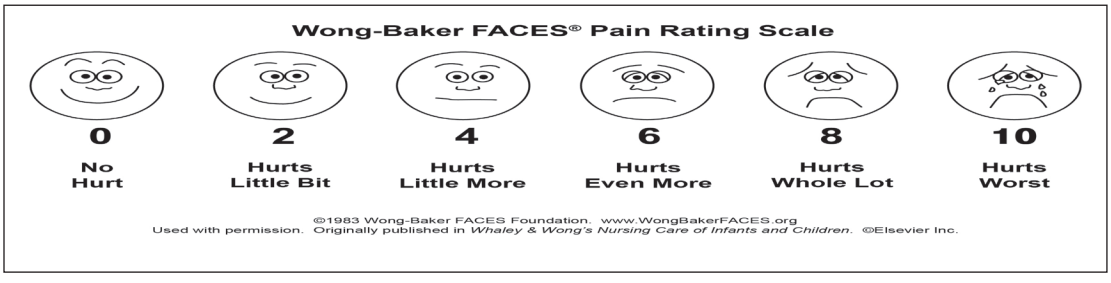
The following parameters were recorded for each treatment: the tooth that was extracted and its root length; the condition of the gums (healthy, redness, infected and swollen, fistulas); the N_2O concentration administered during the treatment. In addition, a dental assistant (blinded to the type of syrup administered) rated the child's behavior according to the Taddio modified Behavioral Pain Scale[13] (Figure 2) at three time-points: prior to treatment, following

Figure 2: modified behavioral pain scale (MBPS)

Behavior Observed	Score
Facial expression	
Definite positive expression (ie, smiling)	0
Neutral expression	1
Slightly negative expression (ie, grimace)	2
Definite negative expression (ie, furrowed brows, eyes closed tightly)	3
Cry	
Laughing or giggling	0
Not crying	1
Moaning, quiet vocalizing, or gentle or whimpering cry	2
Full-lunged cry or sobbing	3
Full-lunged cry, clearly more than baseline†	4
Movements	
Usual movements and activity, resting and relaxed	0
Partial movement or attempt to avoid pain by withdrawing limb when procedure is done	2
Agitation with complex movements involving head, torso, or other limbs, or rigidity	3

*From Taddio et al.[12]
†Used only for postprocedural pain.

Figure 1: Wong-Baker FACES



administration of the local anesthesia, and after the extraction. This 10-point scale assesses pain according to children's facial expression, crying, and movements: a lower score indicates more positive behavior. Uncooperative behavior was considered as a score > 5.

Statistical analysis

Data were analyzed utilizing an SPSS (Statistical package for the social sciences) 15.0 software (SPSS Inc., Chicago. IL., USA).

The t-test was used to assess associations of children's behavior and age with various parameters, such as pain behavior and the Wong-Baker FACES score. The Pearson Chi-Square test was used to assess associations of the treatments administered with such parameters as history of extraction, type of anesthesia, and the need for additional pain relief medicine.

RESULTS

The study comprised 105 children: 43 in the paracetamol group, 33 in the ibuprofen group and 29 in the placebo group. Gender distribution, and mean ages and body weights were similar for the three groups (Table 1).

Table 1: Demographic characteristics of the patients according to study groups

	Paracetamol group	Nurofen group	Placebo group
Number of children	43	33	29
Males, n (%)	18 (42%)	15 (46%)	14 (48%)
Age, mean ± SD	8.6±2.4	9.6±2.2	9.8±2.2
Body weight, mean±SD	26.8±7.2	29.9±7.8	32.7±9.2

Children's sensitivity to pain according to parents' assessment, and parents' expectations of their children's cooperation during treatment were similar between the groups. (Table 2)

Table 2: Parents assessment — sensitivity to pain and cooperation before treatment

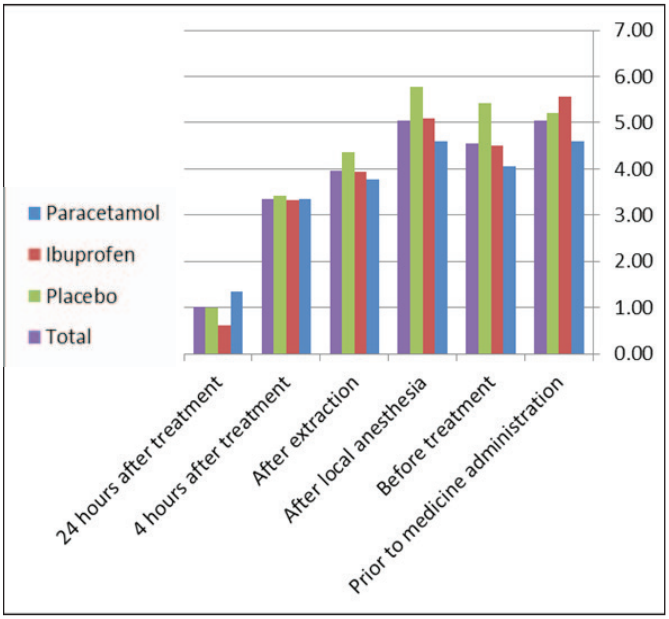
	Paracetamol	Nurofen	Placebo
Sensitivity assessment	1.88±0.66	1.69±0.72	1.75±0.68
cooperation assessment	2.14±0.7	2.36±0.74	2.41±0.86

Data are presented as means +SD

For the following variables, differences between the treatment groups were not statistically significant: the number of siblings, children's place in the family, previous dental treatment, previous experience with N_2O, and the condition of the children's gums. Smaller proportions of children in the paracetamol group had previous extractions. A greater proportion of patients in the placebo than the other groups had full length roots. Greater proportions in the paracetamol than the other groups had less than half roots and had more than one root; however, these differences between the groups were not statistically significant.

Figure 3 shows the FACES scores at the various time points. There were no significant differences between the groups however; the placebo groups demonstrated higher scores after local anesthesia administration and extraction. In addition, the overall "pain issue" expressed by the children even prior to treatment was high.

Figure 3: Figure 3 shows the FACES scores at the various time points.



Pain behavior scores according to the Taddio scale was recorded before treatment, after local anesthetic and after extraction. A trend was found, showing low values before treatment, highest values were observed during the local anesthesia administration, and lower during the extraction. Although no significant differences between the groups was found, the values in the Placebo group were the highest Table 3.

Table 3: Children's behavior (Taddio Behavioral Pain Scale)+ SD

Time of assessment	Paracetamol	Ibuprofen	Placebo	Total
Before treatment	3.12±2.11	3.67±2.01	4.46±2.71	3.63±2.3
During local anesthesia	4.84±2.19	4.94±1.89	5.14±2.16	4.91±2.1
During extraction	3.86±2.1	4.3±2.19	4.79±2.33	4.22±2.21

Parents reported administering an analgesia within four hours following the procedure to 9/43 (20.9%), 2/33 (6.1%) and 12/29 (41.4%) of the children in the paracetamol, ibuprofen and placebo groups, respectively. The difference between the placebo and between the ibuprofen and paracetamol groups was statistically significant (p=0.004). No statistically significant was found between the paracetamol and ibuprofen groups.

DISCUSSION

The main finding of this study is that, in the setting of dental extractions performed with the use of N_2O, a smaller proportion of children who received preemptive oral doses of paracetamol or ibuprofen needed a postoperative analgesic than did children who received a preoperative oral dose of a placebo.

We note that children's assessments of pain according to Wong Baker scale was almost the same (no significant difference) in the

different groups but the placebo groups demonstrated higher scores after local anesthesia administration and extraction. The high levels of scores before administration of medicine may reflect the high level of stress in the different groups.

At 4 hours after extraction the scores were similar to that at baseline. Twenty four hours after extraction the scores were similar and very low.

After four hours the WBS were similar because parents of children from the different groups were instructed to give their children analgesics if they complained about pain within one hour after extraction. At 24 hours after extraction there was no pain in the different groups, this indicates that pain after primary tooth extraction is expected only few hours after extraction.

Children's sensitivity to pain according to parents' assessment, and parents' expectations of their children's cooperation during treatment were similar. This fact emphasizes the effectiveness and validity of the preemptive modality because if the placebo group were more sensitive and not cooperative their parents would tend to give them more analgesics.

According to the Taddio Behavioral Pain Scale the scores were higher for the placebo group before treatment, after local anesthesia and after extraction (Table 3). This demonstrates that children who were less cooperative during treatment tend to need more analgesia after treatment. This group will benefit more from preemptive modality.

Other studies have shown oral paracetamol and NSAIDs to be effective in the postoperative relief of dental pain[15,16]. Moreover, recent publications have confirmed the effectiveness of paracetamol, at the dose of 15 mg/kg, and NSAIDs in reducing pain in children[17,18].

In the current study, both paracetamol and ibuprofen demonstrated benefit in reducing the need for analgesics in children who underwent tooth extractions. We note that in the ibuprofen group, the number of children with a history of previous extractions was higher than in the paracetamol or placebo groups. We would expect that previous dental extractions could increase pain sensitivity and thus the need for an analgesic. Therefore, the low need for analgesics in this group compared to the other groups supports the effectiveness of preemptive Ibuprofen in pain reduction. But dentists must take into consideration the side effects of it (gastric bleeding, gastrointestinal toxicity) compared to paracetamol which has less adverse events[19].

A number of studies have examined the benefit of preemptive analgesia in the dental setting. In a double blind, randomized study of 34 adults who underwent removal of impacted mandibular third molars, and who served as their own controls, postoperative analgesic consumption was less when ketorolac was injected preoperatively and a placebo injected postoperatively than when a placebo was injected preoperatively and ketorolac postoperatively[8]. Further, a prospective, randomized, single-blind, crossover study concluded that preemptive administration of NSAIDs was effective in the management of pain following the surgical removal of impacted third molar teeth[9]. Contrasting with the above, a prospective randomized double-blind trial showed greater delay in pain onset and lower pain intensity among patients undergoing third molar surgery who received postoperative rather than preemptive analgesia, or rather than a placebo[14].

Only a few studies have examined the use of preoperative analgesics in the pediatric dental setting. A recent Cochrane review[10] identified only 5 studies that evaluated the use of preoperative analgesics on pain following dental or orthodontic procedures in children, and that did not use general anesthesia or sedation, including N_2O. All the studies were included in the 2012 Cochrane review of the same subject. The data were deemed not conclusive nor of higher enough quality to determine a benefit of preoperative analgesics in pediatric dental procedures performed under local anesthesia.

The results in this study are comparable to other studies[20] which showed that preemptive use of paracetamol compared to placebo extended the onset of postoperative pain, lowered its intensity and decreased the need for postoperative analgesics after primary tooth extractions in children.

Our study faces some limitations. While many of the demographic, clinical, and operative characteristics examined distributed similarly between the study groups, a number of them differed, specifically: previous experience with tooth extractions, behavior prior and during treatment. A crossover study design would eliminate these differences, as the same children would then receive a preemptive analgesia at one treatment and a placebo at another.

Another limitation of this study is that data collected from parents raises issues of reliability. It is difficult to accurately know the degree to which the parents may themselves have had an influence on the children's report of pain or on administering analgesics. Nonetheless, such error would result in nondifferential misclassification, and thus, would not be expected to affect the conclusion of the study.

CONCLUSIONS

Administration of paracetamol or ibuprofen to children prior to tooth extraction appeared to reduce the likelihood that an analgesic would be needed, compared to the administration of a placebo.

REFERENCES

1. McWhorter AG, Townsend JA. Behavior symposium Workshop A report – current guidelines/revision. Pediatr Dent. Mar-Apr;36(2):152-3. 2014 .
2. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. [Internet]. Vol. 306, Nature. 1983. p. 686–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6656869
3. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence.Pain . 52,. 259–85. 1993.
4. Kaufman E, Epstein JB, Gorsky M, Jackson DL, Kadari A. Preemptive analgesia and local anesthesia as a supplement to general anesthesia: a review. Anesth Prog.;52(1):29–38. 2005.
5. Ong CKS, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: A meta-analysis. Anesth Analg.;100(3):757–73. 2005.
6. Møiniche S, Kehlet H, Dahl JB. A Qualitative and Quantitative Systematic Review of Preemptive Analgesia for Postoperative Pain Relief. Anesthesiology [Internet]. 2002;96(3):725–41. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000542-200203000-00032
7. Mahgoobifard M, Mirmesdagh Y, Imani F, Najafi A, Nataj-Majd M. The Analgesic Efficacy of Preoperative Oral Ibuprofen and Acetaminophen in Children Undergoing Adenotonsillectomy: A Randomized Clinical Trial. Anesthesiol Pain Med [Internet]. 2014;3(3):1–4. Available from: http://www.anesthpain.com/?page=article&article_id=15049
8. Ong CKS, Seymour RA, Chen FG, Ho VCL. Preoperative ketorolac has a preemptive effect for postoperative third molar surgical pain. Int J Oral Maxillofac Surg;33(8):771–6. 2004.
9. Pektas ZO, Sener M, Bayram B, Eroglu T, Bozdogan N, Donmez A, et al. A comparison of pre-emptive analgesic efficacy of diflunisal and lornoxicam for postoperative pain management: a prospective, randomized, single-blind, crossover study. Int J Oral Maxillofac Surg. ;36(2):123–7. 2007.
10. Ashley PF, Parekh S, Moles DR, Anand P, Macdonald LCI. Preoperative analgesics for additional pain relief in children and adolescents having dental treatment. Vol. 2016, Cochrane Database of Systematic Reviews. 2016.
11. Kharouba J, Hawash N, Peretz B, Blumer S, Srour Y, Nassar M, et al. Effect of intravenous paracetamol as pre-emptive compared to preventive analgesia in a pediatric dental setting: a prospective randomized study. Int J Paediatr Dent [Internet]. 2017;1–9. Available from: http://doi.wiley.com/10.1111/ipd.12311
12. Savino F, Vagliano L, Ceratto S, Viviani F, Miniero R, Ricceri F. Pain assessment in children undergoing venipuncture: the Wong–Baker faces scale versus skin conductance fluctuations. PeerJ [Internet]. 2013;1:e37. Available from: https://peerj.com/articles/37
13. Taddio A, Nulman I, Goldbach M, Ipp M, Koren G. Use of lidocaine-prilocaine cream for vaccination pain in infants. J Pediatr ;124(4):643–8. 1994.
14. Kaczmarzyk T, Wichlinski J, Stypulkowska J, Zaleska M, Woron J. Preemptive effect of ketoprofen on postoperative pain following third molar surgery. A prospective, randomized, double-blinded clinical trial. Int J Oral Maxillofac Surg;;39(7):647–52. 2010.
15. Olson NZ, Otero a M, Marrero I, Tirado S, Cooper S, Doyle G, et al. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. J Clin Pharmacol [Internet]. 2001;41(11):1238–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11697757
16. Troullos ES, Freeman RD, Dionne RA. The scientific basis for analgesic use in dentistry. Anesth Prog [Internet]. 1986;33(3):123–38. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2175478&tool=pmcentrez&rendertype=abstract
17. de Martino M, Chiarugi A. Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. Pain Ther [Internet]. 2015;4(2):149–68. Available from: http://link.springer.com/10.1007/s40122-015-0040-z
18. de Martino M, Chiarugi A, Boner A, Montini G, de' Angelis GL. Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal. Drugs;77(12):1295–311. 2017.
19. Haas DA. An update on analgesics for the management of acute postoperative dental pain. J Can Dent Assoc; 68(8):476-82. 2002.
20. Baygin, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post- operative pain in primary tooth extraction. Int J Paediatr Dent. Jul;21(4):306-13. 2011.