


Effect of intravenous paracetamol as pre-emptive compared to preventive analgesia in a pediatric dental setting: a prospective randomized study

JOHNY KHAROUBA¹, NASIR HAWASH², BENJAMIN PERETZ¹, SIGALIT BLUMER¹, YARA SROUR², MARRY NASSAR³, MULHAM SABBABH², ANAN SAFADI², ALEXEY KHOREV² & MOSTAFA SOMRI^{3,4} 

¹Department of Pediatric Dentistry, Faculty of Medicine, The Maurice and Gabriela Goldschleger School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel, ²Anaesthesia Department, Bnai Zion Medical Center, Haifa, Israel, ³Anaesthesia Department and Paediatric Anaesthesia Unit, Bnai Zion Medical Center, Haifa, Israel, and ⁴The Bruce & Ruth Rappaport, Faculty of Medicine, Technion – Institute of Technology, Haifa, Israel

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Background. Efficacy of pre-emptive analgesia compared to preventive regimen, managing post-operative pain is still controversial.

Aim. Evaluating the efficacy of intravenous (IV) paracetamol as pre-emptive analgesia compared to preventive post-treatment administration in pediatric dental setting.

Design. In a prospective trial, 60 noncooperative children of ASA I, II aged 3–10 years who underwent dental rehabilitation under general anaesthesia were randomly divided into two groups. Pre-emptive group ($n = 30$) received 15 mg/kg of IV paracetamol before the start of treatment. Preventive group ($n = 30$) received 15 mg/kg of paracetamol at the end of treatment. Analgesic efficacy was measured by visual analog scale of

faces (VASOF), percentage of children received postoperative analgesia.

Results. The VASOF results in the pre-emptive group were significantly lower compared to the preventive group at 4, 8, 12, and 24 h (0.0146, 0.0188, 0.0085, and 0.0001, respectively). Less children in the pre-emptive group received supplemental fentanyl postoperatively compared to the preventive group (27.6%, 58.6%, respectively, $P = 0.0170$). Time to first rescue dose of fentanyl postoperatively in the pre-emptive group was later than in the preventive group ($P = 0.0432$).

Conclusions. Administration of IV paracetamol pre-emptively provides lower pain scores, and a decreased percentage of children required pain relief and less amount of postoperative opioids, compared to preventive administration.

Introduction

Acute pain is commonly experienced in children after dental rehabilitation. Moreover, a negative experience, caused by postoperative pain, might discourage a child from cooperating at future appointments for dental treatment. Acute pain following oral surgery results from the heightened sensory nociception in the head and oral cavity compared to other parts of the body¹. Consequently, post-surgical dental pain is one of the most studied models in pharmacology and pain research, demonstrating that pre-emptive analgesia or

preventive with a multimodal analgesic approach can be used to attenuate the postoperative pain intensity².

Pre-emptive analgesia approach focuses on the timing of administration of an analgesic medication or technique, which is applied before the painful stimulus to prevent or 'pre-empt' the afferent input which amplifies postoperative pain; thus, effective pre-emptive analgesia should prevent the establishment of central sensitization caused by incisional and inflammatory injuries³. The validity of the pre-emptive analgesic efficacy to reduce postoperative pain can only be evaluated by clinical trials using a pre- versus post-study design, by comparing the same analgesia regimen initiated after surgery^{3,4}.

Whereas the preventive analgesia approach is not time related, the analgesic intervention

Correspondence to:

Prof. Mostafa Somri, Bnai Zion Medical Center,
P. O. Box 4940, 3104802, Haifa, Israel.
E-mail: somri_m@yahoo.com

may or may not be initiated before surgery and is defined by reduced postoperative pain or analgesic consumption relative to another treatment, placebo treatment or no treatment^{5,6}.

Previous studies employing pre-emptive analgesia have demonstrated that pain either subsided or central sensitization was prevented, prior to the painful stimulus. Consequently, reducing post-injury pain and a decreased need for postoperative opioids as analgesia after treatment^{3-5,7}.

Whether pre-emptive analgesia is more effective than preventive regimens in managing postoperative pain is still controversial. Several clinical studies in pediatric dental procedures have shown that pre-emptive analgesia or preventive with a multimodal analgesic approach can be used to attenuate the postoperative pain intensity⁸⁻¹⁰. These three studies, however, compared the efficacy of the following analgesic agents: paracetamol, nuerophren, and ibuprofen only *versus* placebo.

In contrast, a recent meta-analysis of Randomized Controlled Trials (RCT) including 190 children concluded there is lack of evidence to determine any benefit of preoperative analgesics in pediatric dental procedures¹¹.

The discrepancies in these clinical study results were related, in part, to the controversy associated with the definition of pre-emptive and preventive analgesia³ and to methodological differences in the conduct of the clinical trials reported to date¹².

Despite these controversies on the analgesic effect of the pre-emptive and preventive analgesic approaches, clinical trials assessing the efficacy of pre-emptive analgesia are continuously being conducted.

Intravenous (IV) paracetamol administered before dental treatment decreased the postoperative analgesia consumption and lowered the postoperative pain intensity in the adult population in studies compared only with placebo¹³⁻¹⁵.

No previous study, however, has focused on the timing of administration of the IV paracetamol and compared the analgesic efficacy of IV paracetamol administered preoperatively, before the dental treatment

(pre-emptive analgesic approach) with IV paracetamol administered postoperatively, post-dental treatment (preventive approach) in a pediatric dental setting performed under general anesthesia (GA) including intraoperative opioids.

The primary objective of this study was to investigate the post-dental analgesic effect of pre-emptive approach (IV paracetamol administered before the start of the dental treatment) *versus* preventive approach (IV paracetamol administered at the end of the dental treatment); in both approaches, GA was induced combined with an opioid agent administered intraoperatively. We evaluated the analgesic efficacy, of either intervention, in attenuating postoperative pain intensity, reducing percentage of children who required postoperative analgesic dose, decreasing a supplemental postoperative analgesic dose consumption and prolonging time to the first rescue analgesic, in children undergoing dental treatment.

Material and methods

Sample size

An *a priori* power analysis was performed to determine the minimum group size ($n = 25$), before the investigation. The following assumption was made for the power analysis of two-sample study of 30% difference in the intensity level of pain, with a power of 80% and $\alpha = 0.05$. Adding five subjects for an expected 10% dropout rate, the estimated sample size for the study should be 30 participants in each of the two study groups^{16,17}.

Setting and study population

After receiving the approval of the local Institute Ethical Committee of Bnai-Zion Medical Center, Haifa, Israel, registration in Clinical-Trial.gov and obtaining written parental informed consent, 75 noncooperative children of 3–10 years of age who underwent dental rehabilitation under GA were assessed for eligibility.

All children were evaluated by a senior pediatric dentist, who determined a wide

dental treatment, including mostly fillings, stainless steel crowns, space maintainers, fissure sealant, and preventive care, with an estimated duration of more than 1 h. The study included pediatric subjects who were in high stress and did not cooperate with the pediatric dentist according to Houpt cooperation score¹⁸ in a previous treatment session as they failed to undergo dental treatment under local anesthesia alone or in combination with behavioral management or under pharmacological conscious sedation, in the pediatric dental clinic, and thus requiring GA to accomplish dental treatment. Fifteen children failed to meet the inclusion criteria and did not complete the enrollment process; therefore, 60 children of ASA I, II, ages 3–10, were enrolled during the study period April 2015–August 2016.

Children with renal or hepatic insufficiency or with a history of an allergic reaction or sensitivity to paracetamol were excluded from this study.

Anesthesia process

Anesthesia was induced in all children in both groups by inhalation of sevoflurane; IV venflon was inserted after induction of GA and fentanyl administration in a dose of 1–2 $\mu\text{g}/\text{kg}$, with nasal endotracheal intubation facilitated by rocuronium 0.5 mg/kg. Throat pack was also inserted. Anesthesia was maintained with $\text{N}_2\text{O}/\text{O}_2$ (50%–50%) and 2%–3% concentration of sevoflurane and IV fentanyl, as needed during the dental treatment. Patients were ventilated by non-rebreathing technique keeping ETCO_2 between 30 and 45 mmHg. Intraoral local anesthesia was not administered to any patient during the dental rehabilitation.

All patients were monitored intraoperatively with the Datex-Ohmeda S/5TM Anesthesia monitor (Helsinki, Finland).

All children received GA by the same senior anesthesiologists and were operated on by the same surgical dentist team.

Study design

The study cohort was randomly divided into two groups of 30 patients each. Randomization

was based on a computer-generated code prepared at a remote site and sealed in sequentially numbered, opaque envelopes.

Group A (Pre-emptive group – 30 patients) received 15 mg/kg of intravenous paracetamol in 50 mL of normal saline after induction of GA and 15 min before the start of the dental treatment and another 50 mL of normal saline at the end the treatment.

Group B (Preventive group – 30 patients) received intravenous 50 mL of normal saline after induction of GA and before the start of the dental treatment and 15 mg/kg of paracetamol IV in 50 mL of normal saline at the end of the dental treatment.

These IV paracetamol doses in both patient groups were given either preoperatively or postoperatively, as an adjuvant to the IV fentanyl administered intraoperatively at the induction time of GA and as required during treatment process.

All analgesia pharmaceuticals administered by the anesthesiologist were prepared and supplied by another researcher who performed the randomization process; however, was not involved in patient care. The trial was double-blinded, and in that, patients, parents, and anesthesiologist were all blinded to the treatment groups. Nurses and physicians who evaluated postoperative pain and collected data in post-anesthesia care unit (PACU) were blinded to patient allocation.

Patients' pain assessment

Level of pain intensity was measured using the visual analog scale of faces (VASOF)^{19,20} which consists of five cartoon faces corresponding to scores 0–5 (0 = no hurt, 1 = hurts a little bit, 2 = hurts a little more, 3 = hurts even more, 4 = hurts a whole lot, 5 = hurts worst). VASOF was recorded at arrival to PACU (post-anaesthesia care unit), and at 2, 4, 8, 12, 24 h post-treatment. When the VASOF score post-operatively was of ≥ 2 , the child received a rescue dose of intravenous fentanyl of 1–1.5 $\mu\text{g}/\text{kg}$. Postoperatively, total number of patients who needed rescue analgesic doses were documented as well as the amount of fentanyl consumed and

the time to first postoperative rescue analgesia administration.

Total amounts of intraoperative IV fentanyl and paracetamol were recorded as well.

After treatment period

Children were discharged home when they reached six points in the Steward's discharge score²¹ in which the principal elements are consciousness, airway, and movements. Written and verbal instructions for post-treatment were provided to the parents, before the dental treatment, when parental informed consent was obtained. Parents and children who were able to understand were instructed how to use the VASOF pain scale. Parents were instructed when to administer pain medication with oral paracetamol or ibuprofen, according to the obtained VASOF score, as needed, and to record administration time and dose. Parents were also asked about any adverse events during the 24-h postoperative period at home. Follow-up data were collected from parents, who were contacted by phone, by a research coordinator who was blinded to the paracetamol regimen used.

Patient demographic data, such as age, weight, gender, and all collected data were entered into the PC database and analyzed.

The primary outcomes to assess the analgesic efficacy of the pain management approach pre-emptive *versus* preventive administered IV paracetamol in a pediatric dental setting were as follows: postoperative pain intensity according to the VASOF pain score; total number of patients and supplemental postoperative IV fentanyl administered in PACU; time to first rescue analgesia administration; and total patients administered pain relief medication at home.

Statistical analysis

For the continuous variables medians, means, standard deviations, and ranges were calculated. Test for normality was performed by Shapiro–Wilk normality test. The results of the continuous variables between the two

study groups for (pre-emptive *versus* preventive) were analyzed by the Kruskal–Wallis rank test (a nonparametric test for study groups). For the categorical variables, numbers and percentages were calculated. The distributions for the categorical variables between the study groups were compared and analyzed by the chi-square test (a parametric test) or by Fisher–Irwin exact test (a nonparametric test for small numbers).

All statistical tests were analyzed to a significance level of 0.05. Statistical analysis was performed using the STATA 12.0 software (Stata Statistical Software, Release 12; Stata-Corp LP, College Station, TX, USA).

Results

During the study trial, a total of 60 patients were enrolled in the two study groups. Five children were excluded due to lack of follow-up at home (Fig. 1).

In the pre-emptive group: 28 patients were treated with IV paracetamol 15 min before initiation of dental treatment.

In the preventive group: 27 patients were treated with IV paracetamol at the end of the treatment.

Baseline demographic analysis

The baseline demographic variables (age, weight, and gender) were not significantly different between the pre-emptive and preventive study groups ($P > 0.05$; Table 1).

Total intraoperative fentanyl and paracetamol

There was no significant difference in the total amount of intraoperative paracetamol according to patient's body weight between the two groups, with a median amount of 240 mg (range: 165–450 mg) *vs* 250 mg (range: 180–500 mg) in the pre-emptive and the preventive groups, respectively ($P = 0.11$; Table 1).

There was also no significant difference in the total amount of intraoperative fentanyl between the two groups, in the pre-emptive group (median: 30 μ g; range: 25–50 μ g) and

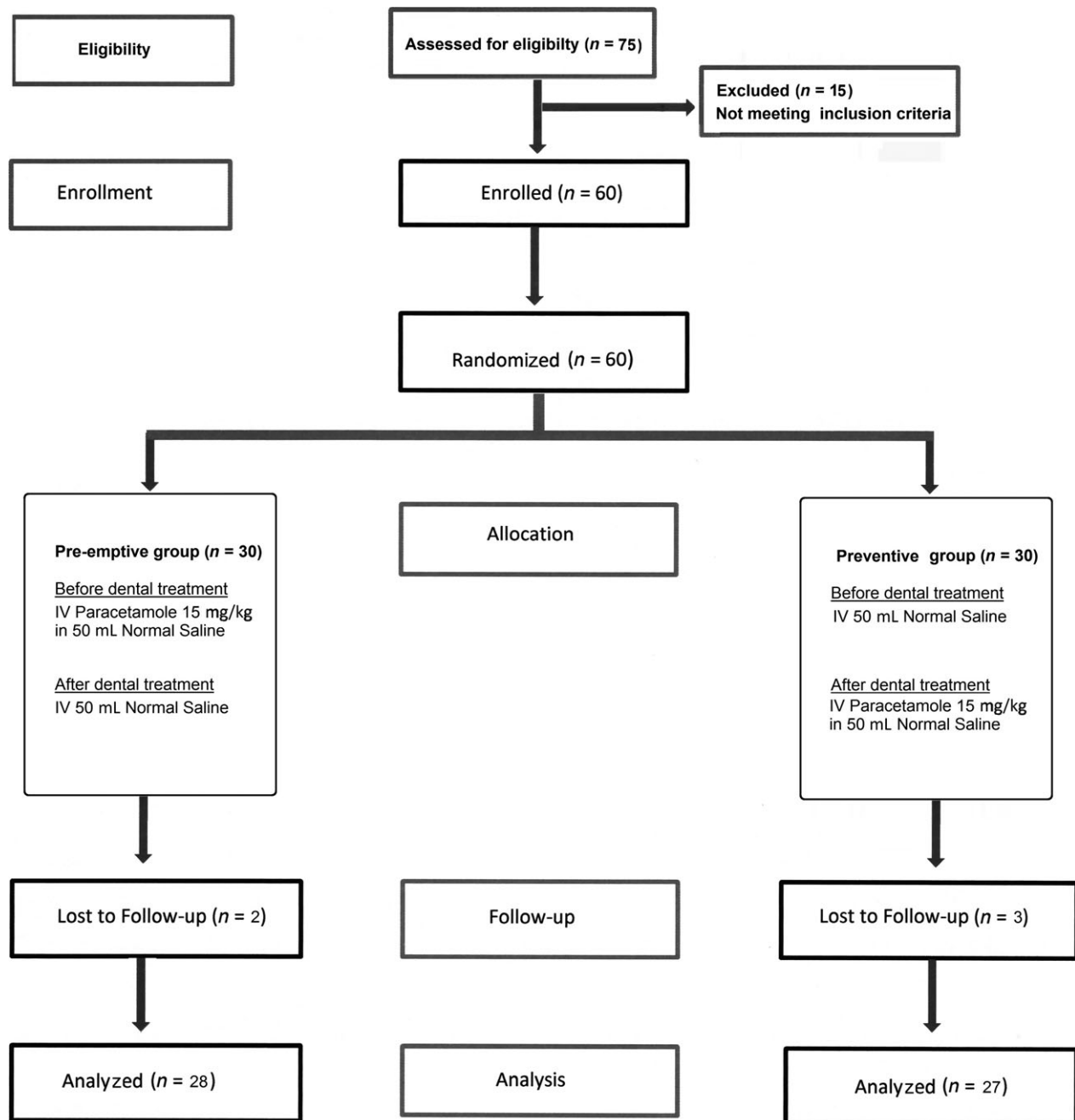


Fig. 1. CONSORT flow diagram of the study.

in the preventive group (median: 35 μg ; range: 20–60 μg ; $P = 0.19$, Table 1).

Pain assessment in PACU

Pain scores according to the VASOF scale measured at six time periods (0, 2, 4, 8, 12, and 24 h post-operation) in both study groups are presented in Table 2. The mean

pain scores for all times were 0.76–1.66 in the pre-emptive study group compared to 1.58–2.48 in the preventive study group.

The VASOF in the pre-emptive study group was significantly lower in four time periods (4, 8, 12, and 24 h) compared to the corresponding rates in the preventive group ($P = 0.0146$, 0.0188, 0.0085, and 0.0001, respectively; Table 2).

Table 1. Demographic data and total intraoperative paracetamol and fentanyl.

Group	Pre-emptive (n = 28)	Preventive (n = 27)	P-value
Age (years)	4.59 ± 1.48	4.52 ± 1.06	*0.8222
Weight (kg)	16.41 ± 3.84	17.55 ± 4.14	*0.1901
Gender			
Male (%)	17 (59)	18 (69)	†0.4120
Female (%)	11 (41)	9 (31)	
Total intraoperative analgesia			
IV Paracetamol (mg)	247.8 ± 58.5	271.4 ± 67.1	*0.1194
IV Fentanyl (µg)	32.9 ± 7.3	35.4 ± 8.5	*0.1989

Values are presented as mean ± SD.

P-value by *Kruskal–Wallis test or †chi-square test.

P < 0.05 (significant).

Pain management in PACU

The percentage of children who received fentanyl postoperatively in PACU in the pre-emptive study group (27.6%) was significantly lower compared to 58.6% of the children in the preventive study group ($P = 0.0170$; Table 3).

The total amount of postoperative rescue fentanyl received in the PACU by children in the pre-emptive group (median: 5 µg; range: 5–10 µg) was significantly lower than administered in the preventive group (median: 15 µg; range: 5–20 µg, $P = 0.0017$; Table 3).

Median time to receive the first postoperative rescue dose of fentanyl in PACU in the pre-emptive group, 70 min (range: 10–120 min) was significantly later than in the preventive group, 25 min (range: 0–120 min, $P = 0.0432$; Table 3).

Treatment with pain relief at home

In the preventive study group, 37.9% received pain relief at home compared to 13.8% in the

Table 3. Pain management data comparison between pre-emptive and preventive groups.

Group	Pre-emptive (n = 28)	Preventive (n = 27)	P-value
Children received fentanyl in PACU (%)	7 (27.6)	15 (58.6)	†0.0170*
Total IV fentanyl in PACU (µg)	6.6 ± 2.3	13.2 ± 4.7	‡0.0017**
Time of first fentanyl in PACU (min)	70.6 ± 37.3	37.1 ± 28.6	‡0.0432*
Treated with pain relief at home (%)	4 (13.8)	10 (38.0)	§0.0700

Values are presented as mean ± SD.

P-value by ‡Kruskal–Wallis rank test or †chi-square test; or §Fisher's exact test.

* $P < 0.05$ (significant) ** $P < 0.01$ (significant).

pre-emptive study group. The difference was nearly significant ($P = 0.0700$; Table 3).

Side effects

Only one child had nausea in the pre-emptive group. In the preventive group, only one child had a fever. There were no other reported side effects in both groups.

Discussion

This study on children undergoing the same dental procedures under GA, demonstrated significantly lower VASOF pain scores (in four time periods) postoperatively among children in the pre-emptive group, receiving IV paracetamol analgesia before treatment, compared to children in the preventive group, receiving analgesia at the end of treatment.

An additional indication to the efficacy of the pre-emptive modality in this study was demonstrated by the higher percent of

Table 2. VASOF values of the pre-emptive and preventive groups.

Time (h)	Arriving in PACU	2 h	4 h	8 h	12 h	24 h
Pre-emptive	1.14 ± 1.16	1.48 ± 1.50	1.55 ± 1.33	1.66 ± 1.34	1.45 ± 1.27	0.76 ± 1.27
Preventive	1.58 ± 1.31	2.03 ± 1.02	2.48 ± 1.21	2.45 ± 1.27	2.21 ± 1.11	2.24 ± 1.30
P-value	†0.078	†0.0985	†0.0146*	†0.0188*	†0.0085**	†0.0001**

Values are presented as mean ± SD.

P-value by †Kruskal–Wallis rank test.

* $P < 0.05$ (significant) ** $P < 0.01$ (significant).

VASOF, visual analog scale of faces.

children in the preventive group (58.6%) administered higher total supplemental fentanyl at the postoperative period for pain control in PACU, as compared to 27.6% of children in the pre-emptive group. Moreover, the first dose of rescue pain medication required was significantly later in the pre-emptive study group.

There is a significant variability in the reported rates of children who experienced pain and were treated for pain after dental treatment, possibly related to the different study designs, such as method of pain assessment, age and medical status of the children, use/nonuse of local anesthesia. Whether pre-emptive or the preventive treatment was administered pre-/intra- or post-dental treatment and types of procedures performed, in addition to the accuracy of the pain evaluation used by their parents²².

The rates of children who experienced a moderate degree of pain intensity in the preventive group in our study (58.6%) were comparable with previous reports on postoperative pain ranging between 36% and 93%, in children after dental treatment under GA^{23,24}. Nonetheless, in our study only 27.6% of the children in the pre-emptive group required postoperative pain relief.

This study indicated that the timing of the administered IV paracetamol is very significant and demonstrated that administering paracetamol before the start of the dental treatment, which is considered a pre-emptive analgesic approach, had a better effect on pain intensity and analgesic requirement at the fourth hour and follow-up in hospital and furthermore, a lower number of children experienced pain at home compared to administering the same analgesic agent at the end of the dental treatment.

Similar results were shown in other studies in pediatric patients undergoing oral surgery with the use of preoperative paracetamol. Baygin *et al.*⁸ showed that pre-emptive use of oral paracetamol compared to placebo extended the onset of postoperative pain, lowered its intensity, and decreased the need for postoperative analgesics, after primary tooth extraction in children. Romej *et al.* investigated the effect of preoperative orally

administered acetaminophen *versus* postoperative rectal acetaminophen showing that the preoperative group required less rescue morphine doses than patients given rectal acetaminophen, after tonsillectomy procedure. They concluded that pre-emptive acetaminophen is a safe, quick, and inexpensive intervention that can readily be incorporated into anesthesia and may enhance analgesia in pediatric tonsillectomy patients²⁵. Moreover, in this study we used paracetamol intravenously which has a more rapid onset and peak effect of 15 min or less compared to the late peak affect achieved after 1 h with oral or rectal paracetamol administration¹⁵.

Our study illustrates that the pre-emptive use of IV paracetamol delayed the onset time of increased pain intensity and pain analgesic requirement with a median of 70 min compared to 25 min in the preventive group. This finding was interesting and comparable to results by Reuben *et al.*²⁶ who demonstrated that patients in the pre-incisional rofecoxib group tolerated a longer time period before taking postoperative analgesics, compared with patients who received rofecoxib at post-incisional time or placebo ($P < 0.0001$).

This study performed in the same pediatric population undergoing similar surgical trauma intensity has demonstrated, using a unique definitive pre-emptive study design attesting to the positive pre-emptive effect of paracetamol. One possible explanation is its mechanism of action through the serotonergic pain pathway, which interrupts continuous pain firing from the surgical site, thus preventing both peripheral and central pain sensitization²⁷.

Another important issue in this study is the well-documented finding that acute pain in children is often inadequately assessed and treated, for different reasons, at home. Previous reports showed that close to 50% of pediatric surgical patients experienced moderate to severe postoperative pain; however, only 33% of these patients had received sufficient analgesia from their parents at home²⁸.

In this study, VASOF (at 8, 12, 24 h) was significantly higher at home, in the preventive group and correspondingly 37.9% *vs* 13.8% ($P = 0.0700$) of children in preventive

versus pre-emptive group, respectively, received pain relief at home. This also, however, indicates that there is a discrepancy between the pain intensity experienced by the child at home and the insufficient pain relief treatment given by the parent at home.

The pros and cons of this form of regime must take into consideration the risk of complications as well as the cost of the agent used. Conventional NSAIDs may be associated with serious unwanted effects (such as bleeding or renal impairment) when used perioperatively²⁹, whereas the anti-inflammatory and analgesic properties of paracetamol have no reports on these adverse events and also are without narcotic-related side effects (e.g., drowsiness, constipation, respiratory depression). These pharmacological characteristics show an advantage in ambulatory dent-alveolar surgical patients, particularly in treatment of mild to moderate pain, and thus can be proposed as an alternative to conventional NSAIDs.

The limitations of this study include the lack of comparison of both groups with placebo and an evaluation of either the pre-emptive effect or side effects with a placebo group.

In conclusion, the timing of administering IV paracetamol before dental rehabilitation (pre-emptive approach) performed under GA may attenuate painful stimulus intensity in the pediatric dental setting, both in hospital and at home, as well as decrease rates of postoperative opioids analgesia and reduce analgesic requirement at hospital, as compared to its preventive administration at the end of the treatment. Based on these findings, further studies are warranted comparing both approaches with a placebo group, to assess pain relief and adverse events in children, also after discharge at home, and means to instruct parents to provide appropriate pain relief treatment at home.

Disclosures

Approval of the local Institute's. Ethical Committee of Bnai-Zion Medical Center, Haifa, Israel (No. 23-15), ClinicaTrial.gov ID NCT02884921 and parental informed consent obtained for each patient.

Why this paper is important for pediatric dentists

- The pre-emptive use of intravenous paracetamol before the start of dental rehabilitation under GA may attenuate painful stimulus intensity and decrease total dosage of pain medication requirements at hospital, compared to its preventive effect.
- The pre-emptive approach delayed the onset of increased pain intensity and time to first rescue analgesia and reduced the rate of children who required postoperative opioid analgesia thus minimizing opioid side effects.
- Despite significantly lower pain intensity scores reported in the pre-emptive group after child discharge home, there were no significant differences in percent of children who received pain relief at home between the two groups. This might indicate discrepancies between pain intensity levels and parent's response at home.

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Conflict of interest

The authors declared that they have no conflict of interest.

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Author contributions

J.K., B.P., S.B., and M.S. conceived the ideas, analyzed the data and led the writing; N.H., S.B., M.N., M.S., A.S., Y.S, and A.K. collecting data and analyzed the data.

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