

Efficacy of Preemptive Analgesia on Postoperative Pain Control in Children Who Underwent Full-Mouth Dental Rehabilitation Under General Anesthesia: A Randomized Controlled Clinical Trial

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Aims: To evaluate the efficacy of intravenous preemptive analgesia on postoperative pain in children undergoing dental rehabilitation under general anesthesia. **Methods:** In this prospective randomized clinical trial, 70 children aged 3 to 7 years were scheduled for dental treatment and randomized into two groups: the control group or the preemptive group. Patients received 15 mg/kg of intravenous paracetamol either before the start of treatment (preemptive group, n = 35) or at the end of treatment (control group, n = 35). Postoperative pain scores were recorded at 1, 2, 4, 6, 8, 12, and 24 hours using the Wong-Baker FACES Pain Rating Scale (WBFS). Additionally, the need for rescue analgesic and the total opioid consumption of the patients were recorded during the first 24 hours postoperative. **Results:** The pain scores in the preemptive group were significantly lower than those in the control group at the postanesthesia care unit and at 2, 4, and 8 hours postoperative ($P < .05$). However, there were no statistically significant differences in pain scores between groups at 12 and 24 hours postoperative. Need for rescue analgesics and total intravenous fentanyl consumption were significantly higher in the control group than in the preemptive group ($P < .05$). The percentage of children who received medication for pain relief at home was higher in the control group than in the preemptive group, but the difference was not statistically significant ($P > .05$). **Conclusion:** Preemptive use of intravenous paracetamol reduces postoperative pain scores and postoperative opioid consumption. However, there is a need to evaluate pain levels in children who receive comprehensive dental treatment under general anesthesia after hospital discharge for effective postoperative pain control. *J Oral Facial Pain Headache* 2021;35:297–302. doi: 10.11607/ofph.2960

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Dental general anesthesia (DGA) is an outpatient procedure that is frequently used by pediatric dentists to provide dental care for young children who show limited cooperation for complicated dental procedures in routine clinical settings.¹ DGA provides a satisfactory clinical environment for performing high-quality dental treatment that can be completed in a single treatment session.¹ Many studies have shown that DGA highly improves oral health-related quality of life (OHRQoL) and body growth in young children.^{2–4} Despite the many advantages of general anesthesia, such as providing safe, painless, and efficient dental care for young children, the anesthetic procedure does have some morbidity and mortality.

Postoperative pain remains the most common morbidity during recovery after dental treatment procedures under general anesthesia.⁵ Effective postoperative pain management may be beneficial for decreasing adverse outcomes such as chronic pain, increased recovery time, and health care costs.⁶ There have been many efforts to control postoperative pain, such as using systemic analgesics during and after the operation and intraoperative topical and local analgesic usage in children.^{7,8} Opioid and nonopioid analgesics are the most frequently used agents for postoperative pain control in pediatric patients. They are usually administered orally and intravenously on a per-demand basis or through patient-controlled analgesia.⁶

Preemptive analgesia is a postoperative pain control method defined as an antinociceptive approach that starts before surgery and prevents the establishment of central sensitization caused by incisional and inflammatory injuries.⁶ Many studies have evaluated the efficacy of preemptive analgesia on postoperative pain in adults and children in various fields of medicine.^{6,9,10} However, there are limited data on preemptive analgesia for postoperative pain control in children receiving comprehensive dental treatment under general anesthesia.⁸

Paracetamol, also known as acetaminophen, is a nonopioid agent that acts primarily on the central nervous system by inhibiting central cyclooxygenase (COX) in the brain, which is highly selective for COX-2 and likely acts through indirect serotonergic pathways.¹¹ The intravenous (IV) formulation of paracetamol is commonly prescribed in pediatrics and widely used as an antipyretic and analgesic agent for the control of fever and acute pain in children. The onset of analgesia and antipyretic action with IV paracetamol is 15 and 30 minutes, respectively.¹² Furthermore, studies have been conducted on the efficacy of paracetamol administered before the start of surgery for postoperative pain control. Kharouba et al⁸ reported that administration of preemptive IV paracetamol resulted in lower pain scores, decreased the need for pain-relieving medications at home, and reduced opioid consumption at the hospital. Contrarily, Song et al⁶ determined that preemptive analgesia using IV paracetamol analgesia with fentanyl provided no advantage for postoperative pain control after corrective osteotomy in pediatric patients.

There is no consensus in the literature regarding the management of postoperative pain in pediatric patients undergoing various types of surgical procedures. The demand for comprehensive dental treatment under general anesthesia for uncooperative children is increasing day by day.¹³⁻¹⁵ Numerous painful dental procedures, including extraction, pulpotomy, pulpectomy, and placement of stainless steel crowns, are performed in patients in a single session.⁵ Thus, it is important to establish a protocol to effectively control postoperative pain in these patients. For this reason, the present study was conducted (1) to assess the efficacy of preemptive IV analgesia for postoperative pain control in children receiving comprehensive dental treatment under general anesthesia and (2) to determine the postoperative analgesic need at hospitals and homes in the same patient population.

Materials and Methods

Sample Size

A power analysis was performed a priori based on a previous study⁸ to determine the minimum sample size. Assuming an α error of .05, a power of 80%, and a dropout rate of 10%, the required sample size was 35 for each group.

Subjects and Clinical Examinations

This randomized controlled clinical study was approved by the Inonu University ethical committee (2019/18) and conducted in accordance with the guidelines of the Declaration of Helsinki. The study protocol was explained to the children's parents, and written informed consent was obtained. The study was registered (Protocol Registration Receipt NCT03852602) at <http://www.clinicaltrials.gov>. Ninety children were evaluated for eligibility. All children were examined by the same pediatric dentist (S.K.) considering the inclusion and exclusion criteria. The inclusion criteria were as follows: aged between 3 and 7 years; no cooperation with the pediatric dentist according to the Frankl behavior rating scale¹⁶ in the dental clinic; and having a need for comprehensive dental treatment including at least one tooth extraction and/or vital endodontic therapy, fillings, stainless steel crowns, space maintainers, or preventive care. The exclusion criteria were: having any other known systemic chronic diseases; allergy to opioid analgesics or general anesthetics; postoperative intensive care unit admission; and renal or hepatic insufficiency.

Twenty of the children were not eligible, and so 70 children participated in this study at the Department of Pediatric Dentistry, Faculty of Dentistry, Aydin Adnan Menderes University, Aydin, Turkey, between February and December 2019.

Study Design

Randomization. Patients were randomized into the control group or the preemptive group via computer-generated randomization. Group allocation was performed using sequentially numbered, opaque, and sealed envelopes. Each envelope included the group allocation and the instructions for the anesthetist in the operating room. All patients underwent the same anesthesia protocol with the same anesthetist (O.K.).

The preemptive group received 15 mg/kg IV paracetamol (Paracerol, Polifarma) in 50 mL of saline 15 minutes before the start of the dental treatment. The control group received 15 mg/kg IV paracetamol in 50 mL of saline at the end of the dental treatment. All analgesic drugs used in the study were administered by a staff nurse who was not assigned to the postanesthesia care unit.

General Anesthesia Procedure

All patients in the study group were intubated by the same blinded anesthetist, who has more than 10 years of experience (O.K.). Anesthesia induction was carried out via a face mask with 8% sevoflurane in 100% oxygen, and an IV line was established through which propofol 1% (Propofol-Lipuro, B. Braun Melsungen) 2 mg/kg; fentanyl (Talinat, VEM) 1 µg/kg; and rocuronium (Myocron, VEM) 0.5 mg/kg were administered via nasotracheal intubation. Patients were monitored during the operation with an anesthesia monitor (Dräger Fabius Plus, Dräger). Anesthesia was maintained with sevoflurane 2% in a mixture of 50% oxygen and nitrous oxide. Patients were extubated and transferred to the postanesthesia care unit (PACU) when they were fully awake.

Dental Treatment Procedure

All dental procedures were performed by the same pediatric dentist (S.K.) during the same treatment session. Decayed teeth underwent either restorative (compomer resin, composite resin) or endodontic (pulpotomy, pulpectomy) procedures. Teeth that could not be restored were then extracted. The decayed, missing, and filled teeth index (DMFT index) of the patients, duration of the dental operation, and duration of anesthesia were recorded.

Postoperative Pain Evaluation

The patients' pain levels were assessed using the Wong-Baker FACES scale,¹⁷ which has been validated for children aged 3 to 7 years. This scale includes six cartoon faces corresponding to scores 0 to 5 (0 = does not hurt; 1 = hurts a little bit; 2 = hurts a little more; 3 = hurts even more; 4 = hurts a whole lot; 5 = hurts worst). Pain levels were recorded upon arrival to the PACU and at 2, 4, 8, 12, and 24 hours postoperative by a blinded investigator (O.K.). In case the patient's postoperative pain score was ≥ 2 ⁸ (moderate to severe pain), the patient was medicated with IV fentanyl (1 µg/kg), which was recorded as a need for rescue analgesic.

Children were discharged from the hospital when their Steward discharge score, which evaluates consciousness, airway, and movements, was ≥ 6 .¹⁸ The parents were asked to grade their satisfaction levels with their child's recovery from 0 to 10 (0 = very dissatisfied; 10 = very satisfied).

Parents were instructed how to use the Wong-Baker FACES scale, when to administer pain medication with oral paracetamol, and to record pain scores and medication administration time on a chart constructed for this study.

The parents were asked about side effects during the postoperative period at home. Data after discharge from the hospital were obtained from parents

via phone calls by a researcher who was blinded to the study groups (P.D.).

Statistical Analysis

Continuous variables were tested for normality using Shapiro-Wilk test. Normally distributed data were expressed as mean \pm SD and analyzed using Student *t* test or a repeated-measures general linear model. Categorical variables are presented as numbers or percentages and were analyzed using chi-square test. All statistical analyses were performed at a significance level of $P < .05$ using SPSS software version 20.0 (IBM).

Results

Demographic and Perioperative Characteristics

Seventy children aged between 3 and 7 years (35 children in each group) were enrolled in this study. There was no loss to follow-up or adverse events during the study period (Fig 1). There were no statistically significant differences between the demographic and perioperative clinical variables (total intraoperative IV paracetamol and fentanyl) of the groups ($P > .05$; Table 1). The recovery times and dmft values of the groups were comparable ($P > .05$; Table 1). Additionally, there were no statistically significant differences between groups in terms of the dental procedures performed ($P > .05$) or the scores for satisfaction with their child's recovery given by parents ($P > .05$).

Postoperative Pain Assessment

The pain scores in the preemptive group were significantly lower than those in the control group upon arrival at the PACU and at 2, 4, and 8 hours postoperative ($P < .05$; Table 2). There were no statistically significant differences in pain scores between the groups at 12 and 24 hours postoperative at home.

Analgesic Requirements at Hospital and Home

The need for rescue analgesic was significantly lower in the preemptive group than in the control group at the hospital (11.4% vs 34.3%, $P < .05$; Table 2).

There were significant differences between the preemptive group and the control group in terms of total IV fentanyl consumption during the hospital stay (2.14 ± 6.50 vs 5.65 ± 8.05 µg/kg, $P < .05$; Table 2). Furthermore, there was a statistically significant difference between the two groups in terms of the time until the first fentanyl administration in the hospital (51.05 ± 17.7 vs 61.88 ± 19.32 minutes for control vs preemptive, respectively, $P < .05$; Table 2). The number of patients who received analgesic medication at home was lower in the preemptive group than

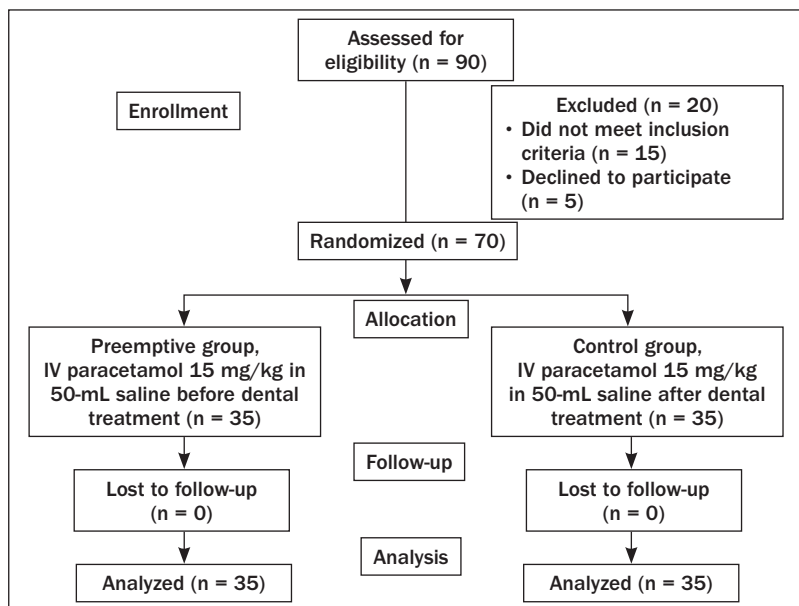


Fig 1 CONSORT (Consolidated Standards of Reporting Trials) flowchart of patient recruitment and follow-up.

Table 1 Comparison of Demographic Data and Perioperative Clinical Variables Between Groups

	Control (C)	Preemptive (P)	P
Age (y)	4.87 ± 1.59	4.72 ± 1.51	0.729
Weight (kg)	18.41 ± 4.29	18.80 ± 5.67	0.791
Gender (male/female), n	23/12	21/14	0.800
ASA classification (I/II), n	28/7	30/5	0.752
Intraoperative IV paracetamol (mg)	273.33 ± 66.24	282.0 ± 85.07	0.693
Intraoperative IV fentanyl (µg)	20.58 ± 5.02	28.84 ± 44.41	0.370
Duration of anesthesia (min)	63.91 ± 18.46	63.04 ± 25.11	0.890
Duration of operation (min)	50.91 ± 18.64	56.0 ± 22.68	0.397
Recovery time (min)	10.20 ± 2.34	9.72 ± 1.98	0.435
dmft	11.83 ± 3.22	11.73 ± 3.30	0.924

Data are reported as mean ± SD unless otherwise indicated. ASA = American Society of Anesthesiologists; dmft: decayed, missing, filled teeth; IV = intravenous.

Table 2 Comparison of Postoperative Pain Scores, Postoperative Pain Management Data, and Parental Satisfaction Levels Between Groups

	Control	Preemptive	P ^a
<i>Postoperative pain scores</i>			
Upon arrival in PACU	1.08 ± 1.34	0.28 ± 0.54	.008^a
2 h	0.37 ± 0.82	0.01 ± 0.01	.027^a
4 h	0.33 ± 0.70	0.08 ± 0.27	.020^a
8 h	0.70 ± 1.12	0.08 ± 0.40	.030^a
12 h	0.37 ± 0.82	0.04 ± 0.20	.064
24 h	0.40 ± 0.76	0.20 ± 0.50	.309
Need for rescue analgesic, n (%)	12 (34.3)	4 (11.4)	.044^c
Total IV fentanyl in hospital, µg/kg	5.65 ± 8.05	2.14 ± 6.50	.044^a
Time to first fentanyl in hospital, min	51.05 ± 17.7	61.88 ± 19.32	.017^a
Need for analgesic at home, n (%)	17 (48.6)	9 (25.7)	.082 ^c
Parent satisfaction level (0–10)	8.94 ± 1.37	9.02 ± 1.04	.769
P value ^b	.012	.015	–

Data are reported as mean ± SD unless otherwise indicated. Significant values are indicated in bold. PACU = postoperative care unit; IV = intravenous.

^aStudent t test.

^bRepeated-measures general linear model for intragroup postoperative pain comparisons upon arrival in PACU and 2, 4, 8, 12, and 24 hours postoperative.

^cChi-square test.

in the control group, but this difference was not statistically significant (respectively, 25.7% vs 48.6%, *P* > .05; Table 2).

Discussion

This prospective randomized controlled clinical trial evaluated the effect of preemptive analgesia on postoperative pain scores, need for rescue analgesic, and need for analgesic at home in children who underwent full-mouth dental rehabilitation under general anesthesia. Children who received 15 mg/kg IV paracetamol before dental treatment demonstrated significantly lower pain scores up to 8 hours postoperative compared to the control group, but not at 12 and 24 hours postoperative. Need for rescue analgesic was significantly higher in the control group than in the preemptive group. Additionally, need for analgesic at home during the postoperative 24 hours was not significantly different between groups.

In the literature, there is a wide range of variability in pain scores reported after dental treatment in children. The discrepancies between the studies may be due to the different study designs, such as pain assessment, type of dental procedure, age, medical status of children, and use/non-use of local anesthesia. Kharouba et al⁸ reported that 27.6% of the children in their preemptive group experienced moderate pain (≥ 2; according to WBFS) after dental rehabilitation; however, the percentage of children who experienced a moderate degree of pain intensity in the present study was lower (11.4% in the preemptive group). These differences between the pain scores of the studies may have resulted from the use of local anesthesia and the different dental treatment procedures performed under general anesthesia. In the study group of the present study, children received at least one painful dental procedure, such as tooth extraction and/or vital endodontic therapy, fillings, and stain-

less steel crowns, and local anesthesia was administered before the painful dental procedures. The use of local anesthesia might have contributed to reducing the postoperative pain intensity in the early postoperative period, which is different from the study by Kharouba et al.⁸ Furthermore, Kharouba et al⁸ performed only restorative or preventive procedures, in contrast to the present study. Keles and Kocaturk⁵ compared the postoperative pain scores of children who received only restorative treatment and those who received at least one primary molar pulpotomy under general anesthesia¹⁹ and reported that the postoperative pain scores were significantly higher in the children who received pulpotomy treatment.

Opioids are the most commonly used drugs for the control of moderate to severe pain at any age. They provide good pain relief with a wide confidence interval and should be used with caution in children younger than 2 months due to a high risk of respiratory depression.²⁰ It is possible to administer opioids intramuscularly, intravenously, or subcutaneously in children. The IV route is the most commonly used; however, opioids have side effects such as nausea, vomiting, urinary retention, hallucinations, somnolence, dizziness, and intestinal obstruction.²⁰ Considering these side effects, there are many efforts to decrease opioid consumption in children.^{21–23} In the present study, 1 µg/kg IV fentanyl was used as the rescue analgesic for moderate to severe postoperative pain.

Studies evaluating the effect of preemptive analgesia on opioid consumption concluded that total consumption of analgesics was a better parameter than the time to first rescue analgesic requirement.^{24,25} In the present study, both parameters were evaluated, as well as the analgesic requirements of the groups at home. Opioid consumption in the preemptive group was significantly lower than in the control group. Moreover, the time to rescue analgesic was longer in the preemptive group, which is in agreement with previous studies.⁸ However, the percentage of children medicated with an analgesic at home was higher in the control group, although there was no statistically significant difference (48.6% in the control group vs 25.7% in the preemptive group). Contrary to these results, Cicvaric et al²⁶ stated that preemptive analgesia with paracetamol infusion was proven to be efficient in terms of postoperative pain control, but did not reduce the overall analgesic administration in children who underwent elective herniorrhaphy. The main reason for the difference between these two studies may be the procedure type conducted under general anesthesia.

Previous studies revealed that parental satisfaction levels related to their child's treatment periods were affected by parameters such as postoperative pain, emergency delirium, and side effects observed in patients during the follow-ups at the hospital and

home.^{27–31} Kocaturk and Keles²⁸ compared the parental satisfaction levels of children who underwent full-mouth dental rehabilitation under propofol- vs sevoflurane-based anesthesia, and propofol resulted in decreased postoperative pain compared to sevoflurane. The parental satisfaction level was higher in the propofol-based anesthesia group compared to the sevoflurane-based anesthesia group due to the lower emergency delirium and pain scores that were observed for the propofol-based anesthetic technique. Contrary to this literature, parental satisfaction levels in the present study were similar in both groups. This could be attributed to the lower pain scores in both groups and the multimodal pain control strategy, including the combination of local anesthesia with preemptive or preventive analgesia in this study.

This study has some limitations. First, there was no placebo group for comparison to the control and preemptive groups; however, not providing analgesia to some patients would have been unethical. Second, the pain score assessment performed at home relied on parents or caregivers; to overcome this problem, the parents were instructed on how to score the pain, and only parents who could perform this scoring successfully were included.

The present results revealed that preemptive analgesic application might have a significant benefit in the DGA setup. However, this might be different from team to team, and the present results cannot be generalized because there may be individually indicated analgesic needs. The findings of this study require further investigation to clarify the effectiveness of preemptive analgesic in young children receiving comprehensive dental rehabilitation under DGA.

Conclusions

This study suggests that children who received IV paracetamol before the start of dental treatment under general anesthesia required less rescue analgesics at follow-up in the hospital. Moreover, a lower number of children received analgesics at home in the preemptive group compared to the control group, although there was no statistically significant difference. Based on these results, it can be concluded that preemptive analgesia provided a comfortable immediate postoperative period, which is vital during recovery in young children and for their parents and/or caregivers.

Clinical Implications

- Postoperative pain control is an important issue in young children receiving full-mouth dental rehabilitation under general anesthesia.

- Preemptive use of IV paracetamol may provide a comfortable postoperative period for children undergoing comprehensive dental treatment under general anesthesia.

Acknowledgments

This study was approved by the Adnan Menderes University Faculty of Dentistry Clinical Investigations Ethics Committee. Informed consent was obtained from all individual participants and from their parents and caregivers. This study did not use any funding. The authors report no conflicts of interest.

Author contributions: S.K. conceived the ideas; S.K., O.K., and P.D. collected the data; S.K., O.K., and P.D. analyzed the data; and S.K. led the writing.

References

- Jiang HF, Qin D, He SL, Wang JH. OHRQoL changes among Chinese preschool children following dental treatment under general anesthesia. *Clin Oral Investig* 2019;24:1997–2004.
- Ferrazzano GF, Sangianantoni S, Mitrano RL, Ingenito A, Alcidi B, Cantile T. Assessing changes in oral health-related quality of life and body growth in 3-5 years old children following dental treatment under general anaesthesia due to severe dental caries. *Eur J Paediatr Dent* 2019;20:214–218.
- Grant CG, Daymont C, Rodd C, et al. Oral health-related quality of life of Canadian preschoolers with severe caries after dental rehabilitation under general anesthesia. *Pediatr Dent* 2019;41:221–228.
- Collado V, Pichot H, Delfosse C, Eschevins C, Nicolas E, Hennequin M. Impact of early childhood caries and its treatment under general anesthesia on orofacial function and quality of life: A prospective comparative study. *Med Oral Patol Oral Cir Bucal* 2017;22:333–341.
- Keles S, Kocaturk O. Immediate postoperative pain and recovery time after pulpotomy performed under general anaesthesia in young children. *Pain Res Manag* 2017;2017:9781501.
- Song IK, Park YH, Lee JH, Kim JT, Choi IH, Kim HS. Randomized controlled trial on preemptive analgesia for acute postoperative pain management in children. *Pediatr Anesth* 2016;26:438–443.
- Leong KJ, Roberts GJ, Ashley PF. Perioperative local anaesthetic in young paediatric patients undergoing extractions under outpatient 'short-case' general anaesthesia. A double-blind randomised controlled trial. *Br Dent J* 2007;203:e11.
- Kharouba J, Hawash N, Peretz B, 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* 2018;28:83–91.
- Kim DH, Kim N, Lee JH, Jo M, Choi YS. Efficacy of preemptive analgesia on acute postoperative pain in children undergoing major orthopedic surgery of the lower extremities. *J Pain Res* 2018;11:2061–2070.
- 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* 2014;4:e15049.
- Nahum E, Friedman M, Kaplan E, Weissbach A, Kadmon G. The hemodynamic effect of intravenous paracetamol in children: A retrospective chart review. *Pediatric Drugs* 2019;21:177–183.
- Khalili GR, Shafa A, Yousefi R. Comparison of the effects of preemptive intravenous and rectal acetaminophen on pain management after inguinal herniorrhaphy in children: A placebo-controlled study. *Middle East J Anaesthesiol* 2016;23:543–548.
- Schroth R J, Quiñonez C, Shwart L, Wagar B. Treating early childhood caries under general anesthesia: A national review of Canadian data. *J Can Dent Assoc* 2016;82:g20.
- Meyer BD, Lee JY, Casey MW. Dental treatment and expenditures under general anesthesia among Medicaid-enrolled children in North Carolina. *Pediatr Dent* 2017;39:439–444.
- Knapp R, Gilchrist F, Rodd HD, Marshman Z. Change in children's oral health-related quality of life following dental treatment under general anaesthesia for the management of dental caries: A systematic review. *Int J Paediatr Dent* 2017;27:302–312.
- Frankl S, Shiere F, Fogels H. Should the parent remain with the child in the dental operator? *J Dent Child* 1962;29:150–163.
- Wong DL, Baker CM. Pain in children: Comparison of assessment scales. *Pediatr Nurs* 1988;14:9–17.
- Steward DJ. A simplified scoring system for the post-operative recovery room. *Can Anaesth Soc J* 1975;22:111–113.
- El Batawi HY. Lidocaine use for pain management during paediatric dental rehabilitation under general anaesthesia. *Eur Arch Paediatr Dent* 2013;14:381–387.
- Thigpen JC, Odle BL, Harirforoosh S. Opioids: A review of pharmacokinetics and pharmacodynamics in neonates, infants, and children. *Eur J Drug Metab Pharmacokinet* 2019;44:591–609.
- Pruitt LCC, Swords DS, Russell KW, Rollins MD, Skarda DE. Prescription vs. consumption: Opioid overprescription to children after common surgical procedures. *J Pediatr Surg* 2019;54:2195–2199.
- D'Souza G, Wren AA, Almgren C, Ross AC, Marshall A, Golianu B. Pharmacological strategies for decreasing opioid therapy and management of side effects from chronic use. *Children (Basel)* 2018;5:163.
- Dervan LA, Yaghmai B, Watson RS, Wolf FM. The use of methadone to facilitate opioid weaning in pediatric critical care patients: A systematic review of the literature and meta-analysis. *Pediatr Anesth* 2017;27:228–239.
- Shen X, Wang F, Xu S, et al. Comparison of the analgesic efficacy of preemptive and preventive tramadol after lumpectomy. *Pharmacol Rep* 2008;60:415–421.
- Helenius LL, Oksanen H, Lastikka M, et al. Preemptive pregabalin in children and adolescents undergoing posterior instrumented spinal fusion: A double-blinded, placebo-controlled, randomized clinical trial. *J Bone Joint Surg* 2020;102:205–212.
- Cicvaric A, Divkovic D, Tot OK, Kvolik S. Effect of pre-emptive paracetamol infusion on postoperative analgesic consumption in children undergoing elective herniorrhaphy. *Turk J Anaesthesiol Reanim* 2018;46:197–200.
- Uezono S, Goto T, Terui K, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. *Anesth Analg* 2000;91:563–566.
- Kocaturk O, Keles S. Recovery characteristics of total intravenous anesthesia with propofol versus sevoflurane anesthesia: A prospective randomized clinical trial. *J Pain Res* 2018;11:1289–1295.
- Keles S, Kocaturk O. Postoperative discomfort and emergence delirium in children undergoing dental rehabilitation under general anesthesia: Comparison of nasal tracheal intubation and laryngeal mask airway. *J Pain Res* 2018;11:103–110.
- Pieters BJ, Penn E, Nicklaus P, Bruegger D, Mehta B, Weatherly R. Emergence delirium and postoperative pain in children undergoing adenotonsillectomy: A comparison of propofol vs sevoflurane anesthesia. *Pediatr Anesth* 2010;20:944–950.
- Chandler JR, Myers D, Mehta D, et al. Emergence delirium in children: a randomized trial to compare total intravenous anesthesia with propofol and remifentanyl to inhalational sevoflurane anesthesia. *Pediatr Anesth* 2013;23:309–315.