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A COMPARISON OF THE EFFECTS OF PRE-EMPTIVE AND INTRAOPERATIVE INTRAVENOUS ACETAMINOPHEN ADMINISTRATION ON PAIN MANAGEMENT AFTER CIRCUMCISION

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Abstract

Aim: The aim of this study was to compare the efficacy of the pre-emptive and intraoperative use of intravenous acetaminophen in post-circumcision pain in children.

Methods: The records of patients who had undergone circumcision were retrospectively evaluated using our database in the Samsun University, Samsun Training and Research Hospital, Department of Pediatric Surgery, Turkey, from May 2021 to May 2022. Patients were divided into two groups based on administration of pre-emptive (Group 1) and intraoperative (Group 2) acetaminophen. Baseline characteristics, vital signs, outcomes, and Face, Legs, Activity, Cry, and Consolability (FLACC) scale scores were then compared between the groups.

Results: Two hundred four patients, 95 (46.6%) in Group 1 and 109 (53.4%) in Group 2, were enrolled in the study. No significant difference was determined in terms of mean body mass index, age, length of stay in the recovery room, operative time, or length of hospital stay. Vital findings exhibited no difference in preoperative, induction, intraoperative, or postoperative recordings. Significant differences were observed between the groups' mean pain scores 30 minutes after surgery ($p = 0.024$). However, no such significant differences were observed at one and three hours after surgery ($p = 0.063$ and $p = 0.708$, respectively). Rescue analgesia was performed in 13 (13.7%) cases in Group 1 and 17 (15.6%) in Group 2 ($p = 0.7$).

Conclusions: Pre-emptive intravenous acetaminophen reduced pain 30 minutes after circumcision. Pre-emptive and intraoperative use of acetaminophen resulted in similar and acceptable efficacy in pain relief one and three hours after surgery.

Keywords: *Acetaminophen, pre-emptive, circumcision, pain, analgesia, pediatrics*

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Introduction

Male circumcision involves the excision of the foreskin from the glans of the penis and is one of the most frequently performed surgical procedures worldwide[1]. However, in common with all surgical procedures, circumcision is a painful event. Post-operative pain is the most frequent side-effect of circumcision, and this and the complications there of are a source of concern on the part of surgeons and anesthesiologists[2]. Increasing awareness of the problem and endeavors to improve pain management in children, both intra- and postoperatively, led to the publication of guidelines in 2018 by the European Society for Paediatric Anaesthesiology Pain Committee[3].

Pre-emptive analgesia, the administration of analgesic medications prior to surgical incision, has been recommended under various surgical conditions by numerous studies. However, the efficacy of pre-emptive analgesia remains unknown, although the results of clinical trials in humans have consistently described it as beneficial[4]. The pre-emptive approach entails the management of pain before it actually occurs, the objective being to minimize postoperative pain by disrupting afferent input. The most efficacious pre-emptive agents in terms of lowering central sensitization are analgesics that act on pain resulting from injuries due to incisions and related inflammation[5].

Similarly, to non-steroidal anti-inflammatory drugs, acetaminophen exhibits both central and peripheral effects. Acetaminophen is a safe analgesic and administered in different forms and by various routes. Its use is particularly recommended for postoperative pain management and in the form of a single therapy aimed at relieving mild postoperative pain without causing major adverse effects[6]. The analgesic effects of intravenous (IV) acetaminophen administration have also been widely examined, especially in children, and acetaminophen has been recommended for pre-emptive analgesia[7].

It is important to identify a cost-effective analgesic agent with acceptable pain-reducing capabilities. The pre-emptive or intraoperative use of acetaminophen can produce differing outcomes in terms of pain relief. However, no previous studies have compared the analgesic effects of these two methods. The purpose of this study was to compare the effects of pre-emptive and intraoperative IV acetaminophen administration on postoperative pain in boys after circumcision.

Materials and Methods

Two hundred four patients who underwent circumcision at the Samsun University, Samsun Training and Research Hospital, Department of Pediatric Surgery, Turkey, between May 2021 and May 2022 were included in the study.

Patient evaluation and selection

All children in the study received 15 mg kg^{-1} IV acetaminophen for pain control, either prior to circumcision (Group 1) or immediately after the incision was made (Group 2).

Inclusion criteria

- Age 1-7 years,
- Being operated using the dorsal slit technique under general anesthesia, and
- Receipt of pre-emptive or intraoperative IV acetaminophen.

Exclusion criteria

- Children aged under one year or over seven,
- Children undergoing circumcision other than with the dorsal slit technique (guillotine, sleeve resection, Plastibell, Mogen clamp, etc.),
- Patients receiving analgesic therapy other than acetaminophen,
- Patients receiving postoperative IV acetaminophen,

- Patients using analgesic, antiepileptic, or sedative drugs, and
- Patients undergoing additional procedures together with circumcision (herniorrhaphy, tonsillectomy, orchiopexy, appendectomy, etc.) were excluded from the study.

Preoperative preparation

Patients were given standard maintenance fluids, depending on their body weight. Group 1 received IV acetaminophen 30 minutes prior to circumcision.

Anesthesia management

All patients were monitored throughout the surgical procedure in terms of electrocardiography, respiratory rate, non-invasive arterial blood pressure, and pulse oximetry. General anesthesia was induced in all cases through the administration of a combination of fentanyl l-2 µg/kg and 1% propofol 2-3 mg/kg. A mixture of 50% nitrous oxide, 50% oxygen, and 2-3% sevoflurane was also employed during anesthesia. Postoperatively, the laryngeal mask was removed once the child began to breathe spontaneously, and all cases were transferred to the recovery room.

Surgical technique

The dorsal slit method was employed in all cases. This entails the separation of the adhesions between the prepuce and the glans. Artery forceps are placed at 10 and 1 o'clock, and both layers of the prepuce are then incised at the 12 o'clock position, leaving a few millimeters of skin proximal to the corona. The surgical method is described in Figure 1. Dorsal slit circumcision was performed on all children's by the same surgeon (SSB).

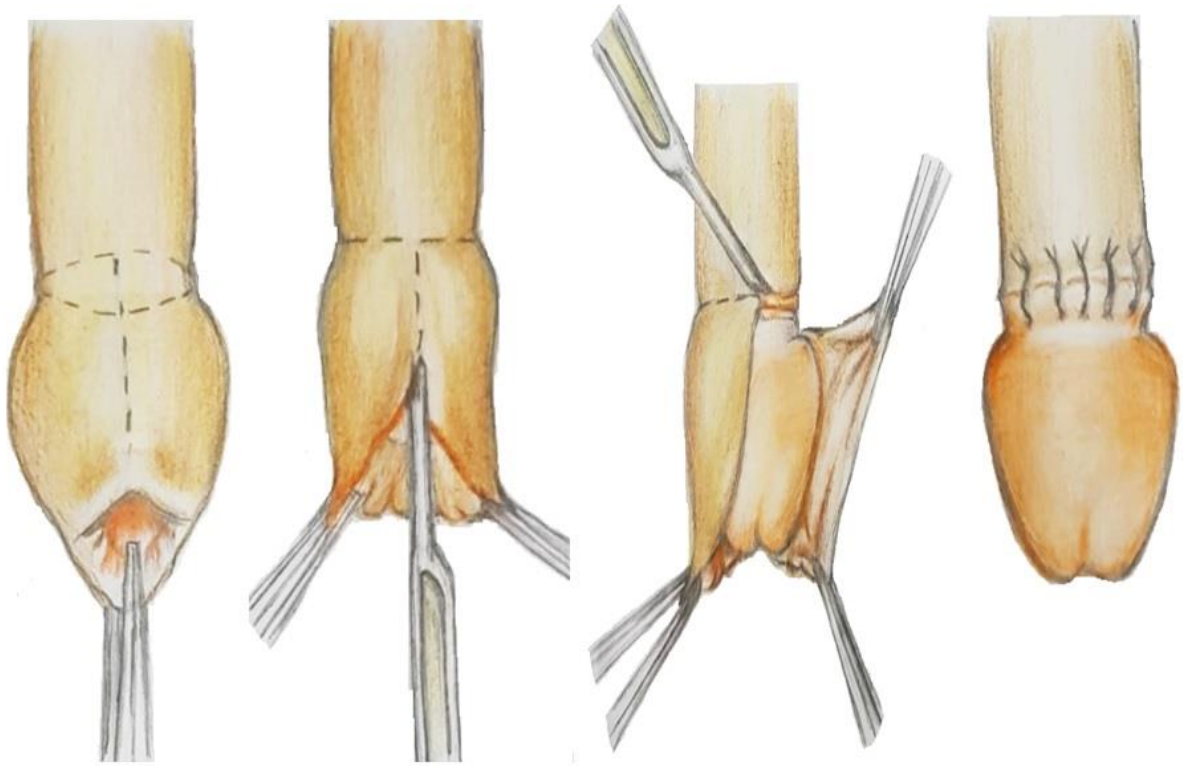

Figure 1. Technic of dorsal slit circumcision (a: The incision line is marked; b: Grasp the foreskin with two artery forceps and the foreskin is cut the dorsal midline; c: The preputial skin is resected leaving a 0.5 cm sleeve to the corona; d: Penil skin is then sutured to the coronal sleeve)

Categories	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Figure 2. Face, Legs, Activity, Cry, Consolability (FLACC) Scale

Evaluation of postoperative pain

Patient pain was assessed using the Face, Legs, Activity, Cry, Consolability (FLACC) scale. This consists of five domains (face, legs, activity, crying, and consolability), each of which is scored 0, 1, or 2, yielding a total scale score from 0 to 10 (Figure 2). Total FLAAC scores were calculated. A score of 0 is interpreted as relaxed/comfortable, 1–3 as mild discomfort, 4–6 as moderate pain, and 7–10 as severe discomfort/pain[8]. Pain scores were recorded 30 minutes, and one and three hours after surgery. Rescue analgesia (IV tramadol, 1-2 mg kg^{-1}) was administered in cases with high postoperative FLAAC scores (>4).

Data collection

Clinical data were analyzed, including body mass index (BMI), age, respiratory rate, heart rate, saturation rate, pain scores, length of stay in the recovery room, rescue analgesia requirements, operative time, and length of hospital stay.

Statistical analysis

Data analysis was performed on SPSS version 25 software (Statistical Package for Social Sciences- IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to determined normality of distribution of measurable data. Continuous data as mean ± standard deviation, and nominal data were expressed as frequencies and percentages. Nominal variables were evaluated using the Chi-square test, while the independent Samples T test was applied to determine the presence of a statistically significant difference between the two groups. A p values lower than 0.05 were regarded as significant.

Table 1. Detailed information of all patients in the study.

Variables	Group 1 (N = 95)	Group 2 (N = 109)	p value
Age (years), mean ± SD	4.1 ± 2.29	3.98 ± 2.27	0.7
Body mass index (kg/m²), mean ± SD	18.62 ± 3.06	18.22 ± 3.29	0.371
Operative time (minute), mean ± SD	26.4 ± 4.37	25.94 ± 3.76	0.426
Recovery time (minute), mean ± SD	35.4 ± 6.12	35.33 ± 5.8	0.874
Hospital stay (hour), mean ± SD	9.04 ± 0.98	9.06 ± 0.94	0.871

Abbrevation: SD, standard deviation.

Results

Two hundred four patients with a mean BMI value was 18.16 ± 3.12 kg/m^2 were included in the study. The patients' mean age of 4.03 ± 2.29 years, mean operative time was 26.15 ± 4.05 minutes, and mean length of hospital stay was 9.05 ± 0.96 hours.

No statistically significant differences were observed between the groups in terms of patient BMI, age, length of stay in the recovery room, operative time, and length of hospital stay. Patient outcomes and characteristics are presented in Table 1. Comparison of children's heart, respiratory, and saturation rates between the groups revealed no difference in preoperative, induction, intraoperative, or postoperative recordings (p >0.05). The vital findings are shown in Table 2. The groups' FLAAC values at 30 min, one hour, and three hours postoperatively were 2.22 ± 1.24 vs. 2.61 ± 1.21, 1.10 ± 0.91 vs. 1.33 ± 0.80, and 0.71 ± 1.34 vs. 0.78 ± 1.43, respectively.

Significant differences were observed between the groups' mean scores of pain immediately after 30 minutes (p = 0.024). However, no such significant differences were observed at one and three hours after surgery (p = 0.063 and p = 0.708, respectively). The detailed FLAAC scores of the groups are shown in Table 3.

During postoperative observation, rescue analgesia was not performed for the first postoperative three hours in order to evaluate the efficacy of acetaminophen administration. Rescue analgesia was applied to patients with higher FLAAC scores (FLAAC >4), 13 (13.7%) children in Group 1 and 17 (15.6%) in Group 2 (p = 0.7). Additionally, no adverse effect of acetaminophen was observed. All of the patients were discharged from the hospital after an uneventful six-hour period.

Table 2. The vital findings of patients in groups. Values are presented as mean ± standard deviation.

Variables	Group 1 (N = 95)	Group 2 (N = 109)	p value
Preoperative heart rate (beats/minutes)	128.5 ± 18.28	125.11 ± 14.99	0.148
Preoperative breath rate (breath/minutes)	24.88 ± 4.78	24.04 ± 5.30	0.24
Preoperative saturation rate (%)	99.68 ± 0.51	99.66 ± 0.49	0.738
Induction heart rate (beats/minutes)	122.21 ± 14.05	120.87 ± 16.45	0.536
Induction breath rate (breath/minutes)	25.30 ± 5.48	24.56 ± 4.85	0.31
Induction saturation rate (%)	99.87 ± 0.33	99.85 ± 0.40	0.696
Intraoperative heart rate (beats/minutes)	118.31 ± 20.26	127.45 ± 85.20	0.309
Intraoperative breath rate (breath/minutes)	24.20 ± 4.90	23.23 ± 4.61	0.151
Intraoperative saturation rate (%)	99.92 ± 0.26	99.87 ± 0.33	0.201
Postoperative heart rate (beats/minutes)	118.27 ± 11.46	118.09 ± 11.03	0.908
Postoperative breath rate (breath/minutes)	24.18 ± 4.32	23.11 ± 4.08	0.068
Postoperative saturation rate (%)	99.85 ± 0.38	99.77 ± 0.44	0.163

Table 3. Pain scores measured on the Face, Legs, Activity, Cry, and Consolability (FLACC) scale at different times.

FLACC scores	Group 1 (N = 95)	Group 2 (N = 109)	p value
30 minutes after surgery, mean ± SD	2.22 ± 1.24	2.61 ± 1.21	0.024
1 hour after surgery, mean ± SD	1.10 ± 0.91	1.33 ± 0.80	0.063
3 hours after surgery, mean ± SD	0.71 ± 1.34	0.78 ± 1.43	0.708

Abbrevation: SD, standard deviation

Discussion

The present study examined the effects of pre-emptive and intraoperative use of IV acetaminophen on postoperative pain relief in children. While the greatest analgesic effect during the first 30 minutes after circumcision was observed in the pre-emptive group, both applications of acetaminophen exhibited similar and acceptable efficacy in pain relief one hour after surgery.

Acetaminophen is frequently employed in the treatment of urological surgery-related postoperative pain[6]. IV, oral, or rectal acetaminophen administration are frequently used to provide analgesia after circumcision, with rare side-effects associated with the use of acetaminophen including anaphylaxis, liver disorders, hypotension, and tachycardia[9]. McNicol et al.[10]'s systematic review and meta-analysis showed that 37% of patients receiving IV acetaminophen experienced a 50% decrease in pain severity over four hours (vs. 16% among those receiving placebo). Additionally, the administration of IV acetaminophen was associated with a lower additional analgesic requirement. The FLAAC scoring system was used for pain evaluation in the present study. Scores of 4-6 are interpreted as representing moderate pain under this system. Mean FLAAC scores were below 3 at all-time points in both groups. Additional analgesia was given to 13 (13.7%) children in Group 1 and 17 (15.6%) in Group 2. In agreement with the previous literature, acetaminophen was seen to provide effective treatment of post-circumcision pain.

Pre-emptive analgesia occupies a dominant place among the various alternatives available for improving postoperative pain control. Pre-emptive analgesia involves analgesic medication being administered prior to tissue injury, in other words before the reception, transmission, modulation, and nociception of the aggressive stimulus, the objective being to prevent hyperalgesia and the resulting pain-amplifying stimulus[11]. Pre-emptive analgesia has been used as an effective pain control method in pediatric surgeries, and acetaminophen is one of the most commonly used drugs for pre-emptive analgesia in pediatric patients[7,9,12-14].

The quality of acetaminophen-related postoperative analgesia methods in circumcision has been investigated in a number of previous studies[15]. Munevveroglu and Gunduz[15] compared the effects of penile block, caudal block, subcutaneous ring block, IV tramadol, and IV acetaminophen on pain management after circumcision. No differences were observed between the pain scores of the five groups at 30, 60, 120, or 180 minutes after surgery. The findings of that study showed that IV acetaminophen provided similar pain palliation to that of invasive analgesia methods.

An examination of the literature shows that the IV form of acetaminophen has generally been compared with the rectal or oral forms[7,14,16,17]. IV acetaminophen has been found to exhibit its analgesic effect more rapidly than the oral and rectal forms. This is attributed to the IV form of acetaminophen reaching peak plasma concentrations and entering the central nervous system more rapidly than the other types[16,18]. The efficacy of IV acetaminophen may vary depending on whether use is preoperative, intraoperative, or postoperative. Pre-emptive use of the IV form of acetaminophen was therefore compared with IV form intraoperative use in the present study. Our search of the literature revealed no previous studies comparing these two methods with one another.

Previous studies have shown that IV acetaminophen can be safely used without causing any pathology in vital findings[9,14]. However, pre-emptive IV acetaminophen use is also thought to be capable of causing various changes in the patient's vital signs during surgery. In the present research, patients' vital signs were therefore recorded in the preoperative, induction, intraoperative and postoperative periods, and no clinically significant abnormality was observed between the groups.

There are a number of limitations to this study, one being its retrospective and sin-

gle-center nature. In addition, the observation and pain recording period was limited to the first three hours postoperatively, and it might have been useful to have extended this to 24 hours. Nonetheless, we think that our research is particularly valuable in terms of its large patient number and role as a pioneering study investigating the effectiveness of IV acetaminophen used for analgesia at different time points.

Conclusion

In conclusion, pre-emptive acetaminophen provides more effective analgesia in the first 30 minutes postoperatively but loses this advantage after one hour. Considering the analgesic efficacy and limited half-life of IV acetaminophen, administered either pre-emptively or intraoperatively, its use may be recommended for effective postoperative pain management in children undergoing circumcision.

Author contributions
All authors read and approved the final manuscript.
SA: Conception of the work, analyzing and acquisition of data, drafting the work, final approval.
SSB: Acquisition of data, literature search, drafting the work, final approval.
GE: Design of the work, acquisition of data, drafting the work, final approval.
EP: Conception of the work, acquisition of data, drafting the work, final approval.
HSC: Design of the work, literature search, analysis of data, drafting the work, final approval.

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

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Ethical approval
This study was carried out in line with the Declaration of Helsinki and it was approved by Samsun University, Clinical Research Ethics Committee (No: 2022/2/1, Date: 01.06.2022).

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