

## Comparison of Rectal and Parenteral Paracetamol Administration in Pain Control After Circumcision

Tutku SOYER\*, Ünase BÜYÜKKOÇAK \*\*, Özkan CESUR \*,  
Yasemin Özkan PEKUZ\*\*, Murat ÇAKMAK\*

\*Department of Pediatric Surgery Kırıkkale University, Faculty of Medicine, Kırıkkale, TURKEY

\*\*Department of Anesthesiology and Reanimation, Kırıkkale University, Faculty of Medicine, Kırıkkale, TURKEY

### Abstract

**Introduction:** A prospective, randomized, double blind, clinical trial was performed to compare the efficacy of rectal and intravenous routes of paracetamol in postcircumcision pain in children.

**Methods:** Patients (n:83) older than 2 years of age were randomized into rectal (RP) and intravenous (IP) paracetamol groups and received either paracetamol 40 mg.kg<sup>-1</sup> rectally or 15 mg.kg<sup>-1</sup> intravenously. The vital findings (heart rate, respiratory rate and blood pressure) were recorded preoperative, peroperative and postoperative period. Postoperative pain was evaluated by CHEOPS scale.

**Results:** Patients were included into RP (n:38) and IP (n:45) groups randomly. The age median was 6 years (range: 3-9 years) and 5 years (range: 3-7 years) in RP and IP groups, respectively. Vital findings did not show any difference in both preoperative, peroperative and postoperative recordings (p>0.05). Median CHEOPS scores did not reveal a statistical difference (p>0.05). CHEOPS scores were higher than 10 in both groups at postoperative 20<sup>th</sup> minutes recording. In IP group, CHEOPS score 4 is obtained at the 180<sup>th</sup> postoperative minute. Rescue analgesia was performed in 24 (63.15%) children in RP group and 18 children (25%) in IP group (p>0.05).

**Conclusion:** The use of paracetamol intravenously is safe and well tolerated by children after circumcision. The intravenous form of paracetamol can be constituted as an alternative analgesic with an improving clinical efficacy in postoperative period. However, efficacy of intravenous paracetamol has no superiority to rectal administration, it can be used in case of oral administration is prohibited or delayed.

**Key words:** intravenous paracetamol, pain, circumcision, children

### Sünnet Sonrası Ağrı Kontrolünde Rektal ve Parenteral Parasetamol Uygulamalarının Karşılaştırılması

#### Özet

**Amaç:** Rektal ve intravenöz parasetamolün sünnet sonrası ağrının giderilmesinde etkinliği karşılaştırılmak amacıyla prospektif, randomize, çift kör bir klinik çalışma yapılmıştır.

**Gereç ve Yöntem:** İki yaşından büyük hastalar (n:83) rektal (RP) ve intravenöz (IP) parasetamol grubu olmak üzere iki gruba rastgele ayrılmış, rektal yolla 40 mg.kg<sup>-1</sup> ya da intravenöz 15 mg.kg<sup>-1</sup> parasetamol verilmiştir. Vital bulgular (kalp hızı, kan basıncı, solunum sayısı) preoperatif, peroperatif ve postoperatif dönemde kayıt edilmiştir. Postoperatif ağrı CHEOPS skalası ile değerlendirilmiştir.

**Sonuçlar:** Olguların 38'i RP gruba, 45'i IP gruba rastgele dahil edildi. Yaş ortancası RP grubunda ve IP grubunda sırasıyla 6 (aralık: 3-7 yaş) ve 5 (aralık: 3-7 yaş) idi. Vital bulgular preoperatif, peroperatif ve postoperatif ölçümlerde fark göstermemekteydi (p>0.05). CHEOPS ortanca skorları istatistiksel fark ortaya koymamaktaydı (p>0.05). Yirminci dakikadaki ölçümlerde her iki grupta da CHEOPS ortancaları 10'un üstündeydi. IP grubunda 180. dakikada CHEOPS ortancası 4 olarak değerlendirildi. Kurtarıcı analjezik RP grubundaki olguların 24'ünde (%63.15) ve IP grubun 18'inde (%25) uygulandı.

**Yorum:** Çocuklarda sünnet sonrası intravenöz parasetamol kullanımı güvenlidir ve iyi tolere edilmektedir. Parasetamolün intravenöz formu, postoperatif dönemde artan klinik etkinliği ile alternatif bir analjezik olarak kabul edilebilir. Her ne kadar, etkinlik bakımından intravenöz form, rektal parasetamole göre üstün değilse de, oral alımın kesildiği ya da geciktiği durumlarda kullanılabilir.

**Anahtar Kelimeler:** intravenöz parasetamol, ağrı, sünnet, çocuk

### Introduction

Circumcision is the most commonly practiced surgical procedure carried out in children. Numerous studies have shown that circumcision causes severe intraoperative and postoperative pain in both newborns and children. Many analgesic regimens have been recommended for postcircumcision pain relief, including penile or caudal block, penile ring infiltration, topical application of eutectic mixture of local anesthetic and administration of acetaminophen<sup>1</sup>.

Acetaminophen is used for relief of postcircumcision pain with a broad margin of safety in children<sup>2</sup>. Paracetamol (*N*-acetyl-*p*-aminophenol, acetaminophen) is the most commonly prescribed drug for the management of mild to moderate pain in children<sup>3</sup>. However, the

optimum route of administration is unclear. The oral and rectal route of paracetamol produces an unpredictable plasma concentration and may not be accepted by all patients<sup>4</sup>. Intravenous (i.v.) route provides less variability in plasma concentrations and can be used in children who are unable to take paracetamol orally<sup>4</sup>. Although i.v. form of paracetamol has been recommended to provide analgesia for mild-moderate pain, there are few studies comparing the clinical efficacy and duration of analgesia in children.

A prospective, randomized, double-blind, clinical trial was performed to compare the efficacy of intravenous versus rectal paracetamol in postcircumcision pain in children.

**Patients and Methods**

Patients older than 2 years of age (ASA Physical Status Classification I) and who prefer elective circumcision under general anesthesia, were enrolled into the study. After obtaining written informed consent, patients were randomized into rectal (RP) and intravenous (IP) paracetamol groups at the preoperative anesthetic evaluation the day before surgery. Patients were assigned consecutive numbers. Patients with odd numbers received rectal paracetamol where others received intravenous form of the medication. Patients who have drug hypersensitivity, severe renal, hepatic, respiratory or cardiac disease, history of seizures, neuromuscular disorder and chronic pain were excluded. All children were fasted and premedicated with i.v. midazolam 0.05 mg.kg<sup>-1</sup> after vascular access. EMLA<sup>®</sup> (5% lidocain HCl and prilocain, Astra Zeneca, Turkey) cream was applied to the dorsum of both hands for vascular access 30 minutes before surgery.

All patients were monitored including electrocardiogram, noninvasive arterial blood pressure, respiratory rate and pulse oximetry (Cardiicap/5<sup>®</sup>, Datex Ohmeda, Louisville, CO, USA) during the operation. Anesthesia was induced with 2 mg.kg<sup>-1</sup> propofol i.v. and maintained by 50% nitrous oxide in oxygen with 3-4% sevoflurane breathing spontaneously via laryngeal mask airway. After induction, patients received either paracetamol 40 mg.kg<sup>-1</sup> (Paranox- S<sup>®</sup>, Sanofi, Turkey) rectally or 15 mg.kg<sup>-1</sup> (Perfalgan<sup>®</sup>, Bristol-Myers Squibb, Germany) intravenously. Since, we aimed to compare the efficacy of rectal and intravenous routes of paracetamol in pain control after circumcision, neither topical eutectic mixture of local anesthetic nor dorsal penil blockade were performed. The technique of sleeve circumcision was performed to all patients by the same surgeon.

The vital findings (heart rate, respiratory rate, blood pressure) were recorded prior anesthetic induction (30 minutes) and during (5 minutes intervals through 30 minutes) and after (at 20<sup>th</sup>, 60<sup>th</sup>, 90<sup>th</sup> and 180<sup>th</sup> minutes) the surgery. The normal range of vital signs<sup>5</sup> were considered as listed in Table 1. The blood pressures of children obtained in concomitant recordings were scored according to normal blood pressure scale for children to obtain a statistical analysis. The blood pressures within normal limits were scored as 0. The pressures lower than normal limits were scored as -1 and higher values were considered as a score of 1.

An anesthesiologist who was blind to which of the route was applied to the patient, evaluated the postoperative pain by CHEOPS scale<sup>6</sup> (Children's Hospital of Eastern Ontario Pain Scale). The parameters of this behavioral scale which was intended for children ages through 1 to 7, were listed Table 2. CHEOPS scores equal or lower than 4 was assessed as no pain and scores between 4-10 were considered as pain. The CHEOPS scores more than 10 should be treated. During postoperative follows, rescue analgesia was not performed for the first postoperative three hours to evaluate the efficacy of different routes of paracetamol administration. Rescue analgesia (rectal paracetamol, 20 mg.kg<sup>-1</sup>) was performed to patients who had still higher scores of CHEOPS (CHEOPS>4) at the end of postoperative three hours.

The primary efficacy variable in this study was pain intensity which was rated by CHEOPS. The vital signs were also considered as the safety variables of two routes. The study was approved by Local Ethical Committee. The vital signs and CHEOPS scores were compared in groups by SPSS 15.0. The p values lower than 0.05 was considered to be significant.

**Table 1:** The scale used to evaluate the vital signs of children

Age	Heart Rate (beats.min <sup>-1</sup> )	Blood Pressure (systolic & diastolic) (mm Hg)	Respiratory Rate (breaths.min <sup>-1</sup> )
Premature	120-170	55-75 35-45	40-70
0-3 mo	100-150	65-85 45-55	35-55
3-6 mo	90-120	70-90 50-65	30-45
6-12 mo	80-120	80-100 55-65	25-40
1-3 yr	70-110	90-105 55-70	20-30
3-6 yr	65-110	95-110 60-75	20-25
6-12 yr	60-95	100-120 60-75	14/22
12 yr	55-85	110-135 65-85	12-18

**Table 2:** CHEOPS scale for postoperative pain assessment in children

Item	Behavioral	Definition
<b>Cry</b>	No cry	1 Child is not crying.
	Moaning	2 Child is moaning or quietly vocalizing silent cry.
	Crying	2 Child is crying, but the cry is gentle or whimpering.
	Scream	3 Child is in a full-lunged cry; sobbing; may be scored with complaint or without complaint.
<b>Facial</b>	Composed	1 Neutral facial expression.
	Grimace	2 Score only if definite negative facial expression.
	Smiling	0 Score only if definite positive facial expression.
<b>Child Verbal</b>	None	1 Child not talking.
	Other complaints	1 Child complains, but not about pain, e.g., "I want to see mommy" or "I am thirsty".
	Pain complaints	2 Child complains about pain.
	Both complaints	2 Child complains about pain and about other things, e.g., "It hurts; I want my mommy".
	Positive	0 Child makes any positive statement or talks about other things without complaint.
<b>Torso</b>	Neutral	1 Body (not limbs) is at rest; torso is inactive.
	Shifting	2 Body is in motion in a shifting or serpentine fashion.
	Tense	2 Body is arched or rigid.
	Shivering	2 Body is shuddering or shaking involuntarily.
	Upright	2 Child is in a vertical or upright position.
	Restrained	2 Body is restrained.
<b>Touch</b>	Not touching	1 Child is not touching or grabbing at wound.
	Reach	2 Child is reaching for but not touching wound.
	Touch	2 Child is gently touching wound or wound area.
	Grab	2 Child is grabbing vigorously at wound.
	Restrained	2 Child's arms are restrained.
<b>Legs</b>	Neutral	1 Legs may be in any position but are relaxed; includes gentle swimming or separate-like movements.
	Squirm/kicking	2 Definitive uneasy or restless movements in the legs and/or striking out with foot or feet.
	Drawn up/tensed	2 Legs tensed and/or pulled up tightly to body and kept there.
	Standing	2 Standing, crouching or kneeling.
	Restrained	2 Child's legs are being held down

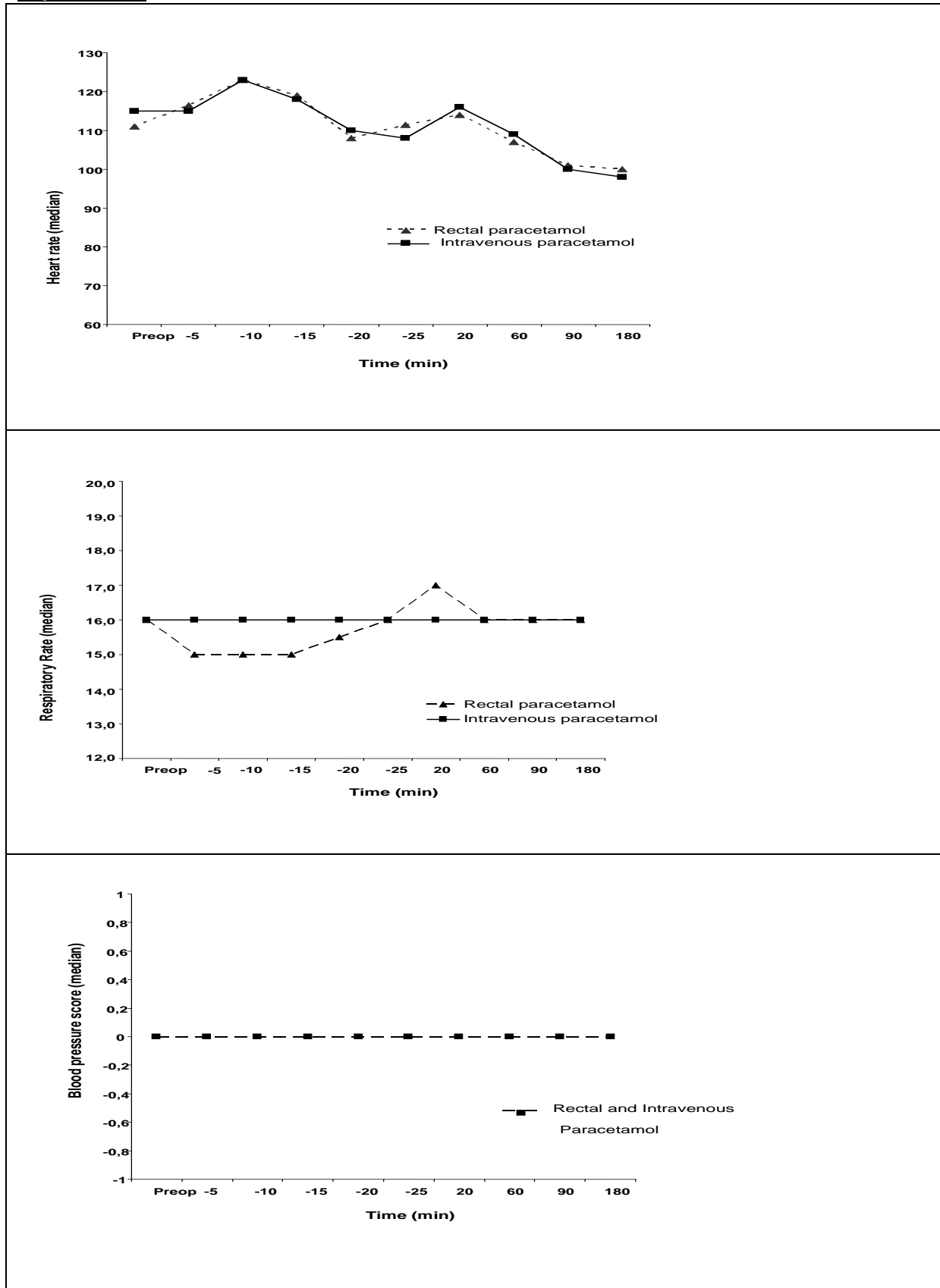
## Results

Eighty three patients who were undergoing elective circumcision were recruited in the study. Thirty eight of patients were included into RP group and 45 of them were included in IP group randomly. The age median was 6 years (range: 3-9 years) and 5 years (range: 3-7 years) in RP and IP groups, respectively. There was no difference between groups in terms of weight percentiles ( RP: 60 p, range: 50-75 p and IP: 75 p, range: 50-95 p,  $p>0.05$ ). The operative course was uneventful and completed with a mean duration of  $29 \pm 4.6$  minutes.

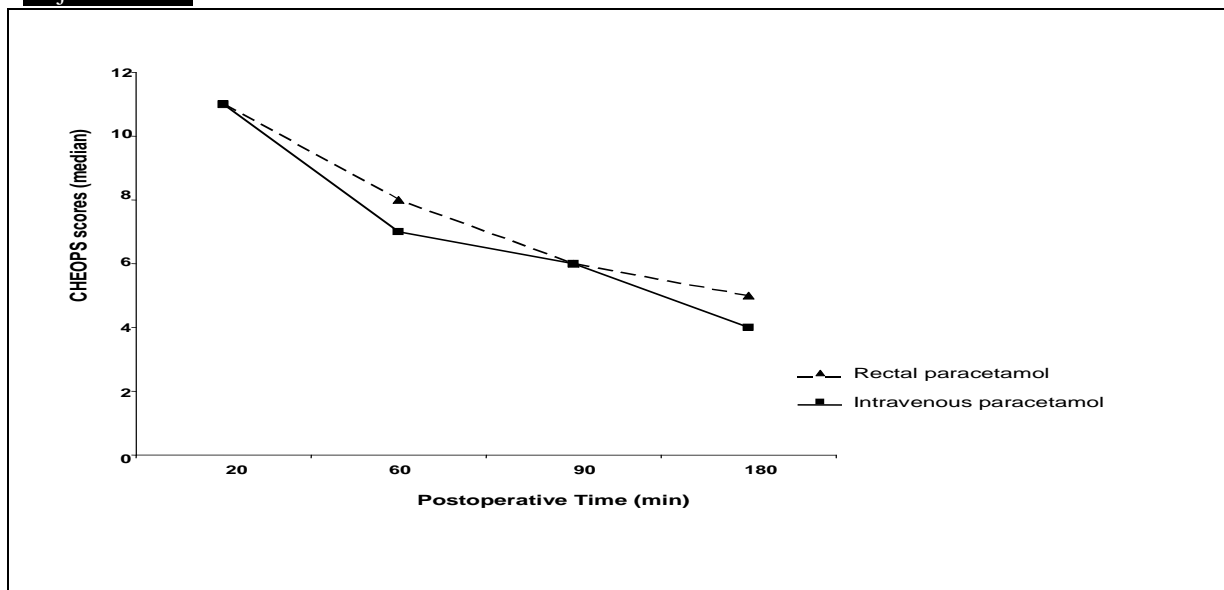
The heart rate, respiratory rate and blood pressure score medians in concomitant recordings in groups were outlined in Figure 1. When heart rate, respiratory rate and blood pressure scores of

children were compared in groups, these vital findings did not show any difference in both preoperative, peroperative and postoperative recordings ( $p>0.05$ ).

Also comparison of median of CHEOPS scores in RP and IR groups, did not reveal a statistical difference ( $p>0.05$ ). The CHEOPS score medians in postoperative recordings in RP and IP groups were shown in Figure 2. CHEOPS scores were higher than 10 in both groups at postoperative 20<sup>th</sup> minutes recording. In IP group, CHEOPS score 4 is obtained at the 180<sup>th</sup> postoperative minute. Rescue analgesia was performed in 24 (63.15%) children in RP group and 18 children (25%) in IP group ( $p>0.05$ ). All of the patients discharged from the hospital after an uneventful 12 hours period.



**Figure 1.** The median of vital findings ( heart rate, respiratory rate and blood pressure scores respectively) of patients in groups in concomitant recording. The (-) values on X axis of graphs demonstrates the preoperative time.



**Figure 2.** The median CHEOPS score in groups in postoperative recordings.

### Discussion

Circumcision is a commonly performed surgical procedure in children. General anesthesia in conjunction with local anesthetics provides both intraoperative and postoperative analgesia. Penile nerve block, application of eutectic mixture of local anesthetic and caudal block are usually used for intraoperative pain relief and also they are used to maintain postoperative analgesia after general anesthesia<sup>7</sup>. Acetaminophen, which was used for relief of mild to moderate pain after minor surgery, did not ameliorate either intraoperative or immediate postoperative pain of circumcision<sup>2</sup>. However, it has been found that acetaminophen provides some benefit after postoperative period<sup>2</sup>. We performed a prospective, randomized, double-blind clinical trial to compare the efficacy of i.v. versus rectal route of paracetamol in postcircumcision pain. Although, a placebo control was usually recommended in analgesic studies to validate the efficacy of methods, it would be unethical to use a placebo group in children where the analgesic effect of paracetamol has been already demonstrated<sup>2,8</sup>. In this study, we aimed to compare the efficacy of two different routes of paracetamol. Therefore, we did not perform a local anesthetic during circumcision. Hence, the main outcome of the study was to control the postoperative pain, all operations were performed under general anesthesia to eliminate the intraoperative pain.

The new formulation of acetaminophen, i.v. paracetamol, might improve prediction of concentration compared to enteral formulations, by eliminating of plasma variability due to absorption<sup>3</sup>. It has been also suggested that oral and rectal paracetamols may not achieve therapeutic levels in some cases<sup>3,9</sup>. Although plasma levels are more predictable in i.v. paracetamol, studies comparing the clinical efficacy of i.v. paracetamol with other routes are limited<sup>4</sup>. Rectal route can be used after

induction of anesthesia with a mean analgesic duration of 4-6 hours<sup>10</sup>. In rectal route, single dose of acetaminophen 40 mg.kg<sup>-1</sup> is used as loading dose and provides plasma concentrations of 10-20 mg.litre<sup>-1</sup><sup>11</sup>. Pharmacokinetic studies on i.v. paracetamol suggest that initial dose of i.v. paracetamol is 15 mg.kg<sup>-1</sup> for children. This dose provides a plasma concentration of 10 mg.litre<sup>-1</sup> for 6 hours<sup>3</sup>. Therefore, we chose to compare the single dose of acetaminophen 40 mg.kg<sup>-1</sup> rectally and 15 mg.kg<sup>-1</sup> intravenously. These doses are associated with similar plasma levels and have been chosen according to previously published studies and pharmacokinetic data<sup>3,4</sup>.

In our study, vital signs recorded intraoperatively and postoperatively demonstrated that, both forms of paracetamol can be used safely and well tolerated by the children. Murat et al reported a clinical trial, comparing the tolerance and analgesic efficacy of i.v. paracetamol after inguinal hernia repair in children<sup>8</sup>. Similar to our results, they found that no clinically significant abnormality in vital signs were observed with this new solution of paracetamol. Also, we did not observe any adverse effect of drug during i.v. administration.

We used CHEOPS scale to perform efficacy assessment in groups. For the first postoperative 20<sup>th</sup> minutes, CHEOPS scores were more than 10 in both groups. During this period, rescue analgesia did not perform in order not to reach the toxic levels. Consistent with our results, Howard et al found that acetaminophen did not ameliorate the immediate postoperative pain in children after circumcision<sup>2</sup>. The period between 60<sup>th</sup> and 180<sup>th</sup> postoperative minutes, mean CHEOPS scores were rated more than 4 in RP and IP groups. The pain intensity did not show significant difference between groups ( $p > 0.05$ ). At the end of the 3 hours period, IP group

**Orijinal Makale**

had a mean CHEOPS score of 4, where mean CHEOPS score was still higher in RP group. However, this difference did not reach a statistical significance ( $p>0.05$ ). Contrary to our results, Capici et al reported that rectal paracetamol provided a longer analgesia (for a period of more than 6 hours) when compared to i.v. paracetamol in children with adenotonsillectomy. They suggested that rectal paracetamol had a slower onset analgesic effect which lasts longer<sup>4</sup>. According to their data, children receiving rectal acetaminophen needed rescue analgesia after a longer period when compared with those receiving i.v. acetaminophen<sup>4</sup>. In our study, we performed rescue analgesia in 63.15% of children in RP group. However, only 25% of children received rescue analgesia at the end of 3 hours in IP group. In this study, no further conclusion is possible about the efficacy of i.v. paracetamol for late postoperative analgesia, but we can propose that parenteral form of paracetamol can be constituted as an alternative analgesic with an advantage of long term pain control until oral administration becomes convenient. On the other hand, it has been proposed that children who underwent circumcision experienced severe pain especially during the first 2 hours and intensity of postoperative pain remarkably decreases after a certain time period<sup>1,12</sup>. We suggest that improved pain relief in IP group may be related with the nature of postcircumcision pain in children. Similar results (decreased CHEOPS scores) in RP group in concomitant recordings may also support our suggestion.

In conclusion, the use of i.v. paracetamol is safe and well tolerated by children after circumcision. The i.v. form of paracetamol can be constituted as an alternative analgesic with an improving clinical efficacy in postoperative period. However, efficacy of i.v. paracetamol has no superiority to rectal administration, it can be used in case of oral administration is prohibited or delayed.

**References**

1. Weksler N, Atlas I, Klein M, Rosenzveig V, Ovaid L, Gurman GM. Is penil block better than caudal epidural block for postcircumcision analgesia. *J Anesth* 2005; 19:36-39
2. Howard CR, Howard FM, Weitzman ML. Acetaminophen analgesia in neonatal circumcision: The effect on pain. *Pediatrics* 1994;93: 641-646
3. Anderson BJ, Pons G, Autret-Leca e, Allegaert K, Boccard E. Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. *Pediatric Anesthesia* 2005;15: 282-292
4. Capici F, Ingelmo PM, Davidson A, Sacchi CA, Milan B, Sperti R, Lorini L, Fumagalli RF. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. *Br J Anaesth* 2008;100: 251-255
5. Mathers LH, Frankel LR. Pediatric Emergencies and Resuscitation, In Kleigman RM, Behrman RE, Jenson HB, Stanton BF, eds. *Nelson Textbook of Pediatrics*, Philadelphia: Saunders, Elsevier, 2007: 387-405
6. Mc Garth PJ, Johnson G, Goodman JT, et al. CHEOPS: A behavioral scale for rating postoperative pain in children. In Fields HL, Dubner R, Carvero F, eds. *Advances in Pain Research and Therapy*. New York: Raven Press, 1985:395-402
7. Geyer J, Ellsbury D, Kleiber C, Litwiller D, Hinton A, Yankowitz J. An evidence-based multidisciplinary protocol for neonatal circumcision pain management. *J Obstet Gynecol Neonatal Nurs* 2002,24: 337-42
8. Murat I, Baujard C, Foussat C, Guyot E, Petel H, Rod B, Ricard C. Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair. *Pediatric Anesthesia* 2005;15:663-670
9. Andersn BJ, Holford NH, Woolard GA, Kanagasundaram S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. *Anesthesiology* 1999;90:411-421
10. Remy C, Marret E, Bonnet F. State of the art of paracetamol in acute pain therapy. *Curr Opin Anaesthesiol* 2006;19: 562-5
11. Howell TK, Patel D. Plasma paracetamol concentrations after different doses of rectal paracetamol in older children. A comparison of 1 gr vs. 40 mg x kg(-1). *Anaesthesia* 2003; 58:69-73
12. Bramwell RGB, Bullen C, Rardford P. Caudal block for postoperative analgesia in children. *Anesthesia* 1982;37: 1024-1028

**Corresponding Author**

Tutku Soyer, MD

Kırıkkale University, Faculty of Medicine,

Department of Pediatric Surgery,

71100, Kırıkkale, Turkey

Tel: 090 532 6651960

E-mail: tutku@sanalofis.net