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RESEARCH ARTICLE

Comparison of preemptive intravenous paracetamol and caudal block in terms of analgesic and hemodynamic parameters in children

Çocuklarda Analjezik ve hemodinamik parametreler açısından preemptif intravenöz parasetamol ve kaudal bloğun karşılaştırılması

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ABSTRACT

Objectives: Paracetamol has a widespread use for fever and symptomatic relief of pain in children. The aim of this study was to compare analgesic effects of preemptive intravenous (i.v.) paracetamol, and caudal block with levobupivacaine.

Materials and methods: A total of 60 children with ASA I-II physical status, aged 5-15 years and undergoing inguinal hernia repair, were randomly allocated to three groups so that each group contained 20 patients. Group P children received i.v. 15mg/kg paracetamol. Group C received only caudal block with levobupivacaine, and Group PC received both i.v. paracetamol, and caudal block with levobupivacaine. Pain level assessed by modified Eastern Ontario Children's Hospital pain scale (mCHEOPs), sedation status by Ramsey sedation scale at postoperative 5, 15, 30 min and 1,3, and 6th hours.

Results: No significant differences were found in age, gender distribution, body weight, ASA status, type and duration of surgery between three groups (p>0.05). Although significant difference were found in mCHEOPs scores within groups by repeated measures, no difference of pain scores was observed between three groups (p>0.05). There were no significant differences in the hemodynamic parameters (heart rate, blood pressure) both within groups and between groups (p>0.05).

Conclusions: Preemptive intravenous paracetamol had similar analgesic effects compared with caudal block with levobupivacaine with regard to postoperative pain scores in children undergoing inguinal hernia repair. No hemodynamic or other adverse effects were observed with intravenous paracetamol. *J Clin Exp Invest 2012; 3(2): 202-208*

Key words: Intravenous paracetamol, caudal block, preemptive analgesia, children, inguinal hernia repair

ÖZET

Amaç: Parasetamol çocuklarda ateş ve akut ağrının semptomatik tedavisi amacıyla yaygın bir şekilde kullanılmaktadır. Bu çalışmada preemptif analjezi amacıyla verilen intravenöz (i.v.) parasetamolü, kaudal blok uygulamasıyla karşılaştırmayı amaçladık.

Gereç ve yöntem: Alt batın cerrahisi operasyonlarında fiziksel durumu ASA I-II olan, 5-15 yaşlarında 60 çocuk rastgele bir şekilde 20'şer çocuktan oluşan 3 gruba ayrıldı. Grup P' ye i.v. 15 mg/kg parasetamol verildi ve salinle kaudal blok yapıldı, Grup K' ya sadece levobupivakainle kaudal blok yapıldı; Grup PK'ya ise hem i.v. parasetamol verildi hem de levobupivakainle kaudal blok yapıldı. Bütün hastalara aynı anestezi tekniği uygulandı. Hastaların ağrısı, Modifiye Eastern Ontario Cocuk Hastanesi ağrı skalası (mCHEOPS) ile, sedasyon durumu ise Ramsey Sedasyon Skalasına göre postoperatif 5, 15, 30. dakikalarda ve 1, 3 ve 6. saatlerde değerlendirildi. İlk analjezik gereksinim zamanları kaydedildi.

Bulgular: Gruplar arasında yaş, cinsiyet, vücut ağırlığı, ASA durumu, ameliyat tipleri ve ameliyat süreleri bakımından anlamlı bir fark bulunmadı (p>0.05). Ağrı skorları bakımından grup içi değişimi anlamlı farklı bulunmakla birlikte (p<0.05) gruplar arasında istatistiksel bir farklılık saptanmadı (p>0.05). Tüm gruplarda mCHEOPS puanlarını en yüksek düzeye postoperatif 15. dakikada ulaştı. Gruplar arasında çeşitli zamanlarda elde edilen postoperatif sedasyon skorları karşılaştırıldığında anlamlı bir farklılık bulunmadı (p>0.05). Hemodinamik veriler (kalp hızı, kan basınçları) değerlendirildiğinde ortalama kan basıncı ve kalp atım hızlarında grup içi ölçümlerde ve gruplar arasında anlamlı bir farklılık saptanmadı (p>0.05).

Sonuç: Çocuklardaki alt batın cerrahilerinde preemptif olarak uygulanan intravenöz parasetamol ve kaudal bloğun benzer biçimde postoperatif ağrı skorlarını azalttığı bulunurken herhangi bir yan etki ve olumsuz hemodinamik etkiye rastlanmadı.

Anahtar kelimeler: İntravenöz parasetamol, kaudal blok, preemptif analjezi, çocuklar, alt batın cerrahisi

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INTRODUCTION

Stimuli from damaged tissue are not transmitted via "hard-wired" routes into central nervous system. On the contrary, nociceptive stimuli start a cascade of changes in the somatosensory system which leads to increased response of both peripheral and central neurons. These changes would cause increased responses against later stimuli. Thus, pain sensation would be more severe and intense.[1]

Preemptive analgesia is a pharmacological strategy based on administration of analgesic interventions before the surgical stimulus in order to attenuate. In various studies of preemptive analgesia, local anesthetics, opioids, paracetamol, non-steroid anti-inflammatory drugs, central and peripheral nerve blocks.[2-4] have been used for this purpose. The preferred drug and its route of administration are still under investigation. It is still investigated which drugs and which route should be preferred for preemptive analgesic techniques.[5]

Paracetamol (acetaminophen) is a non-opioid agent acting primarily on central nervous system via central cyclo-oxygenase inhibition and probably through indirect serotoninergic pathways.[2] 6 It is widely used as an anti-pyretic and analgesic agent for control of fever and acute pain in children. Intravenous (i.v.) Form might be more effective and useful in the postoperative period. Onset of analgesia, and anti-pyretic action with i.v. paracetamol is 15 min and 30 min, respectively.[2,6,7]

Among the regional anesthetic and analgesic techniques, caudal block is generally preferred in pediatric lower abdominal surgery.[8]

In prospective, randomised and double-blind study, we aimed to compare the effects of preemptive intravenous paracetamol and caudal block with levobupivacaine with regard to analgesic efficacy and hemodynamic profile.

MATERIALS AND METHODS

This prospective randomized study includes ASA I-II 60 children aged between 5-15 years undergoing elective inguinal hernia repair. Exclusion criteria were emergency cases, hypersensitivity to any of the study drugs used, active and serious history of liver, lung, kidney and heart, neurological and neuromuscular disease, history of analgesic or any drug abuse, coagulopathy, local infection at caudal region, open wound or multiple attempts at caudal region.

After approval of scientific ethics committee, written and oral informed consent were taken from parents of children.

Children were taken to the premedication room. Three-lead electrocardiography, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), oxygen saturation (SpO2) were monitored with Criticare Poet Plus® 8100 monitor in premedication room. A peripheral vein was cannulated with an appropriate sized venous catheter. No premedication drug was given. We used closed-envelope method to randomly patients into 3 groups in this prospective, double-blind study.

Group P (n=20) received i.v. paracetamol 15 mg/kg infusion (Braun® perfusor compact-type 8714827 pump) in 30 minutes after arrival in the premedication room. After the anesthetic induction, no caudal block was performed.

Group C (n=20) received i.v. 100 ml saline infusion in 30 minutes after arrival in the premedication room. After the anesthetic induction, caudal block was performed with 0.25% levobupivacaine 0.75 ml/kg.

Group PC (n=20) received i.v. paracetamol 15 mg/kg infusion in 30 minutes after arrival in the premedication room. After the anesthetic induction, caudal block was performed using 0.25% levobupivacaine 0.75 ml/kg.

No analgesic drug was given to patients during perioperative period. In the operation room, three-lead electrocardiography, SBP, DBP, MBP, SpO_2 were monitorized with Datex® Engstrom AS/3 monitor. Standard anesthetic induction was propofol 2-3 mg/kg slow bolus injection until the loss of eyelash reflex. Fentanyl 2 µg/kg was used as opioid. Anesthesia was deepened with face mask ventilation in 50% oxygen - 50% air, 4-6% desflurane. Proseal® LMA was placed. Then, we positioned the patient to left-lateral position and caudal epidural space was reached using specific needle by an experienced anesthetist under sterile conditions. Group C and PC received 0.25% levobupivacaine 0.75 ml/kg at the caudal epidural space. Patients were taken onto operation table in the supine position, covered with sterile drape and then surgery started. After first incision, hemodynamic responses up to 20% were accepted as within the normal range. After the last skin suture, all the anesthetic gasses were stopped, and LMA was removed. Patients were taken to the recovery room and kept there for 30 minutes. Levels of sedation and pain were recorded. At the inpatient wards, possible side effects, sedation and pain scores were also recorded. Ramsey Sedation

Score was used for evaluation of postoperative sedation level and mCHEOPS (Modified Eastern Ontario Children's Hospital Pain Scale) was used for postoperative pain level (Table 1 and 2) at 5, 15, 30 min and 1, 3, 6th hours. Analgesic consumption, complications (local or systemic), and side effects were recorded.

If pain level would 5 or over, extra paracetamol 15 mg/kg i.v. was administered postoperatively. Nevertheless tramadol 1 mg/kg i.v. was administered if it would not obtained adequate analgesia. Patients were discharged on the same day, if there would no problem or complication at all.

Statistical analysis

SPSS 12.0 software was used for statistical analysis. Results were given as mean ± standard deviation. Countable data were compared with with Chi-square test and measurable data were compared with Kruskall-Wallis test between 3 groups. ANOVA test and Post Hoc Dunnett's test T3 were used for comparison of repetative data. Hemodynamic data, pain, and sedation scores were repetitively measured over time intervals postoperatively and compared both in-group and inter-group with these tests. $p<0.05$ was accepted as significant.

RESULTS

According to age, weight and operation duration, there were no statistical difference ($p>0.05$). In all 3 groups, male patients were more than females but this was not statistically significant ($p>0.05$) (Table 3).

In-group comparison of pain scores at time intervals with mCHEOPS revealed a significant difference ($F=17,888$, $p<0.001$) but there were no significance when all the measurements were evaluated together ($p>0.05$, Figure 1). Pain scores with mCHEOPS were highest in all 3 groups at the postoperative 15th minutes.

Inter-group comparison of sedation scores at time intervals with Ramsey Sedation Score revealed no significant difference ($p>0.05$).

Inter-group comparison of pain scores at time intervals with mCHEOPS revealed that number of patients needing supplemental analgesics in Groups P and C were higher than in Group PC (the number of patients who received supplemental analgesics 7,5,2 respectively, $p=0.045$). No tramadol was used in groups.

There were no within-group or between-group differences of blood pressure or heart rate among the 3 groups throughout the study ($p>0.05$, Figure 2).

Table 1. mCHEOPS pain scores

Score	0	1	2
Cry	No cry	Crying, moaning	Scream
Facial	Smiling	Composed	Grimace
Verbal	Positive	None or other complaint	Pain complaint
Torso	Neutral	Shifting, tense, upright	Restrained
Lower extremity	Neutral	Kicking, suffering, detraction	Restrained

Table 2. Ramsey Sedation Scores

1	Fully awake and oriented
2	Awake, tendency to sleep
3	Sleeping but easily awakened with verbal commands
4	Sleeping but awakened with physical stimulus
5	Sleeping, cannot be awakened with verbal or physical stimulus

Table 3. Distribution of patients according to age, sex, body weight, duration of surgery

	Group P (n=20)	Group C (n=20)	Group PC (n=20)	*p
Age, Years*	8.6±2.8	6.9±3.0	8.0±3.5	NS
Sex, Male/ Female	16/4	15/5	16/4	NS
Weight, Kg*	25.7±6.6	21.6 ±7.2	24.8±8.5	NS
Operation duration, min*	32.9±21.0	34.8±15.0	53.4±39.2	NS

*Values are presented as mean ± SD, Group P: paracetamol, Group C: caudal block, Group PC: paracetamol + caudal block, NS: not significant ($p>0.05$)

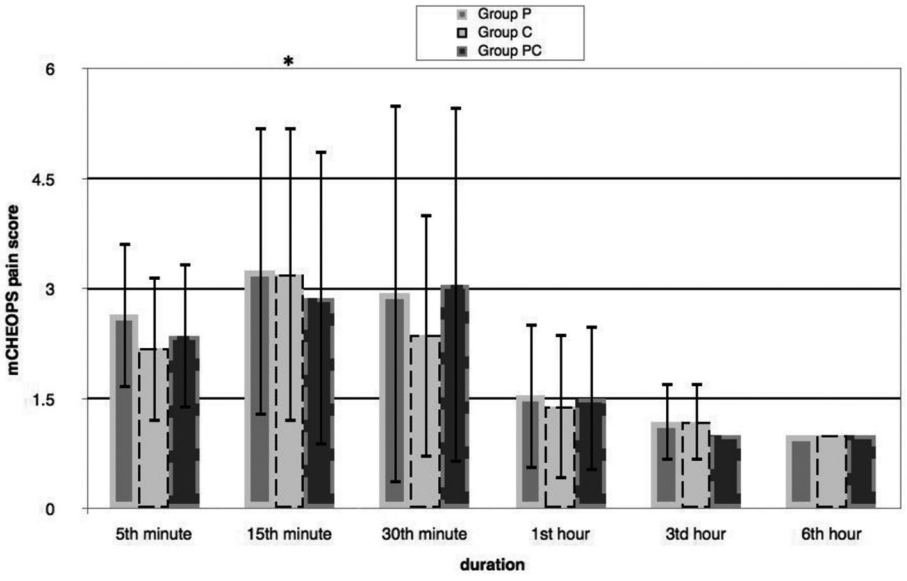

Figure 1. Distribution of mCHEOPS pain scores of groups versus time (mCHEOPS 0-10). Values are expressed as median. *Postoperatively 15 minutes in all groups, the highest level reached mCHEOPS pain score was seen as the time period, $p<0.05$. Group P: only i.v.paracetamol, group C: only caudal block, group PC: both i.v. paracetamol and caudal block.

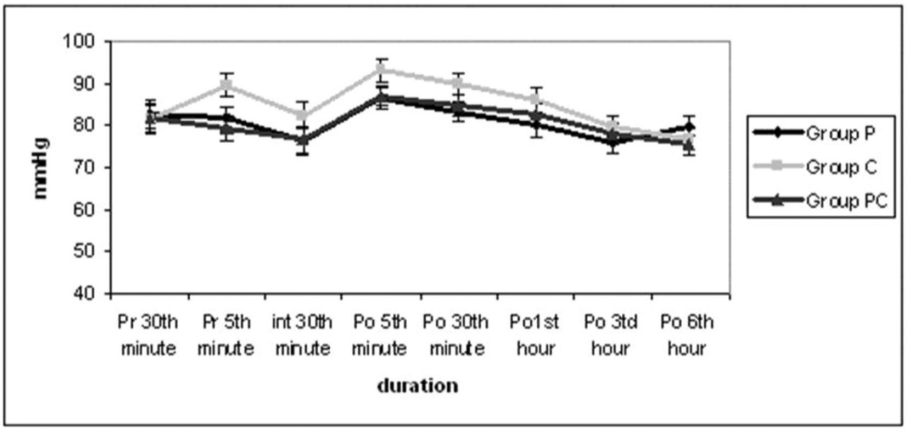

Figure 2. Distribution of mean blood pressure values of groups versus time. Mean blood pressure values between groups were compared, no significant difference was found. Values are expressed as median.

DISCUSSION

We used preemptive i.v. paracetamol for children undergoing elective inguinal hernia repair in our study. 30 minutes before operation, we gave 15 mg/kg i.v. paracetamol. We observed that perioperative hemodynamic parameters, postoperative analgesic efficacy, and side effects were all similar to the caudal anesthetic technique.

In the literature, there were only 4 studies on children with i.v. paracetamol. Murat et al[9] compared analgesic efficacy of 15 mg/kg paracetamol and 30 mg/kg propacetamol on children undergoing elective inguinal hernia repair. Murat et al[9] found that paracetamol and propacetamol on children were comparable, similar. Alshami et al[10] compared analgesic efficacy of i.v. paracetamol, and i.m. meperidine on children undergoing elective tonsillectomy and found that i.v. paracetamol group had the highest pain scores. Again Alshami et al[11] compared analgesic efficacy of i.v. paracetamol and i.m. meperidine on children undergoing elective tonsillectomy, and found that i.v. paracetamol group had sufficient analgesic levels. Paracetamol also provided some benefits like having lesser sedation and shorter duration at the recovery room. Capici et al[12] compared

analgesia duration of rectal and i.v. paracetamol on children undergoing elective adeno-tonsillectomy and found that 40 mg/kg rectal paracetamol had longer duration of action than 15 mg/kg i.v. paracetamol for moderate pain procedures. These above mentioned 4 studies however, did not include preemptive i.v. paracetamol and caudal block comparisons.

The appropriate route of paracetamol administration depends on age. Oral paracetamol administration leads to unpredictable plasma concentrations, also might be unpleasant to some children. Oral paracetamol might be inducing post-operative nausea and vomit, thereby limiting its applicability. Alternative rectal paracetamol route might not be accepted by some patients, therefore, preferred to be given after anesthetic induction; even then it might not reach therapeutic plasma levels in some cases. Whereas i.v. paracetamol shows relatively stable and controlled plasma concentrations.[12] We preferred i.v. route of paracetamol be cause our patients' age average was 7-8 years and i.v. route of paracetamol had obviously more advantages than other routes.

In recent years, there had been numerous experimental and clinical studies associated with preemptive analgesia concept in the anesthetic practice.[4] Dahl et al[13] published a meta-analysis of 80 studies about preemptive treatments. They concluded that preemptive and postoperative administrations of NSAIDs, local anesthetic infiltrations, intravenous opioids, ketamine, epidural, caudal, spinal analgesics were not significantly different in terms of analgesic efficacy. However, the same authors concluded that the evaluation of preemptive analgesia should include not only the timing of preemptive treatment but also duration and efficacy of preemptive analgesics. The studies so far did not include these three factors therefore, could not achieve enough success; they required further reproducible studies. Thus, we planned our study in order to include all three factors.

Onset of analgesia of i.v. paracetamol was nearly 15 minutes, half-life was 2.5 hours, and duration of action was 4-6 hours. It was accepted that analgesic efficacy of paracetamol is directly related to its plasma concentration. One gram i.v. paracetamol is hydrolysed to 0.5 gram paracetamol. Therefore, 15 mg/kg paracetamol equals to 30 mg/kg propacetamol. In children, 30 mg/kg propacetamol forms 10 mg/Litre serum concentration, this is sufficient to overcome mild to moderate pain. 15 mg/kg paracetamol is well-tolerated in children for pain relief. That's why the recommended initial dose is 15 mg/kg.[5,12,14,15] In our study, we assumed that the analgesic efficacy of paracetamol is correlated to its plasma concentration, so we started infusion 15 minutes before the surgery and preferred the dose of 15 mg/kg in order to get the effective plasma concentration. Thus, maximum plasma level of paracetamol was achieved at the beginning of surgery. Group P and group C postoperative pain scores were similar, with similar analgesic efficacies.

We did not use any opioid in this study, because we did not want to interfere with the postoperative analgesic needs. So far opioids were used widely in treating acute postoperative pain. However, serious side effects (respiratory depression, sedation, confusion, urine retention, itching-pruritus, constipation) limited usage of this drug group. In order to decrease opioid need in the postoperative period, non-steroid anti-inflammatory drugs like COX-2 inhibitors and metamizol might be useful. Likewise, unwanted effects of non-steroid anti-inflammatory drugs; impaired platelet function, nephrotoxicity, gastrointestinal side effects, agranulocytosis, sodium retention might also limit their usage.[16-18] Paracetamol is a safe non-opioid analgesic which is known to have a lower incidence of side effects and drug interactions. The most important side effect is hepatoxicity, and hepatic failure is not seen unless recommended doses are overrun.[19-20] In this study, no side effect is seen with the dose of 15 mg/kg i.v. paracetamol. Therefore, we think that paracetamol has a safe profile which is supposed to be tolerated by all the children.

There was no significant difference between pain scores of all groups versus time. However, total number of patients who received supplemental analgesics (7,5,2 respectively) were higher in Group P and Group C than Group PC. The reason of similar total pain scores at postoperative times might be due to the supplemental analgesics in the Group P and C. In groups C and PC where caudal block was performed, no serious complication (dural puncture, intravascular injection, rectum perforation, drug overdose, skin lesion) was seen.[21]

Preemptive analgesia concept became more common in recent years, and further studies are performed with various drugs before various surgical operations. Ong et al[22] published a meta-analysis investigating the efficacy of preemptive analgesia in preventing acute postoperative pain. In this meta-analysis, epidural blocks are compared before, and after surgical incision, 653 patients in the 13 randomized-controlled studies were investigated; 7 studies showed significantly better results

with preemptive blocks, but 6 studies showed no significant difference. Especially, 4 seperate caudal block studies were performed on children with different local anesthetics. Their aim was to show preemptive analgesia and 2 of studies have shown lesser postoperative pain scores whereas the other 2 studies showed no difference.[8,23-25] Møiniche et al[1] reported in a review that preemptive analgesia may provide decreased risk of chronic postoperative pain development and severe acute postoperative pain scores is also decreased.

We did not record any hemodynamic instability or statistical difference in the children which were treated with 15 mg/kg paracetamol (Figure 2) undergoing lower abdominal surgery. In a study, investigating the hemodynamic effects of i.v. paracetamol, they used i.v. paracetamol as an analgesic in major orthopedic surgeries. There were no negative hemodynamic recordings, and hepatic function tests were not negatively affected.[25] In another adult study, where preemptive i.v. paracetamol was used in total abdominal hysterectomy cases, there was also no hemodynamic instability.[2]

In conclusion, preemptive paracetamol and caudal block are both effective in children who are undergoing elective lower abdominal surgery. They significantly decreased postoperative pain scores. Thus, we concluded that although no difference in pain scores and hemodynamic effects was seen, i.v. paracetamol would be the preferred method still, given its safety profile and cost.

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