Ketamin ve Ropivakainin pediatrik hastalarda etkinliği: Plasebo kontrollü, çift kör çalışma

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ÖZET

Ketamin ve Ropivakainin pediatrik hastalarda etkinliği

Randomize, plasebo kontrollü ve çift kör olarak düzenlenen bu çalışmada, ropivakainle kaudal blok altında elektif herni tamiri yapılacak pediatrik hastalarda preemptif intravenöz ketamin ve plasebonun etkilerinin karşılaştırılması ve değerlendirilmesi yapılmıştır.

MATERYAL-METOT: planlı herni tamiri operasyonu geçirecek olan 1- 12 yaşları arasında, ASA I-II grubu 60 hasta çalışmaya dahil edilmiştir. Hastalar randomize olarak 3 gruba ayrılmıştır. Grup K hastalara anestezi indüksiyonundan önce intravenöz yolla 0.5 mg/kg ketamin, Grup R hastalara kaudalden 0.7 mg/kg %0.2 ropivakain ve intravenöz yoldan 2 ml normal salin, Grup RK hastalara kaudalden 0.7 mg/ml %0.2 ropivakain ve intravenöz 0.5 mg/kg ketamin verilmiştir. Anestezi süresince hastaların kalp hızı, end-tidal CO2, pulse oksimetri, kan basınçları ve BIS(bispektral indeks) takibi yapılmıştır. Postopertif analjezi etkinliği Objektif Ağrı Skalası (OPS) ile değerlendirilmiş ve analjezik ihtiyacı operasyon sırasında ve sonrasında kayıt edilmiştir.

BULGULAR: Grup R ve Grup RK arasında fentanil tüketiminde faklılık görülmedi, anestezi sırasında Grup K hastalardaki fentanil tüketimi önemli derecede yüksekti, Grup R ve Grup RK, Grup K ile karşılaştırıldığında OPS değeri önemli derecede yüksek olarak görüldü.

SONUÇ: Elektif herni tamiri yapılan pediatrik hasta grubunda kaudal uygulamalarda uygun dozlarda ropivakain ile peroperatif ve postoperatif dönemlerde tatmin edici analjezi sağlanabilmiş ve yan etki görülmemiştir. Uygulanan ketamin dozlarında ise preemptif etki elde edilememiştir.

Anahtar Kelimeler: preemptif analjezi, ketamin, kaudal blok, pediatrik hastalar

SUMMARY

The Efficacy of Preemptive Ketamine and Ropivacaine in Pediatric Patients: A Placebo Controlled, Double-blind

OBJECTIVE: *We have evaluated and compared the preemptive efficacy of intravenous ketamine with placebo and caudal ropivacaine in pediatric patients going under elective hernia repair.*

METHODS: *60 ASAI-II pediatric patients ages between 1-12. The patients were divided into 3 groups randomly.*

Group K patients had 0.5mg/kg ketamine by intravenous route before induction,Group R patients had 0.7 mg/kg 0.2% ropivacaine caudally and 2ml normal saline intravenously,Group RK patients had 0.7 mg/kg 0.2% ropivacaine caudally and 0.5mg/kg ketamine by intravenous routeAll patients had standard anesthesia technique. Heart rate (HR), pulse oximetry, and systolic and diastolic blood pressure (BP), and BIS (bispectral index) were obtained during anesthesia, In addition, end-tidal carbon dioxide concentration was monitored. The efficacy of postoperative analgesia was documented by objective pain scale (OPS). Analgesic requirements during and after the surgery documented

RESULTS: *While there was no significant differences in fentanyl consumption between the groups GR and GRK, fentanyl consumption was found to be significantly higher in group K during anesthesia.When compared with GR and GRK, GK had significantly higher OPS values. During postoperative period Group K patients demanded for additional analgesics in significantly shorter time than group R and Group K patients. GK patients had consumed significantly higher amounts of acetaminophen after surgery*

CONCLUSION: *Caudal application of ropivacaine in appropriate doses provides satisfactory peroperative and postoperative analgesia with no side effects in pediatric patient group going under elective hernia repair where as ketamine with the applied doses has no preemptive effect.*

Key words: *preemptive analgesia, ketamine, caundal block, pediatric patients.*

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Introduction

The field of pain management in general has grown considerably over the past 30 years. Despite the advances, pain management in certain special populations like pediatric patient group is just beginning to be explored. Basic and clinical research has been improving our understanding and management of children's pain.

Research on ideal technique, ideal drug combination and ideal time of application still keeping on for better results in postoperative pain management.

Regional anesthetic and analgesic techniques especially caudal blockade with different drugs in pediatric population is commonly used. Caudal anesthesia and analgesia is now a standard technique in subxyphoidal pediatric procedures. In order to increase the success and overcome the unwanted effects of local anesthetic drugs alone as systemic toxicity, short duration, different analgesic doses and drug combinations have been tried (Almenrader et al. 2005, Panjabi et al. 2005, Ivani et al. 2002).

Ketamine, NMDA receptor antagonist, has been used preemptively, as an adjuvant to analgesic treatment on the hypothesis of its possible preventive effect on central sensitization (Launo et al. 2004). However the dose, route of application, appropriate patient group even its affectivity are still in debate.

In the presented study, we have evaluated and compared the preemptive efficacy of intravenous ketamine with placebo and caudal ropivacaine in pediatric patients going under elective hernia repair.

Methods:

The study was designed as randomized, placebo-controlled, double-blinded manner.

The randomization was computer based and prepared in double-blinded manner. Solutions were prepared by an anesthesist not involved in any other session of the study. The study blinding was maintained until completion of the study.

Following approval from Ethical committee of Istanbul University, Medical Faculty and written informed consent from the parents of 60 ASAI-II pediatric patients ages between 1-12, who were scheduled for elective hernia repair between the dates June 2005-June 2006 by Pediatric Surgery Department of Medical Faculty of İstanbul University were enrolled in the study. Patients younger than 1 year and older than 12 years, procedures less than 30 minutes and longer than 4 hours, patients with known allergy or hypersensitization to the drugs planned to be used and the patients who have contraindication to regional blockade (infection, sepsis, coagulopathy, anti-aggregant/anticoagulant intake) were excluded from the study.

The patients were divided into 3 groups randomly:

Group K; Group K patients had 0.5mg/kg ketamine by intravenous route before induction, N=20

Group R; Group R patients had 0.7 mg/kg 0.2% ropivacaine caudally and 2ml normal saline intravenously, N=20

Group RK; Group RK patients had 0.7 mg/kg 0.2% ropivacaine caudally and 0.5mg/kg ketamine by intravenous route, N=20

Anesthetic Technique:

All children received 0.5-mg/kg rectal midazolam 20 min before anesthetic induction. After insertion of an IV access, the administration of glucose/saline solution 10 ml/kg, general anesthesia was induced by administering sevoflurane via a facemask. maintenance of anesthesia was realized with sevoflurane at 1 minimum alveolar anesthetic (MAC) concentration and 70% nitrous oxide in oxygen via laryngeal mask. The caudal block was performed under aseptic conditions with a 22-gauge Quincke needle in a left lateral position. Immediately after the anesthetic was injected, the children were turned to a supine position.

Heart rate (HR), pulse oximetry (SpO2), and systolic and diastolic blood pressure (BP), and BIS (bispectral index) were obtained before and after the induction of general anesthesia, after caudal injection, and every 5 min thereafter, intraoperatively. In addition, end-tidal carbon dioxide concentration was monitored. The interval between caudal injection and skin incision was 15 min in all patients.

An intraoperative decrease in BP or HR of more than 30% from preoperative values was defined

as hypotension or bradycardia, respectively, and was treated with rapid infusion of fluids or with atropine 0.01 mg/kg when needed. Respiratory depression was defined as a decrease in SpO2 to <93% requiring supplementary oxygen. An intraoperative increase in BP or HR by >10% was defined as insufficient analgesia and was treated with fentanyl 0.1 mic/kg. At the beginning of skin closure, sevoflurane and nitrous oxide were discontinued. When the children were sufficiently awake, they were taken to the recovery room after the laryngeal mask was removed.

Postoperative analgesia was evaluated with the OPS (objective pain scale). If the OPS (objective pain scale) were equal or higher than 5 the child received rectal paracetamol 2mg/kg.

Evaluation parameters:
Intraoperative propophol consumption and analgesic consumption (fentanyl) were evaluated during surgery.

The efficacy of postoperative analgesia was documented by objective pain scale (OPS). The OPS was based on objective behavioral variables (blood pressure, crying, agitation, motion, and verbal evaluation (Table 1). In addition, the first spontaneous voiding was recorded.

Table 1. Objective pain scores: 3 point, 0-2 evaluation of with respect to changes in blood pressure, crying, movements, agitation and verbal evaluation of the child

Parameter	Value
Blood pressure	
10% preop	0
10% to 20% preop	1
>20% preop	2
Crying	
Not crying	0
Crying but consolable	1
Crying, not consolable	2
Movement	
None	0
Restless	1
Thrashing	2
Agitation	
Asleep or calm	0
Mild	1
Hysterical	2
Verbal evaluation or body language	
Asleep or states no pain	0
Mild pain (cannot localize)	1
Moderate pain (can localize) verbally or by pointing	2

Six hours after caudal injection, the patients were discharged from the recovery room to the ward, where they were monitored for another 8 h. SpO_2, OPS, and sedation scores in the recovery room were recorded by an experienced nurse at the 15^{th}, 30^{th} minutes 2^{nd}, 4^{th}, 8^{th} hours.

Statistical analysis: All values are expressed as means ± SD. Data analysis was performed by factorial analysis of variance (ANOVA). TUKEY was used as the posttest. Results were considered to be statistically significant at $P < 0.05$. After data collection, power analysis was performed for the duration of the block by use of a commercially available program.

Results:
When the demographic features were compared between the groups there were no significant differences between the groups regarding age, weight, gender and duration of surgery (Table 2).

Table 2. Demographic features and duration of surgery There were no significant differences between groups with respect to their age, weight, gender distribution, and duration of surgery

	GK		GR		GRK	
	Avg.	SD	Avg	SD	Avg.	SD
Age (year)	4,1	2,756	2,85	1,278	3	1,076
Weight (Kg)						
Gender (F/M)	18,7	7,446	17,65	5,204	15,85	2,870
Duration of surg.						
(min)	3/12		2/13		0/15	
	62,7		61,3		57,9	

There were no significant differences between the groups regarding propofol consumption during the surgery ($p>0.05$) (Figure 1), while there was no significant differences in fentanyl consumption between the groups GR and GRK, fentanyl consumption was found to be significantly higher in group K (Table3).

When evaluating the pain at the 0th, 30th minu-

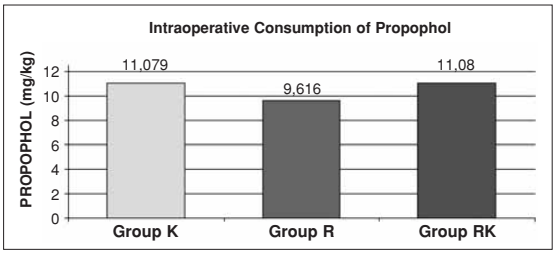


Figure 1. Mean VAS values of groups according to time (*: p<0.05)

Table 3. Intraoperative analgesic consumption: fentanyl consumption in GK found to be significantly higher. There were significant differences between GR and GRK with respect to fentanyl consumption during surgery

	GK		GR		GRK		
Intraoperative	Avg.	Ss	Avg.	SS	Avg.	SS	p
analgesic							
(fentanyl)consumption	1,225	0,5538	0,44	0,5295	0,1	0,1892	α<0,001
(micgr/Kg)	α		α		β		β<0,001
	β		θ		θ		θ<0,05

tes, 2nd h, 4th h and 8th hours GK had significantly higher OPS values (more pain) when compared with GR and GRK, (Table 4, Figure 2). Respectively, GK patients had consumed significantly higher amounts of acetaminophen. There were no significant differences in acetaminophen consumption between groups R and RK. During postoperative period Group K patients demanded for additional analgesic in significantly shorter time than group R and Group K patients (Figure 3).

Only 3 patients from GK had nausea and vomiting those who had higher opioid consumption during surgery.

Discussion:

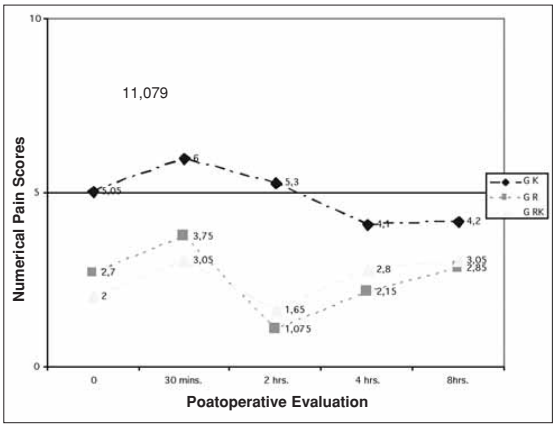
Postoperative pain management is one of the most important issues in the outcome of the surgery. Despite all the developments in anesthetic and regional techniques, newer drugs, drug combinations, its impact in pediatric patient groups may sometimes be under estimated due various reasons like pediatric metabolism, facility problems, pediatric limitation of certain drugs, techniques, lacking knowledge of evaluation parameters.

Caudal blockade is a standard anesthetic techni-

Table 4. Comparison of OPS values between the groups: The OPS values at the 0th, 30th min., 2nd, 4th, and 8th hours are higher in GK

	GK		GR		GRK		
	Avg.	SD	Avg.	SD	Avg.	SD	p
OPS 0	5,05	1,538	2,7	1,218	2	0,9177	α<0,001
		α		α		β	β<0,001
		β		θ		θ	θ>0,05
OPS 30	6	1,124	3,75	1,020	3,05	0,7592	α<0,001
		α		α		β	β<0,001
		β		θ		θ	θ>0,05
OPS 2	5,3	2,227	2,9	1,075	2,75	1,650	α<0,001
		α		α		β	β<0,001
		β		θ		θ	θ>0,05
OPS 4	4,1	1,294	2,15	1,348	2,8	1,105	α<0,001
		α		α		β	β<0,001
		β		θ		θ	θ>0,05
OPS 8	4,2	1,936	2,85	1,226	3,05	1,146	α<0,001
		α		α		β	β<0,001
		β		θ		θ	θ>0,05

Figure 2. Comparison of OPS values between the groups



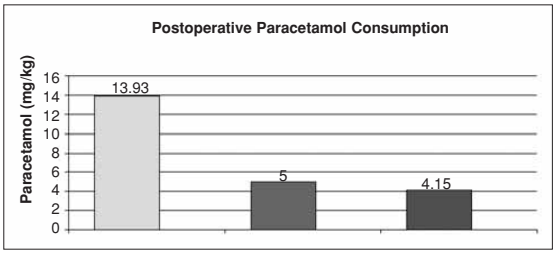


Figure 3. Postoperative paracetamol consumption

que to achieve an adequate level of perioperative analgesia in all subxiphoidal pediatric procedures. Caudal block can be used as an adjunct to general anesthesia or administered at the completetion of surgery to provide postoperative analgesia (De Beer and Thomas 2003). However single injection may have only a relatively short duration of action. Koinig et al (Koinig et al. 1999), who used ropivacaine for caudal blockade, reported that only 52% of children maintained a sufficient level of analgesia for 24 hours when a concentration of 0.5% was used. Placement of a catheter into the extradural space to administer low concentrations for longer periods either at the caudal or lumbar region adds a risk of infection and tends to prevent early mobilization.

Attempts to overcome these problems by combining local anesthetic agents with other drugs like adrenaline, ketamine, clonidine, opioids have met with different degrees of success in prolonging the pain-free period (Turan et al. 2003, Prosser et al. 1997, Cook et al. 1995, Naguib et al. 1991). Ivani et al (Ivani et al. 2000) reported that the duration of analgesia offered by plain ropivacaine 0.2% could be extended by using ropivacaine 0.1% plus clonidine 2 g/kg. In his study group supplementary analgesics were required in only 10% of those children, compared with 45% of the former, when compared with the 100% reported by Koinig et al (Koinig et al. 1999) for ropivacaine 0.25%. Apart than adding miscellaneous agents, use of preemptive analgesia is another method used to increase the quality and the duration of analgesia via central ways. Tissue trauma during surgery modifies the central processing pathway for pain perception. These changes decrease stimulus threshold and amplify postoperative pain. The induction and maintenance of such central sensitization may be dependent on the activation of N-methyl-d-aspartic acid (NMDA) receptors (Kissin 2000). Therefore, preoperative administration of ketamine, an NMDA-receptor antagonist has for a long time has been the gate to preemptive analgesia.

Despite the overwhelming success in animal experiments (Lee et al. 2005, Lee et al. 2001, Nagasaka et al. 2000) clinical reports confirming the preemptive analgesic effects of ketamine in general have not been forthcoming (Becke et al. 2005, Gilabert Morell and Sanchez Perez 2002, Adam et al. 1999).

Though on hypothetical basis it is assumed to be a good preemptive agent, the results from the published data are not satisfactory and the subject is prone to discussion with regard to the population, route of administration, central neurotoxicity and side effects. In addition, preemptive use of ketamine in pediatric patient population is also not very common. In a recent study Kwok et al (Kwok et al. 2004) found that their results demonstrate that a small dose of ketamine, given before skin incision, decreases postoperative pain, reduces morphine consumption, and delays patients' request for analgesia after laparoscopic gynecologic surgery. Evaluating our results, the most important finding of our study was that on the contrary to some published data (Lavand'homme et al. 2005, Launo et al. 2004) we had found out that intravenous administration of ketamine does not have any affect either on peroperative anesthetic demand or postoperative pain and analgesic consumption bringing abroad questionin of the preemptive effect of ketamine. Preoperative caudal ropivacaine administration on the other hand found to be significantly more effective either in peroperative analgesic demand or postoperative pain scores and analgesic demand than intravenous ketamine administration alone.

In addition, addition of intravenous ketamine to caudal ropivacaine didn't reduce peroperative analgesic demand or postoperative analgesic demand or postoperative pain scores Obviously, we cannot come to the conclusion that ketamine doesn't have preemptive effect from the above mentioned data. There may be a number of reasons explaining the in affectivity of ketamine in our study as the dose administered, elimination, pediatric metabolism, time of administration because timing of treatment in preemptive analgesia is an integral part of the concept, the interaction between drug dosage and stimulus intensity must not be overlooked.

Also preemptive dose in pediatric patient population is another important issue for ketamine. The intrinsic analgesic properties of ketamine may have reduced the postoperative pain score. The plasma ketamine concentration producing clinical analgesia is in the order of 100–150 ng/mL (Kwok et al. 2004). Given that ketamine is rapidly distributed, they have calculated that a bolus injection of ketamine 0.15 mg/kg would provide analgesia for less than 5 minutes. Altho-

ugh the dosage was higher in our study our information is lacking to discuss its continuity through out the surgery.

Discussing our results we have to take in consideration that despite ketamine acts via central pathways both at the spinal and supraspinal levels, caudal ropivacaine administration inhibits pain transmission at the spinal level with appropriate timing and dosing, consequently it also inhibits central sensitization and provides postoperative analgesia with low analgesic requirements has a superior preemptive effect in our study group.

Conclusion

Caudal application of ropivacaine in appropriate doses provides satisfactory peroperative and postoperative analgesia with no side effects in pediatric patient group going under elective hernia repair and has superior preemtive effect compared with intravenous ketamine administration.

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