Effects of ketamine added to ropivacaine in pediatric caudal block

Pediyatrik kaudal blokta ropivakaine eklenen ketaminin etkinliği

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Summary

Objectives: We aimed to determine the hemodynamic effects and postoperative pain control quality of ropivacaine and ketamine addition to ropivacaine in children undergoing inguinal hernia repair with caudal anesthesia.

Methods: A total of 45 patients (1-4 years) scheduled to undergo inguinal hernia repair were studied. Anesthesia was induced with sevoflurane in O_2/N_2O and vecuronium was administered to facilitate endotracheal intubation. Anesthesia was maintained with sevoflurane in O_2/N_2O. Patients were randomly divided into three groups. Following endotracheal intubation, we administered 2 mg/kg 0.2% ropivacaine to Group R; 0.5 mg/kg ketamine to Group K; and 2 mg/kg 0.2% ropivacaine plus 0.5 mg/kg ketamine to Group R+K caudally. Pain levels were evaluated via modified CHEOPS, and sedation levels were assessed by the Wilson Sedation Scale.

Results: At the postoperative 45th minute (min), the CHEOPS score was significantly higher in Group R compared to Group K and Group R+K ($p<0.05$). This score was significantly higher in Group R than in Group R+K at the postoperative 60th min ($p<0.05$). The effective analgesic period was significantly higher in Group K (852±309 min) and Group R+K (1032±270 min) than in Group R (435.5±273 min) ($p<0.05$). The analgesic requirement in the first 24 hours postoperatively was lower in Group R+K than the other groups. Sedation scores were below 2 in all groups. There were no significant differences between groups regarding adverse events.

Conclusion: The results of the present study indicate that caudal ropivacaine, ketamine and ropivacaine plus ketamine provided effective postoperative analgesia. Additionally, ketamine combined with ropivacaine lengthened the duration of analgesia while lowering analgesic requirements.

Key words: Caudal block; ketamine; postoperative pain; ropivacaine.

Özet

Amaç: *İnguinal herni onarımı operasyonu geçiren çocuklarda kaudal anestezide ropivakainin ve ropivakaine eklenen ketaminin, hemodinamiye etkisi ve postoperatif ağrı tedavisindeki etkinliliğinin değerlendirilmesi amaçlandı.*

Gereç ve Yöntem: *Çalışmaya 1-4 yaşlarında inguinal herni onarımı planlanan 45 olgu alındı. Anestezi indüksiyonu O_2/N_2O karışımı içinde sevofluran ile yapıldı. Vekuronyum ile yeterli kas gevşekliği sağlanarak endotrakeal entübasyon uygulandı. Anestezi O_2/N_2O hava karışımı içinde sevofluran ile sürdürüldü. Hastalarımız rastgele üç gruba ayrıldı. Endotrakeal entübasyondan sonra, Grup R'ye 2 mg/kg %0.2'lik ropivakain, Grup K'ya 0.5 mg/kg ketamin, Grup R+K'ya 2 mg/kg %0.2'lik ropivakain+0.5 mg/kg ketamin kaudal olarak verildi. Hastaların ağrı düzeyleri modifiye CHEOPS, sedasyon durumu Wilson sedasyon skalası kullanılarak değerlendirildi.*

Bulgular: *Modifiye CHEOPS skorunun, Grup R'de postoperatif 45. dakikada Grup K ve R+K'ya göre, 60. dakikada ise Grup R+K'ya göre anlamlı derecede artmış olduğu saptandı ($p<0.05$). Grup K (852±309 dakika) ve R+K'da (1032±270 dakika), Grup R'ye (435.6±273 dakika) göre analjezi süresinin daha uzun bulundu ($p<0.05$). İlk 24 sa içindeki analjezik gereksinimi olan olgu sayısının Grup R+K'da daha az olduğu belirlendi. Sedasyon skorları tüm gruplarda <2 seyretti. Yan etkiler bakımından gruplar arasında anlamlı farklılıklar yoktu.*

Sonuç: *Çalışmamızda kaudal ropivakain, ketamin ve ropivakain+ketamin ile etkin bir postoperatif analjezinin sağlandığı, ropivakaine eklenen ketaminin analjezi süresini uzattığı ve daha az analjezik gereksinimi doğurduğu saptandı.*

Anahtar sözcükler: Kaudal blok; ketamin; ropivakain; postoperatif ağrı.

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Introduction

The use of regional methods has considerably alleviated the physiological stress arising from inadequate postoperative pain management amongst pediatric patients, their families and medical staff. Orally administered analgesics sometimes provide insufficient pain control and parenteral opioids, besides their higher activity, have certain side effects such as sedation, respiratory depression, constipation, nausea and vomiting that impede their effective use. Additionally, the short dosage interval of these medications imposes additional stress on children.[1] Regional methods of spinal, epidural, caudal anesthesia and peripheral plexus blockage in extremity interventions can be used as adjuvant methods to general anesthesia. Caudal block is the most common method among these. Not only its application straightforward but its higher safety profile also makes caudal block the method of choice.[2] The choice of appropriate agent for the caudal block is important. Agent must be effective, long lasting and safe. Bupivacaine and ropivacaine are accepted agents in caudal block with long lasting effects and well differential nerve blocking capacities at low concentrations.[3,4] The most significant disadvantage of local anesthesia is its short duration due to single administration. To overcome this limitation certain drugs are suggested in combination with the local anesthetic agent.[5-7]

Ropivacaine has been the agent of choice, with its long effective period, well differentiated nerve blocking capacity, and ongoing postoperative analgesic effects with minimal motor block. Additionally, ropivacaine has less central nervous system and cardiac toxicity than bupivacaine.

After further developments in understanding the important roles of N-Methyl D-Aspartate (NMDA) receptor antagonists in analgesia, ketamine, an NMDA antagonist, became the drug of choice in clinical applications.[5] When used in sub-anesthetic doses, ketamine has powerful analgesic effects. Previous studies have demonstrated that caudally administered ketamine and bupivacaine provide protracted postoperative analgesia. Caudal epidural anesthesia is the most common method not only for its easy applicability but also for its intraoperative and postoperative analgesic effects.[1,8]

In the present study, we aimed to evaluate the effects of caudal ropivacaine, ketamine and a combination of these two drugs on hemodynamic parameters and postoperative pain in children that were scheduled to undergo inguinal hernia repair.

Methods

The study protocol was approved by the local ethical committee and informed consent was obtained from the parents of children. Forty-five children with ASA I-II, aged between 1-4 years scheduled to undergo inguinal hernia repair were included. Exclusion criteria for the study were: Mental retardation, Down syndrome, multiple malformations, hepatic, renal and neurological diseases, potential postoperative ventilator requirement, emergent surgical situations, increased intracranial or intraocular pressure, epilepsy. The study population did not receive any premedication.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), peripheral arterial oxygen saturation (SpO_2) and electrocardiograph were monitored. Anesthesia was induced with a facial mask using 8% sevoflurane in a mixture of 50% O_2 and 50% N_2O. A suitable vein at the dorsum of the hand was cannulated (with 24 G cannula). Fluid replacement was administered with 1/3 Izodeks solution (Eczacıbaşı/Baxter, Istanbul, Turkey) at a rate of 3-5 ml/kg/h. After maintaining adequate muscle relaxation with 0.1 mg/kg vecuronium bromide (Organon, Istanbul, Turkey), endotracheal intubation was performed using cuffless tubes. Anesthesia was maintained with 0.5-2.5% sevoflurane in 50% O_2 and 50% N_2O mixture. Vecuronium bromide (0.03 mg/kg) was administered to cases requiring repetitive muscle relaxation.

Patients were randomly divided into three groups using a random rumber table. Following endotracheal intubation, patients were placed in lateral decubitus positoin and, under sterile conditions, caudal epidural anesthesia was performed with a 22-gauge B-bevel needle. After controlling regurgitation of blood and cerebrospinal fluid the ropivacaine group (Group R) was administered 2 mg/kg of 0.2% ropivacaine (Naropin 0.2%, AstraZeneca, Soderalje, Sweden), the ketamine group (Group K) patients

Table 1. Modified CHEOPS[9]

Score	0	1	2
Cry	No cry	Crying/moaning	Scream
Facial expression	Smiling/Positive	Neutral	Grimace
Verbal expression	Positive statement	Negative statemtent	Suffering from pain, another complaint
Torso	Neutral	Variable, taut, upright	Stretched
Legs	Neutral	Kicking	Stretched, continuous move

received 0.5 mg/kg ketamine (Ketalar, Eczacıbaşı, Istanbul, Turkey) and the ropivacaine plus ketamine group (Group R+K) was administered 2 mg/kg 0.2% ropivacaine plus 0.5 mg/kg ketamine over 2-3 min. Immediately after application of caudal block, patients were taken into supine position. SBP, DBP, HR and SpO_2 of the patients were recorded prior to caudal block, after caudal block, at the 5th and 15th min of the surgical interventions and every 15 min until the end of the surgery. A decrease of more than 20% in HR and mean arterial pressure (MAP) from baseline values was accepted as settled caudal block than the surgical procedure was started. Anesthetic agents were discontinued at the end of the surgical procedure and patients were ventilated with 100% O_2. Residual block was antagonized with 0.02 mg/kg atropine sulphate and 0.05 mg/kg neostigmine. Patients were extubated after confirmation of adequate respiratory and muscular activity.

In the recovery room, SpO_2 values were monitored and SBP, DBP and HR values were recorded every 5 min during the first (post-surgical) 15 min. HR, SBP, DBP, respiratory rate (RR), SpO_2, pain and sedation scores were recorded at the postoperative 5th, 15th, 30th and 60th min and the 2nd, 3rd, 4th, 6th, 12th and 24th h. Pain levels were evaluated according to modified CHEOPS (Table 1).[9] Sedation levels were evaluated according to the Wilson sedation scale (Table 2).[10] The degree of motor block was assessed with the 3-point scale (Table 3).

Patients were followed for nausea, vomiting, urinary retention, incontinence, hallucination and negative behaviors. According to modified CHEOPS, values equal to or greater than 4 were accepted as indication of analgesic requirement. The times of first analgesic administration and total analgesic dose during the first 24 h were recorded. Patients suffering from pain received 20 mg/kg of paracetamol via the rectal route in the recovery room. Patients received 20 mg/kg of paracetamol via the oral route when appropriate.

Table 2. Wilson sedation scale[10]

Score	Degree of sedation
1	Fully awake and oriented
2	Drowsy
3	Eyes closed but rousable to command
4	Eyes closed but rousable to mild physical stimulation (earlobe tug)
5	Eyes closed but unrousable to mild physical stimulation

Table 3. Motor block scale

Score	Criteria
0	Free movement of legs, able to stand
1	Possible to move the legs
2	Unable to move legs

Statistical analysis were performed using a commercially available software package Statistical Package for Social Sciences (SPSS, version 12.0). Data were presented as mean ± standard deviation (SD). One Way ANOVA, Post Hoc Tukey HSD, Kruskal Wallis and Mann-Whitney U tests were used for comparison of groups. Intragroup comparisons were performed with Paired-Samples T test and Wilcoxon analysis. In the presence of nausea-vomiting, urinary retention, incontinence, hallucinations and negative behaviors Pearson Chi Square test was applied. A P value smaller than 0.05 was accepted as significant.

Table 4. Age, gender, body weight and duration of surgery of the groups (mean ± SD)

	Group R (n=15)	Group K (n=15)	Group R+K (n=15)
Gender (M/F)	10 / 5	11 / 4	11 / 4
Age (months)	27.53±9.03	25.66±10.72	30.00±13.49
Body weight (kg)	12.40±1.95	12.00±2.44	13.26±3.12
Duration of surgery (min)	41.00±11.68 (30-60)	41.66±11.90 (20-60)	37.00±11.14 (15-50)

Results

There were no statistically significant differences between groups regarding age, sex, body weight and operation durations (p>0.05, Table 4).

According to intragroup analysis, the decrease in SBP (Fig. 1) in Group R after caudal block was statistically significant (p<0.05). The decrease in SBP values of Group K and Group R+K were not statistically significant in all measuring points. On the other hand, inter-group analysis showed that the decrease in SBP within Group R after caudal block was significantly different from Group K and Group R+K (p<0.05). There was a significant increase in Group K at the 5th min of the operation compared with Group R and Group R+K (p<0.05). Intra-group analysis of DBP (Fig. 2) revealed a significant decrease in Group R after caudal block

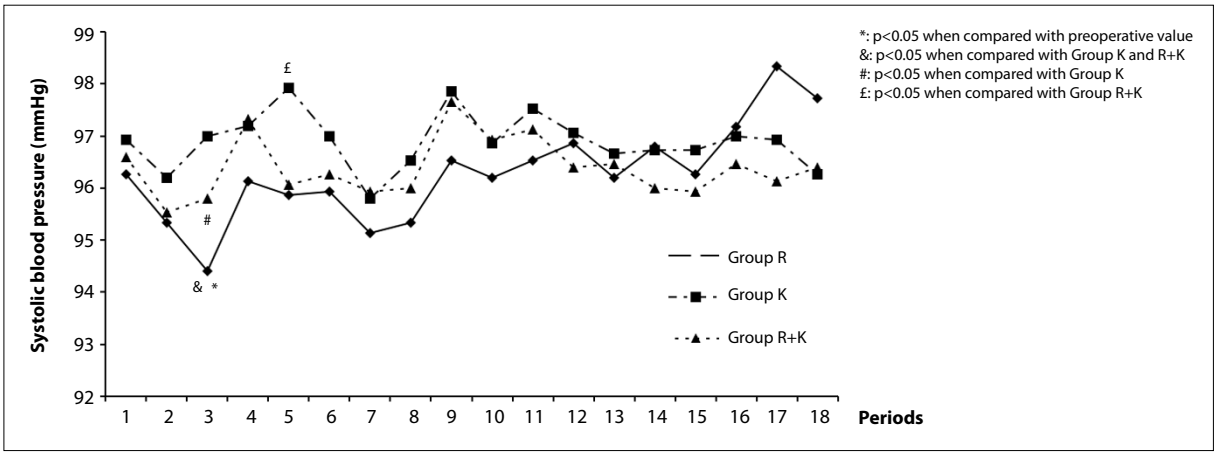

Fig. 1. Systolic blood pressure values: 1: preoperative; 2: prior to caudal block; 3: after caudal block; 4: immediately after started of operation; 5, 6, 7, 8: at the intraoperative 5th, 15th, 30th, 45th min respectively; 9, 10, 11, 12, 13, 14, 16, 17, 18: at the postoperative 5th, 15th, 30th and 60th min and the 2nd, 3rd, 4th, 6th, 12th and 24th h respectively.

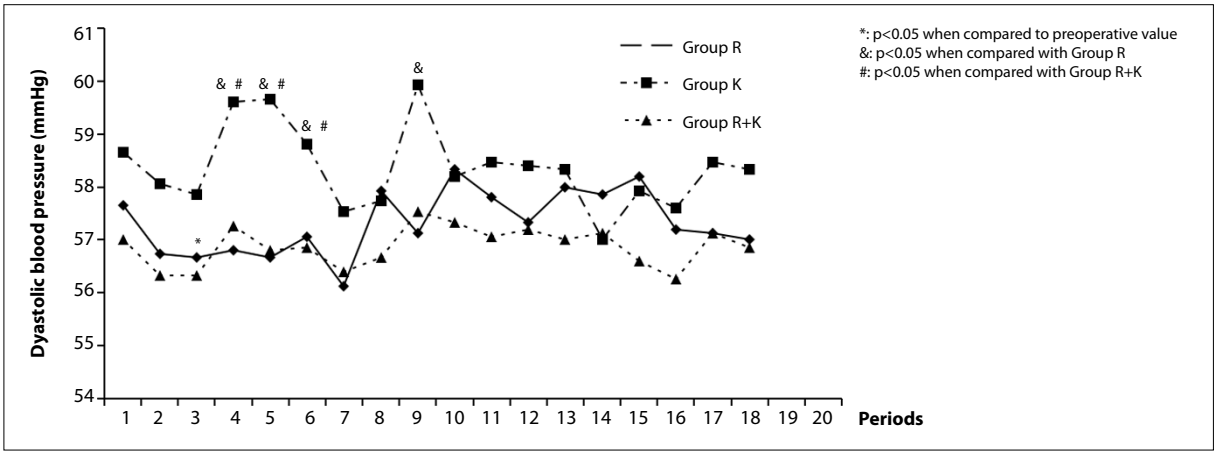

Fig. 2. Dyastolic blood pressure values: 1: preoperative; 2: prior to caudal block; 3: after caudal block; 4: immediately after started of operation; 5, 6, 7, 8: at the intraoperative 5th, 15th, 30th, 45th min respectively; 9, 10, 11, 12, 13, 14, 16, 17, 18: at the postoperative 5th, 15th, 30th and 60th min and the 2nd, 3rd, 4th, 6th, 12th and 24th h respectively.

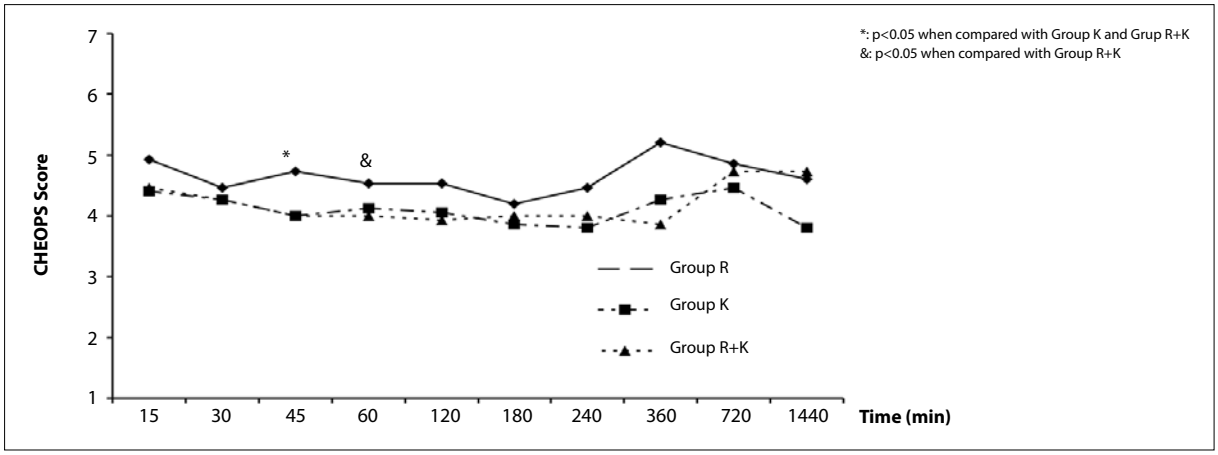

Fig. 3. Postoperative CHEOPS values.

(p<0.05). Inter-group analysis demonstrated significantly higher DBP values in Group K than Group R at the surgical incision point and at the 5th, 15th and 45th min of the operation (p<0.05). Additionally, Group K values were significantly higher than Group R+K at the surgical incision point and at the 5th and 15th min of surgery (p<0.05). There were no statistically significant differences in inter and intra group analysis regarding HR, RR, SpO_2 values (p>0.05). SpO_2 values were above 97% in all of the cases and there were no apneic patients.

There were no significant difference in intra-group analysis of CHEOPS values (p>0.05). Inter-group analysis revealed significant increase in Group R than Group K and Group R+K at the postoperative 45th min. Additionally, there was a significant increase in CHEOPS values in Group R compared with Group R+K at the postoperative 60th min (p<0.05) (Fig. 3). There were no significant differences in either inter or intra group analysis regarding sedation and motor block (p>0.05). There were no deep sedation in any of the patients. However, only one patient in Group R had prolonged motor block for 4 h (Block degree: Scale 2 for the first two hours and 1 for subsequent hours).

Nausea and vomiting were observed in two patients in both Group R and Group K. One patient in Group R suffered from urinary retention which lasted for three hours and recovered without any therapy. Two patients in Group K and one patient in

Table 5. Postoperative side effects

Side effects	Group R (n=15)	Group K (n=15)	Group R+K (n=15)
Nausea-vomiting	1	0	0
Urinary retention	1	0	0
Hallucination	0	2	1
Nystagmus	0	3	1

Table 6. Analgesic durations of the groups and number of patients that required analgesia

	Group R (n=15)	Group K (n=15)	Group R+K (n=15)
Analgesic duration (min)	435.6±273* (180-1200)	852±309 (360-1440)	1032±270 (540-1440)
Number of patients that required analgesia	9**	5	2

* p<0.05 when compared to Group K and R+K; ** p<0.05 when compared with Group R+K.

Group R+K hallucinated. Nystagmus was observed in three patients in Group K and in one patient in Group R+K. There were no significant differences among the groups regarding these adverse events (Table 5).

The mean time until the first analgesic requirement and the number of patients requiring rescue analgesia are given in the Table 6. None of these patients required analgesic agents in the recovery room.

Discussion

The results of the present study indicate that caudal anesthesia with ropivacaine, ketamine provided hemodynamic stability and increased the duration of analgesia while lowering analgesic requirements in children undergoing inguinal hernia repair with general anesthesia.

Analgesia duration provided by ropivacaine was reported to be similar to that of bupivacaine, however ropivacaine produces lesser motor block and cardio toxicity than bupivacaine.[4] Animal studies have demonstrated that tolerability of high dose ropivacaine is better than that of high dose bupivacaine.[11] There is no consensus on the exact dose of ropivacaine in caudal anesthesia. Koining et al. have used two different concentration regimens of ropivacaine (0.75% and 0.5%) for postoperative analgesia. They demonstrated that 0.5% ropivacaine provides adequate analgesia in 52% of the patients for 24 h.[12] In another study by Khalil et al., 1 ml/kg 0.25% of ropivacaine was found to provide 11 h of mean analgesia duration and had an analgesic profile sufficient for 33% of cases in the first 24 h.[13] Ivani et al. have found the analgesia duration to be 271 min (for 1 mg/kg 0.2% ropivacaine).[4] Da Conceicao and Coelho found 0.375% of ropivacaine for the same dosage profile provided 5 h of analgesia.[14] The linear correlation between concentration and analgesia duration in these studies is striking. We used 0.2% ropivacaine (2 mg/kg) in the present study and the mean analgesia duration was calculated as 435 ± 273 min. Six of our cases (40%) did not require analgesia in the first 24 h.

Ketamine is a widely used agent in both anesthesia and pain prevention. It was also reported as an effective agent in postoperative pain control.[1,15,16] Ketamine added to bupivacaine in caudal analgesia as an adjuvant agent was shown to increase analgesia duration. Sample et al. added different doses of ketamine (0.25, 0.5 and 1 mg/kg) to caudally applied bupivacaine (0.25%) for postoperative pain control and found analgesia durations of 7.9, 11 and 16.5 h, respectively. They concluded that 0.5 mg/kg ketamine was the most effective dose with optimal effect duration and minimal side effect profile.[2] Ozbek et al. used caudal ketamine and determined the median time to first analgesia time as 24 h. They stated that their cases did not require any analgesics in the first 6 h since their CHEOPS scores were four.[17] Lee and Sanders demonstrated postoperative analgesia duration of caudal ropivacaine (1 mg/kg 0.2%) and ropivacaine (1 mg/kg 0.2%) plus ketamine (0.25 mg/kg) as 3 and 12 h, respectively.[6] The groups in this study did not demonstrate any significant differences regarding postoperative nausea, vomiting, sedation, hallucination and urinary retention. De Negri and Ivani established an analgesia duration of 291 min with 2 mg/kg 0.2% ropivacaine which was increased to 701 min with 0.2% ropivacaine combined with 0.5 mg/kg S-Ketamine.[18] In all of these previous studies, the addition of caudal ketamine to the regimen increased the analgesia duration. In our study, the mean analgesia duration in Group R+K (2 mg/kg, 0.2% ropivacaine plus 0.5 mg/kg ketamine) was 1032±270 min and only 2 patients (13%) in this group required analgesia in the first 24 h. Analgesia durations of the Group K (0.5 mg/kg ketamine) and the Group R+K were significantly higher than that of the Group R (2 mg/kg, 0.2% ropivacaine) ($p<0.05$). There was no significant difference between Group K and Group R+K regarding analgesia duration ($p>0.05$). Ropivacaine has less pronounced myocardial depressor and dysrhythmic effects than bupivacaine.[19] Da Conceicao and Coelho used a combined dose of 0.375% bupivacaine and ropivacaine at 1 ml/kg dose and found minimal changes in HR, SBP and DBP values.[14] De Negri and Ivani reported that ropivacaine and S-ketamine with ropivacaine had no hemodynamic effects.[18] In our study, SBP and DBP values recorded during the postoperative period were similar to the preoperative values. On the other hand, the ropivacaine group demonstrated decreases in SBP and DBP values after caudal block

compared to the control values. The ketamine and ropivacaine plus ketamine groups did not show any significant differences at any measurement points. The decrease in the ropivacaine group was statistically significant. SBP and DBP values in the ketamine group were higher than the ropivacaine group at the 5th, 15th and 45th min of the operation. HR values were lower than control values in all groups, however these differences were not statistically significant. In contrast to previous studies, none of our cases demonstrated hypotension and bradycardia. Khalil et al. reported no respiratory or hemodynamic changes after caudal block with 0.25% ropivacaine.[13] Similarly, De Negri and Ivani reported no respiratory changes or depression after caudal 0.02% ropivacaine and 0.2% ropivacaine and S-ketamine mixture.[18] In our study, respiratory rates of the cases were between 23-25 per minute, and we did not encounter any respiratory depression.

Ropivacaine has similar sensory effects to bupivacaine, however, its motor block duration is shorter.[14,19] Ivani et al. reported no motor weakness after 0.25% bupivacaine and 0.2% ropivacaine.[4] Conversely, Khalil et al. reported motor weakness continuing for 3 h after 0.25% caudal ropivacaine.[13] In those studies, ketamine was shown to reduce the incidence of motor block when added to the procedure after reducing the dosage of local anesthetic agent. In our study, comparison of motor block scores of the groups revealed no significant difference in both intra-group and inter-group analyses. However, one of the patients that received 0.2% ropivacaine demonstrated 4-h long motor block. None of the previous studies reported sedation with single use of ropivacaine.[15] In our study, sedation scores were lower than 2 and there was no difference between groups. Additionally, we did not observe delirium in any of the groups. Previous studies reported nystagmus after caudal application of ketamine.[17,20] In our study, we observed nystagmus in three patients in the ketamine group (20%) and one in the ropivacaine plus ketamine group (6.6%). Ozbek et al. reported 10.5% vomiting with caudal ketamine.[17] Negri and Ivani reported this side effect in 10.5% of patients that received ropivacaine and in 5.2% of patients that received ropivacaine and S-ketamine.[18] In our groups, nausea and vomiting was observed in two patients in both the ropivacaine and ketamine groups (13.3%). Additionally, we observed urinary retention in only one case in the ropivacaine group (6.6%).

Luz et al. suggested reduced intraoperative anesthetic agent requirement with caudally applied bupivacaine.[3] Consequently, we also think that presurgical application of caudal ropivacaine, ketamine and ropivacaine plus ketamine reduced the intraoperative anesthetic agent requirement.

In conclusion, caudal anesthesia combined with general anesthesia provided a painless and comfortable postoperative period in children undergoing lower abdominal surgery. Data of this study revealed similar results for caudal ketamine (0.5 mg/kg) and ropivacaine (2 mg/kg) added ketamine (0.5 mg/kg). As there was no statistically significant differences for motor block, sedation and side effects, the caudal use of ropivacaine plus ketamine combination has the advantage of increased analgesia duration and hemodynamic stability. Additionally, analgesic requirements are decreased, thus, ropivacaine can safely be used in combination with ketamine in children receiving caudal anesthesia.

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