



# The success rate and complications of awake caudal epidural bupivacaine alone or in combination with intravenous midazolam and ketamine in pre-term infants

Mahin Seyedhejazi<sup>1</sup>, Majed Mashhoori<sup>1</sup>, Rasoul Azarfarin<sup>2</sup>, Daryoush Shekhzadeh<sup>1</sup>, Nasrin Taghizadieh<sup>1</sup>

## ABSTRACT

**Background:** The aim of the present study is to compare the success rate and complications of caudal epidural bupivacaine alone or in combination with intravenous (IV) midazolam and ketamine in awake infants undergoing lower abdominal surgery. **Materials and Methods:** In this double-blind, clinical trial study, 90 infants (aged below 3 months and weight below 5 kg) with American Society of Anaesthesiologists I-II, were divided into three groups of each 30: Group 1 received bupivacaine 0.25%, 1 mL/kg for caudal epidural block; Groups 2 and 3 received caudal block with same dose bupivacaine along with IV pre-treatment with midazolam 0.1 mg/kg or IV midazolam 0.1 mg/kg and ketamine 0.3 mg/kg, respectively. **Results:** The success rates in Groups 2 and 3 were 93.3% and 93.1%, respectively, compared with a caudal block with bupivacaine alone 80%; ( $P = 0.015$ ). There was no significant difference among the three groups in terms of mean systolic and diastolic blood pressures and mean heart rate at intervals of 0, 20, 40 and 60 min ( $P < 0.05$ ). There were no significant differences in the pain scores  $>3$  on the Neonatal Infant Pain Scale at three intervals (30, 60 and 120 min) after surgery among the three groups. The complications such as apnoea or desaturation were not found in any of the studied groups. **Conclusions:** Adding IV ketamine and/or midazolam to bupivacaine caudal epidural block in the conscious infants can positively affect block success rate.

**Key words:** Awake caudal epidural block, bupivacaine, children, ketamine, midazolam

## INTRODUCTION

Caudal epidural block is the most common regional anaesthetic technique in infants and neonates, undergoing surgery in the lower parts of the body, such as inguinal hernia, anal and rectal operations.<sup>[1]</sup> A caudal block before the surgery reduces the need for intravenous (IV) anaesthetic administration, thus decreasing postoperative complications and leading to faster recovery and earlier discharge.<sup>[2]</sup> This method can be useful for pre-term children to reduce the morbidity and mortality after surgery. Caudal block can be used as a separate anaesthetic technique as well<sup>[3]</sup> or together with a subarachnoid block, can reduce the complications of abdominal surgery such as postoperative apnoea in infants with pre-term birth.<sup>[4]</sup> Infants and neonates, especially very premature infants, are at a high risk of apnoea after surgery with general anaesthesia.<sup>[5]</sup> Caudal anaesthesia is used in the premature infants to reduce the possibility of postoperative apnoea and to discontinue the use of general anaesthesia and narcotics.<sup>[6]</sup> Although a caudal block can be done simply and is highly successful in local anaesthesia, the duration of action is short<sup>[7]</sup>, which can be partly overcome by adding complementary drugs for local anaesthetics.<sup>[8]</sup> There is a need for pre-medication in children to eliminate anxiety, analgesia and to prevent

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<sup>1</sup>Department of Anesthesiology, Tabriz University of Medical Sciences, <sup>2</sup>Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

**Address for correspondence:**  
Dr. Majed Mashhoori,  
Tabriz Children Hospital, Sheshkelan Street,  
Tabriz University of Medical Sciences, Tabriz, Iran.  
E-mail: seidhejazi@yahoo.com

bradycardia and psychological effects after surgery. Various medications, including midazolam and ketamine, are used to relax the patient and eliminate the pain in children.<sup>[9,10]</sup> While no serious complications have ever been reported by adding non-narcotic drugs to caudal anaesthesia, further studies are necessary.<sup>[11,12]</sup> Thus, the researcher decided to evaluate the effect of adding IV midazolam and ketamine as a pre-treatment to caudal epidural anaesthesia with bupivacaine on the success rate, pain score and complications in awake infants, undergoing elective surgery at different postoperative intervals, using caudal block.

## MATERIALS AND METHODS

This study was performed on 90 infants (age <3 months, weight <5 kg) with American Society of Anaesthesiologists class I-II after approval by the Institutional Ethics Committee. The children were the candidates for elective surgeries such as inguinal hernia repair, genital and urinary tract surgery, all of which lasted for <1.5 h. Exclusion criteria were as follows: Caudal block contraindications, contraindication for the use of ketamine, midazolam and bupivacaine, the operation time of more than 1.5 h and cardiopulmonary comorbidities.

Patients were divided into three groups of each 30 using randomised blocks. Necessary actions, objectives and processes were explained to the parents and written informed consent was obtained the day before surgery. After the preoperative visit and sufficient time for fasting, patients were taken to the operating room. Demographic characteristics (age, sex, weight and gestational age) and vital signs (heart rate, systolic and diastolic blood pressure) at 0, 20, 40 and 60 min were measured. After few oral dextrose drops (30%) and complete sterilisation, caudal block with bupivacaine 0.25%, 1 mL/kg in lateral position, was done using a 22-gauge needle (in all of the groups).

In this double-blind, randomised study: Group 1 received caudal epidural block plus IV placebo, Group 2 received caudal block along with IV midazolam 0.1 mg/kg and Group 3 received caudal block with IV midazolam 0.1 mg/kg and ketamine 0.3 mg/kg.

The same volume of IV drugs in similar, coded syringes was prepared and the observer was unaware of their types. The infants were examined in terms of block success, complication rate and apnoea. The absence of pain about 15 min after the caudal block was defined as a successful epidural block (tested by pinching the

skin in the inguinal region). Surgery was started from 15 to 20 min after caudal anaesthesia in all the groups. General anaesthesia was induced in the case of regional anaesthesia failure, surgery was continued with general anaesthesia and the case was excluded from the study. Intraoperative and postoperative vital signs (heart rate, systolic and diastolic blood pressure at intervals of 0, 20, 40 and 60 min) and postoperative complications such as arterial oxygen desaturation, apnoea and length of analgesia were measured at intervals of 0, 30, 60 and 120 min. The Neonatal Infant Pain Scale (NIPS), consisting of six behavioural indicators of crying, facial expressions, quality of breathing, muscle strength and movement of the hands, feet and alertness, was used. Scoring of each domain ranged from 0 to 1 except the neonate crying domain, which is scored from 0 to 2. The total score can be between 0 and 7. Based on the pain assessment scale, subjects, whose scores were equal or higher than 4, were placed in the pain group.

Data analysis was done using statistical software SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc. Descriptive statistics indicators such as mean, frequency and standard deviation were calculated. Mean values of systolic and diastolic blood pressure and heart rate at intervals of 0, 20, 40 and 60 min after surgery were compared in the three study groups by using one-way ANOVA and the scores of postoperative pain were analysed using the Chi-square test. The  $P \leq 0.05$  was considered as statistically significant.

## RESULTS

Seventy-nine patients finished the study: Caudal block ( $n = 24$ ), caudal block plus IV midazolam ( $n = 28$ ) and caudal block along with IV midazolam and ketamine ( $n = 27$ ). Eleven patients lost from the study, mostly due to failed caudal epidural block and change to general anaesthesia. No significant difference was seen in age, gender, gestational age and weight among the three groups [Table 1]. However, there were significant differences in the success rate of block among the three groups of caudal block with IV midazolam (93.3%), caudal block along with IV midazolam and ketamine (93.1%) and caudal block alone (80%).

No significant differences were seen in the mean scores of heart rate [Table 2], systolic and diastolic blood pressure at different intervals among the three groups. The only difference was related to caudal anaesthesia with bupivacaine and caudal anaesthesia with bupivacaine — IV midazolam at 40-min interval using Tukey's test [Tables 3 and 4].

**Table 1: Demographic variables in the three study groups**

Groups variable	Caudal with bupivacaine	Caudal with bupivacaine + IV midazolam	Caudal with bupivacaine + IV midazolam + IV ketamine	P
Age (day)	38.83±15.48	45.50±19.69	46.00±19.40	0.197
Weight (g)	3480.00±728.30	3642.86±747.66	3795.19±843.19	0.352
Gestational age (week) (%)				
Term	10 (41.7)	12 (42.9)	17 (63)	0.234
Pre-term	14 (58.3)	16 (57.1)	10 (37)	
Gender (%)				
Male	19 (79.2)	21 (75)	24 (88.9)	0.421
Female	5 (20.8)	7 (25)	3 (11.1)	

IV: Intravenous

There were no statistically significant differences in all the three groups at intervals of 0, 30, 60 and 120 min in comparison with pain after caudal anaesthesia based on NIPS in the subgroups [Table 5].

There were no statistically significant differences in NIPS total scores at three intervals among the three groups, although within the time intervals of 30, 60 and 120 min in 6, 8 and 14 patients, respectively, had scores >4; however, the mean total scores in the groups were not more than 1.17 that were not statistically significant.

Complications of regional anaesthesia and IV drugs, such as prolonged motor block, bradycardia, hypotension, respiratory depression, apnoea and hypoxia, were not observed in any of the groups.

## DISCUSSION

The effect of IV midazolam and/or ketamine on caudal epidural block success rate and complications in awake infants, undergoing lower abdominal surgery, were evaluated in this study. Caudal epidural block is accepted as a safe and proper technique in awake infants,<sup>[8]</sup> the findings of this study also indicated that caudal epidural block in the awake infants is a simple technique and is a more reliable local anaesthetic technique for lower abdominal surgery in pre-term infants. The caudal epidural block with bupivacaine together with IV midazolam and or ketamine in the awake infants had more success rate. In bupivacaine group (Group 1), the success rate was 80% (24 out of 30 patients); by adding the IV midazolam and/or ketamine, the success rate increased to 93%. The findings of this study were consistent with the findings of Peutrell and Hughes,<sup>[9]</sup> that is, the caudal epidural anaesthetic technique with single dose bupivacaine was successful in eight out of nine children with pre-term birth. The difference between the study done by Peutrell and the present study is that the Peutrell study used caudal epidural anaesthesia with the catheter insertion

**Table 2: Mean values of heart rate at different intervals in the three groups**

Group time	Mean ± SD			P
	Caudal with bupivacaine	Caudal with bupivacaine + IV midazolam	Caudal with bupivacaine + IV midazolam + IV ketamine	
0 min	174.08±17.65	169.71±15.48	174.93±18.36	0.487
20 min	159.71±14.71	150.68±13.61	153.48±14.65	0.077
40 min	157.08±19.56	145.59±17.04	149.59±16.74	0.073
60 min	152.29±15.11	143.36±16.48	147.15±17.12	0.15

The significance was  $P \leq 0.05$  using ANOVA test. SD: Standard deviation; IV: Intravenous

**Table 3: Mean systolic blood pressure at different intervals in the three groups**

Group time	Mean ± SD			P
	Caudal with bupivacaine	Caudal with bupivacaine + IV midazolam	Caudal with bupivacaine + IV midazolam + ketamine	
0 min	76.50±16.75	79.70±19.9	70.63±20.33	0.203
20 min	77.75±15.44	76.89±13.98	72.33±9.95	0.287
40 min	77.75±9.57	72.68±6.43	71.26±8.93	0.019*
60 min	75.83±10.79	74.93±8.13	71.26±10.39	0.207

The significance was  $P < 0.05$  using ANOVA test. SD: Standard deviation; IV: Intravenous

**Table 4: Mean diastolic blood pressure at different intervals in the three groups**

Group time	Mean ± SD			P
	Caudal with bupivacaine	Caudal with bupivacaine + IV midazolam	Caudal with bupivacaine + IV midazolam + ketamine	
0 min	36.63±11.26	37.96±13.10	38.63±17.05	0.877
20 min	35.88±11.10	32.61±11.07	30.15±6.21	0.116
40 min	36.04±7.92	31.61±7.59	28.44±6.25	0.002*
60 min	33.92±6.71	32.36±7.15	31.00±7.98	0.37

SD: Standard deviation; IV: Intravenous; \*Significant

technique, while in this study the caudal epidural anaesthesia technique was used without a catheter. Several studies indicate the success rate of the caudal block to be between 89% and 99%.<sup>[10,11]</sup> However, the success rate in neonates can be higher than in infants.

**Table 5: Pain scores of patients in the study groups at different time intervals**

Time	Caudal with bupivacaine		Caudal with bupivacaine + IV midazolam		Caudal with bupivacaine + IV midazolam + ketamine		P
	Pain full (%)	No pain (%)	Pain full (%)	No pain (%)	Pain full (%)	Painless (%)	
NIPS in 30 min	3 (12.50)	21 (87.50)	2 (7.10)	26 (92.9)	1 (3.70)	26 (96.3)	0.504
NIPS in 60 min	2 (8.30)	22 (91.70)	1 (3.60)	27 (96.40)	5 (18.5)	22 (81.5)	0.177
NIPS in 120 min	3 (12.50)	21 (87.50)	4 (14.3)	24 (85.70)	7 (25.9)	20 (74.01)	0.379

IV: Intravenous; NIPS: Neonatal infant pain scale

On the other hand, other studies have shown a higher failure rate of the caudal block in children of <10 kg of body weight. Because of the difficulty in identifying the caudal hiatus, failure rate has been reported in the 11% of subjects.<sup>[12]</sup> Despite the incidence of postoperative apnoea in infants with pre-term birth, caudal epidural anaesthesia with a single dose injection or repeated injection or infusion using a catheter, in the awake children has been proposed safely.<sup>[13,14]</sup> The results of this study showed that there was no significant difference in heart rate at different time intervals in all the three groups, which was different from the findings of Geze *et al.*<sup>[16]</sup> in the awake children using bupivacaine and midazolam that a significant difference in heart rates at time intervals of 5 and 10 min was found. However, this was consistent with the results of the study carried out by Seyedhejazi and Zarrintan<sup>[5]</sup> indicating no significant alterations in heart rate of the subjects in caudal anaesthesia using bupivacaine 20 and 25 min after surgery, and with the study of Spear showing that the caudal block with bupivacaine caused no clinically significant changes in heart rate in the subjects.<sup>[15]</sup>

No clinically significant difference was seen in systolic blood pressure at time intervals of 0, 20, 40 and 60 min among the three groups. Although there was a statistically significant difference at the time interval of 40 min between the two groups of caudal anaesthesia with IV midazolam and caudal anaesthesia group with IV midazolam and ketamine compared with caudal anaesthesia group with bupivacaine, it was clinically significant but unimportant. These findings are consistent with the findings of the studies done by Seyedhejazi and Zarrintan, Arbabi<sup>[5,17]</sup> and Spear, Bouchut and Marhofer.<sup>[15,18,19]</sup>

No clinically significant difference was seen in diastolic blood pressure at time intervals of 0, 20, 40 and 60 min among the three groups. Although there was a statistically significant difference in the time interval of 40 min between the two groups of caudal anaesthesia with midazolam and caudal anaesthesia group with IV midazolam and ketamine compared with caudal anaesthesia group with bupivacaine, it was

clinically significant but seems unimportant. These findings are consistent with the findings of the studies done by Seyedhejazi and Zarrintan, Arbabi<sup>[5,17]</sup> and Spear, Bouchut, Marhofer and Peutrell.<sup>[15,18-20]</sup> Adding midazolam and ketamine to bupivacaine in this study resulted in no significant changes in diastolic blood pressure at the time intervals mentioned; however, in other studies, adding a drug such as S-ketamine, fentanyl, ketamine or midazolam to bupivacaine also led to changes in diastolic blood pressure.<sup>[21]</sup>

The results related to pain scale (NIPS) evaluation in the three study groups at time intervals of 30, 60 and 120 min after the surgery was not significant in any of the subgroups, which is consistent with the findings of a study conducted by Chaudhary *et al.*<sup>[21]</sup> at the intervals of 30 min and 1-h after the surgery. In our study, 3 patients in the bupivacaine group, 2 in the bupivacaine - midazolam group and 1 in the bupivacaine — midazolam with ketamine group had pain at the interval of 30 min. That is, adding IV midazolam and ketamine to caudal bupivacaine was not effective in reducing pain (except in a few patients), which is consistent with the results of Seyedhejazi *et al.* study in which after only using bupivacaine after 4 h, 6 patients were in need of analgesics. It seems that ketamine in the doses used in that study did not cause extra analgesia, it only leads to mild sedation that made caudal block easier with a calm and relatively motionless infant. In this study, 3 patients had a score of >3 at the interval of 3 h in the bupivacaine group. Similar results were seen in the study of Bouchut *et al.* in which only 2 patients in the bupivacaine group needed analgesics after 24 h.<sup>[18]</sup> These findings are consistent with the findings of the study done by Locatelli *et al.*<sup>[22]</sup> showing the analgesic effectiveness of levobupivacaine by adding S-ketamine to bupivacaine; however, there was no significant difference in the pain scale among the study groups. In our study, there was no statistically significant difference among the three groups at different time intervals, adding IV midazolam or ketamine or both to bupivacaine for pain control. In the study of Arbabi *et al.*,<sup>[17]</sup> a significant difference was observed when adding midazolam to bupivacaine at different time intervals compared to S-ketamine

to bupivacaine and bupivacaine alone, considering that general anaesthesia was used in this study as well. The findings of the present study are consistent with the study of Baris *et al.*<sup>[23]</sup> in which there was no significant difference among the three groups receiving bupivacaine and fentanyl (Group 1), bupivacaine with midazolam (Group 2) and bupivacaine alone (Group 3) and pain was measured every 30 min for 4 h after the surgery using the Children's Hospital of Eastern Ontario Pain Scale. None of the subjects in our study suffered from apnoea, nausea, vomiting or a decrease in arterial oxygen saturation that was consistent with Seyedhejazi's findings.<sup>[24]</sup>

## CONCLUSION

This study showed that pre-treatment with IV ketamine and/or midazolam before caudal epidural anaesthesia with bupivacaine in the awake infants can increase the success rate of caudal block without any complications.

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## Conflicts of interest

There are no conflicts of interest.

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