Comparing midazolam-bupivacaine and neostigmine-bupivacaine for caudal anesthesia in children undergoing herniorrhaphy

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Erratum: The name “Amirhossein Farrokhiaski” was mistakenly omitted in the publication of this article and hereby is added.

Abstract

Introduction: Neostigmine and midazolam are each added to bupivacaine for the purpose of caudal anesthesia. In this study, we compared neostigmine and midazolam, each co-administered with bupivacaine, in terms of analgesia and side effects during pediatric inguinal hernia opera.ons.

Materials and methods: We included 60 children 1–6 years old, candidates for elective unilateral herniorrhaphy. After general anesthesia induction with inhaled sevoflurane, a caudal block was performed. Patients were randomly allocated to one of two trial groups: midazolam group received bupivacaine 25% 1ml/kg with midazolam 50µg/kg, and neostigmine group received bupivacaine 25% 1ml/kg with neostigmine 2µg/kg through the caudal route. Heart rate, mean arterial pressure and oxygen saturation were recorded before induction and every five minutes after caudal anesthesia up to 30 minutes. Pain and sedation scores were recorded at 2, 4, 6, 12 and 24 hours after the operation, along with rescue analgesia dosage, vomiting and respiratory depression.

Results: Mean duration of analgesia in the midazolam group was similar to the neostigmine group (18.8±9 vs. 20.4±7.5, P=0.44). The analgesic dosage required was not significantly lower in the neostigmine group compared to the midazolam group (58.3±121.7 VS. 70.8±125.8, P=0.63).The number of patients who needed analgesic agents was similar in both groups (P=0.76). Nausea (P<0.05) and vomiting (P=0ti01)rates were higher in the neostigmine groupti

Conclusion: Midazolam (50µg/kg) compared to neostigmine (2µg/kg) provided higher sedation along with lower incidence of postoperative nausea and vomi.ng.

Keywords

- Midazolam
- Bupivacain
- Neostigminecaudal
- Pediatr

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Introduction

Decreasing the conduction of pain messages in the central nervous system (CNS) is one of the main mechanisms that anesthesia use to control pain. Drugs and procedures may be modified to achieve better pain control.[1, 2]

Transmission of pain messages in the CNS can induce the release of inflammatory mediators, catecholamines, and catabolic hormones, creating a hypermetabolic situation that leads to increased metabolic rate, oxygen usage and depletion of body metabolic hormones.[3]

Uncontrolled pain can induce sympathetic nervous system responses and increase morbidity and mortality. Activation of the sympathetic nervous system can cause increased myocardial oxygen consumption, creating risks of ischemia and myocardial infarction.[2-4] Ileus in the gastrointestinal tract and respiratory impairment have been reported among pediatric patients due to sympathetic responses.[2-4]

There are several options to control postoperative pain in children, such as systemic analgesic agents (narcotic and nonnarcotic drugs) and local analgesia techniques (neuroaxial and peripheral blocks). Neostigmine is a hydrophilic molecule that can decline acetylcholine and create analgesia.[5] Spinal analgesic properties, peripheral and supraspinal activity have been reported with neostigmine usage.[6] Caudal injection of neostigmine has few dose related side effects, such as nausea and vomiting.[7] Hofley et al. reported that intrathecal injections of midazolam on the nociceptive system achieved reactions with GABA system in the rat.[2] Midazolam is an agonist of benzodiazepine GABA receptors at the posterior spinal horn and decreases presynaptic and postsynaptic receptor activity.[8]

Intrathecal injections of midazolam can release endogenous opioids and indirectly have impacts at kappa and sigma receptors.[9] Previous investigations suggested that 50µg/kg is an ideal dosage for epidural injection of midazolam, and that higher dosages are accompanied by more sedation.[10] The present study compared the analgesic effects of midazolam and neostigmine, when coadministered with bupivacaine, on pain and hemodynamic parameters of pediatric patients undergoing herniorrhaphy.

Materials and methods

The present randomized clinical trial was performed on 60 pediatric patients (1–6 years old) with ASA1 criteria who were referred for surgery due to inguinal hernia. The children had not received any premedication and their operation was performed with general anesthesia after obtaining parental consent. Anesthesia induction was completed with a mixture of O_2, N_2O, and halothane. After induction, the patients were placed in a lateral position and a caudal block was performed by an anesthesiologist blinded to groups with a 23 gauge syringe in aseptic conditions. Following an atracurium injection (0.5mg/kg), LMA mask was inserted and anesthesia was continued with halothane ($N_2O_{(70\%)} + O_{2\ (30\%)}$ + 0.5–1 MAC).

Children were randomly placed in two trial groups (randomization was performed by random number table). Patients in the neostigmine group received a caudal block containing bupivacaine 0.25% (1ml/kg) and neostigmine (2µg/kg), and those in the midazolam group received a caudal block containing bupivacaine 0.25% (1ml/kg) and midazolam (50µg/kg).

Changes in heart rate, mean arterial pressure (MAP), and oxygen saturation rate were measured prior to the beginning of anesthesia and every five minutes after caudal block during the operation. The operation began 10 minutes after the caudal block and analgesia was defined as less than 15% changes in hemodynamic parameters during operation in comparison with the preoperative period. The caudal block was considered to be a failure in individuals who had more than 15% variation in hemodynamic parameters, and in patients receiving fentanyl 1 µg/kg intravenously. They were excluded from the study. Ringer lactate was administered intravenously (6 ml/kg/h) during the operation and 4 ml/kg/h after the operation.

If children had less than 15% decline in their MAP and pulse rate, they were monitored at the recovery ward until two hours after the operation and awakening. Sedation rate, pain, arterial oxygen saturation, MAP, heart rate and respiratory rate were monitored and measured at 2, 4, 6, 12 and 24 hours after the operation.

Pain was measured by FLACC table on a 0–10 scale **Table 4**. Children indicating a score higher than 4 received acetaminophen (20mg/kg) syrup for analgesia. Sedation rate was assessed with a four-level index (0–3) **Table 5**.

During the study, patients were assessed for nausea and vomiting by the recovery nurse blinded to groups. Vertigo, itching and respiratory depression (breathing rate below 10 times per minutes), time of first prescription and total analgesic dosage, were all recorded into a checklist.

Data were analyzed using a software package used for statistical analysis (SPSS Version 21, SPSS Inc, Chicago, IL, USA). Quantitative variables were presented as mean±SD and qualitative variables were presented as frequency and percentages. To compare

quantitative variables, mean±SD and percentages were calculated for each group and compared using independent Student's t-tests. Qualitative variables were compared between groups with chi-square. Differences were considered significant at (P≤0.05).

Results

Each trial group contained 30 children. Demographic variables such as age, sex, weight, surgery, and anesthesia duration showed no significant differences between the groups **Table 1.**

Table 1: Comparison of baseline variables between the two trial groups

	Midazolam	Neostigmine	P-value
Age (Mean±SD)	34.2±17.8	38.2±19.2	0.41
Gender (male/female)	15/15	15/15	-
Weight (Mean±SD)	13.2±3.5	14.3±3.6	0.26
Operation duration (Mean±SD)	17.2±6.9	15.5±7.8	0.89
Anesthesia duration (Mean±SD)	32.6±8.1	34.4±9.3	0.42

During perioperative period, mean heart rate in the neostigmine group was significantly lower than in the midazolam group (P<0.05).

After the operation, MAP and mean heart rate in the neostigmine group were significantly lower than the midazolam group (P<0.05) and oxygen saturation showed no significant difference between the groups **Table 2**.

Table 2: Hemodynamic parameters of patients after anesthesia induction

Pre operative			
	Midazolam	**Neostigmine**	**P-value**
MAP (mm Hg)	79.7±11.1	75.5±13.2	0.194
Heart rate (bpm)	127.5±17.9	125.4±15.9	0.633
O_2 saturation rate	98.6±0.6	97.9±2	0.362
Peri operative			
	Midazolam	**Neostigmine**	**P-value**
MAP (mmHg)	73.5±7.5	70.7±8.6	0.181
Heart rate (bpm)	127.3±18.7	113.0±14.8	0.002
O_2 saturation rate	98.6±0.7	98.0±0.9	0.016
Post operative			
	Midazolam	**Neostigmine**	**P-value**
MAP (mmHg)	79.7±6.6	68.1±7.4	0.001
Heart rate (bpm)	112.7±15.5	99.3±11.2	0.001
O_2 saturation rate	97±1.3	97.2±0.6	0.474

Mean pain score in neostigmine group patients showed no significant difference compared to the midazolam group (0.45±0.58 vs. 0.57±0.46, P=0.081). Mean sedation rate in the neostigmine group was significantly lower than in the midazolam group (0.27±0.28 vs. 0.64±0.49, P=0.023). Mean analgesia duration (from caudal anesthesia to the first administration of rescue analgesic) in the midazolam group showed no difference compared to the neostigmine group (18.8±9 vs. 20.4±7.5, P=0.44). The mean amount of analgesic agent used in the midazolam group was not significantly higher than in the neostigmine group (70.8±125.8 vs. 58.3±121.7, P=0.603). The number of patients

who needed analgesic agents was similar in both trial groups (P=0.76).

Nausea (P=0.05) and vomiting (P=0.01) rates were higher in the neostigmine group **Table 3**.

Table 3: Comparison of Nausea and Vomiting between the groups

	Midazolam (% /N)	Neostigmine (% /N)	P-value
Nausea	0	% 7.6	P=0/250
Vomiting	0	% 3.23	P=0.11

Pain was measured by FLACC table on a 0–10 scale **Table 4**.

Children indicating a score higher than 4 received acetaminophen (20mg/kg) syrup for analgesia. Sedation rate was assessed with a four-level index (0–3) **Table 5**.

Table 4: Flacc pain scale

Categories	SCORING		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown withdrawn, disinterested	Frequent to constant frown , clenched jaw , quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking , or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consol ability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Each of the five categories, (F); Face; (L) Legs; (A) Activity; (C)Cry; (C) CONSOL ability, is scored from 0 to 2, which results in a total score between 0 and 10.0 2002, The Regents of the University of Michigan. All Rights Reserved.

Table 5: Ramsay Sedation Assessment Scale

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated, and tranqu
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

From Ramsay *et al.* [10].

Discussion

This study was the first to examine the use of the coudal midazolam among Iranian pediatric patients. Our findings showed that the mean duration of analgesia, usage of rescue analgesics and pain score in the neostigmine group were similar to the midazolam group. Our results were close to those of Kumar et al, who assessed the impact of adding midazolam, neostigmine and ketamine to bupivacaine in caudal anesthesia and concluded that the analgesia duration and sedation rates were higher in neostigmine and midazolam groups respectively.[11] However, Davoudi resulted longer duration of post operative analgesia in neostigmine-bupivacaine than midazolam-bupivacaine group.[19] According to our results, the incidence of nausea and vomiting was higher in the neostigmine group than in the midazolam group. Other studies showed the same results. Canvaro et al 2006, Parkash e al 2006, Kumar et al 2005, Tucker et al 2004 and Abdullatie et al 2001, reported that adding neostigmine to bupivacaine neuroaxially increased nausea and vomiting.[14, 9, 11, 15, 5]

However, Mireskandari et al concluded that the incidence of vomiting was not different between the fentanyl-bupivacaine and the neostigmine-bupivacaine groups and Jarahzadeh et al. reported similar incidence of nausea and vomiting in neostigmine and midazolam groups.[12, 20]

The present study revealed that the midazolam-bupivacaine mixture provided better sedation for patients than the neostigmine-bupivacaine mixture. This is in accordance to Bousoffara's and Parkash's results.[13, 9, 20]

Regarding hemodynamic parameters, we recorded more stability in the midazolam group than in the neostigmine group. The results were significant ($p<0.05$) in postoperative MAP, preoperative and postoperative HR. Reports of similar studies showed that adding midazolam to bupivacaine provides hemodynamic stability while neostigmine causes negative impact on hemodynamic parameters when coadmimistered with bupivacaine.[20]

However, Kumar did not find any difference in hemodynamic parameters between his trial groups.[11]

Other studies demonstrated that midazolam-bupivacaine compared to bupivacaine alone, prolonged duration of analgesia and provided sedation if administered neuroaxially.[16-18, 20-22]

Conclusion

In conclusion, our findings support that adding midazolam (50µg/kg) to bupivacaine provides more sedation, less hemodynamic changes and less nausea and vomiting rates compared to neostigmine (2mg/kg) as adjuvant to bupivacaine in caudal anesthesia.

It is suggested to conduct more studies with greater sample sizes, variety of adjuvant drugs and evaluating other parameters such as sensory motor status, post-operative bladder function and discharge time.

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