British Journal of Medicine & Medical Research
17(12): 1-6, 2016, Article no.BJMMR.27029
ISSN: 2231-0614, NLM ID: 101570965

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Evaluation of Bupivacaine Co-administration with Midazolam or Neostigmine in Pediatric Inguinal Hernia Surgery-A Randomized Clinical Trial Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author JMH designed the study, wrote the protocol and wrote the first draft of the manuscript. Author VS managed the literature searches, analyses of the study, performed the spectroscopy analysis and author HN managed the experimental process. Author DMH identified the species of plant. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/27029
Editor(s):
(1) Alexandre Zanchenko Fonseca, Department of General Surgery, University of Santo Amaro, Brazil.
(2) Nurhan Cucer, Erciyes University, Medical Biology Dept., Turkey.
Reviewers:
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(3) Ramesh Gurunathan, Tuanku Jaafar Hospital, Malaysia.
Complete Peer review History: http://www.sciencedomain.org/review-history/16307

Original Research Article

Received 16th May 2016
Accepted 8th September 2016
Published 23rd September 2016

ABSTRACT

Aims: The aim of this study was to evaluate the analgesic effects of midazolam and neostigmine co-administration with bupivacaine in pediatric inguinal hernia surgery.
Study Design: Randomized, double-blinded clinical study.
Place and Duration of Study: Departments of Anesthesiology, Head and Neck Surgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, between 2012 and 2014.
Methodology: In this double blinded randomized clinical trial study, 90 pediatric patients aged 1-5 years undergoing inguinal hernia surgery were randomly assigned in to 3 groups. Group A

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received bupivacaine with placebo. Group B received caudal block with bupivacaine co-administrated with 50 µgr/kg midazolam. Group C received bupivacaine co-administered with neostigmine 2 µgr/kg. The hemodynamic variables were recorded at the baseline and interoperation. The pain score, sedation score**,** nausea/vomiting and analgesic use were recorded in the recovery phase and after 24 hours too.

Results: Baseline and intraoperative hemodynamic variables such as heart rate and blood pressure were compared between three groups. After 24 hours the pain score and sedation were not different. The anesthesia side effects like nausea and vomiting were the same between the three groups. In recovery room pain and sedation were significantly better in midazolam group (B). Also the analgesic use between group A and B, was different during 24 hours after operation. The most analgesic dose were used in Bupivacaine with Placebo (A) and the least in midazolam group (B).

Our findings demonstrated that pain score in midazolam and neostigmine group was less than bupivacaine group and sedation score was higher in midazolam and neostigmine group. After 24 hours the pain score and sedation were not different. The anesthesia side effects like nausea and vomiting were the same in three groups. Analgesic use was significantly higher in bupivacaine group compare with other two groups.

Conclusion: From the results, midazolam and neostigmine would be appropriate adjuncts to bupivacaine in caudal block during pediatric surgeries.

Keywords: Local anesthesia; caudal block; bupivacaine; neostigmine; midazolam; pediatric surgery.

1. INTRODUCTION

One of the benefits of the regional anesthesia is the reduction of post-operative pain [1-3]. Also, nerve block can reduce opioids administration and its side effects [4,5]. Less pain and lack of opium side effects due to nerve block can reduce time of recovery room and patient's ambulation which can lead to early hospital discharge [6-10]; local anesthesia reduces intraoperative bleeding since the time of surgery is decreased due to better operative condition [11] and avoids adverse effects of general anesthesia such as nausea, sore throat and cognitive dysfunction condition [12].

Caudal epidural anesthesia is a common method used for pediatric lower abdominal surgeries and is a safe and effective method [13,14]; Caudal anesthesia was developed in pediatric anesthesia and this method is excellent for post-operative pain reduction [15,16]; local anesthesia is also an impressive method for reduction of the post-operative stress response in infants and children [17,18]. It is recommended for most of the lower abdominal surgeries [6,7,19,20]. To prolong the analgesic effect that is induced by nerve block, caudal catheters or adding various analgesic agents such as midazolam, neostigmine, ketamine and topical opioids may be needed [3,4,10,13,21-25]. Although opium is effective its use is limited due to respiratory depression and other side effects [9]. Therefore, non opioids agents such as the above mentioned are used.

The aim of the study was to evaluate the analgesic effect of midazolam and neostigmine co-administrated with bupivacaine.

2. MATERIALS AND METHODS

This double blinded randomized clinical trial study was conducted in Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Ninety pediatric patients aged 1-5 years ASA class Iundergoing inguinal hernia surgery were included in this study. This study was approved by the ethics committee and the written informed consent was obtained from all patients parrents. Patients with history of allergic reaction to local anesthesia, sacral infection, bleeding disorder, Aspirin consumption in a week before surgery and neurological or spinal congenital abnormalities were excluded from the study.

The participants were randomly assigned to three groups using random number table. The anaesthesia technician performing the study and the surgeon were blinded to the content of the drugs contained in the syringes. Firstly (0.1 mg/kg) midazolam was administrated as pre-medicine then general anesthesia induction was performed with sodium thiopental 7 mg/kg and Atracurium 0.5 mg/kg, then intubation was done and the patients were placed in the lateral position. Regarding the randomization and based on patients body weight, needle caudal block was done. Group (A) received bupivacaine %0.25 1 ml/kg with placebo (normal saline with

the same volume). Group (B) received caudal block with bupivacaine co-administrated with 50 µgr/kg midazolam and group (C) received bupivacaine co-administrated with neostigmine 2 µgr/kg. Anesthesia was continued with N2O (%70) and halothane (%1.5). The surgery started 10-15 minutes after the caudal block.

Heart rate, blood pressure and arterial oxygen saturation monitoring were continuously performed by a standard monitoring included an electrocardiogram, non‑invasive blood pressure, and pulse oximeter. The heart rate and blood pressure were recorded 15 minutes before anesthesia induction and every 5 minutes after induction. The inadequacy of analgesics during the surgery was defined as increased heart rate more than 15% of baseline heart rate. Adequate analgesia was confirmed with stable hemodynamic symptoms. The duration of anesthesia was recorded. The pain score, sedation score, nausea/vomiting and analgesic use were recorded in the recovery phase and after 24 hours too.

The pain score was assessed on the bases on Modified Objective Pain Score (MOPS): (1: Asleep, 2: no pain, 3:mild pain , 4:moderate pain, 5: Severe pain).

The sedation score was assessed according to this staging: (1 = awake, 2 = responsive to verbal command, 3 = responsive to physical stimulus, 4 = unresponsive to verbal/physical stimulus).

2.1 Statistical Analysis

The data was analyzed using SPSS version 20 computer software. The mean age, weight, blood pressure, pain scores and analgesic use in each group were compared with each other using one-way analysis of variance (ANOVA). The Pearson chi-square test with Fisher's exact test were used to compare the sex ratio. Significance was defined at $p \leq 0.05$.

3. RESULTS

The demographic characteristics of the three groups are presented in Table 1. Baseline and intraoperative hemodynamic variables such as heart rate and blood pressure were also compared between the groups (Table 2). Post-operative side effects and analgesic doses are demonstrated in Table 3. Although there were no significant differences in the 24 hours post-operative sedation, pain score, nausea and vomiting, between three groups but there were significant differences in side effects between three groups in recovery room. Pain and sedation were significantly better in midazolam group (B). Also the analgesic use between group A and B was different during 24 hours after operation. The higher analgesic dose was used in Bupivacaine with Placebo (A) and the least was in midazolam group (B).

4. DISCUSSION

Studies have demonstrated that Spinal anesthesia can reduce post surgeries side effects and induce short term and rapid onset anesthesia. Adjuvant medication such as opioids, midazolam and neostigmine can improve the anesthetic effects of spinal anesthesia [20,26]. Also anesthesia and sedation duration will be prolonged by using adjuvant medication. However, opioids use as an adjuvant may cause vomiting and respiratory depression. Therefore, other medical groups like midazolam and neostigmine have been suggested [9,27,28].

Our findings demonstrated that pain score in the midazolam and neostigmine group was lower than the bupivacaine group; sedation score was higher in the midazolam and neostigmine group. The anesthesia side effects like nausea and vomiting were the same between the three groups. Analgesic use was significantly higher in the bupivacaine group compared with the other two groups.

Table 1. Demographic characteristics between three groups

Variables	Bupivacaine with placebo(A)	Bupivacaine with midazolam (B)	Bupivacaine with neostigmine(C)	p-value
Gender				
Male	27(98.5%)	25(85%)	24(80%)	0.431
Female	3(10.5%)	5(15%)	6(20%)	
Age* (mean ± SD)	29.68 ± 13.36	47.96 ± 13.72	34.46 ± 18.95	0.076
Weight (mean ± SD)	12.28 ±4.56	12.36 ± 5.52	11.21 ± 3.02	0.773

**Age is presented in months*

Table 2. The mean baseline and intraoperative hemodynamic variable changes between three groups

Variables	Bupivacaine with placebo (A)	Bupivacaine with midazolam (B)	Bupivacaine with neostigmine (C)	p-value
Baseline:				
Systolicblood pressure	62.6 ± 6.02	79.66 ± 13.27	65.00 ± 5.83	0.121
Diastolicbloodpressure	30.8 ± 6.79	45.00 ± 14.31	37.4 ± 3.91	0.143
Mean arterial pressure	65.7 ± 4.31	76.5 ± 7.77	61.01 ± 4.54	0.604
Heart rate	126.05 ± 12.51	127.5 ± 23.5	110.93 ± 12.51	0.076
Intraoperative (15 min):				
Systolicblood pressure	60.25 ± 2.73	76.69 ± 20.31	58.2 ± 6.3	0.12
Diastolicbloodpressure	30.00 ± 2.16	42.4 ± 17.7	31.8 ± 2.38	0.143
Mean arterial pressure	59.41 ± 4.53	74.00 ± 6.87	54.32 ± 3.81	0.11
Heart rate	126.15 ± 16.13	113.47 ± 24.71	101.6 ± 16.61	0.009

Table 3. Post-operative side effects and analgesia in recovery room and after 24 hours

Variables	Bupivacaine with placebo (A)	Bupivacaine with midazolam (B)	Bupivacaine with neostigmine (C)	P-value
Recovery room:				
Pain score	1.41 ± 0.79	1.16 ± 0.38	1.33 ± 0.65	0.051
Sedation	1.41 ± 0.66	2.44 ± 0.51	1.88 ± 0.57	0.003
Nausea/vomiting	6.68 ± 1.82	6.6 ± 1.66	6.8 ± 1.52	0.247
Analgesic use	0	0	0	
After 24 hours:				
Pain score	1.17 ± 0.51	1.27 ± 0.58	1.46 ± 0.45	0.117
Sedation	0.4 ± 0.16	0.58 ± 0.29	0.45 ± 0.25	0.118
Nausea/vomiting	3.78 ± 2.43	2.4 ± 2.39	3.00 ± 2.26	0.322
Analgesic use	4.05 ± 2.24	2.8 ± 1.4	3.06 ± 1.54	0.02

In a study by Kumar et al. [29] in 2005, the authors assessed and compared the efficacy of ketamine, midazolam and neostigmine co-administered with bupivacaine in eighty children (ASA status I) aged 5–10 yr patients undergoing unilateral inguinal herniotomy. Their results showed that a single shot caudal co-administration of bupivacaine-neostigmine and bupivacaine-midazolam was associated with an extended duration of postoperative pain relief.

Chattopadhyay et al. [30] in 2013 observed the effect of midazolam as an adjuvant in 90 adult patients aged 18–60 years undergoing infraumbilical surgery. They found that the use of midazolam as adjuvant with the local anesthetic in spinal anaesthesia significantly increases the duration of analgesia and decreases the incidence of postoperative nausea-vomiting.

Chaudhary et al. [31] in 2012 evaluated the efficacy and side effect of caudal Bupivacaine as compared to caudal Midazolam for providing post operative analgesia in 50 patients aged between 1-12 yrs of (ASA) class I and II undergoing infraumbilical surgery. They observed that caudal Bupivacaine and caudal Midazolam were equally effective in controlling postoperative pain in children in the first half an hour of the postoperative period. However significantly lower pain scores were observed in children receiving Bupivacaine at 2, 4 and 8 hours post operatively. They suggested that bupivacaine provides longer duration of postoperative analgesia compared to Midazolam.

In a study by Kulkarni et al. [32] in 2012, the effect of intrathecal midazolam in prolonging post-operative analgesia when used as an adjunct with bupivacaine on 150 adult patients of ASA class I/II scheduled to undergo elective lower abdomen, lower limb, and urological surgeries was evaluated. They suggested that midazolam is a useful adjunct to intrathecal bupivacaine for post-operative analgesia.

Arbabi et al. [33] in 2013, evaluated the effectiveness of adding midazolam or Ketmine to caudal bupivacaine on 60 children with ASA physical status I or II undergoing elective surgery below the umbilicus. They found that addition of Ketamine (0.5 mg/kg) or midazolam (50 µg/kg) to caudal bupivacaine provides significant prolongation of analgesia without producing significant negative side-effects.

The small sample size can be considered as our study limitation, although the sample size of our

study was calculated according to the sample size formula and reached 80% of study power. All of our participants were candidate of inguinal hernia surgery, so it is better in future studies all kinds of lower abdominal surgeries be considered.

5. CONCLUSION

Pain score in the midazolam and neostigmine group was lower than the bupivacaine group and sedation score was higher in the midazolam and neostigmine group; the anesthesia side effects were the same between groups and there were no significant differences in hemodynamic variables between three groups, midazolam and neostigmine would be appropriate adjuncts to bupivacaine in caudal block during pediatric surgeries.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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