Original Article

Comparison of Adding Neostigmine and Fentanyl to Bupivacaine in Caudal Analgesia in Pediatric Inguinal Herniorrhaphy

Omid Aghadavoudi[1], Amir Shafa[1]✉, Zahra Nowrouzi[1]

1. Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: The aim of the present trial was to compare efficacy and adverse effects of neostigmine against fentanyl when used as adjuvant to bupivacaine in caudal anesthesia.

Materials and Methods: A total of 140 children, aged 1-6 year scheduled to elective herniorrhaphy, were enrolled. Exclusion criteria were sacral area infection, history of allergic reactions to local anesthetics, bleeding tendency, neurological or spinal disease and lack of parent consent. Patients were assigned, using permuted block randomization method, into four groups of 35. Children in the first group received a caudal injection of 0.5 ml/kg bupivacaine 0.25% plus fentanyl 1µ/kg. The second group received 0.5 ml/kg bupivacaine 0.25% plus neostigmine 1µ/kg. Patients in the third group received 0.5 ml/kg bupivacaine 0.25% plus combination of fentanyl 1µ/kg and neostigmine 1µ/kg, and those in the fourth group only received 0.5 ml/kg bupivacaine 0.25% concentration. To assess pain intensity, Wong-Baker Scale was used. Time to first analgesic request and the dosage of analgesic agent was recorded. Data were analyzed using SPSS 17.0.

Results: Significant differences were observed among groups in terms of number of patients needing analgesic (p=0.01), time to first analgesic request (p=0.005) and analgesic dose. (p=0.05) The lowest number of requests for analgesia, lowest dose of pethidine and longest time to first analgesic request were in patients receiving combination of bupivacaine, neostigmine and fentanyl.

Conclusion: The present study shows that the combination of fentanyl and neostigmine, could prolong duration of analgesia, and decrease severity of pain when added to bupivacaine.

Keywords: fentanyl, neostigmine, bupivacaine, caudal anesthesia

✉ **Corresponding Author:** Amir Shafa, MD. Assistant Professor of anesthesiology, Isfahan University of Medical Sciences, Isfahan, Iran. Imam Hossein Hospital, Imam Khomeini Ave., Isfahan, Iran.
Email: shafa_amir@yahoo.com

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Introduction

Postoperative pain is one the most common problems in surgical patients that can influence their physical and mental health. So, effective pain management is an essential component of postoperative care (1).

Caudal block is one of the technical advancements that is regularly used in children (1-8). This block is safe, effective and easy with less side effects (9-15). It is the most common block technique used in lower abdominal or lower extremity infant surgeries (1, 3, 5, 6, 16-19). In this method, local anesthetics such as bupivacaine have been injected into the caudal canal providing block in the sacral and lumbar nerve roots.

This approach has several advantages: increased intra and postoperative pain relief, decreased use of narcotic and non- narcotic drugs, rapid awakening, and rapid return of bowel function and reduced length of hospital stay (1, 3, 6, 18).

Usually, different additive agents have been used to increase efficacy and to prolong duration of caudal block such as: epinephrine, midazolam, clonidine, neostigmine, ketamine, morphine, tramadol and fentanyl (4-6, 9, 10, 14, 18, 19). But results of these combinations in the field of effectiveness, duration of improvement, hemodynamic changes and side effects have been very different.

Neostigmine is a cholinesterase inhibitor that facilitates transmission of impulses across the neuromuscular junction, used in myasthenia gravis treatment and to reverse the effects of muscle relaxant (11, 18).

Fentanyl is a potent synthetic opioid with many receptors within CNS. It increases pain threshold, inhibits ascending pain pathways and relieves pain in regional or general anesthesia (2, 12, 19).

The aim of the present double-blind randomized clinical trial was to compare efficacy and adverse effects of neostigmine against fentanyl when used as adjuvant to bupivacaine in caudal anesthesia.

Methods

This double-blind, randomized clinical trial was conducted in Imam Hossein pediatric University hospital of Isfahan, Iran.

The protocol of this study was conformed to Declaration of Helsinki, and was approved by the Ethics Committee at Isfahan University of Medical Sciences. Written informed consent was obtained from parents of children, after they were informed about study objectives. The trial was registered in IRCT (IRCT 2017051126866N3).

A total of 140 children, aged 1-6 year and ASA physical status I, who were scheduled to elective herniorrhaphy, were enrolled. Exclusion criteria were sacral area infection, history of allergic reactions to local anesthetics, bleeding tendency, neurological or spinal disease and lack of parent consent.

Demographic characteristics including age, gender, American Society of Anesthesiologists (ASA) class, weight, date and duration of surgery were recorded for each patient.

Caudal anesthesia

Patients were assigned, using permuted block randomization method, into four groups of 35. Children in the first group received a caudal injection of 0.5 ml/kg bupivacaine 0.25% plus fentanyl 1µ/kg. The second group received 0.5 ml/kg bupivacaine 0.25% plus neostigmine 1µ/kg. Patients in the third group received 0.5 ml/kg bupivacaine 0.25% plus combination of fentanyl 1µ/kg and neostigmine 1µ/kg, and those in the fourth group only received 0.5 ml/kg bupivacaine 0.25% concentration.

All children received intravenous midazolam (0.1 mg/kg) as premedication; intubation was performed after induction of anesthesia with fentanyl 2µ/kg, sodium thiopental 6mg/kg and atracorium 0.5mg/kg. The caudal block was performed after intubation and following aseptic technique in lateral position before the onset of surgery. Patients and the researcher who gathered the data were blinded to the solution and patient group.

During surgery, general anesthesia was maintained using inhaled isoflurane (1.2%) in O_2 50%, air 50%. Heart rate (HR), SpO_2, $ETCO_2$, temperature (T) and blood pressure (BP) was recorded every 15 minutes.

At the end of surgery, intravenous atropine 0.02 mg/kg and neostigmine 0.04 mg/kg was used to reverse neuromuscular block; patients were transferred to recovery after extubation.

Hemodynamic changes and drug side effects (nausea and vomiting) were recorded in recovery room and surgery ward in different time points.

To assess pain intensity, we used the standard pain questionnaire (Wong-Baker Scale). Also, the time to first analgesic request and the dosage of analgesic agent was recorded.

Intravenous pethidine (1-1.5 mg/kg) was administered for patients suffering postoperative pain, and intravenous ondansetrone (0.15 mg/kg) was used for patient with postoperative nausea and vomiting.

Statistical analysis

Data were entered into the Statistical Package for the Social Sciences software version 17.0 (SPSS Inc. Chicago, IL, USA). The data were analyzed using one-way analysis of variance (ANOVA), The Chi-squared test or Fisher's exact test, when appropriate. A *p*-value less than 0.05 were considered as significant.

Results

Baseline characteristics (gender, age, weight, ASA score, duration of anesthesia, surgery) were not significantly different in the four groups (Table 1).

Significant differences were observed among groups in terms of number of patients needing analgesic (p=0.01), time to first analgesic request (p=0.005) and analgesic dose. (p=0.05) The lowest number of requests for analgesia, lowest dose of pethidine and longest time to first analgesic request were in patients receiving combination of bupivacaine, neostigmine and fentanyl (Table 2).

There were no significant differences in preoperative, intraoperative and recovery hemodynamic changes (systolic and diastolic BP, MAP and HR) among the four groups.

Intraoperative and postoperative SpO2 levels were significantly different among the four groups. Furthermore, pre-operative and intraoperative ETCO2 levels were significantly different among the four groups.

We observed significant difference in post-operative Wong-Baker pain score in 15^{th}, 30^{th}, 45^{th} min and 2^{nd}, 4^{th}, 6^{th} and 12^{th} hour between four groups. The lowest pain score was in patients

Table 1: Demographic and surgical profile.

Variable	Bupivacaine and fentanyl (N=34)	Bupivacaine and neostigmine (N=35)	Bupivacaine, fentanyl, and neostigmine (N=36)	Bupivacaine (N=34)	P-value
Age (years) Mean ± SD	2.6 ± 1.4	3.2 ± 1.7	3.1 ± 1.6	3 ± 1.6	0.383
Gender :					
Number (%)	31 (91.2%)	30 (87.7%)	30 (83.3%)	32 (94.1%)	0.498
male	3 (8.8%)	5 (14.3%)	6 (16.7%)	2 (5.9%)	
female					
Weight (kg)	13.3 ± 4.1	13.1 ± 4.1	13.6 ± 4.1	13.8 ± 3.8	0.803
Duration of anesthesia (minute)	61.5 ± 12.9	58.1 ± 6.8	61.9 ± 8.3	59.4 ± 7.8	0.263
Duration of surgery (minute)	47.6 ± 11.9	43.1 ± 8.9	45.7 ± 8.4	44.4 ± 7.5	0.338

Table 2: Comparison of postoperative analgesic administration.

Variable	**Bupivacaine and fentanyl (N=34)**	**Bupivacaine and neostigmine (N=35)**	**Bupivacaine, fentanyl, and neostigmine (N=36)**	**Bupivacaine (N=34)**	**P-value**
Patients without need to analgesia (in 12hours), number (%)	22 (64.7%)	18 (51.4%)	٢8 (77.8%)	14 (41.2%)	0.01
Time to first analgesic request (minute)	571.32±212.3	533±226.2	620.97±192.1	433.68±253.6	0.005
Pethidine dose (mg)	2.35±3.6	3.03±3.4	1.5±3.1	4.05±3.8	0.05

receiving combination of bupivacaine, neostigmine and fentanyl ($p<0.001$) (Table 3).

Significant differences were observed in nausea ($p=0.006$) and vomiting ($p=0.12$) among the four groups. Frequency of nausea and vomiting was lowest in patients receiving bupivacaine, and highest in those receiving a combination of bupivacaine, neostigmine and fentanyl (Table 4).

Table 3: Comparison of postoperative pain score (Wong-Baker).

	Bupivacaine and fentanyl (N=34)	**Bupivacaine and neostigmine (N=35)**	**Bupivacaine, fentanyl, and neostigmine (N=36)**	**Bupivacaine (N=34)**	**P-value**
15 minute	1.65	1.71	1.44	2.29	0.038
30 minute	2.06	2.51	2.11	2.53	0.017
45 minute	2.65	3.31	2.72	3.29	0.029
2 hour	3.12	3.71	2.94	3.94	0.004
4 hour	4.53	5.14	3.33	4.88	0.001
6 hour	3.82	4.34	2.83	5.03	< 0.001
12 hour	2.70	3.20	1.89	4.12	< 0.001

Table 4: Comparison of postoperative nausea and vomiting.

Variable	Bupivacaine and fentanyl (N=34)	Bupivacaine and neostigmine (N=35)	Bupivacaine, fentanyl, and neostigmine (N=36)	Bupivacaine (N=34)	P-value
Nausea Number (%)	6 (17.6%)	2 (5.7%)	7 (19.4%)	0 (0%)	0.006
Vomiting Number (%)	4 (11.8%)	2 (5.7%)	7 (19.4%)	0 (0%)	0.012

Duration of recovery time was not significantly different among the four groups. (p>0.05).

Discussion

Caudal block is one of the most effective methods for postoperative pain management. It is usually performed during lower abdominal and lower extremities surgeries in children, using a local anesthetic, with or without additive agents (1-8, 18, 19).

To the best of our knowledge, this is the first study to compare the efficacy of fentanyl, neostigmine and their combination in caudal block.

The present study shows that the combination of fentanyl and neostigmine, could prolong duration of analgesia, and decrease severity of pain when added to bupivacaine. However, our results indicate that this combination may increase the rate of nausea and vomiting.

Regarding average pain score, the combination of fentanyl and neostigmine resulted in more favorable pain relief when added to bupivacaine.

Some previous studies showed that adding fentanyl to bupivacaine resulted in lower pain score when compared to bupivacaine alone (15-17, 19).

Our present study shows that adding neostigmine to bupivacaine yields better analgesia than bupivacaine alone, which is consistent with prior studies (1, 14, 18), however adding fentanyl to bupivacaine is associated with more frequent nausea and vomiting.

Neostigmine caudal analgesic effect was observed in previous studies through a direct effect on the spinal cord after diffusion from dura to CSF or through peripheral anti-nociceptive effect on surgery site after systemic absorption. Moreover, intra-thecal neostigmine can cause analgesia by preventing the break- down of acetylcholine in the spinal dorsal horn (11, 14).

In our study patients receiving a combination of bupivacaine, fentanyl and neostigmine experienced more nausea and vomiting, in comparison with other groups. Group receiving bupivacaine and fentanyl was associated with more frequent nausea and vomiting than those receiving bupivacaine and neostigmine. Patients receiving bupivacaine alone experienced the least frequent nausea and vomiting among other groups. However, vomiting was controlled with a single dose of ondansetron in each group.

In some studies, increase rates of nausea and vomiting was observed in intra-thecal neostigmine. yet the rate has been higher than our present study, which may be due to higher dose of neostigmine (≥2µ/kg) (14); on the other hand, in other studies vomiting did not increase in patients receiving bupivacaine and neostigmine, compared to those receiving bupivacaine alone (11).

Some limitations of our study are small sample size and short postoperative assessment.

Conclusion

The present study shows that the combination of fentanyl and neostigmine, could prolong duration of analgesia, and decrease severity of pain when added to bupivacaine in caudal anesthesia.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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