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Comparison between caudal dexmedetomidine and nalbuphine in children undergoing hypospadias surgery: a prospective randomized double blind controlled study

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Keypoints

Dexmedetomidine and nalbuphine are additives used safely in caudal epidural analgesia/anesthesia in children to improve and prolong the analgesic profile of caudal analgesia. Dexmedetomidine is associated with better and prolonged analgesic profile in children undergoing hypospadias surgery, there were no increased adverse effects in this randomized controlled study.

Abstract

Background and objectives

Caudal epidural analgesia is widely used in children, many additives are used to improve the analgesic profile of this block. The main objective of the study was to investigate the efficacy of adding dexmedetomidine or nalbuphine to local anesthetic in children undergoing hypospadias surgery.

Patients and methods

After ethical approval, this randomized controlled study was carried out in Cairo University hospitals; 60 patients with American Society of Anesthesiologists classification (ASA) I, aged 2-7 years were randomly assigned into one of three groups: group B (control group) (n = 20) received caudal bupivacaine 1 ml/kg with concentration of 0.25%, group BD (n = 20) received caudal bupivacaine 0.25% mixed with 2 µg/kg dexmedetomidine and group BN (n = 20) received caudal bupivacaine 0.25% mixed with nalbuphine 0.2 mg/kg body weight. Pain and sedation was assessed postoperatively. First time of rescue analgesic, total dose of rescue analgesic and side effects were observed for 24 h.

Results

Postoperative FLACC pain scores were significantly less in BD group and to a lesser extent in BN group than in B group ($p < 0.001$) . Patients in BD and BN groups were more sedated in the first 6 hours than in control group but there was no statistically significant difference between BD and BN groups regarding sedation. The first time for postoperative analgesic requirement was significantly longer in BD group (16.89±0.74 hours), BN group (6.70±0.38 hours) and B (control) group (4.84±0.70 hours) ($p < 0.001$).

Conclusion

Dexmedetomidine was more effective and provided longer duration of analgesia than nalbuphine when added to caudal bupivacaine.

Keywords: caudal analgesia, dexmedetomidine, nalbuphine, postoperative

Introduction

Postoperative pain control is a cornerstone in management of anesthesia, various methods are used to control postoperative pain in children, one of the most reliable, popular and safe techniques is the caudal block which provides proper analgesia for lower abdominal surgical procedures with one disadvantage which is the short lived duration of action of the single shot caudal block [1]. Various adjuvants have been used to prolong the duration of action of the single shot caudal block, such as opioids, ketamine and α_2 agonists [2]. Dexmedetomidine (DEX) is a selective α_2 adrenergic agonist with analgesic and anxiolytic properties, it is a safe and effective adjuvant to many anesthetic techniques such as intrathecal or epidural [3]. Its effects are resulting from activation of α_2 adrenergic receptors, and depending on their location; their stimulation in the central nervous system (CNS) result in inhibition of calcium influx in the nerve terminals with subsequent inhibition of the neurotransmitter release thus facilitating analgesia [4].

Nalbuphine is a mixed κ-agonist and μ-antagonist opioid of the phenanthrene group; it is related in its chemical structure to the opioid antagonist naloxone and oxymorphone. It leads to stimulation of spinal and supraspinal opioid receptors which leads to good analgesia with minimal sedation, minimal nausea and vomiting, less respiratory depression and stable cardiovascular functions [5]. Its safety and efficacy has been established in the clinical field [6] and its safety and efficacy also established via the epidural route [7].

Nalbuphine being an agonist antagonist opioid is less likely to cause side effects such as pruritus, respiratory depression, urinary retention, excessive sedation, because of its action at kappa receptors.

The aim of this randomized double blind controlled trial was to compare the duration of post-operative analgesia, sedation and any side effects of single shot caudal epidural dexmedetomidine versus nalbuphine mixed with bupivacaine in children undergoing hernia repair.

Patients and methods

After obtaining informed written parental or guardian consent, and obtaining approval from Research Ethics Committee of anesthesiology department, this prospective randomized double blind controlled parallel-group with allocation ratio of (1:1:1) was conducted in Cairo university hospitals. A total of 60 patients with American Society of Anesthesiologists (ASA) physical status classification I, aged 2-7 years old, of both sex, undergoing elective hypospadias surgery under general anesthesia were enrolled in this study. Exclusion criteria include: asthmatic, cardiac patients, abnormalities of coagulation profile, mental retardation, allergy to any of the study drugs, infection at the site of injection and congenital abnormality of the sacrum, fig

ure 1 shows flowchart of the participants in the study. All patients randomly assigned using computer randomization program www.randomizer.org and numbers concealed in opaque closed envelopes into 3 equal groups 20 patients in each group: group B (control group) (n = 20) received caudal bupivacaine 0.25% , group BD (n = 20) received caudal bupivacaine 0.25% mixed with 2 μg/kg dexmedetomidine and group BN (n = 20) received caudal bupivacaine 0.25% mixed with nalbuphine 0.2 mg/kg body weight. The total volume of mixture injected caudally was remained constant in the 3 groups which is 1 ml/kg body weight with maximum dose of bupivacaine of 2 mg/kg. All patients were kept fasting according ASA guidelines; 2 hours for clear fluids, 4 hours for breast milk and 6 hours for milk formula or light meals. Also, all patients were premedicated with intramuscular injection of 0.1 mg/kg midazolam and 0.01 mg/kg atropine half an hour before transferring to the operating room (OR). On arrival to the OR standard monitors were applied including non-invasive blood pressure (NIBP), electrocardiogram (ECG) and pulse oximetry.

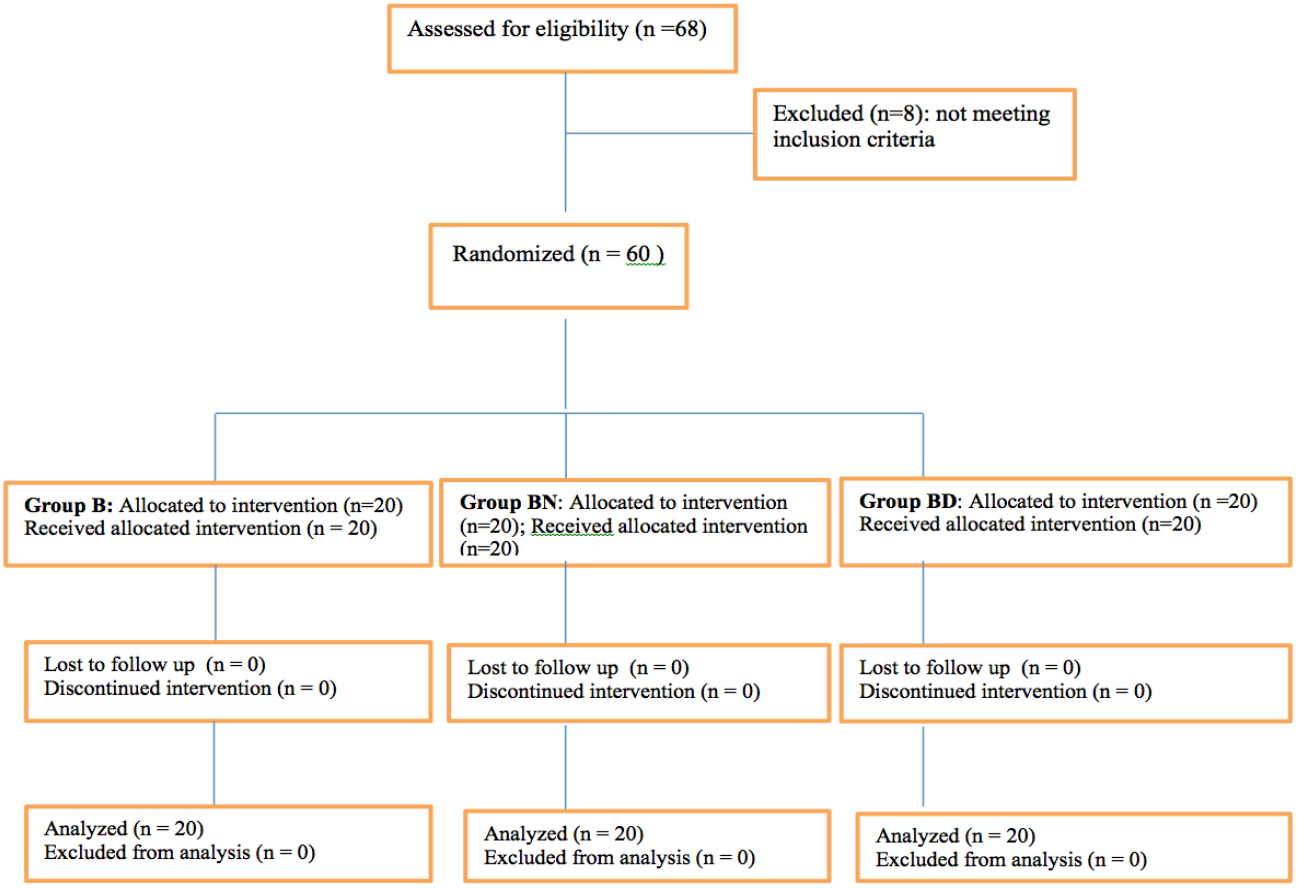

Figure 1. CONSORT Flow participant diagram

Then general anesthesia was induced using inhalation of 8% sevoflurane in 100% oxygen, intravenous line was inserted and tracheal intubation by appropriate size endotracheal tube was facilitated by intravenous atracurium 0.5 mg/kg. Anesthesia was maintained using 2% sevoflurane in 50% oxygen and 50% air with controlled mechanical ventilation to keep end tidal carbon dioxide between 30-35 mmHg. Thereafter, patients were positioned in a lateral decubitus and under complete aseptic technique caudal injection was done using 25 G needle, proper placement of the needle was confirmed by whooshing test [8]. After negative aspiration for blood or cerebrospinal fluid; patients of group B (control group) were received 1 ml/kg plain bupivacaine 0.25%, patients of group BD were received dexmedetomidine (Precedex 100 µg/ml, Hospira®) 2 µg/kg in 1ml/kg plain bupivacaine 0.25% and patients of group BN were received nalbuphine (Nalufin® ampoules 20 mg/ml, Amoun pharmaceutical, Egypt) 0.2 mg/kg in 1ml/kg plain bupivacaine 0.25%. Mean arterial blood pressure (MAP), heart rate (HR) and oxygen saturation (SpO_2) were documented every 5 minutes thought the procedure. By the end of surgery inhalational anesthesia was discontinued and the residual muscle relaxant effect was antagonized with neostigmine 0.05 µg/kg, given with atropine 0.02 mg/kg, and the endotracheal tube was removed after return of spontaneous breathing and the patient was opening eyes then the patient was transferred to the post-anesthesia care unit (PACU), all care givers; anesthetist, surgeon, PACU nurse, as well as patients' parents or guardians were unaware of caudal drug given. In the PACU, pain scores were evaluated by the "Face, Leg, Activity, Cry, Consolability" FLACC pain scale (table 1) [9]; FLACC pain scale is a measurement used to assess pain in children between the ages of 2 months and 7 years or in individuals who are unable to communicate their pain. The scale is scored in a range of 0–10, with 0 representing no pain while 10 is the worst pain.

	Score		
Parameters	0	1	2
Face	No particular expression or smile	Occasional grimace or frown; withdrawn, Disinterested	Frequent to constant frown, clenched jaw, quivering chin
Leg	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
Crying	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs; frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Score: 0, no pain; 1–3, mild pain; 4–7, moderate pain; 8–10, severe pain, FLACC: Face, legs, Activity, Cry, and Consolability.

Table 1. FLACC behavioral pain assessment scale [9]

The scale has five criteria that are each assigned a score of 0, 1, or 2. The time to first analgesic request [which was defined as the time from extubation till the first complaint of pain (Pain Score ≥4)] was also recorded. Sedation was assessed using a modified observer's assessment of alertness/sedation score (table 2) [10].

Responsiveness	Score
Agitated	6
Responds readily to name spoken in normal tone ("Alert")	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

Table 2. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) [10]

Pain and sedation scores evaluated and recorded at 0 (on arrival to PACU), 2, 4, 6, 9, 12, 18 and 24 hours.

Any side effects such as nausea and vomiting, hypotension (MAP 20% decrease from baseline), bradycardia (HR 20% decrease from baseline) and respiratory depression (SpO_2 < 92%) were also evaluated and recorded. The primary outcome was the time to first analgesic request (i.e. pain score ≥4), the secondary outcome was to assess sedation score, hemodynamic and demographic data.

For control of postoperative pain; acetaminophen intravenous infusion of 15 mg/kg was given if the recorded pain score was 4 or more (with minimum 4 h time interval between successive doses of acetaminophen and rescue analgesia with intravenous meperidine 0.5 mg/kg if the pain score was 4 or more within this time interval). Sample size calculation based on a previous study [11] and was done using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows.

The primary outcome was duration of analgesia (time to first analgesic), and to detect a difference in the average time to first analgesic as small as 1.5 times its standard deviation with a power of 0.8 and an α error of 0.05; 15 patients were needed in each arm we increased it to 20 patients to increase the power of the study.

Statistical analysis:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22. Data was summarized using mean ± standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between groups were done ANOVA with post hoc test in normally distributed quantitative variables while non-parametrical Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables.

For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

Results

There was no statistically significant difference between the two groups regarding demographic data (age, sex, weight and duration of anesthesia) (table 2).

No adverse effects were recorded in the first 24 hours in all patients.

No postoperative hallucination, nausea, vomiting, allergy or significant heart rate and blood pressure changes were reported.

Postoperative FLACC pain scores were significantly less in BD group and to a lesser extent in BN group than in B group ($p < 0.001$) (Table 3).

Age (years)	4.40±1.13	4.30±1.36	4.12±1.06	0.761
Weight (kg)	20.60±4.43	20.60±4.48	20.55±3.91	0.999
Duration of procedure (min)	67.85±7.41	69.55±6.11	67.40±7.28	0.591

Table 3. Demographic data of patients and duration of procedure. Data are presented as mean ± SD (standard deviation) and count and %.

Patients in BD and BN groups were more sedated in the first 6 hours than in control group but there was no statistically significant difference between BD and BN groups regarding sedation (Table 4).

	B group (control)	BD group	BN group	P value
FLACC score				
▪ **0h on arrival to PACU**	0.70±0.66	0.70±0.66	0.70±0.66	1
▪ **2h**	2.95±0.22	0.85±0.59*	1.75±0.79*#	< 0.001
▪ **4h**	4.15±0.37	1.75±0.79*	1.30±0.57*	< 0.001
▪ **6h**	4.05±0.22	1.31±0.57*	1.50±0.51*	< 0.001
▪ **9h**	3.65±0.67	1.50±0.52*	2.40±0.50*#	< 0.001
▪ **12h**	3.50±0.51	2.20±0.41*	2.95±0.22*#	< 0.001
▪ **18h**	2.55±0.51	1.56±0.50*	2.40±0.50#	< 0.001
▪ **24h**	1.55±0.51	0.70±0.47*	1.70±0.47#	< 0.001

Table 4. Postoperative FLACC score over time points. Data are presented as mean ± SD (standard deviation), FLACC: Face, legs, Activity, Cry, and Consolability. PACU: Postanesthesia care unit. *: statistically significant compared to corresponding value in control group (P<0.05), #: statistically significant compared to corresponding value in BD group (P<0.05).

The first time for postoperative analgesic requirement was significantly longer in BD group (16.89±0.74 hours) and to a lesser extent in BN group (6.70±0.38 hours) than the B (control) group (4.84±0.70 hours) ($p < 0.001$).

The total dose of postoperative supplementary analgesia (intravenous paracetamol) in the first 24 hours was significantly lower in BD group (128.75±32.72 mg) and to a lesser extent in BN group (263.25±69.99 mg) than in the control group (276.25±94.41 mg) ($P < 0.001$) (Table 5).

Second rescue analgesic meperidine was not required in any patient in the three groups (Table 6).

	B group (control)	BD group	BN group	P value
MOAA/S score				
▪ **0h on arrival to PACU**	3.15±0.37	2.95±0.22	3.40±0.50#	0.002
▪ **2h**	4.45±0.51	4.00±0.00*	4.45±0.50#	0.001
▪ **4h**	4.85±0.37	4.45±0.50*	4.80±0.41#	0.009
▪ **6h**	4.86±0.37	4.70±0.47	4.45±0.51*	0.024
▪ **9h**	4.85±0.38	4.65±0.49	4.80±0.41	0.309
▪ **12h**	4.84±0.38	4.83±0.40	4.90±0.39	0.410
▪ **18h**	5.00±0.00	5.00±0.00	5.00±0.00	----
▪ **24h**	5.00±0.00	5.00±0.00	5.00±0.00	----

Table 5. Postoperative MOAA/S score over time points. Data are presented as mean ± SD (standard deviation), MOAA/S score: modified observer's assessment of alertness/sedation score. PACU: Postanesthesia care unit. *: statistically significant compared to corresponding value in control group (P<0.05), #: statistically significant compared to corresponding value in BD group (P<0.05)

	B group (control)	BD group	BN group	P value
Time to rescue analgesic (h)	4.84±0.70	16.89±0.74*	6.70±0.38*#	< 0.001
Total dose of paracetamol in the first 24 hours (mg)	276.25±94.41	128.75±32.72*	263.25±69.99*	< 0.001

Table 6. Time to 1st rescue analgesic and total dose of paracetamol in the 1st 24 hour. Data are presented as mean ± SD (standard deviation), *: statistically significant compared to corresponding value in control group (P<0.05), #: statistically significant compared to corresponding value in BD group (P<0.05).

Discussion

The present study was designed to compare the duration of postoperative analgesia between caudally administrated DEX and nalbuphine added to bupivacaine, and we found that the mean duration of postoperative analgesia was significantly prolonged with DEX, and to a lesser extent with nalbuphine than plain bupivacaine. There was reduced postoperative FLACC pain scores in BD group, and to a lesser extent BN group than B group, also, there was reduced analgesic requirements during the first 24 hours, in the form of paracetamol injection, in BD group compared to BN and B groups.

Wide range of additives are used to prolong the duration of single shot caudal epidural analgesia/anesthesia [12], DEX is a highly selective α_2 agonist with sedative and analgesic properties. It has been administrated via the epidural route in many trials [13, 14]. Nalbuphine is a

mixed agonist-antagonist opioid which has antagonist effect at mu receptor and agonist at kappa receptors. There are few reports of neuraxial administration of nalbuphine, but no reports of neurotoxicity [15].

The findings of our study are almost similar with observations of El- Hennawy *et al*. [16], who compared the effect of single shot caudal epidural injection of DEX, clonidine or placebo (normal saline) added to bupivacaine, and concluded that the duration of analgesia was significantly prolonged with dexmedetomidine, and to a lesser extent with clonidine than with plain bupivacaine, without significant increase in the incidence of side-effects.

Also, in line with our study Xiang et al [17] studied the effects of caudal DEX and concluded that the addition of DEX to bupivacaine reduced the
response to hernial sac traction in the inguinal hernia repair in pediatric patients, besides it prolonged the duration of postoperative analgesia.

Furthermore, El Shamaa et al. [18] studied the effects of adding caudal DEX or morphine to bupivacaine in children undergoing infra-umbilical surgeries and concluded that there was a significant prolonged duration of postoperative analgesia in DEX group than in morphine group.

Similar to our trial, Saadawy *et al*. [14], who studied the effect of dexmedetomidine on caudal bupivacaine characteristics, they found no
significant changes in the hemodynamic variables among their groups and prolonged postoperative analgesia with dexmedetomidine compared to bupivacaine alone.

In a previous trial [19] we studied the effect of caudal nalbuphine added to levobupivacaine in pediatric patients undergoing hernia repair and we found that there was a significant prolongation of postoperative analgesia in levobupivacaine-nalbuphine group than in levobupivacaine group with hemodynamic stability. But the duration of analgesia was shorter than in DEX group in our present study.

Limitations to our study that we used doses of caudal DEX and nalbuphine comparable to that of the intravenous use; thus our results may reflect systemic absorption effects. We cannot conclude this with certainty, because we did not measure blood levels of DEX or nalbuphine.

Conclusion

The results of this clinical trial had demonstrated that addition of DEX to caudal local anesthetic bupivacaine produced longer duration of postoperative analgesia in pediatric patients undergoing hypospadias surgeries and to a lesser extent in nalbuphine group with stable hemodynamic variables and no side effects.

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