International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2020; 3(1): 06-11
Received: 04-11-2019
Accepted: 06-12-2019

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Effect of addition of dexmedetomidine to caudal bupivacaine on postoperative analgesia in paediatric patients

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DOI: https://doi.org/10.33545/26643766.2020.v3.i1a.62

Abstract
Caudal epidural analgesia is one of the most commonly performed regional techniques in paediatric anaesthesia for intra and post-operative analgesia. However, the duration of analgesia is limited by the duration of action of local anaesthetics. Addition of opioids like morphine, fentanyl is associated with side effects like respiratory depression, urinary retention and pruritus. Dexmedetomidine a α2 agonist is known for its analgesic effects with lesser side effects. Hence, this study was conducted to know the efficacy and safety of addition of dexmedetomidine to bupivacaine in a single shot caudal block in children. This study was conducted among 60 children in the age group of 1 – 10 years coming for various elective infraumbilical surgical procedures. They were divided into two groups of 30 each. Group B received caudal 0.25% bupivacaine 1ml/kg and group D received caudal 0.25% bupivacaine 1ml/kg with dexmedetomidine 1 µg/kg. The pain score in the two groups were similar up to 2 hours after surgery but was higher in group B at the end of 3rd and 4th hour compared with group D. This study showed that the addition of dexmedetomidine in the dose of 1µg/kg to 0.25% bupivacaine 1ml/kg reduced the anaesthetic requirement, prolonged the duration of analgesia with less post operative analgesic requirement after a single shot caudal block with minimal side effects in children.

Keywords: Caudal, bupivacaine, dexmedetomidine, children

Introduction
Pain is defined by the international association for study of pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'' [1]. Pain experienced by infants and children often goes unrecognised, even neglected because they cannot express it [2].
Pain perception actually begins before birth. Surgical pain not only causes immediate nociceptive response but also results in changes in nociceptive activation pathways leading to hypersensitivity, hyperalgesia and allodynia [3].
In paediatric patients, optimum pain relief is a big challenge because it is difficult to differentiate restlessness or crying due to pain from that of hunger or fear. An effective therapy to block or modify the physiological responses to painful stimulus is an essential component of paediatric anaesthesia practice [4].
Regional anaesthetic techniques can reduce the requirement of inhaled anaesthetics and opioids, attenuate the stress response to surgery, facilitate a rapid, smooth recovery and provide good immediate postoperative analgesia with less systemic analgesic requirement [5].
Caudal epidural block is one of the most popular, reliable and safe techniques in paediatric anaesthesia that can be used with general anaesthesia for intra and postoperative analgesia in patients undergoing various surgeries. It is relatively simple technique with good success rate [5, 6]. The main disadvantage of caudal analgesia is duration of action after a single injection which is limited by duration of action of local anaesthetics [7]. Placement of a catheter has an inherent risk of infection. Prolongation of caudal analgesia using a 'single-shot' technique has been achieved by the addition of various adjuvants such as opioids, ketamine, neostigmine, midazolam and α_2 agonists. Many of these adjutants have side effects like respiratory depression, vomiting, pruritus etc [8, 9].
Among the α_2 agonists clonidine and dexmedetomidine are commonly used. Clonidine has been extensively used in all types of regional anaesthetic techniques [10]. Dexmedetomidine is a highly selective α_2 agonist with sedative and analgesic properties with minimal respiratory depression. It has a α_2/α_1 selectivity ratio of (1600:1) which is eight times more potent than clonidine (200:1).

It is shorter acting drug than clonidine with a distribution half- life of 9 min and elimination half- life of 2 hours [11, 12]. This study was undertaken to assess the efficacy of addition of dexmedetomidine to the caudal bupivacaine in prolonging the postoperative analagesia in paediatric surgeries and its safety.

Methodology

This study included 60 children, of both genders, coming for various elective infra-umbilical surgical procedures such as herniotomy, circumcision, orchidopexy, urethroplasty etc. After obtaining clearance from the hospital ethical committee a written informed consent was obtained from parents before commencing the study.

Sampling procedure

Paediatric patients undergoing infraumbilical surgeries fulfilling the inclusion criteria were selected for the study and randomly allocated to two different groups B and D of thirty each. Randomization was done by simple lottery method. All health-care personnel, the patients, and their parents or guardians were blinded to the caudal medications administered. All medications were prepared by anaesthesiologists not participating in the study except for preparing the drugs. The anaesthesiologist who administered anaesthesia also monitored the patient peri-operatively, but was unaware of the study drug.

Equipment

- A tray containing sterile towel, bowl, betadine solution, swabs, sponge holding forceps.
- 23 G hypodermic needle, 10 ml syringes, normal saline for dilution.
- Drugs: Bupivacaine 0.25% vial, Dexmedetomidine 100µg/ml ampoule.
- Appropriate size airways and masks.
- Appropriate size Laryngeal Mask Airway (LMA), Jackson Rees circuit.
- Intravenous cannula 22 G or 24 G
- Working laryngoscope, appropriate size blades.
- Paediatric size self-inflating bag.
- Suction apparatus.
- Drugs necessary for resuscitation were kept ready.

Anaesthesia protocol

The following standard anaesthesia regimen was followed:
All patients were visited on the pre-operative day and relevant demographic data collected. A thorough preoperative evaluation was done including history, general physical examination, systemic examination, airway assessment and spine. Baseline vital parameters were noted. Relevant laboratory investigations were done in all patients. Informed consent was obtained from the appropriate person.

Pre-operative fasting: Solid foods were restricted for 6 hours, breast milk for 4 hours and clear fluids for 2 hours prior to surgery.

Pre-medication: All patients were pre-medicated with syrup Midazolam 0.5mg/kg, 30 min prior to induction.

Monitoring: In the operation theatre standard monitoring was instituted. The continuous monitoring of Heart rate (HR), Electrocardiogram (ECG), Mean Arterial Pressure (MAP), Oxygen Saturation (SpO_2) and End tidal Carbon dioxide ($EtCO_2$) were done and recorded before surgery and every 5 min till the end of surgery.
Induction of anaesthesia was achieved with 50% N_2O and 1-3% halothane in oxygen using Jackson Rees circuit. Intravenous access was secured and an appropriate crystalloid infusion was started according to the calculated requirements. An appropriate sized Laryngeal Mask Airway (LMA) was inserted. After the insertion of LMA, halothane concentration was titrated in 50% nitrous oxide and oxygen to maintain adequate depth of anaesthesia While the patient was breathing spontaneously, he/she was gently placed in left lateral position; vitals were checked again including adequacy of breathing. Under strict aseptic conditions, sacral hiatus was identified by running the thumb up from coccyx towards the sacrum. After identifying the sacral hiatus, a 23 G hypodermic needle with its bevel facing anteriorly was inserted at an angle of 60-70° to the skin till the sacro-coccygeal membrane was pierced, when a distinct "pop" was felt. The needle was now lowered to an angle of 20° and advanced 2-3 mm to make sure that the entire bevel was inside the space. After negative aspiration for blood and CSF, to rule out intravascular or subarachnoid placement of needle the study drug was injected according to the group allocated.
Group B (n = 30) received Bupivacaine 0.25%, 1ml/kg + 0.5ml normal saline
Group D (n = 30) received Bupivacaine 0.25%, 1ml/kg + Dexmedetomidine 1µg/kg making the volume 0.5 ml.
After the injection was complete, the needle was removed and the child was placed in supine position.
The inhaled concentration of halothane was adjusted to achieve haemodynamic changes within 30% of the baseline values. No other narcotics, analgesics or sedatives were used intra-operatively. An intraoperative decrease of MAP or HR by 30% from the baseline value was defined as hypotension or bradycardia respectively and was treated by fluid bolus, ephedrine or atropine, as necessary. Occurrence of intraoperative hypotension, bradycardia and the maximum maintenance concentration of halothane (%) was recorded.
Surgical incision was made 10 min after the completion of caudal block. An intraoperative increase in mean arterial pressure (MAP) or heart rate (HR) by 20% of pre-incision value was defined as insufficient analgesia and was treated with a rescue opioid fentanyl 1µg/kg IV. Those cases were eliminated from the study.

Results

The different surgical procedures performed during the study in the two groups are shown in table 1. 14 (46.7%) children in group B and 12 (40%) in group D underwent inguinal herniotomy. Circumcision was done in 12 (40%) and 7 (23%) cases in group B and D respectively, while urethroplasty accounted for 2 (6.7%) and 8 (26.7%) cases in group B and D respectively. Orchidopexy, chordee correction and fulguration of posterior urethral valves accounted for the remaining cases.

Table 1: Type of Surgical Procedure

Type of Surgery	Group B n (%)	Group D n (%)
Circumcision	12 (40)	7 (23)
Herniotomy	14 (46.7)	12 (40)
Orchidopexy	2 (6.7)	1 (3.3)
Urethroplasty	2 (6.7)	8 (26.7)
Chordee correction	0 (0)	1 (3.3)
PUV Fulguration	0 (0)	1 (3.3)

The Paediatric observational FLACC Pain Score was below 4 at the end of first and second hour in both the groups and did not require any analgesia.

At the end of third and fourth hour, 3 (10%) and 10 (30%) of the patients in group B had a pain score of ≥ 4 respectively and required rescue analgesic whereas none of the patients had a score of ≥ 4 in group D. The difference is statistically highly significant.

The pain score was ≥ 4 in 1 (3.3%) of patients in group B and 12 (40%) in group D by the end of eighth hour. The difference is statistically highly significant.

At the end of 12th, group B had 20 (66.7%) patients with pain score of ≥ 4 while group D had 1 (3.3%) patient with similar pain score. The difference is statistically highly significant. At the end of 16th hour group B had 2 (6.7%) patients with pain score of ≥ 4 while group D had 1 (3.3%) patient with similar pain score. The difference is statistically not significant. At the end of 24th hour, group B had 15 (50%) patients with pain score of ≥ 4 and group D had 8 (26.7%) with similar pain score respectively, the difference being statistically significant. The distribution of subjects in the two study groups according to FLACC pain score 0 (no pain), 1 -3 (mild pain), and ≥ 4 (moderate pain) at various monitoring intervals are shown in charts 1 and 2.

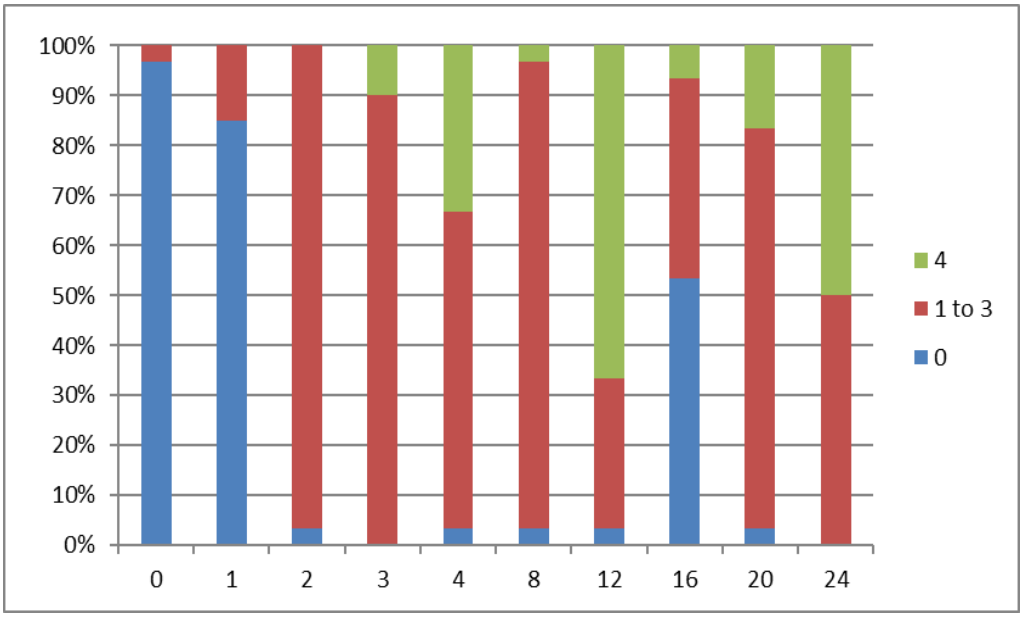

Chart 1: Group B Changes in FLACC score

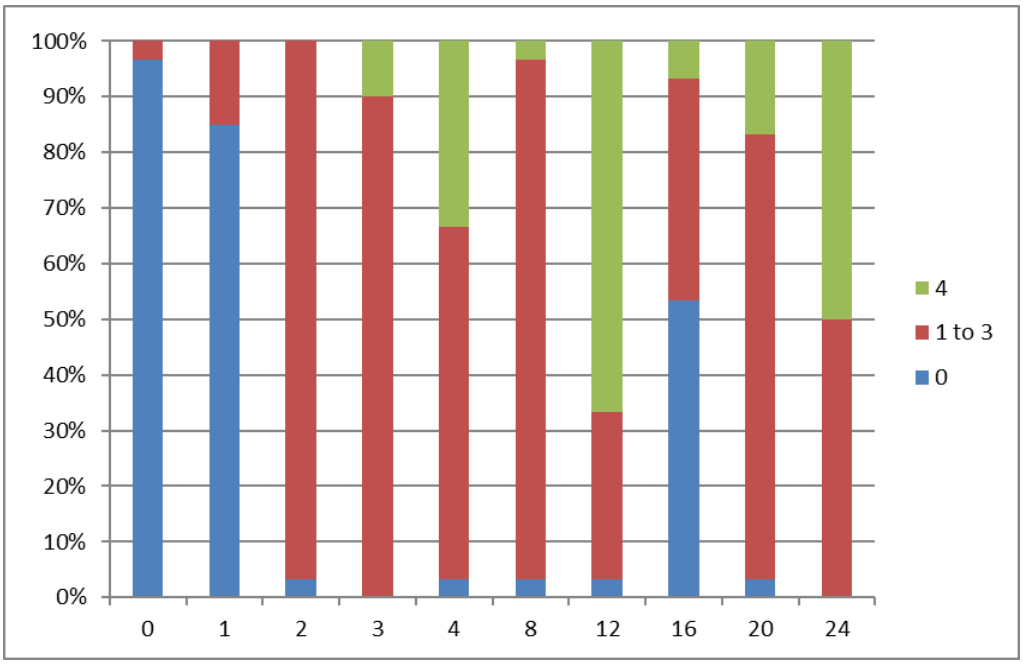

Chart 2: Group D Changes in FLACC score

Table 2: The changes in FLACC Score

Time interval hrs	Mean Rank Group B	Mean Rank Group D	P Value	Statistical Significance
0	31	30	0.317	NS
1	35.42	25.58	0.005	S
2	40.07	20.93	0.001	HS
3	42.72	18.28	0.001	HS
4	38.58	22.42	0.001	HS
8	21.95	39.05	0.001	HS
12	42.43	18.57	0.001	HS
16	30.7	30.3	0.923	NS
20	25.82	35.18	0.027	S
24	35.98	25.02	0.009	S

The total duration of post-operative analgesia in group B was 298 ± 44.6 minutes with a range of 230 – 405 minutes, while in group D, it was 598.17 ± 78.33 minutes with a range of 485 – 755 minutes. This difference between the two groups is highly significant.

Table 3: Duration of Analgesia

Group	Mean duration of analgesia (min) (Range)	Standard Deviation	Range Min	p value	Statistical Significance
B	298.17	± 44.58	230 – 405	0.001	HS
D	598.17	± 78.33	485 – 755		

The total number of rescue analgesics used in the form of paracetamol suppository 30 mg per kg whenever FLACC pain score was ≥4 is depicted in table 4. In group B, 14 (46.7%) children required two doses and 16 (53.3%) required three doses of rescue analgesics. In group D, 3 (10%) children required only single dose, 26 (86.6%) required two and only one child required three doses of rescue analgesics. The difference is statistically highly significant as depicted in table 4.

Table 4: No of Rescue Analgesics

No of Rescue Analgesic	Group B n (%)	Group D n (%)	P value	Statistical Significance
1	0 (0)	3 (10)	0.001	HS
2	14 (46.7)	26 (86.6)		
3	16 (53.3)	1 (3.3)		

Discussion

Post-operative analgesia provides not only pain relief but also inhibits trauma- induced nociceptive impulses so as to blunt autonomic reflexes. It allows the patients to breathe freely and ambulate early to enhance early restoration of function [4]. Historically, because of the wrong notion that the children neither suffer or feel pain, nor respond to or remember the painful experiences to the same degree that adult did, they have been undertreated for pain.

Systemic analgesics (opioids and NSAIDs), used for providing post-operative analgesia, are associated with risk of gastro-intestinal bleeding, precipitation of asthma, thrombocytopenia, nausea and vomiting, sedation, respiratory depression, nephrotoxicity etc. The regional techniques avoid most of these problems and it is possible to achieve analgesia with minimum of drug dose and complications.

Caudal epidural blockade is one of the most popular regional blocks used in paediatric anaesthesia. Caudal block is safe and reliable technique, easy to perform and has been found to be very effective in children, especially in infra-umbilical surgeries when combined with general anaesthesia [4]. It allows rapid recovery from anaesthesia with good post-operative analgesia. The main disadvantage of this technique is that its efficacy is limited by the duration of action of the local anaesthetic. Caudal epidural catheter placement is not popular because of the risk of infection. Various additives to local anaesthetic solutions have been used to prolong the duration of single-shot caudal anaesthesia [8, 9].

Hence, several studies have reported caudal use of opioids, ketamine, midazolam, neostigmine, α_2 agonists and other drugs in children to improve postoperative analgesia. Although the use of caudal opioids did prolong the duration of analgesia, it was associated with side-effects like respiratory depression, pruritus, urinary retention and nausea/vomiting. Hence other drugs like α_2 agonists have been used to improve analgesia in the postoperative period while avoiding the side-effects associated with opioid use.

Among the α_2 agonists clonidine and dexmedetomidine are commonly used. Clonidine has been extensively used in all types of regional anaesthetic techniques. Dexmedetomidine is a highly selective α_2 agonist especially for the 2A subtype with sedative and analgesic properties and minimal respiratory depression. It has a α_2/α_1 selectivity ratio of (1600:1) which is eight times more potent than clonidine (200:1). It is shorter acting drug than clonidine with a distribution half life of 9 min and elimination half life of 2 hours. Dexmedetomidine is a preservative-free solution and contains no additives or stabilizers. Epidural dexmedetomidine has been used in the range of 1.5–2 µg/kg without any incidence of neurological deficits.

In our study we have used a single dose of 0.25% bupivacaine 1ml/kg. Armitage has recommended 0.25% bupivacaine in a dose of 0.5 ml/kg for lumbo-sacral, 1 ml/kg for thoraco-lumbar 1.25 ml/kg for mid-thoracic level of block and the plasma bupivacaine levels were always below 1.2µg/ml, which was below the toxic levels. Gunter *et al* have reported that 0.175% bupivacaine offered the best combination of effectiveness and rapid recovery and discharge for paediatric surgical outpatients.

However, Jamali *et al*. [10] and Cook *et al*. [9] used 0.25% bupivacaine 1ml/kg for paediatric herniotomy and orchidopexy respectively, as a single shot caudal block. Higher concentration can produce motor blockade in the immediate post-operative period and delay discharge. Since

all our patients were monitored for 24 hours post-operatively in the hospital, 0.25% bupivacaine was used which gives a better quality of analgesia.

El-Hennawy *et al*. compared bupivacaine 0.25% 1ml/kg alone and dexmedetomidine 2µg/kg or clonidine 2 µg/kg with bupivacaine 0.25%, 1ml/kg caudally. They concluded that the addition of dexmedetomidine or clonidine to caudal bupivacaine significantly promoted analgesia time [16 (14–18) and 12 (3–21) h respectively] than the use of bupivacaine alone [5 (4–6) h] with a $p<0.001$.

Saadawy *et al*. [12] showed that the duration of analgesia was significantly longer with dexmedetomidine administration 1µg/kg with bupivacaine 0.25% 1ml/kg (18.5 h) than plain bupivacaine 0.25% 1ml/kg (6.2 h) ($p<0.001$) and the incidence of agitation following sevoflurane anaesthesia was significantly lower with dexmedetomidine ($p<0.05$).

Neogi *et al*. [13] compared ropivacaine 0.25% 1ml/kg alone and dexmedetomidine 1µg/kg or clonidine 1µg/kg with ropivacaine 0.25% 1ml/kg caudally. The mean duration of analgesia was 6.32±0.46 hours in the ropivacaine group, 13.17±0.68 hours in the clonidine group and 15.26±0.86 hours in the dexmedetomidine group. They concluded that addition of both clonidine and dexmedetomidine to ropivacaine administered caudally significantly increases the duration of analgesia.

Anand *et al*. [14] also studied ropivacaine 0.25% 1ml/kg and ropivacaine 0.25% 1ml/kg with dexmedetomidine 2 µg/kg caudally. The mean duration of post operative analgesia in the ropivacaine group was 5.5 hours and in the ropivacaine - dexmedetomidine group 14.5 hours with a p value of < 0.001.

In the present study also there is a prolongation in the duration of post-operative analgesia in the dexmedetomidine group (598.17 ± 78.33 minutes) compared to the bupivacaine group (298 ± 44.6 minutes). This difference between the two groups is highly significant, both clinically and statistically.

In this study, the FLACC Pain Scale was chosen to assess post-operative pain. Previous studies of paediatric postoperative caudal analgesia have used the Children's Hospital of Eastern Ontario Pain Scale, the Children and Infants Postoperative Pain Scale, or the Objective Pain Scale. However, several of these studies observed no significant difference in postoperative observational pain score [11]. The FLACC Pain Scale, being an observational and behavioural pain measurement score, is reliable and validated for children aged 2months – 7 years.

The time to first analgesic requirement or total duration of post-operative analgesia in bupivacaine group was 4.96 ± 0.74 h with a range of 3.83 - 6.75 h, while in dexmedetomidine group; it was 9.96 ± 1.33 h with a range of 8.08 – 12.58 h. This difference between the two groups is highly significant.

The FLACC pain score never reached ≥ 4 during the first two hours in both the groups. At the end of third and fourth hour, 3 (10%) and 10 (30%) patients in group B had a pain score of ≥4 and required rescue analgesic whereas none of the patients had a score of ≥ 4 in group D. This difference between the two groups is highly significant. During the remaining time interval except at the end of 8th and 20th hour group B patients achieved higher FLACC score than group D.

Similar prolongation of postoperative analgesia was seen in different studies. The duration of analgesia achieved by the addition of dexmedetomidine to bupivacaine varies widely in these studies (13.9 - 21.3 hours). This may be the result of a number of factors: dose of dexmedetomidine used; differences in premedication and volatile anaesthetics used; type of surgery; indications for rescue analgesia; assessment of pain and statistical analysis.

In bupivacaine group 14 (46.7%) and 16 (53.3%) children required two and three doses of rescue analgesics respectively. Where as in dexmedetomidine group 3 (10%), 26 (86.6%) and 1 (3.3%) children required one, two and three doses of rescue analgesics respectively. The difference is statistically highly significant.

Conclusion

The present study demonstrated that caudal administration of bupivacaine 0.25% (1ml/kg) with dexmedetomidine (1 µg/kg) resulted in reduced anaesthetic requirement, prolongation of the duration of analgesia and less post-operative analgesic requirement compared with 0.25% bupivacaine (1ml/kg) alone, without any significant difference in the hemodynamic parameters or increase in the incidence of side-effects in children undergoing lower abdominal surgeries. Hence low dose dexmedetomidine safely prolongs the duration of post-operative analgesia when it is added to bupivacaine for caudal block for lower abdominal paediatric surgeries.

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