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Effect of Intranasal Dexmedetomidine on Duration of Anesthesia and Postoperative Analgesia after Bupivacaine Caudal Epidural Anesthesia in Children Undergoing Infraumbilical Surgeries

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Abstract

Background: Caudal epidural analgesia a commonly practiced regional anesthesia in children undergoing infraumbilical surgeries but, provides short duration of action after single shot of anesthesia. *Objective:* To explore the effect of intranasal dexmedetomidine on the duration of anesthesia and postoperative analgesia, in pediatric patients undergoing infraumbilical surgery, under single-shotcaudal epidural block. *Methodology:* Pediatric patients (n = 60) were randomly assigned to two Groups—A and B, Group A received intranasal dexmedetomidine (1 µg/kg of body weight) with caudal bupivacaine (0.25%, 1 ml/kg of body weight) and Group B received same, without dexmedetomidine. Vitals were recorded at regular time intervals. Postoperative anesthesia, analgesia, and sedation levels were measured by Modified Bromage Scale, FLACC scale, and Ramsay Sedation Scale. Statistical analysis wasdone using MedCalc version 17. *P* - value of < 0.05 was considered statistically significant. *Results:* Study groups were equivalent in terms of demographics and vitals. Duration of anesthesia in Group A and B were found to be 215.83 ± 16.19 mins and 137.17 ± 15.52 min, respectively, and significant difference was identified between the groups. The time from caudal block to first rescue analgesia was 12.47 ± 2.16 hour sin Group A and 3.55 ± 1.18 hours in Group B; significant variance existed between both the groups ($p < 0.001$). Mean sedation scores were significantly more in Group A, compared to Group B ($p < 0.001$). *Conclusion:* Intranasal dexmedetomidine (1 µg/kg) with bupivacaine (0.25 %) via caudal epidural, lengthens the duration of anesthesia and analgesia in pediatric patients, as compared to sole administration of bupivacaine, without side effects.

Keywords: Pediatric anesthesia; Analgesia; Caudal epidural; Dexmedetomidine; Bupivacaine.

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Introduction

In pediatric patients, anesthesia administration and pain management are two potential challenges to the medical professionals. The procedural pain among pediatric patients is often neglected and under estimated due to in calculable beliefs, myths, and complications in its evaluation and treatment. Anesthesiologists usually use either general, regional, or local anesthesia and each

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method has its unique set of problems.[1] Generally, anesthesia technique will be opted based on type of surgery, patient condition, duration of surgery, safety, and cost effectiveness. Regional anesthesia has many benefits compared to general anesthesia: It provides excellent muscle relaxation and reduces post-operative analgesia.[1] Regional anesthesia practices are superior to general opioid analgesia, with reverence to analgesia safety profile and adverse effects.[2]

In pediatric patients, the most favored regional anesthetic procedure for infraumbilical surgeries is caudal epidural anesthesia.[3] Usually, the block is used either by a single shot injection or as the continuous infusion. Single shot technique is the traditionally preferred peri-operative pain management for regional anesthesia; however, it has a few limitations such as short duration of anesthesia and postoperative analgesia.[4] Thus, to improve analgesic duration and quality of the block, several adjuvants such as clonidine, fentanyl, neostigmine, dexmedetomidine, midazolam, and ketamine have been explored.[5–8] However, all these adjuvants have presented side effects, for example prolonged sedation, respiratory depression, and neurotoxicity, specific to the type and dose of adjuvant used.[5–8] The ideal adjuvant is still a subject of contention and, the search for a drug that offers maximal analgesia with minimal undesirable effects for caudal block in children is continues.

In recent years, dexmedetomidine has been establishedas one of the commonly used medicinal drug in anesthesia practice due to its hemodynamic stability, anxiolytic, sedative, analgesic, and neuroprotective effects.[9] High selectivity of dexmedetomidine to α2 A receptors has been exploited in various regional anesthesia practices and yet, numerous avenues remain under explored, intranasal being one of them.[9]

In recent times, dexmedetomidine has been studied extensively in diverse settings and routes.[10–12] Several researchers have studied its effect as an adjunct to the local anesthetic in caudal epidural anesthesia.[13–15] Dexmedetomidineas adjuvant, when used with spinal or epidural anesthesia, extends the duration of anesthesia and post-operative analgesia.[10]

According to the published literature, intravenous shot of dexmedetomidine plays a significant rolein prolonging anesthesia duration and postoperative analgesia, following neuraxial blocks.[10,16] Intranasal route of administration of dexmedetomidine has been shown to have high bioavailability on par with intravenous administration, with reduced side effects.[17] Hence, this study intended to explore the effect of intranasal dexmedetomidine on the duration of anesthesia and postoperative analgesia in pediatric patients or subjects undergoing infraumbilical surgery under single-shot caudal epidural block.

Materials and Methods

Study Design

This one-year prospective, randomized, case-controlled study was conducted in the Anesthesiology department of a tertiary medical college, after receiving ethical clearance from institutional ethics board for the period *January–December 2017*. Prior to study initiation, informed consent was taken from all the parents or legal guardian of the children.

Study Subjects and Selection Criteria

The study involved 60 children aged between *6 months* and *10 years*, belonging to American Society of Anesthesiologists (ASA) I and II Grades, Body Mass Index (BMI) > *25 kgs*, planned for elective infraumbilical surgeries under caudal epidural anesthesia. Patients with contra indications to caudal epidural block, upper or lower respiratory tract infection, known allergy to dexmedetomidine or bupivacaine, and ASA Grade III or more, were excepted from the study.

Grouping

Subjects were randomly divided into two Groups, with 30 in each Group, through a computerized random-number generator. Group A patients received intranasal dexmedetomidine [*1 μg/kg* of Body Weight (BW)] with caudal bupivacaine (0.25%). It was given in two divided doses into each nostril, using an atomizer connected to a tuberculin syringe. Group B received the same received Normal Saline intranasally, without dexmedetomidine. Anesthesia was maintained with oxygen, nitrous oxide, and isoflurane (0.2%). The study medications were prepared by an anesthesiologist, who was not involved in the study and administered by a medical professional in anesthesia, who was blind to the identity of the drug.

Study Procedure

Anin-depth pre-anesthetic examination was done, one day prior to the surgery. Full medical history was elicited, and diligent physical check-up was

carried out. Preoperatively, routine investigations such as Complete Blood Count (CBC), Clotting Time (CT) and Bleeding Time (BT) were evaluated. All the subjects received pre-medications—glycopyrrolate (*0.005 mg/kg*) and ketamine (*1 mg/kg*) intravenously, in the pre-operative holding area after *4 hours* of fasting period before shifting to operating theatre. In the operation theatre, the baseline readings of the vital signs [peripheral capillary oxygen saturation (SpO_2), Echocardiogram (ECG), Heart Rate (HR), and Blood Pressure (BP)], were recorded. Later, pre-medication ketamine (*1 mg/kg*) was repeated along with midazolam (*0.05 mg/kg*) and fentanyl (*1 μg/kg*). The local anesthetic drug, Bupivacaine (0.25%, *1 ml/kg* of B.W.) was administered to each subject *thru* caudal epidural block. In supine position, the study drug—dexmedetomidine, and normal saline were administered to Groups A and B, respectively. The vitals (hemodynamics) BP, HR and SpO_2 were monitored regularly at every *10 minutes* interval, during and after surgery.

In this study, a decline in mean arterial pressure > 20% was demarcated as hypotension and was treated with Intravenous (I.V.) fluids. Decrease in HR > 20%, was considered as bradycardia and was treated with glycopyrrolate (*0.005 mg/kg*). Adequate analgesia was defined as 'hemodynamic stability', as designated by the absence of an increase in HR or systolic BP of more than 20% compared with the baseline value and, from the intra-operative requirements of the inhalational agents. At the end of the surgical procedure, all the patients were moved to the recovery room and hemodynamics were observed for *2 hours*, before returning them to the ward.

Duration of caudal block (motor block *i.e.*, the duration from the administration of the block to the return), hemodynamics–HR and BP (noted every *10 minutes*, till end of surgery), post-operative pain (time for first rescue analgesia) and the level of sedation (at the end of surgery), were recorded. Total motor block duration was evaluated using the Modified Bromage Scale (Bromage PR, 1965)[18] by eliciting the response to tickling of the toes or passively flexing the knee joint, every half hourly until regression of motor block.

Post-operative pain was evaluated at *0.5, 1, 2, 4,* and *6 hours* or, until the primary rescue analgesic was given using the FLACC score (face, legs, activity, cry, and consolability scale).[19,20] The sedation level in children was assessed with Ramsay Sedation Score[21] at the end of the surgery, at *2 hours*, *6 hours*, and *12 hours*, postoperatively. In addition, side effects (if any), were recorded and any untoward or unexpected intra-operative events were treated and documented.

Statistical Analysis

Microsoft Excel was used to tabulate the data and MedCalc version 17 was adopted to analyze the data. The data were expressed as mean and standard deviation. Student unpaired '*t*'-test was performed to determine significance difference in study parameters between the two Groups. *p*- value of < 0.05 was considered statistically significant.

Results

Table 1 shows presents the demographic characteristics and baseline vitals of study participants. A total of 60 pediatric patients, 30 in each Group (Group A and B) with mean age of *18–21 months* completed this prospective study. Gender distribution among the groups were comparable. In both the groups, the minimum and maximum age were *10–12 months* and *33–40 months*, respectively. Further, in both the groups, minimum weight was similar *i.e.*, *10 kg* whereas, the maximum weight was different. The maximum weight in Group A and B was *19 kg* and *17 kg*, respectively. No significant difference could be detected between the groups, with respect to age and weight ($p > 0.05$). For baseline vitals such as HR, SBP, DBP and SpO_2, no significant variance was found between the two Groups.

Table 1: Demographic characteristics and baseline vitals of the pediatric patients

Demographics		Group A	Group B	*p* value
Gender	Male	11 (36.6%)	15 (50%)	NA
	Female	19 (63.3%)	15 (50%)	
Age (*months*)		21.23 ± 8.89	18.80 ± 6.30	0.22
Weight (*kgs*)		12.93 ± 2.26	12.4 ± 32.19	0.38
HR (*beats/minute*)		118.53 ± 12.80	120.20 ± 8.42	0.47
SBP (*mmHg*)		97.27 ± 5.16	96.27 ± 4.78	0.43
DBP (*mmHg*)		63.67 ± 4.37	65.00 ± 5.06	0.27
SpO_2 (*mmHg*)		100 ± 0.00	100 ± 0.00	1

HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SpO_2: Peripheral Capillary Oxygen Saturation; NA: Not Applicable; Group A: Patients Received Intra-nasal Dexmedetomidine; Group B: Patients who received saline.

Heart Rate (*HR*)

In both the groups, there was a fall in HR from '*0' minute* to *120 minutes* shows in Table 2. However, the fall in HR did not require any

therapeutic intervention. When the mean HR at each time interval was compared with the baseline mean HR, a significant variance in the mean HR was noticed between different time intervals ($p < 0.05$).

SBP

In both the groups, the mean SBP was stable for baseline until *20 minutes*, thereafter, there was slight down fall in the mean SBP till *120 minutes* shows in Table 2. However, the fall did not warrant any aggressive treatment and was treated with intravenous fluids. No significant difference in the mean SBP was found at each time interval when compared with the baseline SBP; however, a strong significant variance in the mean SBP was noticed when baseline was compared with mean SBP at *60, 90,* and *120 minutes* ($p < 0.05$).

DBP

For both the groups the mean DBP was constant and there was no change shows in Table 2. In both the groups no significant difference in the mean DBP was found at each interval when compared with the baseline SBP ($p > 0.05$).

Shows in Table 3 presents the postoperative pain or analgesia score assessed using the FLACC scale at *0.5, 1, 2, 4, and 6 hours* or until the first rescue analgesic was given. In this study, all the pediatric patients in Group A (dexmedetomidine) did not report any postoperative pain till *6 hours*, post which few of the children reported postoperative pain. In the Group A children, the analgesia lasted for more than *14–16 hours*, and in Group B, it lasted for just *6 hours*.

Shows in Table 4 presents the sedation level in children at the end of the surgery at *0, 6,* and *12 hours* postoperatively. In Group A, at '*0' hours*, all

Table 2: Heart Rate, SBP, DBP of study participants at different time intervals

Time (*Minutes*)	Group A	Group B	Group A	Group B	Group A	Group B
	Heart Rate		SBP		DBP	
Baseline	118.53 ± 12.80	124.20 ± 8.42	97.27 ± 5.16	96.27 ± 4.78	63.67 ± 4.37	65.00 ± 5.06
0	118.70 ± 11.26	114.13 ± 11.65*	97.40 ± 5.12	96.27 ± 4.78	63.67 ± 4.37	65.00 ± 5.06
5	113.03 ± 10.62	112.27 ± 10.43*	97.27 ± 5.16	96.27 ± 4.78	63.67 ± 4.37	65.00 ± 5.06
10	109.77 ± 10.69*	110.20 ± 10.30*	97.27 ± 5.16	96.27 ± 4.78	63.67 ± 4.37	65.00 ± 5.06
20	112.93 ± 10.90	109.13 ± 11.65*	97.27 ± 5.16	96.27 ± 4.78	63.67 ± 4.37	65.00 ± 5.06
30	110.77 ± 10.98*	107.13 ± 11.65*	95.27 ± 5.16	94.27 ± 4.78	63.60 ± 4.41	65.00 ± 5.06
60	108.80 ± 10.96*	105.13 ± 11.65*	93.27 ± 5.16*	92.27 ± 4.78*	63.67 ± 4.37	65.00 ± 5.06
90	106.87 ± 10.92*	103.13 ± 11.65*	91.27 ± 5.16*	90.27 ± 4.78*	63.67 ± 4.37	65.00 ± 5.06
120	104.87 ± 10.92*	101.13 ± 11.65*	89.27 ± 5.16*	88.27 ± 4.78*	63.67 ± 4.37	65.00 ± 5.06

Group A: Patients received Intranasal dexmedetomidine; Group B: Patients who received saline; NA: Not Applicable; SBP: Systolic Blood Pressure; DBP = Diastolic Blood Pressure '**' = $p < 0.05$

Table 3: FLACC Score for all the participants at different time intervals

Time (*Hours*)	FLACC Score	Group A	Group B
0	0	30	30
2	0	30	23
	1	–	2
4	0	30	–
	2	–	6
	3	–	2
	4	–	17
6	0	30	–
	4	–	8
8	0	29	–
	4	1	–
10	0	24	–
	4	5	–
12	0	13	–
	4	11	–
14	0	7	–
16	0	4	–
	4	7	–

Group A: Patients received intra-nasal dexmedetomidine; Group B: Patients who received saline.

the patients responded to the commands (Score 3), and after *6* and *12 hours*, they appeared oriented, co-operative, and calm (Score 2). In Group B at '*0' hours*, half of the participants responded to only commands and the others were co-operative and calm (Score 2 and 3); however, after *6 hours*, majority of the subjects were anxious and agitated or restless, or both (Score 1). According to the results in Group A and Group B, the sedative effect was decreased with the increased time interval.

Table 4: Ramsay Sedation Scorefor all the Participants at Different Time Intervals

Time (*hours*)	Ramsay Sedation Score	Group A	Group B
0	2	–	17
	3	30	13
6	1	–	24
	2	30	6
12	1	–	28
	2	30	2

Group A: Patients received intra-nasal dexmedetomidine; Group B: Patients who received saline.

According to the results, the mean duration of motor block in Group A was nearly *215 minutes* while, in Group B, it was *137 minutes*. Time from caudal block to first rescue analgesic is nearly *12 hours* in Group A and *3.5 hours* in Group B. The duration of motor block was more in Group A compared to Group Band is statistically significant ($p < 0.01$). Further, a significant difference in postoperative analgesia was found between both the Groups shows in Table 5. None of the patients showed any significant hypotension or bradycardia.

Table 5: Comparison of duration of caudal block and sedation level between Group A and Group B.

	Group A	Group B	*p* value
Duration of caudal block (Modified Bromage Scale)			
Motor block duration (*minutes*)	215.83 ± 16.19	137.17 ± 15.52	< 0.0001
Time from caudal block to first Rescue analgesic (*hours*)	12.47 ± 2.16	3.55 ± 1.18	< 0.0001
The Sedation Level (Ramsay Sedation Score)			
Time (hours)	**Ramsay Sedation Score**		
0	3 ± 0.00	2.43 ± 0.00	< 0.001
6	2 ± 0.00	1.2 ± 0.40	< 0.001
12	2 ± 0.00	1.06 ± 0.25	< 0.001

Group A: Patients received intra-nasal dexmedetomidine; Group B: Patients who received saline.

Discussion

In modern anesthesia practice, regional anesthesia is primarily used to avoid postoperative analgesia among pediatric patients.[22] Conventionally, it was believed that infants require very little or no analgesia; however, poor analgesia in infants can cause behavioral changes that might affect future responses to pain in early childhood. Consequently, advanced regional anesthesia techniques such as caudal epidural analgesia, are preferred for children of all ages.[3,23] The published reports disclose that addition of intrathecal additives to the regional anesthetics increases post-operative analgesia and prolongs the duration of anesthesia. As this is simple and effective, hence, it has received wide acceptance.[5–8]

The literature revealed that dexmedetomidine, when administered intravenously to post-surgical patients, demonstrates sedative and analgesic effects.[10] In the current study, we used intranasal dexmedetomidine in pediatric patients undergoing infraumbilical surgery under single-shot caudal epidural block. As per published reports, rapid or bolus administration of intravenous dexmedetomidine can result in sudden hypertension and bradycardia until the central sympatholytic activity dominates hemodynamic parameters. Mahmoud *et al.*,[5] reported moderate reduction in hemodynamic parameters, HR, and BP[24] with intravenous administration of dexmedetomidine. Our study circumvented the same problem faced with intravenous administration of dexmedetomidine. This could be attributed to the slow rise in plasma concentration after an intranasal administration.

In this study, we demonstrated prolonged duration of anesthesia and postoperative analgesia in dexmedetomidine group without any episodes of post-operative complications. We infer that the study drug, dexmedetomidine is effective when administered intra-nasally and has a wide safety margin in pediatric patients. These findings are in line with reports of Saadawy *et al.*, (2009)[26] and Anand *et al.*, (2011).[27] Saadawy *et al.* (2009), reported significant prolongation in the duration of caudal analgesia with the addition of dexmedetomidine to 0.25% bupivacaine, compared to 0.25% bupivacaine alone among pediatric patients having unilateral inguinal hernia/orchidopexy.[26] Similarly, Anand *et al.*, (2011) reported prolongedor extended duration of sedation and post-operative pain relief with the drug dexmedetomidine and caudal ropivacaine in pediatric patients undergoing lower abdomen surgery.[27]

The duration of caudal block assessed using Modified Bromage Scale was significantly higher in dexmedetomidine group compared to the normal

saline group. These findings are in harmony with Nazir and Jain (2016),[28] where the Bromage scores were significantly higher in the patients belonging to the age group *18–60 yrs.*, who received dexmedetomidine as adjuvant to bupivacaine compared to bupivacaine, alone. In epidural caudal block, the duration of pain not only depend on the volume and concentration of anesthesia but also on the adjuvant concentration that was used.[28,29]

In this study, pediatric patients who received dexmedetomidine for infraumbilical surgery have displayed reduced FLACC score for the postoperative pain, when compared with normal saline group. These results are analogous to the finding of Parameswari *et al.*, (2010),[30] who reported significantly lower FLACC scores in patients administered with adjuvant (clonidine) along with bupivacaine, when compared with the patients administered with bupivacaine and saline. Further, the sedation (Ramsay) score was higher in patients administered with dexmedetomidine, when compared to the patients administered with normal saline. These findings are comparable with the study findings of Refaee *et al.* (2019), who reported higher sedation score in dexmedetomidine-administered patients compared to patients who received bupivacaine (*0.5 ml/kg*) and normal saline.[31] Thus, the study was successful in establishing the advantages of using dexmedetomidine, intranasally, to prolong the duration of anesthesia and analgesia in caudal epidural anesthesia when used at a dose of *1 μg/kg* of body weight.

Limitations

Although no major complications or side effects were noticed in our study, further studies are obligatory to rule-out any long-term or short-term adverse effects of intra-nasal dexmedetomidine. Besides, the study involved only pediatric patients and the effect in adults and older patients undergoing infraumbilical surgery is not known. Further, futures studies need to be carried out using smaller doses of dexmedetomidine to assess whether similar results can be achieved with lesser complications.

Conclusion

The current study findings demonstrate that combination of dexmedetomidine at a dose of *1 μg/kg* with bupivacaine (0.25%) via caudal epidural, prolongs the duration of anesthesia and analgesia, in pediatric patients compared to bupivacaine solely, without side effects.

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Conflicts of interest: None declared.

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