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Analgesic Efficacy and Safety of Dexmedetomidine as an Adjuvant to Caudal Levobupivacaine for Infraumbilical Surgeries in Children

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Çocuklarda İnfraumbilikal Cerrahilerde Kaudal Levobupivakaine Adjuvan Olarak Deksmedetomidin Eklenmesinin Analjezik Etkinlik ve Güvenirliği

ABSTRACT

Objective: *Postoperative pain management is becoming an integral part of anaesthesia care. Single shot caudal block is a common technique for paediatric analgesia but with the disadvantage of short duration of action. Several adjuvants have been used to prolong the duration of caudal analgesia. So we designed this study using dexmedetomidine as an adjuvant with levobupicaine for caudal block to assess analgesic efficacy, duration of postoperative analgesia, hemodynamic stability and any adverse effects in children.*
Methods: *After getting approval by Institutional Ethical Committee and written informed consent from parents, this prospective, double blind trial was carried on 80 children aged between 1 to 12 years scheduled for elective subumbilical surgeries that were allocated randomly into one of two groups. Children in Group A received 0.25% levobupivacaine 1 mL kg^{-1} body weight with 0.5 mL normal saline and in Group B received 0.25% levobupivacaine 1 mL kg^{-1} body weight with dexmedetomidine 1 mL kg^{-1} in 0.5 mL normal saline as caudal drug mixture.*
Results: *The mean duration of analgesia in Group A was 324.±55.6 min and in Group B was 678±170.9 min which was statistically significant (p<0.001). The total analgesic requirement over 24 hours and the mean pain score was also lesser in group B.*
Conclusion: *Dexmedetomidine in doses of 1 µg kg^{-1} as an adjuvant to 0.25% levobupivacaine for caudal block in pediatric infraumbilical surgeries provides significant prolonged postoperative analgesia and better quality of sleep without any increase in adverse effects.*

Keywords: *Caudal block, levobupivacaine, dexmedetomidine, infraumblical surgeries*

ÖZ

Amaç: *Ameliyat sonrası ağrı yönetimi, anestezi bakımının ayrılmaz bir parçası haline gelmektedir. Tek seferlik kaudal blok, pediatrik analjezi için yaygın bir tekniktir, ancak kısa etki süresi dezavantajıdır. Kaudal analjezi süresini uzatmak için pek çok adjuvan kullanılmıştır. Bu nedenle bu çalışmayı, çocuklarda kaudal blokta kullanılan levobupivakaine adjuvan olarak deksmedetomidin eklenmesinin analjezik etkinliği, postoperatif analjezi süresi, hemodinamik stabilite ve herhangi bir yan etkisi olup olmadığını değerlendirmek için tasarladık.*
Yöntem: *Kurumsal etik kurul onayı ve ebeveynlerden yazılı bilgilendirilmiş onam alındıktan sonra bu prospektif, çift kör çalışma, 1-12 yaş arası elektif subumblikal cerrahi planlanan 80 çocuk, rastgele iki gruptan birine dahil edilerek gerçekleştirildi. Grup A'daki çocuklara 0.5 mL normal salin ile birlikte %0.25 levobupivakain 1 mL kg^{-1}, Grup B'ye ise 0.5 mL normal salin içinde 1 µg kg^{-1} deksmedetomidin ile birlikte %0.25 levobupivakain 1 mL kg^{-1} olacak şekilde kaudal ilaç karışımı verildi.*
Bulgular: *Ortalama analjezi süresi Grup A'da 324±55.6 dk ve Grup B'de 678±170.9 dk olup fark istatistiksel olarak anlamlıydı (p<0.001). 24 saat boyunca toplam analjezik gereksinimi ve ortalama ağrı skoru da Grup B'de daha azdı.*
Sonuç: *Pediatrik infraumbilikal cerrahilerde kaudal blok için %0.25 levobupivakaine adjuvan olarak 1 µg kg^{-1} dozda deksmedetomidin eklenmesi yan etkilerde herhangi bir artış olmaksızın anlamlı dercede uzun postoperatif analjezi ve daha iyi uyku kalitesi sağlamıştır.*

Anahtar kelimeler: *Kaudal blok, levobupivakain, deksmedetomidin, infraumblikal cerrahi*

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INTRODUCTION

Pain is one of the most unpleasant, underdiagnosed and misunderstood sensation which can only be felt but not expressed, particularly in children who completely depends on their guardians for their well being. Inadequate and inappropriate management of postoperative analgesia in children can result in long term physical, psychosocial, and behavioral complications [1]. Till date various techniques have been developed for providing analgesia in pediatric patients but under treatment is still present and it has been attributed to the fear of respiratory depression with opioid use, needle stick injury and difficult pain measurement especially in very small children [2].

Though, after the introduction of caudal block by Campbell in 1933, it has developed as one of the most commonly used regional method for providing post-operative analgesia in paediatric patients as it is easier to perform and extensively safe. It also mitigates the requirement of volatile agents and opioids when combined with general anaesthesia [3]. But the limited duration of analgesia is the main drawback of single shot caudal block, even with use of different local anaesthetic agents e.g., lignocaine, bupivacaine, ropivacaine, levobupivacaine. Therefore, prolongation of duration of these regional techniques is desirable [4].

Recently, Levobupivacaine, an S enantiomer of bupivacaine, is believed to have a safer pharmacologic profile with decreased cardiovascular and neurologic adverse effects attributed to its faster protein binding rate. Levobupivacaine is as efficacious as bupivacaine and found to cause further vasoconstriction in lower concentrations thereby enhancing the sensory blockage with lesser toxicity [5]. Therefore, Levobupivacaine is recognized to deliver equivalent analgesia to bupivacaine but with less motor block.

Various adjuvants to local anesthetics have been investigated for prolongation of caudal block. Adjuvants such as epinephrine, α-2 adrenergic agonists, opioids, ketamine, neostigmine, midazolam, fentanyl and clonidine have been used in the search of ideal agent which remains still elusive [6,7]. Dexmedetomidine which has analgesic and sedative properties, is an extremely selective α-2 receptor agonist with α-2/α-1 ratio of 1600:1 and due to which it is eight times more potent than clonidine having major advantage over clonidine [8].

Some studies have shown that addition of dexmedetomidine to ropivacaine/bupivacaine in regional blocks prolongs the duration of analgesia with minimal side effects. However, there is a scarcity of literature on the use of dexmedetomidine as an adjuvant to levobupivacaine for extension of single shot caudal block. So, we planned this clinical trial to evaluate the analgesic efficacy of dexmedetomidine 1 μg kg^{-1} as an adjuvant to 0.25% levobupivacaine in caudal block in terms of duration of analgesia, pain intensity, level of sedation and side effects.

MATERIAL and METHODS

This prospective, randomized, double blind, clinical study was carried out as per the biomedical research guidelines of Indian Council of Medical Research and in agreement with the principles of Declaration of Helsinki 2013. After the Institutional Ethical Committee (ECR/836/Inst/PB/2016) approval dated 13/02/18 and registering the trial with the Clinical Trial Registry of India (CTRI/2018/07/014769), this study was done on 80 paediatric patients of ASA Grade I or II, aged 1-12 years who were scheduled for elective infra-umbilical surgeries under general anaesthesia with written informed consent from their parents. Patients with history of developmental or mental retardation, known allergy to study drugs, coagulation disorders, coexisting medical or neurological diseases, sacral bone abnormality and any sign of infection at the block site were excluded from study. Preanesthetic assessment was done on the day before surgery and parents were asked to ensure child's preoperative fasting (minimum 2 hours for clear liquid and 6 hours for semisolid or solid). On the day of surgery, all the patients were premedicated with oral midazolam 0.5 mg kg^{-1}, 45 minutes before induction of anesthesia. In the operation room, routine monitors including pulse oximetry, electrocardiogram, and noninvasive blood pressure (NIBP) monitoring were instituted and the baseline vitals were recorded. Intravenous (IV) line was placed with appropriate size cannula and IV fluid infused at the rate of 4 mL kg^{-1} h^{-1}. Intravenous glycopyrrolate

0.005 mg kg^{-1} body weight was administered as premedication. Then standard inhalational anaesthesia technique was used for induction of anaesthesia. Neuromuscular blocking agent atracurium 0.5 mg kg^{-1} body weight was given to facilitate endotracheal intubation. Maintenance of anesthesia was done with 40% O_2:60% N_2O mixture and sevoflurane 1-2%. After induction of anaesthesia, child was moved to lateral decubitus position for blind caudal block. With a sterile procedure, the caudal space was recognized using standard landmarks technique and a 22 G short, hypodermic needle was inserted into the caudal space. Test aspiration was done and the study drug was injected following confirmation of absence of blood/ cerebrospinal fluid.

These patients were randomly divided into 2 groups of 40 each and randomization was done using a computer generated excel spread sheet randomization program. Sequentially numbered sealed opaque envelopes naming the drug to be administered were opened shortly before the induction of anaesthesia. The drugs for use in the caudal space were prepared by an anaesthesiologist who was not contributing in the study and the caudal block was given by another anesthaesiologist who was blinded to the drug that was injected. Children in Group A received 0.25% levobupivacaine in the dose of 1 mL kg^{-1} body weight with 0.5 mL normal saline and Group B received 0.25% levobupivacaine in the dose of 1 mL kg^{-1} body weight with dexmedetomidine 1 µg kg^{-1} in 0.5 mL normal saline as caudal drug mixture. The time of placement of caudal block was recorded and surgery was allowed after 10 minutes of caudal block. In case the block was inadequate as suggested by limb movement on surgical incision or tachycardia, patients were managed with additional fentanyl 1 µg kg^{-1} and excluded from the study. Failure of the caudal block was not found in any of our patients. As per standard protocol heart rate, NIBP, oxygen saturation and temperature were recorded before induction and then every 5 minutes for first half an hour and then every 10 minutes until the end of surgery. The manifestation of intraoperative hypotension i.e., fall in systolic blood pressure >20% of the baseline, requiring a fluid bolus and bradycardia requiring atropine was recorded. After completion of surgery, the residual neuromuscular blockage was reversed using intravenous glycopyrrolate (0.002 mg kg^{-1}) and neostigmine (0.05 mg kg^{-1}). After extubation, patients were shifted to recovery and were monitored for vital signs (heart rate, respiratory rate and peripheral oxygen saturation).

Postoperatively the Face, Legs, Activity, Cry and Consolability (FLACC) pain scale was used to assess pain immediately and at 2, 4, 6, 12, 18 and 24 hours of the postoperative period [9]. Intravenous paracetamol 15 mg kg^{-1} was given as rescue analgesia whenever the FLACC score ≥4 was observed. Duration of analgesia and the 24 hours total analgesic consumption were also recorded. Ramsay sedation score was used to assess the level of sedation at 15, 30 and 60 minutes after extubation and thereafter hourly until the sedation score became 2 or less in each patient [10]. Any other side effects like nausea, vomiting and respiratory depression were monitored and managed accordingly. Postoperative respiratory depression was defined as respiratory rate <10/min or fall in SpO_2<93% requiring supplement oxygen or assisted ventilation.

Statistical Analysis

The duration of analgesia was taken as primary outcome measure for the sample size calculation. Based on former clinical data to detect the mean difference of 4 hours between two groups in duration of analgesia and 80% power along with 5% probability of type 1 error, sample size of 80 patients (40 in each group) was considered acceptable. After completion of trial, all the outcomes were evaluated by using IBM SPSS Statistics for Windows, Version 17.0 (Chicago: SPSS Inc.). Numerical variables were analysed using Student's unpaired t-test and Pearson's chi square (χ^2) test was used for categorical values. Non parametric numerical variables within the two groups were analyzed by using the Mann-Whitney U test. For all statistical analyses, p value <0.05 was taken as significant.

RESULTS

In this study, a total of 80 patients were enrolled and screened for eligibility to participate in this clinical trial. All the 80 patients were allocated to one of the two study groups and there was no drop out in the

study. Regarding demographic data including age, weight, and sex and duration of surgery (Table I) and type of surgery (Table II), no statistically significant difference was found between the two groups. Intraoperative hemodynamic parameters i.e., HR, NIBP, oxygen saturation and temperature were also comparable in both the groups.

Table I. Comparison of demographic data and duration of surgery

Variables	Group A (n=40)	Group B (n=40)	p value
Age (years) (mean±SD)	4.30±2.757	4.38±2.862	0.905
Weight (kg) (mean±SD)	16.58±6.3	16.83±6.4	0.861
Sex (male/female) (n)	35/5	36/4	0.723
Duration of surgery (min) (mean±SD)	45.1±12.8	45.1±12.8	1.00

**p value >0.05 is insignificant.*

Table II. Type of surgeries in the two groups

Type of Surgery	Group A (n=40)	Group B (n=40)	p value
Chordee (%,n)	5% (2)	5% (2)	
Hypospadias (%,n)	25% (10)	32.5% (13)	
Inguinal Hernia (%,n)	55% (22)	47.5% (19)	0.962
Phimosis (%,n)	5% (2)	5% (2)	
Undescended Testis (%,n)	10% (4)	10% (4)	

**p value >0.05 is insignificant.*

Duration of analgesia was demarcated as time between administration of caudal block and the time to first request for rescue analgesia. The mean duration of analgesia in group A was 324±55.6 minutes (mean 5.4 hours) with confidence interval of mean 306.19-341.81 while in group B it was 678±170.9 minutes (mean 11.3 hours) with confidence interval of mean 623.34-732.66. The statistically difference in their mean duration of analgesia was found to be highly significant (Table III).

Table III. Mean duration of analgesia and total analgesic consumption among two groups

	Group A (n=40)	Group B (n=40)	p value	Significance
Duration of analgesia (minutes) (mean±SD)	324±55.7	678±170.9	0.000	HS
Total analgesic consumption (mg) (mean±SD)	392.3±187.5	268.9±111.8	0.000	HS

**HS-highly significant, p value <0.01 is considered highly significant.*

In present study, the FLACC pain scale was measured in PACU at 0 hour and at 2, 4, 6, 8, 12, 16, 24 hours of the post-operative period. FLACC score was statistically non significant among two groups in PACU at 0 hour. The patients in group A showed increase in FLACC pain score at 4 hours and 6 hours whereas the patients in group B had low FLACC score at above intervals. This difference on statistical analysis was found highly significant. However, in group B, there was increase in FLACC score at 8th hour i.e., 3.10±0.8. After receiving rescue analgesia, FLACC score decreased in both the groups. Thus, the difference between mean FLACC Score was statistically significant at 2, 4, 6, 8, 12 and 16 hours while it was comparable at 24 hours postoperatively among two groups (Figure 1).

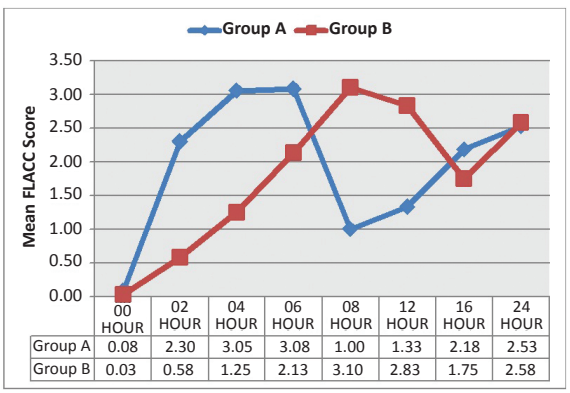
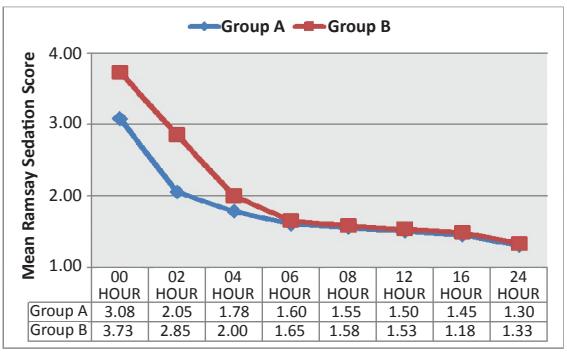


Figure 1. Face, Legs, Activity, Cry and Consolability (FLACC) score during postoperative period

Rescue analgesia was used when FLACC score was ≥4. The mean number of doses of rescue analgesia that was required in group A was 1.60±0.501 and in group B was 1.00±0.00 and the difference was found statistically significant among two groups. Most of the patients in group B (90%) required only single dose of rescue analgesia (except 10% who required second dose in first 24 hours period) whereas in group B, 42.5% patients required single rescue analgesia dose and 55% patients needed two doses of rescue analgesia in 24 hours post-operative period. Only one patient in group A required three doses of rescue analgesia. Mean total analgesic consumption in group A was 392.3±187.5 mg and in group B was 268.9±111.8 mg and the difference among two groups was found statistically significant.

There was also statistically significant difference

regarding level of sedation among the two study groups. The mean RSS score in group B was statistically significant higher as compared to group A at 0, 2 and 4 hours postoperatively. But after 4 hours, RSS was comparable between two groups as shown in (Figure 2). In our study, the intraoperative and postoperative period was uneventful in both groups. No episodes of hypotension, bradycardia, or respiratory depression requiring intervention in any of the patients in the two groups were noted.



	00 HOUR	02 HOUR	04 HOUR	06 HOUR	08 HOUR	12 HOUR	16 HOUR	24 HOUR
Group A	3.08	2.05	1.78	1.60	1.55	1.50	1.45	1.30
Group B	3.73	2.85	2.00	1.65	1.58	1.53	1.18	1.33

Figure 2. Mean Ramsay Sedation Score (RSS) at different time intervals during postoperative period

DISCUSSION

Caudal epidural analgesia is most common, dependable, and safe method in paediatric anaesthesia that can provide satisfactory analgesia for a variety of infra-umbilical surgeries. The main drawback of caudal block is the shorter duration of analgesia after a single injection. The use of repeated doses or infusions of local anaesthetics through caudal catheter is not common in clinical practice due to risk of infection. So, prolongation of single shot caudal analgesia technique has been accomplished by the use of different adjuvants with local anaesthetics [7]. Use of "double caudal" procedure has recently been promoted whereby the caudal is "topped up" at the end of the surgery again [11].

Dexmedetomidine during neuraxial use causes direct stimulation of pre and postsynaptic α-2 adrenoreceptors in the spinal cord thereby by activating spinal cholinergic neurons resulting in acetylcholine release and preventing the release of nociceptive neurotransmitters resulting in analgesia. This effect correlates with the concentration of dexmedetomidine in the cerebrospinal fluid but not that in the plasma [12,13].

In present study, we used levobupivacaine in dosage of 1 mL kg^{-1} of 0.25% levobupivacaine i.e., 2.5 mg kg^{-1}. Clinically, its use in paediatric regional anaesthesia is well established. A study conducted by Frawley et al. [14] had concluded that levobupivacaine at a recommended dose of 2.5 mg kg^{-1} is an effective drug for caudal anaesthesia in children and the faster onset of action was suitable for achieving surgical anaesthesia and this postoperative analgesia was established in greater than 97.5% of patients. We used dexmedetomidine in dosage of 1 μg kg^{-1} as an adjuvant because it has a favorable safety profile with better haemodynamic stability which is in concordance with the reports published by several authors [12,15]. In recent study on different doses of dexmedetomidine (1 μg kg^{-1} and 2 μg kg^{-1}) as an adjuvant to caudal analgesia done by Al Zaben et al. [16] had found that use of higher doses of dexmedetomidine had increased the incidence of side effects without any additional prolongation in duration of analgesia. Sufficient data regarding the effects of different concentrations of dexmedetomidine used to prolong caudal analgesia is still lacking.

In children dexmedetomidine has been safely used without any significant respiratory or hemodynamic side effects. Although hemodynamic adverse effects appear to be less marked in paediatrics than adults but this may be dose dependent as found by Konakci et al [17]. Our study also confirms this finding as there was no significant difference in hemodynamics with the use of dexmedetomidine with levobupivacaine in caudal anesthesia similar to other authors [12,15].

The main outcome of our study was the prolongation of caudal analgesia with addition of dexmedetomidine to caudal levobupivacaine with mean duration of 11.3 hours as compared to levobupivacaine alone (5.4 hours). Tandale et al. [18] also found the significant prolongation in duration of analgesia with mean of 12.8 hours in patients with caudal levobupivacaine 0.25% with dexmedetomidine and 7.3 hours with levobupivacaine 0.25% alone. Our findings were also supported with study done by Fares et al. [13] who found mean duration of analgesia of 8.38 hours and

19.2 hours in patients receiving caudal bupivacaine 0.25% alone and in combination with dexmedetomidine 1 µg kg^{-1} respectively.

Nasreen et al., [19] also showed prolongation in duration of analgesia with use of dexmedetomidine (1 µg kg^{-1}) as an adjuvant to caudal levobupivacine (0.75 mL kg^{-1} of 0.125% levobupivacaine). Mean duration of analgesia was statistically prolonged (1299 ± 145 min) in Group B (dexmedetomidine with levobupivacaine) as compared to Group A (levobupivacaine) (348±36 min). Comparable analgesic duration with lower concentration of levobupivacine could be attributed to the harness of ultrasound in this study, leading to precise deposition of drug.

Moreover, the mean number of rescue analgesic doses and total analgesic requirement were also significantly lower in group B as compared to Group A in present study and these results were also in agreement with study done by Goyal et al. [20] and Kamal et al. [21].

In our study, pain intensity was measured by using FLACC Scale. FLACC scale is easy to use, reliable and valid which has been recognized in miscellaneous settings and in different patient population [22]. In present study, the difference of mean FLACC score among two groups was statistically significant at 2, 4, 6, 8, 12 and 16 hours except at 0 hour and at 24 hours in PACU. Similar results were also observed by Nasreen et al. [19] where the mean FLACC score was >4 in patients of Group A (levobupivacaine alone) after 5 hours as compared to group B (dexmedetomidine & levobupivacaine) and the two groups showed a statistically significant difference of FLACC score at all times in the postoperative period. Tandale et al. [18] also observed a significant reduction in the FLACC scale among patients receiving dexmedetomidine vis-a-vis levobupivacaine.

In this present clinical trial, mean sedation score was more in the group B at 0, 2 and 4 hours postoperatively as compared to Group A but all the patients were easily arousable by verbal contact and none of them experienced any respiratory depression. Some other authors also noted higher sedation scores in patients receiving dexmedetomidine as caudal additive in the postoperative period [13,18].

In our study none of the patient in either group had any side effects like nausea/vomiting, hypotension, bradycardia and respiratory depression within the observation period. A study conducted by Kamal et al.,[21] also found no episodes of clinically significant postoperative complications with use of dexmedetomidine 2 µg kg^{-1} as adjuvant to ropivacaine (0.25%).

There are few limitations in this present study. Firstly, the enrollment of children with wide range of age group (1 to 12 years) who has variable thresholds for pain and capability to communicate pain, could have led to difference in the pain measurement. Secondly, due to difference in degree of surgical trauma (variable surgical procedures) might have led to variability in pain score in this study. Thirdly, as with use of all adjuvants in regional blocks, the analgesic action of dexmedetomidine through systemic absorption cannot be entirely ruled out from present study since we did not include intravenous dexmedetomidine as control group. Lastly, although we did not encounter even a single block failure, it will be safer and precise to conduct the procedure under ultrasound guidance.

CONCLUSION

Hence, we conclude that dexmedetomidine is an effective adjuvant to levobupivacaine for caudal block in pediatric infraumbilical surgeries in terms of prolonged postoperative analgesia, decreased rescue analgesic consumption and better quality of sleep without any adverse effects. This can contribute significantly to better patient comfort and safety.

Ethics Committee Approval: Institutional Ethical Committee (ECR/836/Inst/PB/2016) approval dated 13/02/18.
Conflict of Interest: None
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Informed Consent: Written informed consent obtained from their parents.

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