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A Prospective Comparative Study of Efficacy and Safety of Dexmedetomidine as an Adjuvant to Caudal Levobupivacaine Versus Levobupivacaine Alone in Paediatric Patient

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Abstract

Background: As the day care surgery becomes popular, caudal epidural block has become routine intervention in children and infants. But the major limitation with this technique is duration of analgesia after single injection, which is limited by the pharmacology of local anaesthetic agent used. To prolong the duration of caudal analgesia various adjuvants such as opioids, ketamine midazolam and α2 agonists are used with single shot technique.We have deigned this study to elucidate the efficacy and safety of dexmedetomidine as an adjuvant to caudal Levobupivacaine versus Levobupivacaine alone in paediatric patient. *Material and Method:* Present study is a randomized, prospective comparative study conducted at department of anaesthesia.Based on exclusion and inclusion criteria 80 patients were enrolled for this study. The patients were randomly allocated into two groups.Group L:- 0.75 ml/kg Levobupivacaine 0.25%, diluted in normal saline 0.9% Group LD: - 0.75 ml/kg Levobupivacaine 0.25% with Dexmedetomidine 1 µg/kg. Various parameters like cardiovascular parameter, duration of analgesia, FLACC score and adverse drug reaction was recorded and compared. *Result:* Both groups were comparable to each other with respect to age, sex, weight, duration of surgery and ASA scare, The P value was more than 0.05 which was statistically insignificant.After induction at 5 min, heart rate was 105.26 + 11.61 /min in group L and 106.52 + 15.22/min in group LD. The P value was 0.2162. After 15min of induction the heart rate was 107.27 + 14.41 in group L and 108.36 + 14.24/min in group LD. The P value was 0.2019 which is not significant. The time of analgesia was 342.8 + 12.4 mins in group L and in group LD it was 486.40 + 14.6 mins. Duration of analgesia was longer in group LD and is significant statistically. *Discussion and Conclusion:* From present study we can conclude that caudal administration of 1 µg /kg dexmedetomidine along with 0.75 ml/kg Levobupivacaine is resulted in prolongation of the duration of analgesia, less post-operative analgesic requirement as compared with 0.75ml/kg Levobupivacaine alone. There is no significant difference in hemodynamic parameters and increase incidence of adverse drug reaction.

Keywords: Dexmedetomidine; Levobupivacaine; caudal block; paediatric patient.

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Introduction

Management of pain is most important aspect in post-operative patient care. Effective pain management remains a challenge in paediatric patients [1,2]. An effective therapy to stop or change the physiological responses to painful stimulus is an essential component of paediatric anaesthesia procedure [3]. Caudal epidural block is the single most popular regional anaesthesia technique for

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infant and children, who is undergoing surgical procedure like, orchidopexy, inguinal hernia repair, circumcision and minor lower extremity and perineal surgery.

As the day care surgery become popular, caudal epidural block has become routine intervention in children and infants [4,5]. But the major limitation with this technique is duration of analgesia after single injection, which is limited by the pharmacology of local anaesthetic agent used. To prolong the duration of caudal analgesia various adjuvants such as opioids, ketamine midazolam and α2 agonists are used with single shot technique.

Levobupivacaine is the pure s(-) enantiomer of bupivacaine. Bupivacaine is used widely for regional anaesthesia, but is associated with severe neurological and cardio vascular adverse effect. Bupivacaine is a racemic mixture and adverse effect is due to its dextro R(+) isomer, but Levobupivacaine S(-) isomer is safe. Levobupivacaine is widely used now in India.

Dexmedetomidine is a stereoisomer of medetomidine; it is a highly selective α2 – receptor (AR) agonist with a high selective α2/α1 ratio (1620:1). As an adjuvant to local anaesthetic agent in the spinal cord, it activates α-2c and α2 ARs situated in the neurons of superficial dorsal horn especially lamina II and reduces release of pronociceptive transmitter substance P and glutamate, from primary efferent terminals. It hyper polarizes spinal interneurons via G- Protein mediated activation of K^+ channel. Post synaptic activation of α2 ARs results in sympatholytic effect so the duration of analgesia is prolonged and stress response to surgery may get attenuated [7,8]. various study has been conducted on efficacy and safety of dexmedetomidine in children between age 1 month to 17 years, it is found to be effective as analgesic and providing sedation. Most of the side effect are haemodynamic and in older children not required drug intervention. Neonates are vulnerable to hypothermia [9,10,11]. Based on above literatures and various published studies, it is evident that dexmedetomidine is effective an adjuvant to local anaesthetic agents. But there are very few studies are available for it use along with Levobupivacaine in paediatric patients. Sowe have deigned this study to elucidate the efficacy and safety of dexmedetomidine as an adjuvant to caudal Levobupivacaine versus Levobupivacaine alone in paediatric patient.

Materials and methods

Present study is a randomized, prospective comparative study conducted at department of anaesthesia Rangaraya medical college Kakinada Andhra Pradesh, from January 2017 to December 2018.

Subject

In present study patients were enrolled randomly who were admitted for elective infra-umbilical surgical procedure such as orchidopexy, circumcision, hernia repairetc, as per exclusion and inclusion criteria.

Inclusion criteria

Age: 1 month to 7 yrs

Both sexes.

ASA score I and II

Elective infraumbilical surgery

Exclusion criteria

Infection at the site of block

Bony deformity

Allergy to drug

Bleeding disorder, → cardiac and neurological abnormality, use of opioid analgesic before surgery

Sample size: Based on the result of previous studies, assuming an α- error 0.05 and power of 80% sample size was calculated to be 40. For this calculation we have used clicalc. Com sample size calculator [12,13].

Method: Based on exclusion and inclusion criteria 80 patients were enrolled for this study. The patients were randomly allocated into two groups. The randomization was done by computer generated randomization table. Each group consists of 40 patients – Group L and Group LD. All person involved in providing medication were blinded. Anaesthesiologist who prepared the drug was not aware about the study of drug.

All patients were evaluated on the pre-operativeday which includeshistory, general examination, systemic examination, assessment of airway and spine. Relevant demographic data was collected, and Lab investigation was done.

Solid food was restricted for 6 hours, breast milk for fours and clear fluid for 2 hr before surgery. All the patients were pre-medicated with syrup midazolam 0.5 mg/kg, 30 min prior to induction. In the operation theatre, after receiving the patient, heart rate (HR), Electrocardiogram (ECG), Mean

arterial pressure (MAP), oxygen saturation (SpO_2) were monitored continuously, before surgery and every 5 min during surgery. According to holiday Segar formula, ringer lactate was started as maintenance fluid. After proper preoxygenation patients were induced with intravenous propofol 2 mg/kg till loss of eyelash reflex and jaw relaxation [14].

For maintenance of anaesthesia oxygen, nitrous oxide and Sevoflurane was used ventilation was controlled via face mask attached to Jackson Rees circuit. The concentration of inhaled Sevoflurane was adjusted to achieve hemodynamic changes up to the 30% of base line values (Lower limit). No other analgesic, sedative or narcotic was given to the patient and post induction vital was recorded. Patient was gently placed in left lateral position, under strict aseptic conditions, sacral hiatus was identified and a 23 G hypodermic needle with its bevel facing anteriorly was inserted, and block was performed by loss of resistance to air technique, drug was injected according to the group allocated.

Group L :- 0.75 ml/kg Levobupivacaine 0.25%, diluted in normal saline 0.9%

Group LD :- 0.75 ml/kg Levobupivacaine 0.25% with Dexmedetomidine 1µg/kg.

Residents who were preparing the drug were aware of the children's age and weight. Surgical incision was made 10 min after the completion of caudal block. An intra-operative increase in mean arterial pressure or heart rate by 20% of pre- incision value was defined as insufficient analgesia and was eliminated from the study.

At the end of surgery anaesthetic agent was discontinued and LMA removed in deeper plane of anaesthesia. 100% oxygen inhalation through a face mask was administrated for 3-5 mins. Once the vital was stable, and child was awake, shifted to post-operative room and kept in left lateral position. On arrival in post-operative room child was monitored for four hours with SPO2, respiratory rate, blood pressure and Heart rate, every 5 min, after that child was shifted to ward. Any complication like nausea, vomiting, vascular and dural puncture was noted.

For assessment of post-operative analgesia, we used paediatric observational FLACC pain scale. Pain intensity was assessed at arrival, than every hourly till the time of discharge from the PACU and then every 4 hourly for the first 24 hours after caudle block [15].

FLACC Score

0 = No pain

1-3 = mild pain

4-7 = moderate pain

8-10 = severe pain

If the FLACC score was noted above 4 at anytime, paracetamol rescue analgesia (15 mg/kg) intravenously was given. The duration of adequate caudal analgesia was defined as time interval between the administration of caudal block and first requirement of rescue analgesia, which was recorded.

Ethics: - Present study is approved by institutional ethics committee and before enrolment of patient to this study and written informed consent was obtained from parent/ garden of all patients.

Statistical analysis

Data obtained were tabulated into excel sheet and was analysed by using SPPS version 16 soft were. Results were expressed as mean and the groups were compared by using unpaired t test and chi-square test. For all the P value of equal to 0.05 and less was considered for statistical significance.

Results

As per table -1 mean age of the patients in group L was 2.9 ± 784 yrs and group LD it was 2.809 ± 1.84 yrs. The P value was 0.4157776 which is more than 0.05. The weight of the patients in group LD it was 14.32 ± 4.4 kg.

The p value was 0.25355 which is more than 0.05. Out of 40 patients in group L 38 were male and 2 were female, in group LD 37 were male and 3 were female child,the P value was 0.692348.

Table 1: Demographic profile of both the groups.

Pt characteristics.	Gr. L(n=40 (Mean+SD)	Gr. LD(n=40) (Mean+SD)	p value.
Age (years)	2.9 + 1.784	2.809 + 1.84	0.415776
Weight (kg)	13.52 + 4.14	14.32 + 4.16	0.25355
Sex(m/f)	38/2	39/1	0.556
Duration of surgery in (min)	45.32 + 11.93	42 + 7.60	0.1280
ASA I/II	36/4	37/3	0.692348

In group L 36 patients ASA score was I and in 4 patients ASA score was II. In Group LD ratio of number of patient with ASAI/II was 37/3.

From table-2 it is clear that mean heart rate of patient at base line in group L was 105.6 ± 2.27 and in group LD it was 104.182 ± 12.42 having p value 0.18795. At zero min before induction it was 105.26 ± 11.61 per min in group L and 104.26 ± 14.20/min in group LD. After induction at 5 min, heart rate was 105.26 ± 11.61 /min in group L and 106.52 ± 15.22/min in group LD. The P value was 0.2162. After 15 min of induction the heart rate was 107.27 ± 14.41 in group L and 108.36 ± 14.24/min in group LD. The p value was 0.2019 which is not significant. After 60 min the heart rate in group L was 94.36 ± 20.47/min and in group LD it was 96 ± 16.32/min which were not significant statistically. After 90 min of induction the heart rate in group L patients were 98.346 ± 16.32 and Group LD it was 96.2 ± 2.32 which was not significant statistically.

As per table-3 the mean arterial pressure in group L at base line was 70.45 + 3.9093 mm of Hg and in group LD it was 71.42 ± 4.9993 mm of Hg. The p value was 0.215 which is not significant statistically. At zero min before induction the mean arterial BP was 69.73 ± 4.93 mm of Hg in group L and 70.53 mm of hg in group LD. This was again not significant statistically. After 5 min of induction mean arterial blood pressure was 68.23 ± 4.47 mm of hg in group L and 66.43 + 8.32 mm of hg in group LD. This was not significant statistically. After 15min mean arterial blood pressure in group L was 67.07 ± 5.01193 mm of Hg and in group LD it was 61.90 ± 3.24 mm of hg. The P value was <0.0001 which is significant statistically.

At 30 min the mean arterial blood pressure in group L was 65.45 ± 4.90 mm of hg and in group LD it was 60.92 ± 4.01 mm of Hg which was significant statistically. At 60 min the mean arterial blood pressure in group L was 67.82 mm of Hg and group LD it was 61.24 ± 4.02 mm Hg. This difference was significant statistically. At 90 min the mean arterial blood pressure was 68.62 ± 4.32 mm of Hg in group L and 64.24 ± 3.74 mm of Hg in group LD this difference was again significant statistically.

Regarding various anaesthesia logical parameters between two groups, as per table-4, the FLACC score was 0 at 1st hour in both groups which was not significant statistically.

After two hour the mean FLACC score was 4.85 ± 0.35 in group L and 1.95A ± 0.73 in group LD. This difference was significant statistically. At 3 hr it was 2.02 ± 0.884 in group and 0.025 ± 0.5 in group LD. At 4hr it was 1.95 ± 0.62 and 0.005 ± 0.156 in group L and group LD respectively, At 5 hours the score was 2.95 ± 0.82 in group L and 0.84 ± 0.42 In group LD. At 6 hr it was 2.89 ± 0.37 in group L and 1.02 ± 0.63 in group LD. All these difference in both groups was statistically significant.

The time of analgesia was 342.8 ± 12.4 mins in group L and in group LD it was 486.40 ± 14.6 mins.

Table 2: changes in the heart rate throughout the studied duration.

Time interval	Gr L (mean+SD)	Gr LD (mean+SD)	p value
Base Line	105.6 + 12.27	104.182 + 12.42	0.18795
0	105.01 + 10.27	104.26 + 14.20	0.2162
5 min	105.26 + 11.61	106.52 + 15.22	0.110989
15 min	107.27 + 14.41	108.36 + 14.24	0.2019
30 min	104.36 + 17.62	103.44 + 12.3	0.412
60 min	94.36 + 20.17	96 + 16.32	0.210
90 min	98.346 + 16.32	96.1 + 2.32	0.112

Table 3: Mean arterial blood pressure changes through the study period.

Time	Gr L (mean+SD)	Gr LD (mean+SD)	p value
Base line	70.47 + 3.90	71.42 + 4.99	0.215458
0	69.73 + 4.93	70.53 + 4.97	0.270562
5 min	68.23 + 6.47	66.43 + 8.32	0.210462
15 min	67.07 + 5.011	61.9 + 3.24	<0.0001
30 min	65.24 + 4.99	60.92 + 4.01	<0.05
60 min	67.82 + 2.3	61.29 + 4.02	0.024
90 min	68.62 + 4.32	64.24 + 3.742	0.0428

Table 4: comparisons of various anaesthesia parameters between groups.

Variables		Gr. L(n=40 Mean +SD)	Gr. LD(n=40 Mean +SD)	p
FLACC Score	1 hr	0	0	0.5
	2 hr	4.385 + 0.35	1.95 + 0.73	0.0001
	3 hr	2.02 +0.884	0.025 + 0.50	<0.00001
	4 hr	1.95 + 0.62	0.005 + 0.156	<0.0001
	5 hr	2.95 + 0.82	0.84 + 0.42	<0.0001
	6 hr	2.89 + 0.37	1.02 + 63	<0.0001
2. Duration of Analgesia		342.8 + 12.4	486.40 + 14.6	<0.05
3. Rescue analgesia required by the patient Number (%)		31 (77.5%)	8 (20%))	-

Table 5: Incidence of Adverse drug reaction

Characteristics	Gr L (mean+SD)	Gr LD (mean+SD)
Hypotension	2 (5%)	1 (2.5%)
Bradycardia	2 (5%)	0
Respiratory depression	1 (2.5%)	0
Hypothermia	1 (2.5%)	2 (2.5%)
Vomiting	1 (2.5%)	1 (2.5%)

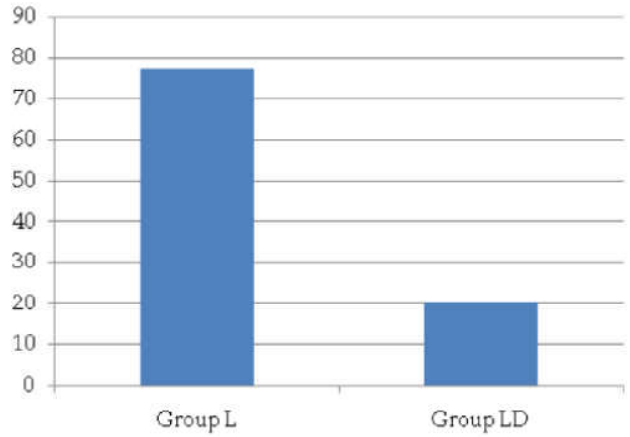

Chart 1: Rescue analgesia required by the patient in two groups (%)

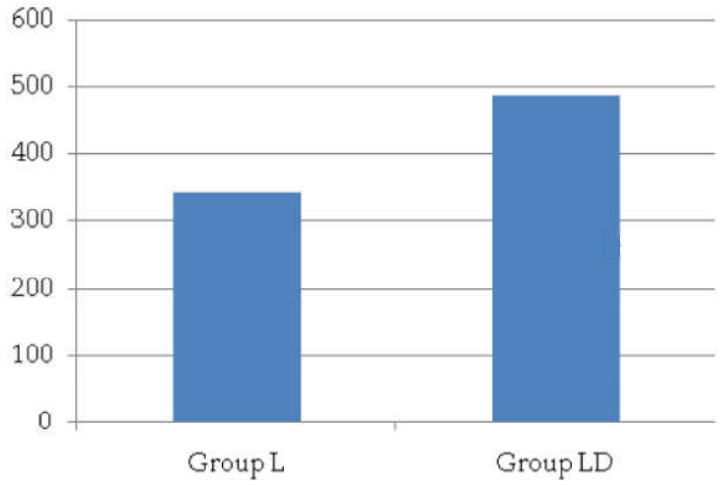

Chart 2: Duration of Analgesia in two group

Duration of analgesia was longer in group LD and is significant statistically. Out of 40 patients in group L 31 (77.5%) patients requires rescue analgesia and in group LD only 8 patients (20%) required rescue the analgesia.

As per table-5 Hypotension was present in 2 patients in group L and 1 patient in group LD. Bradycardia was present in two patients in group L and no patient in group LD has developed Bradycardia. Respiratory depression was absent in group LD but one patient in group L having respiratory depression Hypothermia was present in two patients in group LD and one patients in group L. Vomiting was present in one patients in each group.

Discussion

To achievea satisfactory post-operative analgesia various adjutants are used along with local anaesthetic agents. Dexmedetomidine is a α2 Areceptor blockers which acts at spinal cord level and produces analgesia without effecting the cardiorespiratory profile of patients, various study has been done regarding efficacy of dexmedetomidine along with local anaesthetic agent and the result of the study is encouraging for anaesthesiologist. Elfawal et al. has concluded from his study that dexmedetomidine is a suitable adjutant to Levobupivacaine with stable haemodynamic effects [16].

Present study has been conducted to elucidate the efficacy and safety of dexmedetomidine as an adjuvant to Levobupivacaine in paediatric patients.

Patients were divided into two groups and both groups were comparable to each other with respect to age, sex, weight, duration of surgery and ASA scare, The p value was more than 0.05 which was statistically insignificant. This finding corroborates with the work of Elfawal et al. and Thandale SR et al. [16,17]

In our study we have found that both groups are comparable to each other with respect to heart rate and there is no Bradycardia which requires clinical intervention, this finding corroborates with finding of Modified A et al. [18]. There is statistically significant difference regarding mean arterial blood pressure between two group without any clinical significant. Which is supported by the work of Thandale et al and Trifa M et al. [17,19]

In present study we have observed that there is significant decrease in FLACC in group LD in the first 6hr, in comparison to group L. This finding corroborates with work of Bhaskardutt et al. and Elfawal et al. [12,20].

Duration of analgesia was 342.8 ± 12.4 min in group L and 486.40 ± 14.6 min, which is significant higher in group LD. ZhenzhenTu et al. in his metaanalysis results agreed that dexmedetomidine prolong the duration of analgesia and reduces the requirement of rescue analgesia. This study supports our finding [21]. In present study in Levobupivacaine group 77.5% patients required rescue analgesia but in dexmedetomidine adjuvant group only 20% required rescue analgesia. Which corroborates with the finding of Meenakshi KNP et al. and A1 zaben KR et al. [22,23].

α2 adrenergic agonists have been studied for adverse drug reactions, Paris A et al. and Coskuner I et al were reported that there was not serious side effect was observed by the use of dexmedetomidine. Zhen Zhen TV et al. in his metaanalysis has observed that use of dexmedetomidine as an adjuvant along with local anaesthetic agent is not associated with serious side effect but there was no significant difference in the incidence of nausea vomiting, this finding corroborates with our studies we have observed that incidence of hypothermia was higher in Dexmedetomidine adjuvant group than levobupivacaine alone group [21,24]. This was found in young children which is supported by the work at finkel JC et al. [26]

Conclusion

From present study we can conclude that caudal administration of 1 µg/kg dexmedetomidine along with 0.75 ml/kg Levobupivacaine is resulted in prolongation of the duration of analgesia, less post-operative analgesic requirement as compared with 0.75 ml/kg Levobupivacaine alone. There is no significant difference in hemodynamic parameters and increase incidence of adverse drug reaction.

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