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Comparison of Caudal Analgesia between Levobupivacaine and Levobupivacaine with Clonidine in Children: A Randomised Control Study

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Abstract: Addition of clonidine to levobupivacaine (0.25%) can potentially enhance analgesia without producing prolonged motor blockade.The aim of this study was to evaluate the efficacy of caudal levobupivacaine alone or in combination with clonidine in children undergoing infra-umbilical surgeries. This study was a prospective, randomized, double blind study and sixty children of ASA grade I and II of either sex aged 2-8yr were randomized into 2 groups. Group L received 1 ml/kg of 0.25% levobupivacaine and Group LC received 1 µg/kg of clonidine in combination with 1 ml/kg of 0.25% levobupivacaine caudally after general anaesthesia was induced. Hemodynamic variables (HR, SpO2, RR and NIBP) were monitored in all patients. Duration of analgesia & motor blockade, degree of motor blockade, pain score by FLACC scale and sedation score were recorded at preset time intervals along with various complications like nausea, vomiting, hypotension, bradycardia & respiratory depression. Student's t test was done for statistical analysis by SPSS 17 Software. Mean duration of analgesia was maximum in group LC (503.66±89.53 min) than in group L (237.66± 49.59 min). Degree & duration of motor blockade were comparable in both groups and higher seadation was found in group LC patients. HR, SBP& DBP were lower in group LC as compared to group L. Addition of clonidine to levobupivacaine resulted in a longer duration of analgesia and a higher sedation score as compared to caudal levobupivacaine alone.

Keywords: caudal analgesia, clonidine, levobupivacaine.

INTRODUCTION

Children suffer post-operative pain in the same way as adults; the main difference is that factors such as fear, anxiety and lack of social support can further exaggerate physical pain in children. It has been shown that children, who experience pain in early life, show long-term changes in terms of pain perception and related behaviours [1, 2].

Several advances in developmental neurobiology and pharmacology, knowledge of new analgesics and newer applications of old analgesics in the last two decades have helped the paediatric anaesthesiologist in managing pain in children more efficiently.

Regional anaesthesia provides excellent post-operative analgesia and attenuation of stress response in children. It is safer, easier to perform and cost effective and should be used in all cases where possible [3,4]. In 1967, Fortuna from Brazil reported a series of 170 patients between the ages of 1–10 years who received caudal epidural anesthesia [5].

Single dose injection in caudal anaesthesia is the most effective and most prevalent form of regional block in children [6]. Bupivacaine is the most commonly used local anaesthetic for caudal analgesia. Levobupivacaine is a S enantiomer of bupivacaine and having less cardiotoxicity. It is as effective as bupivacaine for the management of post-operative pain [7].

Prolongation of caudal analgesia using a single shot technique has been achieved by the addition of various adjuvants [8, 9]. Clonidine is an imidazoline derivative with α_2 agonistic activity. After its administration into subarachnoid or epidural space, clonidine provides a substantial antinociceptive effect by acting on the α_2 receptors in the dorsal horn of spinal cord and brain stem nuclei implicated in pain. The aim of our study was to assess and compare the efficacy of

levobupivacaine and levobupivacaine with clonidine used as caudal epidural anaesthetic in paediatric age group (2-8 years) for elective infra-umbilical surgeries.

METHODS

The study was a prospective, double-blind, randomized, and controlled trial. After approval of the institutional ethics committee, children in the age group of 2–8 years under ASA status I and II, scheduled for elective infraumbilical surgeries were enrolled in the study. Children with bleeding disorders, neuromuscular diseases, allergy to local anaesthetic, unwilling parents, bony abnormalities of the spine, and infection at the site of caudal analgesia were excluded from the study. Sixty children were randomly allocated in to 2 groups: group L, group LC, based on sealed envelope technique.

Group L (n=30)	0.25% Levobupivacaine hydrochloride (1ml/kg) + normal saline 0.5 ml
Group LC (n=30)	0.25%Levobupivacaine hydrochloride (1ml/kg)+ inj.clonidine hydrochloride1µg/kg made upto 0.5 ml in NS

Uniform premedication of inj. glycopyrrolate 0.01 mg/kg iv and Inj. midazolam 0.05 mg/kg iv was given 15 minutes before induction of anaesthesia. Intradermal sensitivity test to levobupivacaine was performed. Once the child was brought to the operation theatre, baseline monitoring like heart rate, SBP, DBP (systolic& diastolic blood pressure), RR, ECG & SPO2 were recorded. An intravenous line was placed in children for fluid infusion of lactated ringer solution. Induction of anaesthesia was achieved with 50% N2O and sevoflurane in oxygen using Jackson Rees circuit. One minute before placement in lateral decubitus position, an injection of ketamine (1 mg/kg) was given .The patient was placed in left lateral decubitus position, & mask ventilation continued. Caudal space was identified and the appropriate drug was injected, as per the group, using a 24G needle. Haemodynamic Data were recorded at preinduction, and intervals of 5 min till 30 min after which readings were recorded every 10 min till 1 hour. After 1 hour, readings were taken at 2, 4 and 8 hours.

After 15 min for full effect of caudal block, surgeon was allowed to start the procedure. Effectiveness of block was assessed by haemodynamic stability and decreased requirement for inhalational anaesthetics. No other narcotics, analgesics or sedatives were used intra-operatively. After the commencement of surgery, sevoflurane concentration was gradually decreased and then discontinued.

If there was an increase in heart rate more than 30% of the pre-procedural heart rate at the time of surgical incision, or if there was a failure of caudal block as perceived by an increased modified Bromage score, or if the child required additional supplemental doses of ketamine for analgesia, the case was excluded from the study and supplemental analgesia in the form of further doses of ketamine was given. At the end of surgery N_2O was discontinued and 100% oxygen was administered for 3-5 minutes. Once the vitals were stable and child was awake, the child was shifted to the post- operative recovery room. After arrival to the recovery room, the child was monitored for four hours with SpO2, respiratory rate, NIBP and heart rate. After that the child was shifted to the ward.

Bradycardia: a heart rate of 30% of baseline value or less was treated by inj. atropine 0.01 mg/kg

Hypotension: a fall in systolic BP 30% or greater from the base line value was treated by inj. mephentermine IV, intravenous fluids (crystalloids) as per requirement and oxygen by face mask.

Sensory blockade was assessed by surgeon just before the start of surgery. Degree of Motor Blockade was assessed by patient's movement of leg and feet till no further change was observed. This was classified into four grades according to the Modified Bromage scale.

Table-1: Modified bromage scale [10]

Leg movement	Points
No motor block, able to stand unassisted or complete flexion of ankle, knee and thigh flexion in non-walking child or at wake up evaluation	0
Unable to stand assisted or partial knee flexion with complete thigh flexion in non-walking child or at wake up evaluation	1
Unable to flex the knee but can flex the ankle	2
No movement or complete motor blockade in a fully awake child	3

Duration of Motor Blockade defined as Time from onset of Motor Blockade (taken from administration of caudal block) to Modified Bromage scale 1.

Each child's pain intensity was assessed at 1 hour, 2 hours, 4hours and 8 hours post operatively by using the paediatric observational FLACC pain scale which was first put forward by Merkel *et al*.[11].

Table-2: FLACC Pain Scale

parameters	0	1	2
face	No expression	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw.
legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up.
activity	Lying quiet	Squirming, shifting back and forth, tense.	Arched, rigid, jerking
cry	No cry	Moans or whimpers	Crying steadily, screams
consolability	Content, relaxed	Reassurance, hugging	Difficult to console.

Score 0, no pain; 1-3, mild pain; 4-7, moderate pain; 8-10, severe pain

If score was noted at any time to be 4 or more, paracetamol suppository 15mg/kg rectally was administered to achieve a FLACC scale score of 3 or less.

The duration of analgesia was defined as time interval between the administration of caudal block and the first requirement of supplementary analgesia for the patient and was recorded.

Table-3: Four point sedation score [12]

1	asleep, not arousable by verbal contact
2	asleep, arousable by verbal contact
3	drowsy not sleeping
4	alert/aware

Patient sedation score was defined as

Other complications like respiratory depression, pruritus, vomiting if present, were noted. Statistical analysis was carried out by using student t' test for the intra and inter group comparison by statistics calculation software SPSS version 17; p-value >0.05 was considered to be statistically insignificant and p-value<0.05 was considered to be statistically significant.

RESULTS

Table-4: Demographic Data &Duration of surgery in 2 groups (mean±SD)

S. NO	Variables	Group L	Group LC
1	Age (months)	58.46±24.08	60.60±23.33
2	Weight(kg)	14.06± 2.61	14.46±2.81
3	Sex Ratio(M:F)	27:3	26:4
4.	Duration of surgery(min)	34.33± 8.38	31.16± 6.25

Table-5: Type of surgery in 2 groups

Type of Surgery	Group L	Group LC
Circumscision	7	7
Herniotomy	9	12
Urethroplasty	7	2
Others(skin grafting, CTEV)	7	9

As shown in table no 4 demographic variables were comparable statistically in both groups. Maximum number of patients was operated for herniotomy in both groups as shown in table no.5. Basal recordings such as mean heart rate, SBP, DBP, respiratory rate and SpO_2 were also comparable (p>0.05). Mean durations of analgesia were 237.66± 49.59 min for Group L and 503.66±89.53 min for Group LC respectively. Statistically the difference was highly significant (p<0.05) (table no.6).

Table-6: The mean duration of analgesia in both groups

Parameter	Group L	Group LC	P value
Duration of analgesia (min)	237.66 ± 49.59	503.66±89.53	0.00

Table-7: Duration of Motor Blockade and Modified Bromage Score in both groups

Modified Bromage Scores	Group L Mean ± SD	Group LC Mean ± SD	P value
At the time of shifting	1.90 ± 0.40	1.80 ± 0.55	0.426(#)
75 min	1.93 ± 0.45	1.73 ± 0.45	0.090(#)
90 min	1.53 ± 0.62	1.46 ± 0.50	0.653(#)
120 min	1.13 ± 0.50	0.90 ± 0.60	0.112(#)
180 min	0.06 ± 0.25	0.13 ± 0.34	0.398(#)
Duration of Motor Blockade (min)	106.83±27.80	99.33±30.27	0.322(#)

The above mentioned table.7 shown that the Modified Bromage Score at time periods of shifting, 75 min, 90 min, 120 min and 180 min after induction were 1.90 ± 0.40, 1.90 ± 0.45, 1.53 ± 0.62 ,1.13 ± 0.50 and 0.06 ± 0.25 for group L and 1.80 ± 0.55,1.73 ± 0.44,1.46 ± 0.50,0.90 ± 0.60,0.13 ± 0.34 for group LC. The above table shown that the mean duration of motor of blockade in both the groups were 106.86± 27.80 min for Group L and 99.33±30.27 min for Group LC. The difference between Modified Bromage scores and the duration of motor block between the two groups at various time intervals was statistically insignificant.

Table-8: FLACC scoring (Mean± SD) in both groups

FLACC scores	Group L	Group LC	P value
60 min	0.66±0.66	0.93±0.78	0.160
120 min	1.53±0.93	1.56±0.62	0.872
240 min	3.53±1.22	2.20±0.48	0.000
480 min	4.46±0.937	2.96±0.85	0.000
FLACC at the time of first analgesia request	4.16±0.69	3.16±0.74	.000($)

The above table shown the mean duration of FLACC scores at 60 min, 120 min, 240 min and 480 min after induction to be 0.66±0.66, 1.53±0.93, 3.53±1.22, 4.46±0.937 for group L and 0.93±0.78,1.56±0.62,2.20±0.48 and 2.96±0.85 for Group LC patients. Above given table shown the Mean±SD FLACC scores of the two groups at the time of first analgesia request to be 4.16±0.69 and 3.16±0.74 for group L and Group LC respectively. There was significant decrease (P<0.05) in the FLACC of Group LC as compared to Group L at 240 min and 480 min after induction.

The above table shown that patients of Group LC had significantly lower FLACC scores at the time of first analgesia request (p< 0.05).

Table-9: Comparison of Sedation Score (Mean ± SD) in both the groups

Sedation score	Group L Mean ± SD	Group LC Mean ± SD	P value
At the time of shifting	3.13 ± 0.73	2.63 ± 0.71	0.01($)
75 min	3.50 ± 0.50	3.06 ± 0.73	0.011($)
90 min	4.00 ± 0.00	3.43 ± 0.62	0.000($)
120 min	4.00 ± 0.00	3.83 ± 0.37	0.023($)
240 min	4.00 ± 0.00	4.00 ± 0.00	-

The above table shown the mean sedation scores of both groups at the time of shifting, at 75 min,90 min, at 120 min and at 240 min which were 3.13 ± 0.73,3.50 ± 0.50, 4.00 ± 0.00 ,4.00 ± 0.00 and 4.00 ± 0.00 for Group L and 2.63 ± 0.71, 3.06 ± 0.73, 3.43 ± 0.62, 3.83 ± 0.37 and 4.00 ± 0.00 for Group LC respectively. There was statistically significant difference in the sedation scores of both groups at the time of shifting, 75 min, 90 min and 120 min after induction. Group LC had significantly lower sedation scores as compared to Group L.

There was significant decrease in heart rate at 30 min after induction in LC reaching preinduction levels after 4 hours. SBP was lower in group in LC at 30 and 40 min while DBP was lower at 15,30, 40 & 60 min after induction in group LC.(p<0.05).

No significant hypotension or bradycardia was observed in any patient. One subject in group LC had complaints of vomiting & 2 subjects in L group had complaints of postoperative shivering. No other complications were noted in both groups.

DISCUSSION

Many studies however indicate that pain in children is underestimated by health care professionals, and, therefore, children receive sub-therapeutic doses of analgesics [13]. Clonidine, an alpha 2 agonists which was introduced into paediatric practice in 1973 for the treatment of migraine, has expanded in clinical role to

be used as a sedative, premedicant and analgesic [14]. Several studies [7, 15] state that levobupivacaine, which is the enantiomer of the pure racemic bupivacaine S (-) is less toxic, provides similar analgesic effect as bupivacaine, and causes less motor block. Out of the various studies in which levobupivacaine have been used, concentrations range from 0.125% to 0.25% with drug volumes even up to 1.25 ml/kg. Literature reviews proved that a concentration of 0.25% 1 ml/kg levobupivacaine provided best combination of qualities [16]. Even though clonidine has been used in doses ranging from 1-5 µg/kg, we chose a dose of 1 µg/kg in our study as other studies like Klimscha *et al*. [17] have shown that increasing the dose from 1 µg/kg to 2 µg/kg did not enhance the analgesic effect of clonidine but increased the incidence of side effects like respiratory depression, bradycardia and hypotension while increasing the dose.

Jamali *et al*.[18] used clonidine& epinephrine with 1 ml/kg of 0.25% bupivacaine and observed that the duration of analgesia was significantly longer with clonidine (987±573 min). Other studies like El Hennawy *et al*. [9], Disma N *et al*.[19] & Singh J *et al*. [20] have also demonstrated a significant increase in the duration of analgesia with the addition of clonidine. In our study duration of analgesia was more in group LC as compared to control group. Clonidine blocks Aδ and C fibres manifesting as an increase in Potassium conductance in isolated neurons thus intensifying local anaesthetic conduction block. Duration of motor blockade was comparable in both groups ($p > 0.05$). Our results are in accordance with Cook *et al*. [21] who compared the effects of adrenaline, clonidine and ketamine on duration of analgesia, motor block and concluded that there was no difference in the duration of motor blocks in adrenaline, clonidine (2 µg/kg) & ketamine when added to bupivacaine 0.25%. Our study supported by study done by Ivani G *et al*. [22] & Laha A *et al*. [23].

Modified Bromage scores were comparable in both groups ($p > 0.05$). Our study results are in accordance with Akin A *et al*. [24]. FLACC scores was decrease in clonidine group at 240 min and 480 min after induction ($p<0.05$) as compared to the control group. Singh J *et al*. [20] & El Hennawy *et al*. [9] also observed similar results. Patients in Group LC had higher sedation as compared to Group L .Similar results observed by study done by Upadhyay *et al*. [25] & Chatrath V *et al*. [26]. Sedation after epidural clonidine results from activation of α2- adrenoceptors in the locus coeruleus, an important modulator of vigilance. This resulting in increased activity of inhibitory interneurons such as GABA-ergic pathways to produce CNS depression.

Mean HR, SBP & DBP was less in clonidine group. Our study results are in accordance with results of Klimscha *et al*. [17]. It was observed that one subject in the clonidine group had vomiting and 2 patients in group L had shievering. These findings are similar to findings of Bergendahl H *et al*. [27].

CONCLUSION

The addition of clonidine 1mcg/kg to 0.25% levobupivacaine provided increased duration and better quality of pain relief with no motor blocakade. Althogh it produce sedation, it is a good adjuvent for caudal analgesia in paediatric patients.

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