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A Clinical Comparative Study between Caudal Levobupivacaine-Clonidine and Ropivacaine- Clonidine for Postoperative Analgesia in Paediatric Subumbilical Surgeries

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Abstract

Context: The use of clonidine as adjuvant to newer anaesthetic agents like levobupivacaine or ropivacaine in caudal block enhance postoperative analgesia. *Aims:* the purpose of the study was to compare the efficacy of levobupivacaine 0.25% with clonidine 1 mcg/kg to that of ropivacaine 0.25% with clonidine 1 mcg/kg with respect to post-operative analgesia following caudal administration in children. *Settings and Design:* Prospective, double blinded, randomized controlled trial. *Materials and Methods:* sixty children aged 2-6 years, of American Society of Anesthesiologists (ASA) physical status I or II, undergoing subumbilical surgeries were randomly allocated to two groups. After induction with general anaesthesia, Group L received 1 ml/kg of 0.25% levobupivacaine with clonidine 1 mcg/kg and Group R received 1 ml/kg of 0.25% ropivacaine with clonidine 1 mcg/kg caudally. Duration of analgesia (primary outcome), pain scores, number of rescue analgesic doses and side effects if any were recorded. *Statistical analysis used:* All the results were tabulated and analysed statistically. After checking for normality assumption, Student's t test was used for numerical data and Chi-square test for categorical data. p values<0.05 were considered significant. *Results:* Groups were comparable with respect to age, weight, sex, type and duration of surgery. Mean duration of analgesia in Group L was 11.05±0.26 versus 10.86±0.22 hours in Group R, hence comparable between the two groups. None of the groups had nausea, vomiting, bradycardia or hypotension and no significant sedation was noted. *Conclusion:* Clonidine(1 mcg/kg) when used as an adjuvant in caudal block along with either levobupivacaine 0.25% or ropivacaine 0.25% produces similar post-operative analgesia with fewer side effects.

Keywords: Levobupivacaine; Ropivacaine; Clonidine; Caudal block; CHIPPS score.

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Introduction

Caudal block is one of the simplest and safe technique used for surgical anaesthesia in children undergoing subumbilical surgery. It provides excellent pain relief with minimum side effects. As children are not cooperative, caudal block is usually administered in combination with general anaesthesia. This makes detection of early symptoms of systemic toxicity due to accidental intravascular injection of local anaesthetics extremely difficult [6].

Bupivacaine is the most commonly used local anaesthetic agent. It is a racemic mixture of R and S enantiomers, of which R enantiomer is cardiotoxic. Newer local anaesthetics like levobupivacaine and

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ropivacaine are S-enantiomers, which provide wider margin of safety by reducing the occurrence of cardiotoxicity and neurotoxicity [4].

Usage of local anaesthetic agent alone in caudal block provides shorter duration of analgesia. Prolongation of analgesia can be achieved by the addition of various adjutants and amongst them opioids are most widely used. Strict regulations on opioid use (in India) [17] and unpleasant side effects (respiratory depression) [10] has compelled the clinician to use non opioid drugs. Clonidine, an alpha 2 adrenergic agonist produces analgesia without significant respiratory depression [20]. Previous studies have demonstrated that when clonidine was used as an additive to levobupivacaine and ropivacaine in paediatric patients, resulted in prolongation of duration of analgesia significantly [11,16].

To the best of our knowledge, there have been no studies published, comparing levobupivacaine with clonidine and ropivacaine with clonidine for caudal analgesia in paediatric population. The primary aim of this prospective, randomized, double blinded study was to compare the duration of analgesia and secondary aim to measure the number of rescue analgesic doses and any side effects.

Materials and Methods

Following due permission from the Hospital Ethics Committee and written informed consent from parents, this, randomized, double-blinded clinical study was conducted on 60 paediatric patients, aged 2-6 years, of either sex and American Society of Anesthesiologists (ASA) physical status I or II, undergoing subumbilical surgeries (inguinal hernia repair or orchidopexy). Children with history of developmental delay or mental retardation, neurological disorders, pre-existing bleeding disorders, cardiac diseases, sacral abnormalities, infection at caudal injection site and hypersensitivity to local anaesthetic (amide) drugs were excluded from the study.

A pre-anaesthesia evaluation was done day before the surgery, anaesthetic technique and perioperative course were explained to the parents. Patients were randomly allocated to one of the two groups (30 in each) by computer-generated random list which were delivered in sequentially numbered opaque sealed envelopes.

Group L: Received caudal mixture of 1 ml/kg Levobupivacaine 0.25% with preservative free Clonidine 1 mcg/kg.

Group R: Received caudal mixture of 1 ml/kg Ropivacaine 0.25% with preservative free Clonidine 1 mcg/kg.

The investigator who open the sealed envelope, prepared the solutions for caudal administration as per the group mentioned and labelled it as caudal solution without revealing the group or drug. Further he was not involved in the follow-up of the study. Another investigator, who is not aware of the composition of the caudal solution, performed the caudal block and recorded the observations intra operatively.

In our institute, all paediatric patients had intravenous access secured on the previous day of surgery. On the day of surgery, in the preoperative room, patients were re-examined, nil per oral status was confirmed and baseline vitals were recorded. An infusion of Ringer Lactate was started, midazolam (50 mcg/kg) and glycopyrrolate (5 mcg/kg) were given intravenously. Patients were then shifted to operating room, multiparameter monitor were attached and induction of general anaesthesia was done with fentanyl (1 mcg/kg intravenous), propofol (2.5 mg/kg intravenous) and an appropriate size I gel was inserted. Anaesthesia was maintained with mixture of oxygen and air (50:50) and sevoflurane was adjusted to maintain an end-tidal concentration of 1.5–2%, based on intraoperative haemodynamics. Patients were then placed in the lateral position and under all aseptic precautions caudal block was performed using a short bevelled 23G needle. Needle position was confirmed by the characteristic 'pop' sensed during penetration of sacrococcygeal ligament, followed by "whoosh" test (using 0.5 ml of air) as per our institutional practice. After negative aspiration for blood and cerebrospinal fluid, the study drug prepared was injected caudally and the time was noted. All the blocks were performed by same anaesthesiologist throughout the study. The surgical incision was made 15 minutes after caudal placement of the drug. Gross movements or any intraoperative increase in heart rate or mean arterial pressure by more than 15% after 15 minutes of caudal block was defined as inadequate analgesia and additional dose of intravenous fentanyl 1 mcg/kg was given. The intraoperative hemodynamic and respiratory parameters were monitored and documented every 5 min till awakening. The duration of surgery and anaesthesia were noted. At the end of the surgery, inhalation agent was discontinued. I gel was removed, once the children were sufficiently awake. They were then shifted to post- anaesthesia care unit (PACU) for continuous monitoring. Heart rate, mean arterial pressure, SpO_2 (oxygen

saturation), post operative pain status and side effects were recorded by blinded observer (Senior Resident) every 15 minutes for first two hours, every 30 minutes for next four hours and thereafter hourly till 24 hours. Post operative pain status was assessed using Child and Infant post-operative Pain scale (CHIPPS) Score 3 [Table 1]. The degree of sedation was graded using University of Michigan Sedation scale (UMSS) 14 and was assessed every 15 minutes for first 2 hours only.

The primary outcome of the study i.e. the duration of analgesia (the time duration from caudal placement of drug until the requirement of first rescue analgesia) was recorded. Rescue analgesia was given with intravenous paracetamol 15 mg/kg, when CHIPPS score was ≥ 4. Secondary outcome such as the number of rescue analgesic doses required for first 24 hours, adverse effects like post operative nausea and vomiting, respiratory depression (a decrease in SpO_2 to < 92% requiring supplemental oxygen), hypotension (fall in mean arterial blood pressure > 20% of the baseline value) and bradycardia (fall in heart rate > 20% of the baseline value) were recorded. Next day the patients were discharged and the parents were given phone numbers to inform any untoward incidents.

Based on the pilot study, sample size was determined using Open EPI software. The mean duration of analgesia expected for levobupivacaine – clonidine and ropivacaine – clonidine group were 11.05±0.26 and 10.86±0.22 hours respectively. This indicated a sample size of 26 subjects would be required in each group at an alpha error of 0.05 and power of 80%. We, therefore recruited 30 patients in each group. Statistical analysis was performed using the statistical package SPSSv19.0 [IBM India Pvt Ltd, Bangalore, India]. The categorical data were represented as numbers and percentages and numerical data were represented as mean and standard deviation. The data collected were analysed for normal distribution by one-way analysis (and were normally distributed). Student's t-test was used for Numerical data and Chi-square test for categorical data. Significance was defined as p value<0.05.

Table 1: Children and Infants Post-operative Pain Scale (CHIPPS)

	CHIPPS score	
Item	**Response**	**Score**
Crying	None	0
	Moaning	1
	Screaming	2
Facial expression	Relaxed/smiling	0
	Wry mouth	1
	Grimace (mouth and eyes)	2
Posture of the trunk	Neutral	0
	Variable	1
	Rear up	2
Posture of the legs	Neutral/released	0
	Kicking about	1
	Tightened	2
Motor restlessness	None	0
	Moderate	1
	Restless	2

Table 2: Patient characteristics, type and duration of surgery

Variables	Group L	Group R
Age in years Mean±SD	4.23±1.3	4.47±1.46
Weight (in kilograms) Mean±SD	13.70±2.32	13.73±2.48
Sex ratio Male: Female	24:6	22:8
ASA physical status(I/II)	26/4	25/5
Type of surgery		
Inguinal hernia repair	27	28
Orchidopexy	3	2
Duration of surgery (in minutes) Mean±SD	51.5±5.59	49.83±5.65

SD = Standard Deviation

Group L= Levobupivacaine - Clonidine, Group R= Ropivacaine - Clonidine

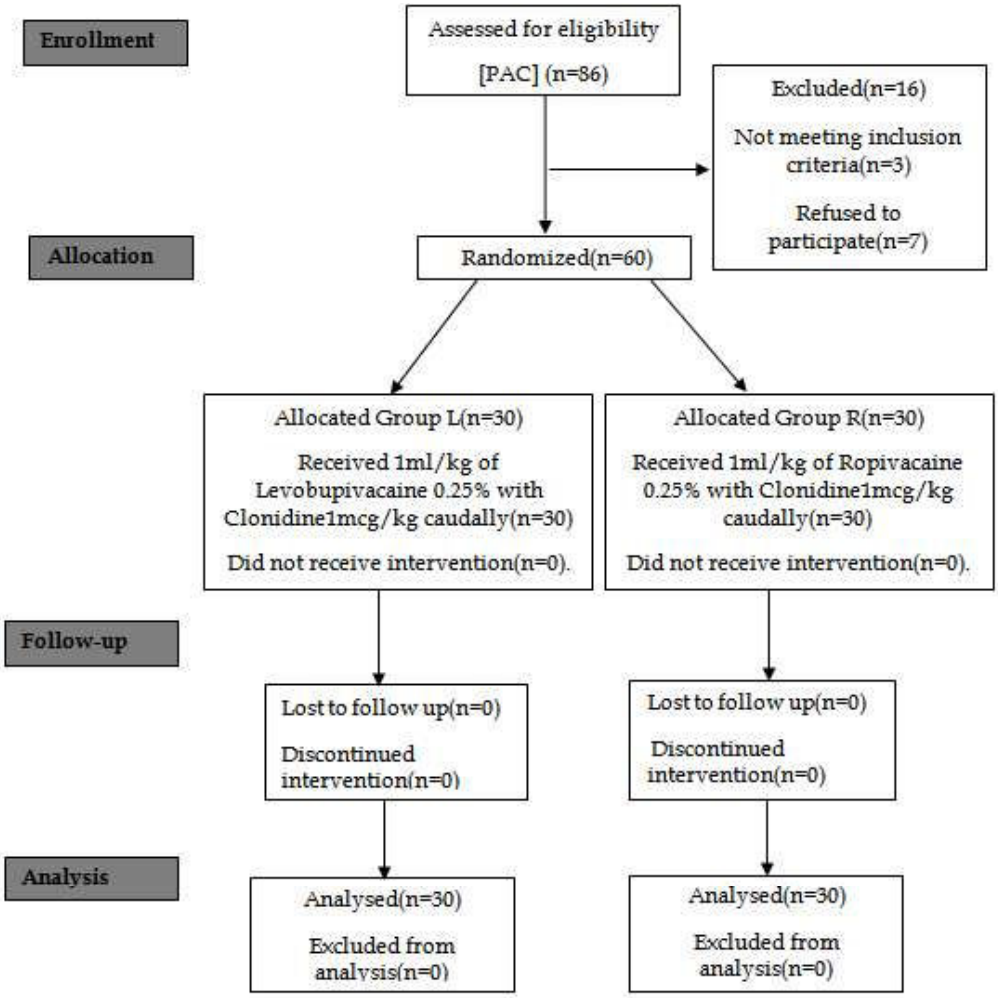

Fig. 1: Consolidated Standards of Reporting Trials flow diagram showing patient progress through the study phases

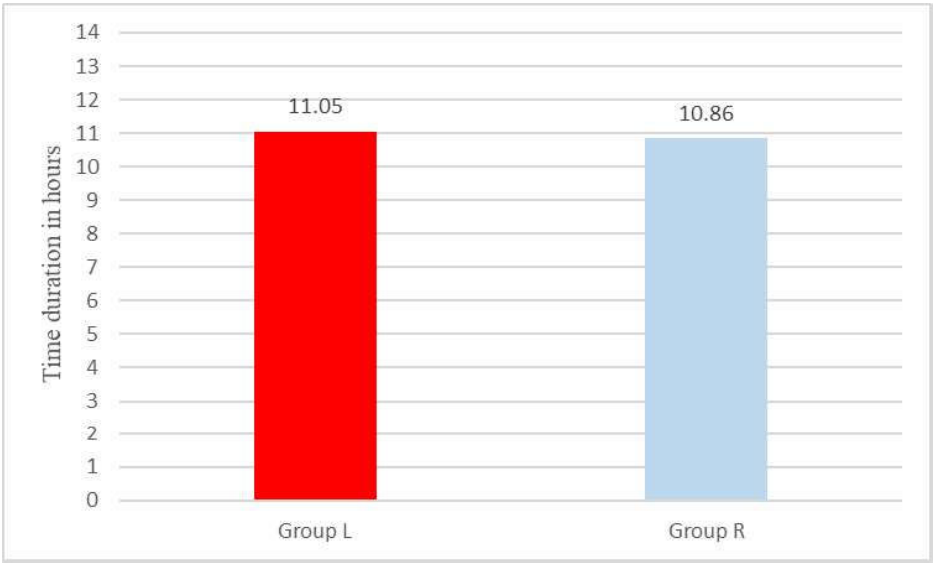

Fig. 2: Comparison of mean duration of analgesia (in hours)

Table 3: The comparison of sedation scores of patients in both the groups

UMSS score	Group L	Group R
0	8	10
1	20	18
2	2	2
3	0	0
4	0	0

UMSS=University of Michigan Sedation Scale

Group L= Levobupivacaine - Clonidine, Group R= Ropivacaine - Clonidine

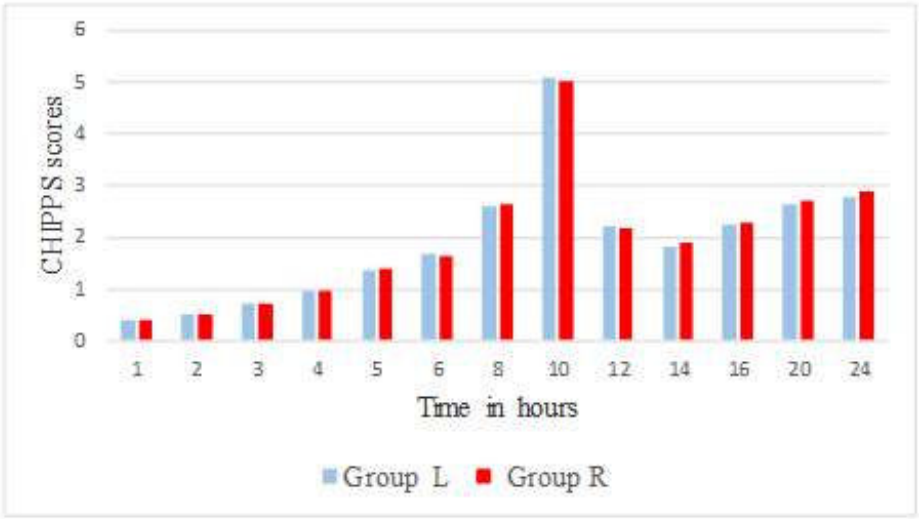

Fig. 3: The comparison of mean Children and Infants Postoperative Pain Scale (CHIPPS) scores in Group L and Group R.

Group L= Levobupivacaine - Clonidine, Group R= Ropivacaine – Clonidine.

Table 4: Duration of analgesia in the published literature

References	Authors	Surgery	Clonidine (mcg/kg)	Local anaesthetic agent	Duration of analgesia (in hours)	Pain Scale used
9	Kanaujia S K and colleagues	Lower abdominal surgeries	1 mcg/kg	Levobupivacaine 0.25% (1 ml/kg)	10.39±0.38	FLACC
16	Potti R L and colleagues	Hypospadiasis repair,inguinal herniotomy	1 mcg/kg	Levobupivacaine 0.25%(1 ml/kg)	16.68±4.7	CHIPPS
15	Manickam A and colleagues	Subumbilical and urological surgeries	1 mcg/kg	Ropivacaine 0.1% (1 ml/kg)	9.8	FLACC
2	Bajwa SJS and colleagues	Inguinal Hernia repair	2 mcg/kg	Ropivacaine 0.25% (0.5 ml/kg)	13.4±3.4	OPS

FLACC: Face, Legs, Activity, Cry, Consolability OPS: Objective Pain Score CHIPPS: Children and Infants Postoperative Pain Scale.

Results

Figure 1 shows the flow of patients through the trial. The groups were comparable with respect to age, weight, gender, ASA physical status, type of surgery and mean duration of surgery as conveyed by Table 2. All the caudal blocks were regarded successful as none required additional doses of intravenous fentanyl. Intraoperative haemodynamic parameters were within 20% of baseline value in both the groups.

The mean duration of analgesia (primary outcome) in group L was 11.05±0.26 and in group R was 10.86±0.22 hours respectively, implying no much difference in duration of analgesia (p value =0.84) between the groups [Fig. 2]. CHIPPS

score were comparable between the groups throughout the study period [Fig. 3]. Both the group required only one dose of rescue analgesic in the first 24 hours.

As evident from the Table 3, Sedation scores were lower as well as similar in both the groups and difference was not statistically significant. There were no complications in the 60 study patients, like nausea, vomiting, bradycardia, hypotension and respiratory depression in the post operative period.

Discussion

Ropivacaine and levobupivacaine are the newer local anaesthetic agents, which are associated with reduced systemic toxicity and hence has greater margin of safety [13]. Clonidine an alpha 2 adrenoreceptor antagonist is one of the widely used adjuvant in caudal block to prolong the duration of analgesia. Clonidine when given neuraxially, its analgesic effect was more pronounced, suggesting spinal mode of action. Sharp and colleagues, in their study found that, a lesser volume of bupivacaine (0.5 ml/kg) after caudal injection may not deliver the clonidine up to the spinal cord, there by leaving only direct action on nerve roots in the caudal area [19]. Further studies on ropivacaine showed that 1 ml/kg 0.25% ropivacaine when administered caudally, produces a maximal plasma concentration of 0.72±0.24 mg/lit(litre), which is way much lower than the maximal plasma concentration of ropivacaine (2.2±0.8 mg/lit) tolerated in adult volunteers [7]. Ingelmo P and colleagues in their study about relative analgesic potencies of levobupivacaine and ropivacaine for caudal anaesthesia in children found that the potency ratio at Effective Dose(ED)50 was 0.92 and at ED95 was 0.89, suggesting similar potency between the two anaesthestic agent in caudal block [8]. Therefore, we chose 1 ml/kg of 0.25% ropivacaine and levobupivacaine. Various doses of clonidine have been used caudally (1–5 mcg/kg), we selected a dose of 1 mcg/kg as it produces similar effect and fewer adverse effects when compared to 2 mcg/kg of clonidine [5].

In the present study, the primary outcome was the duration of analgesia (time duration from administration of caudal block to first requirement of rescue analgesia) which was comparable between the groups (around 11 hours). The duration of analgesia in other studies varied between 5.8 hours to 16.5 hours. This wide range of variation might be due to the difference in the dosage of clonidine, dosage and concentration of local anaesthetics agents, use of various premedication, different scales of pain assessment, indication for rescue analgesia and drugs used for rescue analgesia. Non standardised surgeries and anaesthetic techniques might be the other major factors. [1,2,9,15,16] [Table 4].

Sedation after clonidine is due to alpha 2 adrenoreceptor activation in locus ceruleus, an important modulator of vigilance, resulting in increased activity of inhibitory interneurons to produce central nervous system depression. It is dose-dependent as demonstrated by Lee and colleagues in their study on adding 2 mcg/kg of clonidine [12]. As we used lower dose of clonidine in our study, we had lower sedation scores in both the groups score and all the patients were easily arousable, which are consistent with the findings of previous studies [9,15,16]. Hypotension and bradycardia are the two haemodynamic side effects of clonidine in neuaxial blocks. This is due to stimulation of alpha 2 inhibitory neurons in the medullary vasomotor centre of the brainstem causing a decrease in sympathetic outflow. These are more pronounced in adults and with higher dose of clonidine. Because of lower dose of clonidine (1 mcg/kg) in our study, heart rate and mean arterial pressure were maintained within 20% of the baseline value and were comparable between the groups, which were similar to the previous study [29]. There have been documentation of respiratory depression with the use of caudal clonidine, which were more pronounced in neonates; 20 None of the patients in our study suffered this side effect [9,15,16]. A systematic review and meta-analysis by Yang Y and colleagues on Clonidine as additive to local anaesthetics for paediatric neuraxial blocks, demonstrated the increase in the duration of post operative analgesia, lesser number of rescue analgesic requirement and fewer side effects when lower doses were used. We found similar results in our study [20].

The standardised method of premedication, anaesthesia and analgesia are strengths of our study. Further we used CHIPPS score for pain assessment, which is a simple, objective and validated scale for assessing post-operative pain in children aged 1-6 years [3]. The pain was assessed for 24 hours postoperatively by anaesthesiologists and didn't involve parents. This was to prevent any bias or inconsistency in treating pain among kids. Ours was a single centric study with a small sample size. We didn't measure the motor blockage characteristics. We included children undergoing both inguinal hernia and orchidopexy, thus surgeries were non standardised. These were the limitations of our study.

Conclusion

Clonidine (1 mcg/kg) when added to levobupivacaine 0.25% and ropivacaine 0.25% in paediatric caudal block had similar post operative analgesia with fewer side effects and either combination can be used safely in children undergoing sub umbilical surgery.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Appendix

University of Michigan Sedation Scale (UMSS).

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