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Clinical Comparative Study between Caudal Levobupivacaine-Clonidine and Ropivacaine- Clonidine for Post-Operative Analgesia

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Abstract
Background: *The provision of adequate analgesia is necessary after any surgery and is all the more important in children. Pain after surgery is inevitable. It has been recognized for some time that management of acute pain, especially postoperative pain, has been consistently and systematically inadequate, situation being worse in children.* ***Methodology****: After careful pre-anaesthetic check-up children posted for elective sub-umbilical surgeries between age groups of 3-8yrs of ASA I & II were randomly divided into 2 equal groups.Group L received levobupivacaine 0.25% 1ml/kg + 2mcg/kg clonidine and Group R received ropivacaine 0.25% 1ml/kg + 2mcg/kg clonidine. Following intrathecal administration of these drugs, intraoperative hemodynamic changes, postoperative pain relieving quality and rescue analgesia were studied. Hemodynamic parameters were monitored in the intraoperative and postoperative period. Incidence of side effects were also noted.* ***Conclusion****: Addition of clonidine as an adjuvant to both the groups were significantly increase in Post-operative analgesic quality with perioperative hemodynamic stability with minimum side effects. Thus making it evident the clonidine as an adjuvant to Ropivacaine and levobupivacaine can be safely used for single shot caudal block in children undergoing elective subumbilical surgeries.*
Keywords*: Levobupivacaine, Ropivacaine, Caudal, clonidine, Analgesia.*

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I. Introduction

The provision of adequate analgesia is necessary during peri-operative period and it is all the more important in children.[1] There is a well-defined pathway for sensation in the new-born infant. Nociception is associated with signs of distress even in new-born.[2]The density of nociceptive nerve endings in the skin of new-born infantsis similar to or greater than that in adults. Pain after surgery is inevitable. Relieving pain has been the focus of continuing human effort. However, it has been recognized for some time that the management of acute pain, especially postoperative pain, has been consistently and systematically inadequate. If anything, the situation in children has been even worse, who have long been under-medicated for acute pain.[3]Caudal anaesthesia was first described at the turn of last century by Fernand Cathelin and Jean Anthanase Sicard inyear 1895. It was predated by lumbar approach to epidural block by almost a decade. Since its first description in 1933 for paediatric urological interventions, it has evolved to become the most popular regional anaesthetic technique for use in children.[6]It prides great analgesia during surgery as well as postoperatively in subumbilical surgeries in children.[7]It is a simple technique to perform and remains corner stone in paediatric regional anaesthesia. It is new amino amide local anaesthetic (Pure S - enantiomer) introduced in to clinical practice in 1988.It has shorter propyl (C3H7) substituent on piperidine nitrogen atom. It has low lipid solubility**.** So, it has following advantages: At lower concentration, there is greater degree of separation between motor and sensory block. (differential sensory/motor block) So, it produces more pronounced effect of blocking A delta and C fibers (mediating pain sensation) than A motor fibers. So, at lower concentration, it produce prolonged analgesia without producing motor blockade.It produces less motor blockade because rate of blockade of A motor fibersdepends on the physiochemical properties of individual drug i.e. high PKa and low lipid solubility. The PKa of Bupivacaine and Ropivacaine are identical but because of lowlipid solubility, Ropivacaine produce blockade of A motor fibers more slowly than Bupivacaine.so, it carries advantage in children as children find motor block extremely unpleasant in post-operative period. Thus, Ropivacaine allows early mobilization after surgery.[8] It is pure S-enantiomer so, has less affinity for cardiac sodium and potassium channel. So, it produces significantly less depression of cardiac conductivity (less QRS complex widening) as compared to Bupivacaine.

Thus, it is less cardiactoxic compared toBupivacaine. These positive properties favor the use of Ropivacaine for caudal epidural analgesia for lower abdominal surgery in children. Levobupivacaine, a pure S-enantiomer of Bupivacaine has recently been introduced with a potentially reduced toxic profile compared to Bupivacaine. Various pharmacokinetic, animal and clinical studies not only confirm the cardiac toxicity of racemic bupivacaine but experimental studies with levobupivacaine also indicate lower cardiovascular depressant effect and central nervous toxicity. The rationale for replacing racemic bupivacaine with the s-enantiomers levobupivacaine and ropivacaine is to provide a wider margin of safety with the same analgesic efficacy and less postoperative motor block[9] Levobupivacaine and ropivacaine are associated with less risk for cardiac and central nervous system toxicity and are also less likely to results in unwanted postoperative motor blockade. Clonidine is an alpha-2-adrenergic agonist and stimulation of presynaptic alpha-2 adrenergic receptors cause the inhibition of release of norepinephrine from the sympathetic terminals at periphery and noradrenergic neurons in CNS. These alpha 2 receptors are located on the superficial laminae of spinal cord and brainstem nuclei responsible for pain. So, analgesia may be produced at spinal and brainstem level. Clonidine like local anaesthetics also causes the blockade of conduction of nerve fibers. At spinal cord level, it also decreases the noxious afferent inputs through interaction with the alpha-2 adrenoreceptors. It also reduces the release of substance P and excitatory amino acid in spinal cord from peripheral nerve stimulation by noxious stimuli, suggesting presynaptic inhibitory mechanism. It also hyperpolarizes the neurons in the dorsal horn and render them less responsible to afferent stimuli. In addition to brainstem and peripheral site of action, neuraxial administration of clonidine inhibits the sympathetic preganglionic neurons in spinal cord resulting in hypotension.

Objectives

Levobupivacaine 0.25% 1ml/kg+ Clonidine 2mcg/kg, Ropivacaine 0.25% 1ml/kg+ clonidine 2mcg/kg, with respect to: Post-operative pain relieving quality, To study the intra-operative hemodynamics.

II. Review Of Literature

Pain is a protective mechanism designed to alert the body to potentially injurious stimulus. Pain has been continuing focus in anaesthesia. Untreated acute, recurrent or chronic pain related to medical conditions may have significant physiological and psychological consequences in children.Pain evokes negative physiological, metabolic and behavioral responses in children including increasing heart rate, respiratory rate, blood pressure and increased release of catecholamines, glucagon and corticosteroids. This catabolic state induced by acute pain may be more damaging in infants and young children who have higher metabolic rates and less nutritional reserves than adults. Pain leads to anorexia, causing poor nutritional intake and delayed wound healing, impaired mobility, sleep disturbances, irritability and developmental regression. Pain causes significant morbidity and increased risk of mortality. The lack of clinical research and training in paediatric pain problems has allowed the continued invisibility in this area. The complexity of pain assessment in children has also lead to under-treatment of pain. Infants and toddlers cannot express verbally their discomfort while young children may not want to as they are unaware of pain relief. Gupta et al (2014**)** conducted a study on sixty patients of either sex, age 1-6 years, ASA grade I or II undergoing lower abdominal surgeries who were randomly assigned to two group of 30 each, Group A received inj.ropivacaine 0.2% withclonidine 2mcg/kg and Group B received inj.ropivacaine 0.2% with dexmeditomidine 2mcg/kg after induction with general anesthesia. Hemodynamic parameters were observed before, during, and after the surgical procedure. Postoperative analgesic duration, total dose of rescue analgesia, pain score and any side effects were looked for and recorded. They found addition dexmeditomidine or clonidine to caudal ropivacaine significantly promoted analgesia time. Also, there was statistically significant difference between dexmeditomidine and clonidine as regard to duration of analgesia. No significant difference was observed in incidence of hemodynamic changes or side effects. Addition of dexmeditomidine or clonidine to caudal ropivacaine significantly promoted analgesia in children undergoing subumbilicalsurgeries with significant advantages of dexmeditomidine over clonidine and without an increase in incidence of side effects Laha et al (2012) conducted a study on 30 ASA1 pediatric patients, aged 2- 11years, undergoing infraumbilical surgery were randomly allocated to receive a caudal injection of either plain ropivacain 0.2% 1ml/kg (group A) or mixture ofropivacaine 0.2% 1ml/kg with clonidine 2mcg/kg (group B). Objective pain score and need for supplemental analgesics were compared during first 24 hours postoperatively. Manickam et al (2012) conducted a study on sixty children in the age group of 1–6 years undergoing subumbilical surgeries were included in the study. Group A received 1 ml/kg of 0.1% ropivacaine, group B received 1 ml/kg of 0.1% ropivacaine with clonidine 1 mcg/kg, and group C received 1ml/kg of 0.2% ropivacaine. The mean duration of analgesia was 243.7 ± 99.29 min in group A, 590.25 ± 83.93 min in group B, and 388.25 ± 82.35 min in group C. Bajwa et al (2010) conducted a study on 44 ASA-I paediatric patients between the ages of 1 and 9 years, scheduled for elective hernia surgery, were enrolled in this randomised double-blind study. The caudal block was administered with ropivacaine 0.25% (Group I) and ropivacaine

0.25% and clonidine 2 mcg/kg. Da Conceicao et al (1998**)** Studied 60 children, randomly allocated in a double -blind manner, to receive one of two local anaesthetics: 0.375% of Ropivacaine 1.0 ml/kg or 0.375% Bupivacaine 1.0 ml/. The extent of motor block in the recovery room was scored as 1-3. The Ropivacaine group showed a shorter duration of motor block than the Bupivacaine group ($p < 0.05$). Local anaesthetics prevent generation and conduction of nerve impulses in all excitable tissues. It affects the permeability of the nerve to Na+ and K+. During the resting phase, interior of the peripheral nerve fiber has a potential difference of about -70mV relative to the outside. When the nerve is stimulated there is a rapid increase in the membrane potential to approximately +20mV, followed by immediate restoration of the resting level.

III. Material And Methods

Patients undergoing subumbilical surgeries at Nalanda medical college and Hospital, Patna, Bihar. were included in the study after obtaining written informed consent from the parents. 30 in each group (2 groups),

Study was done on 60 children of physical status ASA1 and 2, aged between 3-8years, undergoing subumbilical surgeries .They were randomly included in groups having equal numbers by using a closed envelope technique and they received caudal epidural block with the following drugs:Group L (Levobupivacaine-Clonidine)-Levobupivacaine 0.25%1ml/kg-2mcg/kg clonidine. Group R (Ropivacaine-Clonidine)-Ropivacaine 0.25% 1ml/kg 2mcg/kg clonidine.

After pre anesthetic evaluation on the previous day of surgery. Basic laboratory investigations was carried out. The entire procedure was explained to the patient and parents. All patients were evaluated one day prior to the surgery with a detailed general physical examination, systemic examination including airway and spine examination. Baseline parameters were recorded. Routine laboratory investigations like complete blood picture, urine routine, bleeding and clotting time, HIV, HBs Ag status and chest x-ray if needed. Informed consent for the procedure was acquired from the parent with clear fasting guidelines (solid foods stopped 6hrs before, milk 4 hours and water 2 -3 hours prior to surgery).The assessment was done within 15s in the postoperative period, score between 0-3- pain free situation4 and above- analgesic requirement with increasing urgency as scores increase.

Inclusion criteria

Patients of either sex, Patients of age between 3-8 yearsPatients of ASA status I & II, Patients scheduled for lower abdominal surgeries with written informed consent.

Exclusion criteria

Patients with known hypersensitivity to local anesthetics.Grossly abnormal sacrum anatomy, Bleeding diathesis, Pre-existing neurological, neuromuscular disease.Local sepsis, ASA > II,

Patient characteristics were analyzed with the student t test for continuous variables and the chi square test for categorical variables. Data is represented as Mean ± standard deviation for continuous data and frequency (percentage %) or median (range) for categorical data.

IV. Results

Distribution of study group based on their age

GROUPS	N	Mean age	Std. Deviation	Minimum age	Maximum Age
ROPIVACAINE AND CLONIDINE	30	5.47	1.46	3	8
LEVOBUPIVACAINEAND CLONIDINE	30	5.23	1.30	3	8
TOTAL	60	5.35	1.38	3	8

The men age is1.46 years in ropivacaine and clonidine and 1.30 years in levobupivacaine and clonidine. There is no significant difference in age of patients in both the groups ($p>0.05$). Both thegroups are similar with respect to age distribution.

Difference in mean weight of the patients between the two groups

GROUPS	MEAN	STANDARD DEVIATION	t VALUE	p VALUE
ROPIVACAINE AND CLONIDINE	13.73	2.48	0.0484	0.9616
LEVOBUPIVACAINE AND CLONIDINE	13.70	2.32		

The mean weight is 13.73kg in Ropivacaine and clonidine group and 13.70kg in levobupivacaine and clonidine

group. There is no significant difference in body weight of patients in both the groups (P>0.05).

Duration of anaesthesia between the two groups

GROUPS	MEAN	STANDARD DEVIATION	t VALUE	p VALUE
ROPIVACAINE AND CLONIDINE	66.17	6.25	0.2056	0.8378
LEVOBUPIVACAINE AND CLONIDINE	66.50	6.18		

The mean duration of anesthesia was 66.17 min in Ropivacaine and Clonidine, and 66.50 min in Levobupivacaine and Clonidine. There is no significant difference in the mean duration of surgery in both the groups (p>0.05).

Difference in RSS score between the two groups

RSS SCORE	MEAN	STANDARD DEVIATION	T VALUE	P VALUE
ROPIVACAINE AND CLONIDINE	2.03	0.80	0.3305	0.7422
LEVOBUPIVACAINE AND CLONIDINE	2.1	0.84		

Mean sedation score was 2.03 in ropivacaine and clonidine group and 2.1 in levobupivacaine and clonidine group.There is no statistically significant difference in the sedation score in both the groups (p>0.05) The mean systolic blood pressure was 98.57, 91.37, 94.1, 87.73, 87.23, 98.82 mmHg in ropivacaine and clonidine group. 98.87, 94.1, 90.4, 88.8, 88.5 mmHg in levobupivacaine and clonidine group. There is no statistically significant difference in mean systolic blood pressure in both the groups (p>0.05) The mean diastolic blood pressure was61.83, 56.83, 55.3, 55.17, 54.25 mmHg in ropivacaine and clonidine group and 62.47, 58.43, 55.47, 54.90, 58 mmHg in levobupivacaine and clonidine group. There is no statistically significant difference in mean diastolic blood pressure in both the groups (p>0.05)The mean arterial pressure was 62.3, 62.63, 63, 63.13, 63.6, 63.83, 64.06, 64.43, 63.13, 63.6, 63.83, 64.06 mmHg in ropivacaine and clonidine group and 62.4, 62.63, 63.13, 63.37, 63.73, 64.1, 64.33, 64.43, 63.37, 63.73, 64.1, 64.33mmHg in levobupivacaine and clonidine group. There is no statistically significant difference in mean arterial pressure in both the groups (p>0.05)Only 2 children in each group had sedation. Other side effects like pruritus, urinary retention, respiratory depression, hypotension, bradycardia were not observed in both the groups.

V. Discussion

The study population was randomly divided into 2 groups by closed envelop method of 30 each who received caudal epidural block with the following drugs: Group L (Levobupivacaine-clonidine)-Levobupivacaine 0.25% 1 ml/kg with 2mcg/kg clonidine. Group R (Ropivacaine-clonidine)-Ropivacaine 0.25%1ml/kg with 2mcg/kg clonidine. Hypothesis made before starting the study

The hypothesis made before starting the study was that the addition of clonidine to ropivacaine and levobupivacaine will prolong the duration of analgesia when compared to plain drugs and to compare duration of analgesia and side-effects of the study drugs. Caudal anaesthesia is one of the most popular regional block in children. This technique is a useful adjuvant to general anesthesia and for providing post-operative analgesia after infra-umbilical surgeries. Bupivacaine, levobupivacaine and ropivacaine are widely utilised in caudal block. As established by several authors, metameric spread depends on volume of the injected mixture, while the desired density of the block depends on the concentration of the anaesthetic. However, concentration must be established in order to avoid anaesthetic toxicity. The Levobupivacaine and ropivacaine are associated with less risk for cardiac and central nervous system toxicity and are also less likely to results in unwanted postoperative motor blockade. The rationale for replacing racemic bupivacaine with the s-enantiomers levobupivacaine and ropivacaine is to provide a wider margin of safety with the same analgesic efficacy and less postoperative motor block.[9] The main disadvantage of caudal anesthesia is shorter duration of action after a single injection of local anesthetic solution. The use of caudal catheters to administer repeated doses or infusion of local anaesthetic solution is not popular, partly because of concern about infection. The use of opioids significantly prolongs the duration of analgesia but carries with it a number of unpleasant side-effects (nausea, vomiting, pruritus, urinary retention) as well as the risk of late respiratory depression. In a retrospective review of 138 children given caudal morphine 0.07mg/kg, there were 11 cases of clinically important hypoventilation (8%). Locatelli et al. found that addition of 0.5mg/kg of s-neostigmine to caudal levobupivacaine 0.175% significantly decreases the need for rescue analgesia in children undergoing abdominal and urological surgery compared with levobupivacaine 0.2% alone. Ingelmo P et al. in there study about relative analgesic potencies

of levobupivacaine and ropivacaine for caudal anaesthesia in children found that in children receiving 1 MAC of sevoflurane, there were no significant difference in the ED for caudal levobupivacaine and ropivacaine. The potency ratio at ED was 0.92 and 0.89 at ED, indicating that caudal levobupivacaine and ropivacaine have a similar potency. There is no statistically significant difference in Sp02 both the groups of our study both intra-operatively and post-operatively. This consistent with studies conducted by Parameshwari A et al., Koul A et al., Shulka U et al., where they found no significant changes in Sp02 both intra-operatively and post-operatively. Another study conducted by Potti R L et al mean duration of analgesia was16.68 ± 4.7 hours, which was more than that in our study, This wide variability might be due to differences in the dose of clonidine and the local anesthetic agents used, use of various premedication, indications for rescue analgesia, drugs used for rescue analgesia, anddifferent scales of pain assessment and different statistical analysis. Potti R L et al. in their study found that the requirement of rescue analgesic was lesser in clonidine group compared with plain levobupivacaine or levobupivacaine withi.v clonidine. Manickam A et al in their study found that requirement of rescue analgesia was lesser in clonidine group compared to ropivacaine alone. Parameshwari A et al. in their study found that requirement of rescue analgesiawas lesser in clonidine group compared to bupivacaine alone. Epidural clonidine has been associated with sedation reflecting systemic absorption and action on higher centers. A delayed sedation might as well as be due to the cephalad migration of the drug in the cerebrospinal fluid. Sedation is a desired effect in most children, thus reducing the requirement of sedatives and anxiolytics in the postoperative period. However, in our study, the mean sedation scores in both the groups were comparable. We used clonidine in a dose of 2 μg/kg and this might explain the sedation in our study groups.

VI. Conclusion

This study suggests that addition of clonidine (2mcg/kg) as anadjuvant to 0.25% ropivacaine (1ml/kg) and 0.25% levobupivacaine (1ml/kg) through caudal route increased duration and quality of analgesia without perioperative hemodynamic instability and any significant side-effects.

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