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Analgesic Effect of Caudal Bupivacaine with or without Clonidine in Pediatric Patient

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ABSTRACT

Background: Caudal analgesia has long been the cornerstone to successful pain management in children undergoing abdominal and lower limb surgeries. Its analgesic duration with single shot injection is however limited. So adjuvants are used with local anesthetics in an attempt to increase the duration of caudal analgesia.This study aims to investigate the duration of analgesia provided by Clonidine when added to caudal Bupivacaine.

Methods: A randomized, double blinded, comparative study was conducted on 64 patients, aged two to seven years, scheduled for unilateral inguinal hernia repair. Patients were randomly allocated into two groups of 32 each, with group A receiving bupivacaine two milligram/kilogram and group B receiving bupivacaine two milligram/kilogram with one microgram/kilogramclonidine, (total volume of injectate was one milliliter/kilogram). Duration of analgesia, hemodynamic response and adverse effects, if any were noted.

Results: Mean duration of analgesia in group A was 264.12 ± 68.77 minutes and in group B was 520 ± 57.37 minutes, p-value <0.001.Incidence of vomiting was 9% in group A compared to 6% in group B.

Conclusions: Clonidineas an adjuvant to caudal bupivacaine prolongs the duration of analgesia without increasing the adverse effects.

Keywords: Bupivacaine; caudal analgesia; clonidine;pediatric.

INTRODUCTION

Caudal block is an invaluable regional anesthetic technique in children undergoing abdominal and lower limb surgeries. A successful block not only provides sound analgesia but also reduces need of general anesthetic and blunts stress response to surgery. However, its beneficial effects is shadowed by the limited period of analgesia with sole local anesthetic injection.[1] So, adjuvants are used to prolong the duration of analgesia.

Opioids are the widely preferred adjuvants but it is not without side effects.[1,2] Hence the search for an adjuvant, that can safely prolong analgesia, has led to the use of clonidine.Clonidine, a selective alpha-2 agonist, provides analgesia based on its anti-nociceptive processing at the level of spinal cord.[3] Studies investigating its analgesic property in our population are limited.

Main objective of this study was to determine the analgesic effect of clonidine as an adjuvant to bupivacaine. The secondary objectives was to assess hemodynamic alterations and adverse effects.

METHODS

This is a randomized, double blinded, parallel group, interventional study conducted over a period of three months following ethical approval from Institutional Review Board. A thorough pre-anesthetic evaluation was done a day prior to surgery and all necessary investigations carried out.Written informed consent was obtained from the guardians of children who met the inclusion criteria.

Patients aged two to seven years planned for elective unilateral inguinal hernia repair belonging to American Society of Anesthesiologists physical status I and II were included. The exclusion criteria were parent's refusal, neurological deficit, coagulopathy, known allergy to study drugs, infection at the injection site and obvious spinal deformity.

Based on a previous study by Parameswori et al,[4] taking

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mean duration of analgesia as the primary outcome variable with effect size (d) of 304.7 minutes and standard deviation (SD) of 350.93, a sample size of 28 was obtained in each group. The size was increased to 32 in each group considering the dropouts and block failure that may occur.

For allocation of patients, computerized random allocation sequence was generated which was concealed in sequentially numbered, sealed, opaque envelopes and was opened only at the time of intervention. A trained staff prepared the study drugs in a sterile way and was not involved in the study thereafter. The patients along with anesthesia provider, who assigned the intervention and measured the outcome variables intra- and post-operatively, were blinded to which intervention patients received.

Patients were kept nil per oral eight hours for fried, fatty foods or meat, six hours for light meal and two hours for clear liquids. In the operation room, standard monitoring in the form of electrocardiogram, non-invasive blood pressure, pulse oximetry and temperature were done. Baseline heart rate (HR) and mean arterial pressure (MAP) were noted. Following appropriate-sized intravenous cannulation, intravenous fluid was started. Anesthesia was induced either intravenously by propofolor by inhalation with halothane and oxygen using Jackson Ree's modification of Ayre's T-piece circuit with facemask. Suitable Laryngeal mask airway (LMA) was placed once adequate depth of anesthesia was achieved andthen anesthesia maintained with inhalational agent and oxygen with assisted ventilation.

Caudal block was performed in lateral position under aseptic conditions with a 23 gauge sterile needle using landmark and loss of resistance technique.Group A receivedbupivacaine(Anawin:BupivacaineHydrochloride 0.5%, Neon Laboratories Ltd, Mumbai, India) two milligram/kilogram (mg/kg) and Group B received bupivacaine two mg/kg with onemicrogram/kilogram (mcg/kg) clonidine (Cloneon: Clonidine Hydrochloride 150 mcg/ml, Neon Laboratories Ltd, Mumbai, India). Total volume maintained at one milliliter/kilogram (ml/kg),[5] in both the groups and to do so sterile normal saline was used along with the study drugs.Surgical procedure was allowed to commence after 10 minutes of caudal block.HR and MAP were recorded every five minutes intraoperatively. At the end of surgery, LMA was removed in deep plane of anesthesia and patients were shifted to recovery bay. Other analgesics were not administered intraoperatively. Duration of analgesia was defined as the time from administration of the study drug to first need of rescue analgesic when Face, Legs, Activity, Cry, Consolability (FLACC)[6] score was ≥ four. In the post-operative ward, the intensity of pain was measured using FLACC scale, hourly till the score reached four at which point intravenous Inj. Paracetamol 15 mg/kg was given.

Table 1.FLACC Scale.

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	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 quietly, normal position moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry, (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Conso-lability	Content, relaxed	Reassured by occasional touching hugging or being talked to, distractable	Difficulty to console or comfort

Interpretation of FLACC score: Score 0 = relaxed and comfortable, Score 1-3 = mild discomfort, Score 4-6 = moderate pain, Score 7-10 = severe pain or discomfort or both

Adverse effects of study drugs (vomiting, sedation, and bradycardia) were recorded if any. Bradycardia was defined as fall in HR of more than 20% of baseline. Sedation was assessed at the same time of FLACC assessment using a four point patient sedation score.(1: Asleep not arousable by verbal command, 2: Asleep arousable by verbal command, 3: Drowsy/ not sleeping, 4: Alert/awake).

Statistical package for social science version 20 (SPSS Inc. Chicago, IL) was used for analysis of data. Data were expressed as mean, standard deviation. Student's t-test was used for continuous parametric data like age, weight, heart rate, mean arterial pressure and duration of analgesia.Chi-square test was used to compare gender distribution and incidence of adverse effects. Level of significance was set as $p < 0.05$.

RESULTS

A total of 64 patients meeting the inclusion criteria were enrolled in the study. Patient's age, gender, weight, duration of surgery (Table 2) and hemodynamics (HR and MAP) were comparable between the two groups.

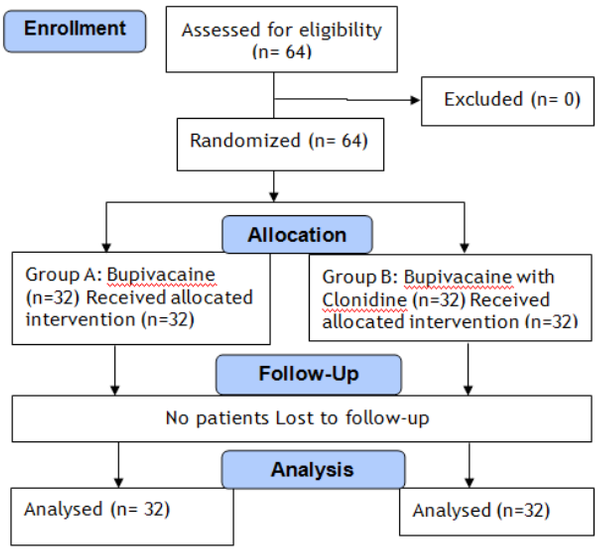

Figure 1. Flow Diagram of study.

Table 2.Demographic data of the patients.

Variables		Group A (n=30)	Group B (n=30)	p-value
Age (years)*		3.60 ± 1.673	4.10 ± 1.738	0.245
Gender†	Male	30	30	0.694
	Female	2	2	
Weight (kilograms)*		14.12 ± 2.55	15.01± 3.48	0.24
Duration of surgery (minutes)*		24.37 ± 8.86	27.90 ± 12.63	0.201

** mean ± standard deviation† number*

Mean duration of analgesia in group A was 264.12 ± 68.77 minutes and in group B was 520 ± 57.37 minutes with p-value <0.001 (Figure 2).

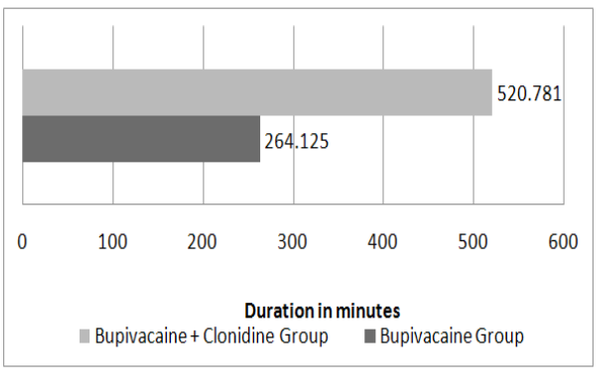

Figure 2. Mean duration of analgesia.

The intensity of pain measured using FLACC scale was significantly lower in group B patients receiving bupivacaine-clonidine from 2nd hour after surgery with p-value < 0.05 (Figure 3). The patients in bupivacaine group reached a score of 4 by 6th hour of surgery and rescue analgesic was given and study concluded, so data up to that time was available and interpreted.

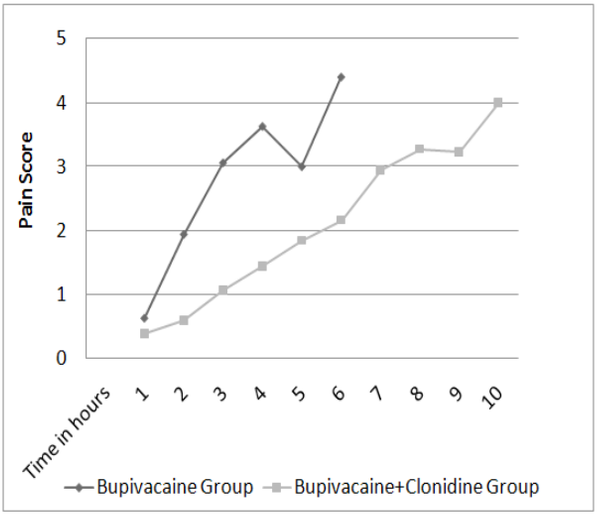

Figure 3. FLACC score at different time interval between two groups.

Sedation score was also assessed along with FLACC scale at same time interval. The score at 2nd hour after the surgery was 2.78 ± 0.94 in bupivacaine group and 2.28 ± 0.88 in bupivacaine with clonidine group with p-value of 0.03. Similarly, the sedation score at 3rd hour after surgery was 3.94 ± 2.50 in bupivacaine group and 3.25 ± 0.95 in bupivacaine with clonidine group with p-value <0.001 From 4th hour, the sedation scores were comparable between the groups with no statistical significant difference (Figure 4).

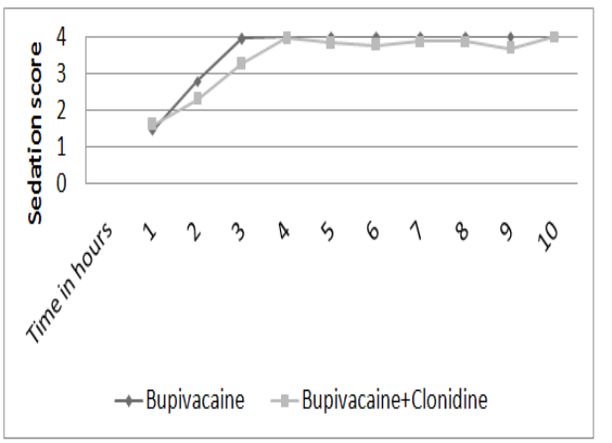

Figure 4. Sedation Score at different time interval between two groups.

During the course of study, three patients in bupivacaine group and two patients in bupivacaine with clonidine group had vomiting. However no other adverse effects

like bradycardia, hypotension, seizure and respiratory depression were observed.

DISCUSSION

The quest to enhance perioperative outcome can only be complete with adequate pain management, more so in children where it becomes sensitive and challenging. Poor perioperative pain management in children can lead to constant irritation, crying, inability to cough and feed well, restricted mobility, delayed wound healing and behavioral and psychological changes in the long run. These effects can be even more distressing for the parents.

So, the aim always has been to alleviate these issues opting a better pain management technique that provides sound perioperative analgesia and hence smooth recovery. Use of adjuvants in caudal block aims to achieve extended period of quality analgesia and hence overcome the adverse issues associated with inadequate pain management. Various postulations have been made regarding mechanism of analgesia provided by caudal clonidine. It exerts an anti-nociceptive action by suppression of the spinal cord nociceptive neurons. Another possible mechanism is that it easily crosses the blood-brain barrier, and may interact with alpha adrenoceptors involved in the activation of inhibitory G-proteins, at spinal and supra-spinal sites within the central nervous system. Clonidine is also believed to suppress neurotransmission in peripheral sensory $A_{delta}$and C nerve fibres.[3]

In our study, the addition of clonidine one mcg/kg to caudal bupivacaine resulted in prolonged duration of post-operative analgesia in children undergoing inguinal hernia repair.Similar result was observed in study by Parameswari et al[4] where a longer duration of analgesia was noted compared to ours. Probable reasons could be selection of a younger age group of patients of one to three years, use of oral midazolam as premedication, use of nitrous oxide and fentanyl intraoperatively. Meghani et al[8] also reported prolonged post-operative analgesia in clonidine group as compared to bupivacaine. The intraoperative use of nitrous oxide and the longer time intervals for the assessment of pain could have accounted for extended period of analgesia than in our study.The finding of our study was in agreement to studies done by Upadhyaya et al,[9] Tripi et al,[10] Jamali et al,[11] Klimscha et al,[12] Singh et al,[7] and Hager et al,[13] all of which revealed longer duration of analgesia when clonidine was used as an adjuvant to caudal bupivacaine in children undergoing sub-umbilical surgeries.

Various factors like age of patients, dose of study drugs, premedication, volatile anesthetic agents, type and duration of surgery, indication for rescue analgesic and assessment of pain could account of variations seen in duration of analgesia in different studies.[4]

Lak et al[14] chose two mcg/kg clonidine as caudal adjuvant to 0.125% bupivacaine, however the mean duration of analgesia in both the groups was short compared to our study and others which may be due to the use of less concentrated bupivacaine thatmay not be potentiated by clonidine.[15] Sharpe et al[16] speculated that, low volume of bupivacaine (0.5 ml/kg) may not be sufficient to deliver clonidine up to the spinal cord. So drug volume of one ml/kg was chosen along with the basis of Armitage regimen that recommends one ml/kg volume of caudal analgesic to achieve a lumbosacral block. Klimscha et al[12] concluded that increasing the dose from one to two mcg/kg did not enhance the analgesic effect of clonidine. With that evidence, a dose of one mcg/kg of clonidine was chosen considering the fact that this dose would suffice to achieve adequate period of analgesia without increasing adverse effects.

The intensity of pain was assessed using behavioral pain assessment tool, FLACC scale. We chose FLACC scale as it is easy to use, validated and provides objective evaluation.[6] Low FLACC scale scores were noted in patients receiving bupivacaine with clonidine, thus the prolonged duration of analgesia. The findings were in agreement with other studies where FLACC scale was used and lower sedation scores were reported in patients receiving clonidine as adjuvant.[4,7,10]

No clinically and statistically significant changes in intraoperative hemodynamics was detected. Parameswari et al,[4] Meghani et al[8] also found no such differences in heart rate and blood pressure. During the course of this present study, three patients in bupivacaine group and two patients in bupivacaine with clonidine group had vomiting. Meghani Y et al[8] observed vomiting in nine patients in clonidine group and three in bupivacaine group. Sharpe et al[16] reported two incidence of vomiting in both the groups. No other adverse effects like bradycardia, hypotension, seizures and respiratory depression were noted which was comparable with studies done by Parameswari et al,[4] Lak et al[14].

Sedation after epidural clonidine results from activation of alpha-2 adrenoceptors in the locus coeruleus, an important modulator of vigilance. This suppresses the spontaneous firing rate of the nucleus, thereby resulting in increased activity of inhibitory inter-neurons such as gamma amino butyric acid GABA-ergic pathways, to produce central nervous system depression.[1] Dose dependent sedation with clonidine could be due to systemic absorption and vascular redistribution.

We observed a slight deeper level of sedation at second and third hour after the surgery in bupivacaine with clonidine group with the difference being statistically significant. But clinically, these patients were not deeply sedated andwere easily arousable by verbal command. Koul et al[17] also noted the same, where a similar sedation score was used. Klimscha et al,[12] concluded although sedation was slightly more pronounced in clonidine group however it only made the children look more comfortable and was appreciated by parents and ward staffs not regarding as an adverse effect. Gupta et al[18] found that number of patients who were relatively more sedated was higher in clonidine group but were easily arousable. Lee et al[19] found longer period of sedation in children who received clonidine where duration of sedation was very similar to the respective duration of caudal analgesia. Hence it could not be concluded reliably that, the longer duration of sedation was caused entirely by the sedative effect of clonidine.

We did not assess the frequency and amount of rescue analgesics used postoperatively which would have helped in determining the analgesic efficacy of clonidine. Also the study was concluded once the FLACC score reached four and further assessment was not done.

CONCLUSIONS

Thus, it can be concluded that clonidine one mcg/kg, when used as an adjunct to bupivacaine for caudal analgesia in a volume of one ml/kg prolongs the duration of postoperative analgesia without increasing the adverse effects.

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