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Effects of Adding Clonidine to Bupivacaine for Caudal Analgesia in children

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ABSTRACT
Caudal epidural analgesia with bupivacaine is very popular in paediatric anaesthesia for providing intra and postoperative analgesia. Several adjuvants have been used to prolong the action of caudal bupivacaine. We evaluated the effect of clonidine added to caudal bupivacaine in prolonging the analgesia in children undergoing sub-umbilical surgery. 80 children in the age group two to eight belonging to American Society of Anaesthesiologists Physical Status I & II undergoing lower abdominal surgeries were prospectively randomized to one of two groups of 40: caudal analgesia with 1 ml/kg of 0.25% bupivacaine in normal saline (Group B) or caudal analgesia with 1 ml/kg of 0.25% bupivacainewith1 µg/kg of clonidine in normal saline (Group BC).Post-operative pain was assessed for 24 hours using the Observational Pain/Discomfort Scale (OPS). The mean duration of analgesia was significantly longer in Group BC(12.18 hour) than in Group B (4.85 hour); P < 0.05. The pain score assessed using OPS scale was compared between the two groups and children in Group BC had lower pain scores, which was found to be statistically significant. The requirement of rescue medicine was lesser in Group BC. Clonidine in a dose of 1 µg/kg added to 0.25% bupivacaine for caudal analgesia during sub-umbilical surgeries significantly prolongs the duration of analgesia of bupivacaine without any major side effects.
Keywords: *Bupivacaine, Caudal analgesia, Clonidine.*

INTRODUCTION

Caudal blockade is the most popular regional anaesthetic technique used in children. Campbell (1933) is credited with the first series of paediatric caudal block but it was not for another 30 years that it gained popularity when Spiegel (1962) described its use.

Bupivacaine is the most commonly used local anaesthetic for this purpose. It is a local anaesthetic of the amide type synthesised by Ekenstam and his colleagues in 1957 and used clinically by U.Telivao since 1963. The limitation of bupivacaine is the short duration of action, about four to six hours when administered as a 'single shot technique'. Several adjuvants such as opioids, ketamine, midazolam, clonidine and neostigmine have been used with bupivacaine to prolong its action[1-5] and thus extend the duration of post-operative analgesia provided by the 'single shot' caudal technique.

Clonidine, anα2 agonist has been used extensively in neuraxial blocks[6-9]and peripheral nerve blocks to prolong the action of bupivacaine. It is one of the most commonly used additives with bupivacaine for caudal analgesia in children[15] Controlled trials of a single injection of caudal-epidural clonidine in children over the age of one year, show wide variation in analgesic duration and sedation. The discrepancy among trials arises from differences in study design; type and volume of local anesthetics, assessment of pain and inclusion of wide age range, and surgical procedures invoking variable pain intensity. In general, caudal blocks with bupivacaine plus clonidine appear to provide analgesia that lasts one-half to two times longer than bupivacaine alone.

We conducted this study to assess the effect of clonidine in prolonging the action of bupivacaine when used for caudal epidural analgesia in children undergoing sub-umbilical surgeries.

AIMS AND OBJECTIVES

- To compare the analgesic effect in terms of duration of analgesia of caudal bupivacaine alone and bupivacaine-clonidine combination administered at 1 ml / kg body weight with clonidine at a dose of 1µg/kgin children aged 2 to 8 years undergoing elective lower abdominal surgeries.
- To compare the incidence of side effects in the two groups

MATERIALS AND METHODS

The present study was a prospective, observational study conducted at the Paediatric Surgery department of Sree Avittam Thirunal Hospital aligned to the Government Medical College, Thiruvananthapuram after approval of the Hospital Ethical Committee. After getting written informed consent from the parents, 80 children in the age group two to eight belonging to American Society of Anaesthesiologists Physical Status I & II undergoing lower abdominal surgeries were prospectively divided into two groups of 40, B and BC andcaudal analgesia with 1 ml/kg of 0.25% bupivacaine in normal saline (Group B) or caudal analgesia with 1 ml/kg of 0.25% bupivacaine with 1 µg/kg of clonidine in normal saline (Group BC).Children with history of allergy to drugs including local anaesthetics, history of bleeding diathesis, pre-existing neurological or spine disease, infection at the site of injection, sacral anomalies were excluded from the study.

All the patients included in the study underwent a detailed pre-anaesthetic check up. Milk and solid foods were restricted after midnight but clear fluids were allowed upto 2-3 hours prior to induction. Premedication was with triclorofos sodium 75mg/kg given orally 11/2 hours prior to surgery. After attaching all pre induction monitors freely flowing venous line was set up using 24G or 22G cannula either with the patient awake or under gas-oxygen-sevoflurane through awell fitting mask, depending on the degree of co-operation of the patient. A 5% dextrose with 1/4 normal saline was set up and the fluid admini-stered according to calculated requirements. Atropine 0.02mg/kg was given after intravenous cannulation in the theatre along with injection ondansetron 0.15 mg/kg. Induction was done with 5-7 mg/kg of thiopentone sodium intravenously and then maintained on oxygen-nitrous oxide-sevoflurane in sufficiently deep plane of anaesthesia with the patient on spontaneous ventilation. Fresh gas flow was kept at 2-3 times the minute ventilation. Continuous ECG and oxygen saturation monitoring was done. Blood pressure was monitored using a mercury sphygmomanometer with acuff of appropriate size. A precordial stethoscope was also attached for monitoring.

Caudal block

After induction of anaesthesia and when all vital signs were stable, the child was gently placed in the lateral position, with the legs flexed at the hip. The vital signs were checked again. The back was

cleaned using povidone-iodine and spirit and then draped. Caudal block was performed under strict aseptic precautions. Sacral hiatus was identified by running the thumb up from the coccyx towards sacrum. A 22G scalp vein needle with its bevel facing anteriorly was inserted at an angle of 60 degrees to the skin till the sacrococcygeal membrane was pierced, when a distinct pop was felt. Then the needle was advanced an additional 2mm in a plane parallel to the spinal axis. Aspiration was done to exclude bone marrow, dural puncture or vessel puncture.

Then the drug was administered slowly. The volume of the dead space of the needle and the tubing was replaced. After the injection was complete, needle was removed, sterile dressing given and the patient placed in the supine position. A close watch was kept on the adequacy of the airway throughout the procedure. No analgesic was given by any route preoperatively and intraoperatively unless otherwise indicated. Anaesthesia was maintained with 1% to 2% sevoflurane titrated to depth and 66% nitrous oxide in oxygen through a face mask with the patient on spontaneous ventilation throughout surgery.

Intraoperative monitoring was done with continuous electrocardiography, pulse oximetry and precordial stethoscope. Arterial blood pressure was recorded every 5 minutes with a mercury sphygmomanometer. Pulse rate and respiratory rate were also continuously monitored. The time of caudal block and duration of surgery was noted. Anaesthetic agents were discontinued at the completion of skin closure.100% oxygen through face mask was administered for 3-5 minutes. Once the vital signs were stable the child was shifted to the recovery room and placed in semi-prone position. The time from discontinuation of anaesthetic to spontaneous eye opening was noted. When the children maintained good colour without oxygenation or external airway support they were transferred to the post operative ward for further monitoring ensuring full oxygen saturation and stable haemodynamics.

Post operative Assessment

Assessment was done for a period of 24 hours after caudal block The Observational pain / discomfort scale (OPS) (Table 1) was used for assessment of post operative pain.Minimum score was taken as 5 and maximum score 15. If OPS> 11, rescue analgesia was given.

Table 1 Observational pain /discomfort scale (OPS)

	NONE	MODERATE	SEVERE
Crying	1	2	3
Facial expression	1	2	3
Position of torso	1	2	3
Position of legs	1	2	3
Motor restlessness	1	2	3

Minimum score-5 Maximum score-15 If OPS> 11 Give analgesia

These assessments were made at 1,2,4,8,12 and 24 hours after caudal block.

Requirement of analgesia

Supplementary analgesia using oral paracetamol 15mg/kg was given to patients who had a pain score equal to or more than 11 anytime during 24 hours.

Side effects

1. Sedation: The time from discontinuation of anaesthesia to spontaneous eye opening was noted.
2. Motor weakness: The duration of motor block was assessed by determining when the children began to move their legs.
3. Delay in micturition: the time of first micturition was noted.
4. Any episode of hypotension, respiratory depression, convulsions were also noted.

Patients were discharged 2 days after the surgical procedure in the absence of any complications.

Statistical Analysis

Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 10. Data are expressed in its frequency and percentage as well as mean and standard deviation. To elucidate the associations and comparisons between different parameters, Chi square (0) test was used as nonparametric test. Student's t-test was used to compare mean values between two groups. Mann Whitney's U test was employed to compare nonparametric variable between two groups. For all statistical evaluations, a two-tailed probability of value< 0.05 was considered significant.

RESULTS

The two groups were similar with regards to age, weight, and duration of surgeryshowing that the two groups were comparable (table 2)

Table 2. Comparision of Age, Weight and Duration of Surgery between two groups

Parameter	Group	Mean	± SD	t value	p value
Age	Bupivacaine Alone	3.01	1.18	- 0.848	> 0.05
	Bupivacaine + Clonidine	3.24	1.19		
Weight (Kg)	Bupivacaine Alone	12.15	2.57	- 0.454	> 0.05
	Bupivacaine + Clonidine	12.40	2.35		
Duration of Surgery (min)	Bupivacaine Alone	18.63	7.51	- 1.869	> 0.05
	Bupivacaine + Clonidine	22.00	8.61		

Gender has no significance with regards to the two groups.

Table 3. Distribution of gender in two groups

	Group B	**Group BC**
	Bupivacaine Alone	Bupivacaine + Clonidine
Male	30	32
	75.00%	80.00%
Female	10	8
	25.00%	20.00%

Chi square = 0.287; P > 0.05

Herniotomy, Circumcision and Orchipexy were the three surgical procedures.

Table 4. Comparison of surgical procedure in two groups

	Group B	**Group BC**
	Bupivacaine Alone	Bupivacaine + Clonidine
Herniotomy	28	23
	70.00%	57.50%
Circumcision	11	15
	27.50%	37.50%
Orchipexy	1	2
	2.50%	5.00%

Chi square = 1.910; P > 0.05

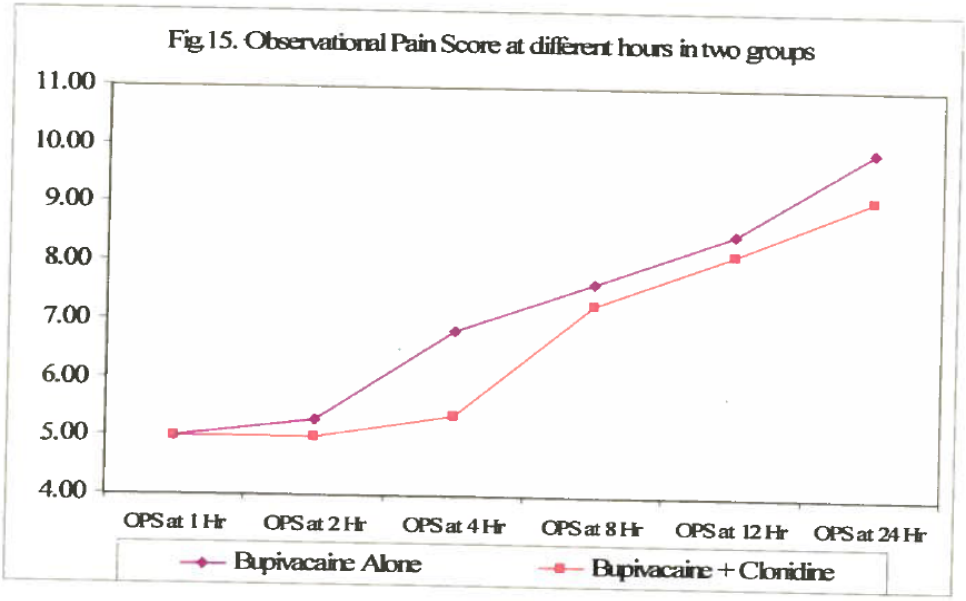
The Observational pain discomfort score (OPS) was assessed at 1,2,4,8,12, and 24 hours after caudal block. At 1 hour, none of the cases in the two groups showed any sign of pain (score 5). Further OPS scores were recorded at 2,4,8,12 and 24 hours after caudal block and recorded as in Table 5.

Table 5 Mann Whitney U test comparing observational pain score at different hours between two groups

Observational Pain Score	Bupivacaine Alone			Bupivacaine + Clonidine			Mann Whitney U value	p value
	Mean	Median	± SD	Mean	Median	± SD		
OPS at 1 Hr	5.00	5.00	0.00	5.00	5.00	0.00	800.00	> 0.05
OPS at 2 Hr	5.30	5.00	0.61	5.00	5.00	0.00	620.00	< 0.01
OPS at 4 Hr	6.83	7.00	0.90	5.38	5.00	0.63	189.50	< 0.001
OPS at 8 Hr	7.65	8.00	0.62	7.30	7.00	1.11	612.50	< 0.05
OPS at 12 Hr	8.50	8.00	0.72	8.18	8.00	1.30	629.00	> 0.05
OPS at 24 Hr	9.95	10.00	1.47	9.13	9.00	1.30	548.50	< 0.05

The observed difference among the groups were statistically significant at 2hr, 4 hr , 8hr and 12 hr and group BC had superior analgesia over group B when mean pain scores were assessed. At 24 hr there was no clinically significant difference even though the clonidine group showed lower scores.

The graph 1 clearly demonstrates that the clonidine- bupivacaine group had lower pain scores compared to the bupivacaine only group during the 24 hr observation period.



The time to first rescue analgesia was greater than 10 hr in all patients in the clonidine-bupivacaine group showing the prolongation of analgesia by the addition of clonidine to bupivacaine, which was highly significant statistically. ($p<0.001$) While considering the time for first analgesia in 24 hours, the mean time requirement in the clonidine-bupivacaine group was 12.18 hour while it was 4.85 hour in the only bupivacaine group and the difference was found to be statistically significant, showing that clonidine was highly effective in prolonging analgesia after surgery.

Also the average time for spontaneous eye opening was prolonged in the clonidine group (43.38) vs(22.63) in the only bupivacaine group in minutes. This may be due to the sedative effect of clonidine or may even be due to the superior analgesia provided by clonidine. The time for leg movement was slightly prolonged in the clonidine group (105.25 vs 94.45) minutes and it was found to be statistically significant. The reason may be the sedative effect or superior analgesia of clonidine, rather than prolongation of motor block by clonidine. The average time for micturition was almost the same in the two groups and it was found to be statistically not significant. Table 6.shows the analysis of side effects profile between the two groups.

Table 6. Student's 't' test comparing different side-effects between two groups

Parameter	Group	Mean	± SD	t value	p value
Time for First Analgesia (Hrs)	Bupivacaine Alone	4.85	1.00	- 27.476	< 0.001
	Bupivacaine + Clonidine	12.18	1.36		
Time for Eye Opening (min)	Bupivacaine Alone	22.63	5.66	- 9.925	< 0.001
	Bupivacaine + Clonidine	43.38	11.95		
Time for Leg Movement (min)	Bupivacaine Alone	94.25	26.64	- 2.139	< 0.05
	Bupivacaine + Clonidine	105.25	18.67		
Micturition	Bupivacaine Alone	4.50	0.72	1.737	> 0.05
	Bupivacaine + Clonidine	4.24	0.59		

DISCUSSION

Inadequate treatment of pain in children can result in short and long -term morbidity. So the provision of postoperative analgesia is mandatory during the administration of any anaesthetic. In this study caudal block using bupivacaine alone, and bupivacaine-clonidine combination was used for providing postoperative analgesia.

Only patients of American Society of Anaesthes-iologists Physical Status I & II undergoing elective lower abdominal surgeries were included in the study. This avoided variations in the duration of surgery and anaesthesia. Since the spread of analgesia is unpredictable and failure rate is also high in children older than 8 years, children belonging to 2 to 8 year age group alone were included in this study. Other than the test drugs no other analgesics were administered either preoperatively or intraoperatively to prevent additive effect unless otherwise indicated.

Induction with thiopentone sodium and maintenance with sevoflurane- nitrous oxide and oxygen was followed in all cases. All the caudal blocks were performed using the same technique and same type of needle. Though several formulae have been described for calculation of dose of local anaeasthetic, the simple and satisfactory Armitage formula[11]was used.

Gunter et al[12] concluded that 0.175% bupivacaine offered the best combination of effectiveness and rapid recovery and discharge for paediatric surgical outpatients. However Cook et a1[13] and Findl ow et a1[14] used 0.25% bupivacaine for paediatric day care orchiopexy. Higher concentrations can produce motor blockade in immediate postoperative period delaying discharge. Since all children undergoing lower abdominal surgeries are observed in our hospital for 24 hours mandatorily 0.25% bupivacaine was used in this study for postoperative analgesia. W. Klimscha[15] and colleagues" concluded that addition of 1µg/kg clonidine to bupivacaine significantly prolonged the duration of analgesia. So 0.25% bupivacaine alone and in combination with clonidine 1µg/kg was administered in this study. Assessment and qualification of postoperative pain is obviously difficult in paediatric age group. Manifestations of pain in children are multivariate and include behavioural, cognitive and physiological aspects. Since the study included preverbal children, self report measures like visual analogue scales could not be used for pain assessment and hence the simple Observational pain/discomfort scale (OPS) was used for pain assessment in this study. This study confirmed the finding of previous workers that the addition of clonidine 1 µg/kg to 0.25% bupiva-caine prolonged the duration of caudal block more than that with 0.25 % bupivacaine alone (mean duration of analgesia 12.18 hr vs 4.85 hr). This was comparable to that reported previously.

Clonidine an alpha-2 adrenergic agonist produces analgesia without significant respiratory depression after systemic, epidural or intrathecal administration. Clonidine's analgesic effect is more pronounced after neuraxial injection, which suggests a spinal mode of action and makes this route of administration preferable. The data from the present study was consistent with that of

similar studies with regard to the duration of analgesia.

Dose dependent sedation usually accompanies the use of clonidine for regional anaesthesia and likely reflects systemic absorption and vascular redistribution to higher centres rather than the cephalad migration of clonidine in the cerebrospinal fluid. In the present study, sedation causing obstructive apnoea and oxygen desaturation was notseen. However increased sedation was noted in the clonidine-bupivacaine group.But since sedation made the children look more comfortable it was appreciated by the parents and nursing staff and was not regarded as an adverse effect.

The most undesirable side effects of neuraxial clonidine administration are hypotension and bradycardia. Since cardiac output in younger children depends on heart rate, a major concern of the present study was haemodynamic safety. However no significant decrease of mean arterial pressure from baseline values occurred in any group.So also there were no significant episodes of bradycardia. The reason may be the atropine premedication used in the patients. Neuraxial clonidine prolongs motor blockade of local anaesthetics and can delay recovery of bladder function.But these effects were minimal in the present study possibly due to the low dose of clonidine used.

In conclusion, the present study demonstrates that for caudal blockade the addition of clonidine 1μg/kg to 0.25 % bupivacaine significantly prolongs the duration of analgesia without any significant clinical adverse effects. These findings were consistent with other similar studies done using caudal clonidine.[16]Clonidine appears to be an attractive adjuvant to local anaesthetics for prolonging post operative analgesia without much adverse effects. Further studies are needed to find the optimum dose of clonidine for caudal analgesia though 1-5 μg/kg is the dose recommended in the literature. The dose of clonidine used in the present study (1 μg/kg) was the minimum effective dose and that may be the reason for the lack of any serious adverse effects while providing adequate analgesia.

SUMMARY

Caudal epidural analgesia has become widely accepted as a means of providing intra operative and postoperative pain relief in children. To compare the postoperative caudal analgesia with 0.25% bupivacaine alone and its combination with clonidine, 80 children aged 2 to 8 years scheduled for lower abdominal surgeries were allocated randomly into 2 groups. Group B received 0.25% bupivacaine 1 ml / kg in saline, Group BC received 0.25% bupvacaine 1 ml / kg with and clonidine 1 μg/kg in saline. Postoperative pain was assessed using the Observational pain/ discomfort scale(OPS) and oral paracetamol 15mg / kg was administered if this score reached 11 or more. The duration of analgesia was longer in children receiving clonidine and bupivacaine together. There were differences between the groups in the incidence of motor block and postoperative sedation. These were more in the clonidine bupivacaine group than in the only bupivacaine group. Respiratory depression, hypotension or convulsions were not observed in groups administered with clonidine.

CONCLUSION

Caudal administration of bupivacaine with the addition of clonidine resulted in superior analgesia with a longer period without demand for analgesics compared with caudal bupivacaine alone. The side effects though minor were more pronounced with bupivacaine-clonidine combination.

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