

The Association of Clonidine with Bupivacaine in Caudal Analgesia for Children

Ojiakor S C^{*1,2} Edomwonyi N P^{3,4} Umeh B U O^{1,2}

¹Department of Anaesthesiology, Nnamdi Azikiwe University, Awka, Anambra State.

²Department of Anaesthesiology, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State.

³Department of Anaesthesiology, University of Benin, Benin City, Edo State.

⁴Department of Anaesthesiology, University of Benin Teaching Hospital, Benin City, Edo State.

*Corresponding Author: Dr. Samuel C Ojiakor, Department of Anaesthesiology, Nnamdi Azikiwe University/Nnamdi Azikiwe University Teaching, Anambra State. +2348037408192

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Abstract

Caudal epidural block is increasingly used in children to provide analgesia. However, the short duration of analgesia with local anaesthetic necessitated the addition of adjuncts like clonidine which actually prolonged the duration of analgesia but may be associated with significant sedation, hypotension and respiratory depression. In this study, we investigated the safety of 1.5µg/kg clonidine added to bupivacaine in caudal blockade in children.

Fifty two children, ASA I or II, aged between 2- 6 years undergoing unilateral herniotomy were randomly allocated into two groups to receive 0.75mls/kg of 0.25% plain bupivacaine with either saline or 1.5µg/kg clonidine as a single shot caudal blockade. Incidences of sedation using University of Michigan Sedation scale, hypotension, respiratory depression and delay in return of motor function was assessed. We observed that there was no statistical or clinical difference in the incidence of sedation between the groups. Haemodynamic changes were similar in both groups and there was no delay in return of motor functions.

This study concluded that 1.5µg/kg of clonidine added to bupivacaine for caudal analgesia did not increase the incidence of adverse effects.

Keywords: Association, clonidine, bupivacaine, caudal block, sedation, adverse effects.

INTRODUCTION

One of the cardinal goals of post operative pain management is to reduce or abolish pain with minimum or no side effects. Over the years various regional anaesthesia techniques have been deployed for the provision of postoperative analgesia¹⁻². Caudal epidural blockade using local anaesthetics have been used routinely and has proved useful in children for surgical procedures below the umbilicus because it is relatively easy to perform and combines a high success rate with low risk of complication.²⁻³ Clonidine, an alpha-2 agonist was initially used as an

antihypertensive but has now been found to possess significant analgesic property which were demonstrated in several studies.^{6-12&15} A number of mechanisms have been suggested on how clonidine induced its effects⁶⁻⁹. It inhibits spinal substance P release and nociceptive neurons firing produced by noxious stimulation⁷. It crosses the blood brain barrier causing a direct suppression of spinal neurons and interacting with alpha-2 adrenoceptors which mediates sedation, analgesia and sympatholysis at spinal and supraspinal sites thereby inhibiting neurotransmission in the peripheral sensory A δ and C fibers through a slow retrograde axonal transport along the nerves⁶⁻⁸. Additionally, clonidine induces vasoconstriction through interaction with alpha-2 adrenoceptors located at peripheral vascular smooth muscles, thereby delaying the absorption and elimination of local anaesthetics⁹.

The aim of this study was to compare the characteristics of caudal block, haemodynamic changes and sedation following the addition of clonidine to bupivacaine in relation to bupivacaine alone among children undergoing unilateral herniotomy.

METHOD

The study was initiated after obtaining approval from NAUTH Ethics & Research Committee. It was a prospective, double blind and randomized study conducted from April – December 2015 at Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, South East, Nigeria.

Written informed consent was obtained from parental/guardian of the fifty two children who are aged between 2- 6 years of ASA I or II physical status enrolled for elective unilateral herniotomy. Patients with bilateral inguinoscrotal hernia, sacral deformities, infection at the sacral area, neurological diseases and bleeding disorders were excluded. All the patients were randomly divided into two groups. Randomization was done by picking random numbers from a sealed bag. The sample size was determined by power analysis

Group I received a mixture of 0.75ml/kg of plain bupivacaine (0.25%) and saline while group II received a combination of 1.5 μ g/kg clonidine and 0.75ml/kg of plain bupivacaine (0.25%) in one syringe. Anaesthesia was induced in a stepwise increase of halothane 1-3% in 100% oxygen using a tight fitting face mask and Jackson-Rees breathing circuit. Following loss of consciousness, intravenous access was secured with size 24G cannula and normal saline was commenced at a rate of 10 ml/kg in the first 1 hour. Thereafter, patient was positioned in the left lateral decubitus position with the knees drawn up to the chest. Under strict aseptic conditions, sacral hiatus was identified by running up the thumb from the coccyx towards the sacrum. The sacral hiatus is the third point of the equilateral triangle formed with two posterior superior iliac spines (dimples on the skin). After sacral hiatus was identified, a size 22 gauge short bevel hypodermic needle was inserted into the sacral hiatus at angle 60⁰ to the skin. The needle was then slightly advanced cranially while readjusting the angle until a characteristic “give” was felt which indicated the penetration of the sacro-coccygeal membrane, subsequently a sudden loss of resistance as the needle was advanced further about 2 mm cephalad indicated entrance of the needle into the caudal epidural space. Subcutaneous needle placement was ruled out by absence of subcutaneous emphysema using a 2ml air in fluid syringe while dural puncture and intravascular puncture was ruled out by negative aspiration test for cerebrospinal fluid and blood respectively. All the caudal blocks were performed by the investigator. Thereafter syringes of

study solution of either 0.75 ml/kg of bupivacaine (0.25%) plus saline (0.1ml/kg) or 0.75 ml/kg of bupivacaine (0.25%) plus 1.5 µg/kg (0.1 ml/kg) clonidine prepared by another anaesthesiologists was administered by the investigator who was blinded to the drug composition. Dressing was applied to the skin puncture site and the patient was returned to supine position and surgery commenced. Anaesthesia was maintained with 0.5 -1 % halothane in 100% oxygen with the patient breathing spontaneously via face mask connected to Jackson Rees circuit at a flow rate of 2.5 – 3 minute volume. Haemodynamic parameters changes were documented, heart rate less than 70beats/minute and SPO_2 less than 92% were considered as bradycardia and respiratory depression respectively during surgery and in the postoperative period to be managed by the administration of 0.01mg/kg of atropine and supplemental oxygen if they occur. Sedation was assessed for all the children at 30 minutes, 1 hour, 2 hours and 3 hours at the end of surgery using University of Michigan Sedation Scale (UMSS)¹⁸, time of emergence from anaesthesia as well as time to resume motor function and voiding.

At the end of surgery, oropharynx was suctioned and halothane was discontinued but 100% oxygen was continued for about 15 to 20 minutes till full recovery. The patients were positioned laterally and transported to post-anaesthesia care unit and subsequently transported to the ward on full recovery.

Statistical Analysis

Data were analyzed with SPSS (Statistical Package for the Social Sciences) Version 17. Continuous data were summarized as mean and standard deviations (SD), and dichotomous data, as counts and frequencies. Parametric data were evaluated by using Student's t-test and Fisher's exact tests. A *P* value of < 0.05 was considered statistically significant

RESULTS

The two groups were comparable in age, weight and height (Table 1).

The mean time interval from end of surgery to emergence and the mean duration of surgery was comparable in both groups with no statistically significant differences. *P*= 0.292 and 0.695 respectively. Time to successfully place caudal block was 13.93 ± 0.92 minutes in the bupivacaine–saline (BS) group and 14.00 ± 0.85 minutes in bupivacaine–clonidine (BC) group and the differences were not statistically significant.(*P* =0.791) (Table II)

Table I: Patients demographic characteristics (Mean ±SD)

Parameters	Group BS N=26	Group BC N=26	P value	Level of significance
Age (yrs)	3.38 ± 1.55	3.81± 1.36	0.307	NS
Weight (kg)	14.44 ± 3.89	15.06 ± 2-67	0.507	NS
Height (cm)	90.27± 9.45	90.35± 7.83	0.975	NS
ASA				
I	15 (57.7%)	19 (73.1%)		
II	11 (42.3%)	7 (26.9%)		

N S-Not significant

ASA–American Society of Anesthesiologist physical status

Table II: Time interval for successful caudal placement from induction, duration of surgery and time of emergence from end of surgery. (Mean±SD)

Parameter	Group BS N=26	Group BC N=26	Pvalue	Significance
Caudal interval (mins)	13.93± 0.9	14.00± 0.85	0.791	NS
Range	(12-15 min)	(12- 15 min)		
Surgery duration (mins)	53.60± 11.45	50.15± 5.83	0.292	NS
Range	(44-73 mins)	(43-71min)		
Time of emergence (mins)	20.11± 3.91	20.49± 2.51	0.695	NS
Range	(19-36min)	(20-32min)		

NS - Not Significant

The sedation scores throughout the period of sedation assessment as shown in table II were comparable in the two groups. In the first 30 minutes after surgery the sedation scores were 1.35 ± 0.49 in group BS and 1.46 ± 0.51 in group BC. (P= 0.406) At 2 hours of assessment, sedation scores was less than 1 in both groups and the differences were not statistically significant. P= 0.409 The mean time to first spontaneous voiding were 1.88 ± 0.4 and 1.96 ± 1.2 hours in groups BS and BC respectively and the differences were not statistically significant. P= 0.597 (Table III).

Table III: Sedation Scores (Mean ± SD)

Parameter	Group BS N = 26	Group BC N = 26	P Value	Level of Significance
30 mins	1.35±0.49	1.46±0.51	0.406	NS
1 hr	1.20±0.43	1.27±0.45	0.660	NS
2 hrs	0.65±0.43	0.77±0.44	0.409	NS
3 hrs	0.35±0.48	0.42±0.50	0.577	NS

NS - Not Significant

Table IV shows that mean time to first spontaneous voiding and ambulation was similar in the two groups.

Table IV: Time to First Ambulation and Voiding (Mean ±SD)

Parameter	Group BS N = 26	Group BC N = 26	P Value	Level of significance
Ambulation (hours)	2.38±0.9	2.54±1.2	0.605	NS
First Void (hours)	1.88±0.4	1.96±1.2	0.597	NS

NS - Not Significant

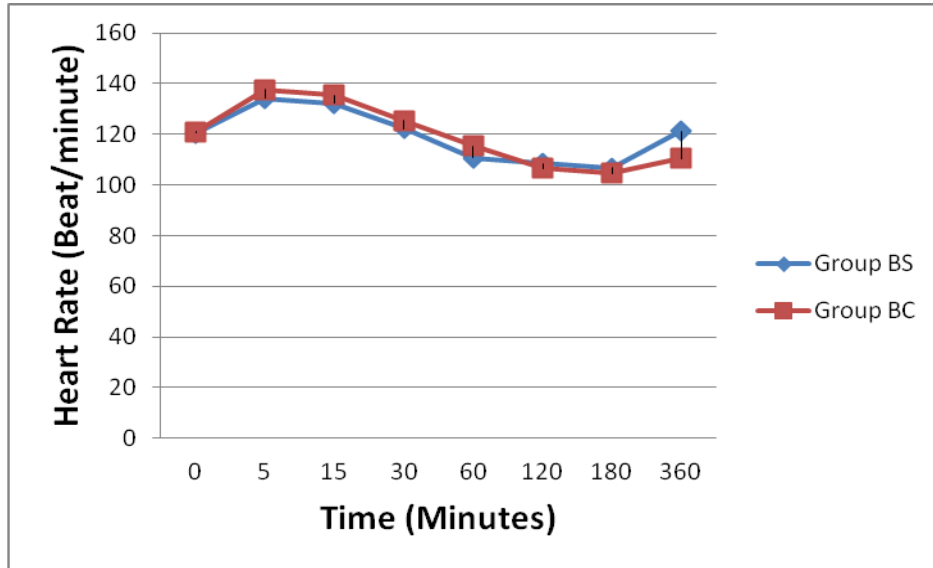
Table V shows the baseline vital signs which were comparable in the two groups. The intraoperative and postoperative haemodynamic changes including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and respiratory rate represented in figures 1, 2, 3, 4 and 5 did not show any significant differences between the two groups. No episode of bradycardia or hypotension was observed and at no point during the study was there a fall in Oxygen saturation below 92% in either group.

Table V: Baseline vital signs (Mean ± SD)

Parameter	Group BS N = 26	Group BC N = 26	P value	Level of significance
Heart rate/min	120.31±14.84	122.39±14.33	0.452	NS
Resp rate /min	26.62± 3.43	25.31± 2.52	0.742	NS
SBP (mmHg)	97.66± 12.15	95.15±13.01	0.480	NS
DBP (mmHg)	54.73± 8.50	53.58± 8.89	0.727	NS
MAP	68.11± 8.35	69.08± 8.80	0.690	NS

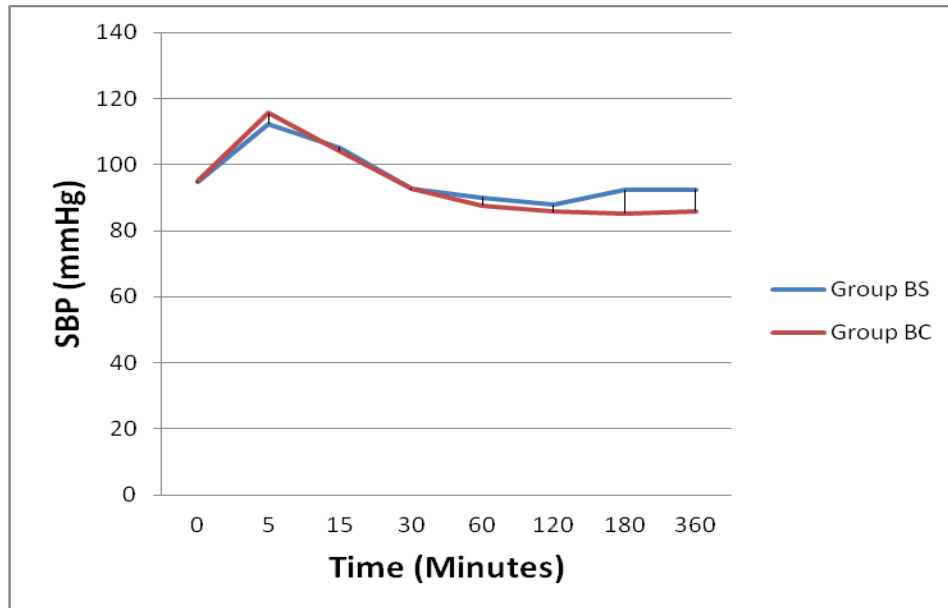
NS-Not Significant. Resp-Respiratory, SBP- Systolic blood pressure, DBP- Diastolic blood pressure, MAP- Mean arterial pressure.

Figure I: Mean Heart Rate Changes



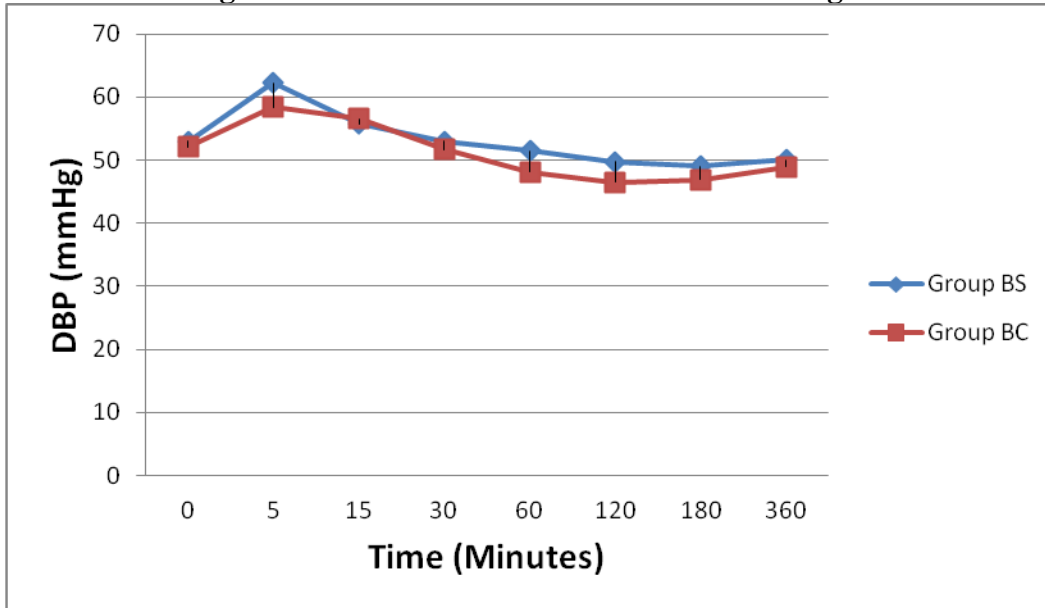
BS – Bupivacaine – Saline
BC – Bupivacaine – Clonidine

Figure 2: Mean Systolic Blood Pressure Changes



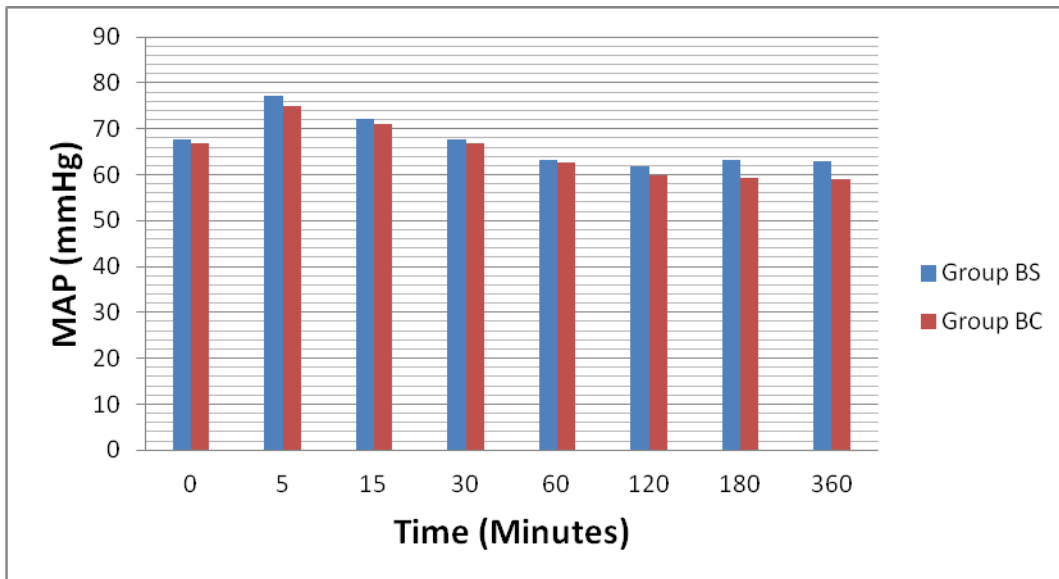
BS – Bupivacaine – Saline
BC – Bupivacaine – Clonidine
SBP – Systolic Blood Pressure

Figure 3: Mean Diastolic Blood Pressure Changes



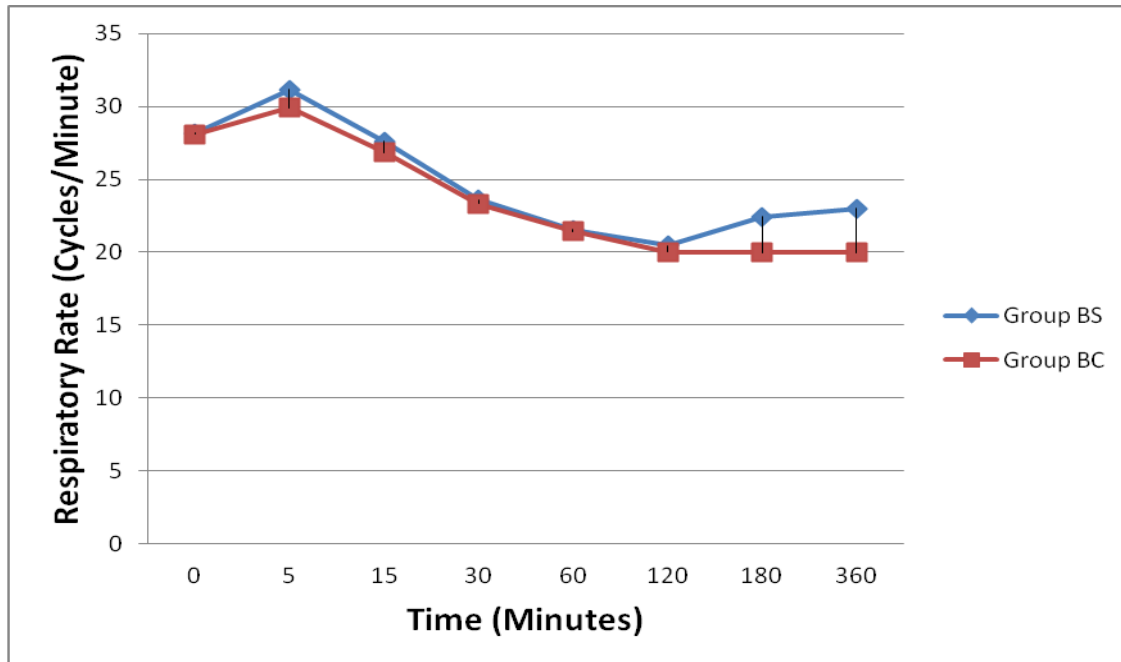
BS – Bupivacaine – Saline
BC – Bupivacaine – Clonidine
DBP – Diastolic Blood Pressure

Figure 4: Mean Arterial Pressure Changes



BS - Bupivacaine – Saline
BC – Bupivacaine – Clonidine
MAP – Mean Arterial Pressure

Figure 5: Mean Respiratory Rate Changes



BS – Bupivacaine – Saline
 BC – Bupivacaine – Clonidine

DISCUSSION

The ease of performance combined with high success rate made caudal epidural block using local anaesthetic the most common regional anaesthesia technique for sub-umbilical surgical procedures in children²⁻⁴. Clonidine as an adjunct to local anaesthetic have been documented to effectively prolong the duration of analgesia of caudal block unfortunately, it was noted to be associated with undesirable effects such as sedation, respiratory depression and hypotension⁵⁻⁸. Sedation was observed in both groups in the first 1 hour of the postoperative period with no statistical significant difference. The sedation scores progressively reduced from 1.35 ± 0.49 (BS) and 1.46 ± 0.51 (BC) ($p = 0.406$) to 0.35 ± 0.48 (BS) and 0.42 ± 0.50 (BC) ($p = 0.406$) respectively after 3 hours of evaluation. This result was consistent with the findings by Jamali and colleagues⁹ who reported no significant sedation with the use of $1 \mu\text{g}/\text{kg}$ of clonidine. Additionally Koul and colleagues¹⁰ did also not observe any significant incidence of sedation in their study when they used $2 \mu\text{g}/\text{kg}$ of clonidine. Another study by Lee and colleague¹¹ reported a significant longer sedation period when $2 \mu\text{g}/\text{kg}$ of clonidine was used in their study. However, it was discovered that the patients were premedicated with trimeperazine a sedative which may have contributed to the longer sedation period. Furthermore, no incidence of respiratory depression was observed and at no point was there a decrease in SPO_2 less than 92% or respiratory rate less than 16 cycles per minute. Although some studies^{13&14} observed profound sedation with doses as high as $5 \mu\text{g}/\text{kg}$ of clonidine but was not appreciated with the use of $1.5 \mu\text{g}/\text{kg}$ deployed in this study and this goes to validates the safety of low dose caudal clonidine

Incidences of hypotension and bradycardia have been reported in some studies¹²⁻¹⁴ as part of the most common side effects with neuraxial clonidine. The combined central and sympatholytic effects of clonidine plus that of the local anaesthetics may lead to exaggerated haemodynamic response than either of the drug alone. In our study, hypotension or bradycardia were not observed in any of the groups and the magnitude of change was similar between the two groups with no statistical significant differences. This findings is in agreement with report of Meghani and co-workers¹⁵ they noted in their study that the addition of 1-2 µg/kg to bupivacaine caudal analgesia did not significantly decrease the heart rate or blood pressure intra and postoperatively. However, the use of higher dose of clonidine (5 µg/kg) in a study carried out by Motsch and colleagues¹² resulted in a marked decrease in the systolic blood pressure and heart rate during the first 3 hours of the postoperative period compared with the patients in the control group. ($P < 0.05$) Also Gubina et al¹³ in a prospective randomized study of 24 middle aged patients undergoing thoracotomy for lung surgery using 300 – 460 µg of clonidine for epidural analgesia found that regardless the excellent analgesia achieved, there was profound decrease in blood pressure and heart rate requiring intervention. Our observation and that of other studies^{16&17} suggests that caudal clonidine in doses of 1-2 µg/kg did not significantly alter the haemodynamic variables.

Other side effects associated with neuraxial blockade includes, urinary retention and delay in return of motor function. The results from this study showed that, there were no detectable differences in the mean time to emergence from anaesthesia, time to first voiding and ambulation between the two groups. The mean time to first ambulation was 2.54 ± 1.17 and 2.38 ± 0.94 hours for groups BC and BS respectively. ($p = 0.605$) Also the mean time to first voiding was 1.96 ± 0.59 and 1.88 ± 0.43 hours for groups BC and BS respectively. ($p = 0.597$) This result was in agreement with those of Koul and colleagues¹⁰ who demonstrated that the addition of 2 µg/kg of clonidine to 1 ml/kg of 0.25% bupivacaine did not result in any incidence of urinary retention and the mean time to first voiding was 4.7 hours for the clonidine group and 4.8 hours for the control group.

Our study was not without a limitation in that a total of three different consultant paediatric surgeons and two Senior Registrars performed the surgeries which may have accounted for the wide ranges in the duration of exposure to anaesthesia and surgery.

Based on the interest generated in the last decade on paediatric day case procedures, we recommend the routine addition of clonidine to local anaesthetics caudal block because it enables the anaesthesiologists to employ light general anaesthesia which correspondingly enhance rapid emergence and better recovery profile.

CONCLUSION

This study demonstrated that the dose of 1.5 µg/kg clonidine added to 0.75ml/kg of 0.5% of bupivacaine for caudal block in children undergoing herniotomy did not increase the incidences of adverse effects.

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Conflict of interest:

The authors' declare that they have no conflict of interest.

Authors' contribution:

Ojiakor S C developed the study, conceptualize the design and implementation of the work, and overall revision of the manuscript was done by Edomwonyi N P and Umeh B U O.

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