Pediatric Anesthesia and Critical Care Journal 2017;5(2):95-102
doi:10.14587/paccj.2017.15

PACCJ

Caudal bupivacaine and midazolam versus bupivacaine alone for pain relief in paediatric ambulatory groin surgeries

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Keypoints

Midazolam has been demonstrated to possess analgesic property when deposited in the epidural space. We explored the analgesic benefits of caudal midazolam as an adjuvant to caudal bupivacaine in ambulatory paediatric groin procedures, and studied the recovery and side effects of the drug. Caudal bupivacaine midazolam injection provides superior quality of analgesia in children undergoing ambulatory groin procedures compared to bupivacaine alone with satisfactory recovery profile.

Abstract

Introduction

Adequate pain control after ambulatory surgery remains a major challenge. Midazolam as adjunct to local anaesthetics in caudal epidural analgesia has been found effective with minimal side effects. This study was carried out to evaluate its analgesic efficacy and recovery profile in children who underwent ambulatory groin surgeries.

Materials and Methods

Eighty-six children aged between one and six years who presented for herniotomies or orchidopexies at our ambulatory facility were randomized to receive either a caudal epidural injection of bupivacaine (1ml/kg of 0.125%) alone (group B), or with 50µg/kg of midazolam (group M) after induction of general anaesthesia. Postoperatively, time to first analgesia, number of doses of paracetamol administered within the first 24 hours, sedation scores within the first hour, and time to home readiness were recorded.

Results

The study and control groups had comparable sociodemographic characteristics. The mean time to first request for analgesic was significantly longer (p = 0.0001) in group M (477.67 min ± 53.79 min) compared to group B (243.79 min ± 44.00 min). The number of doses of post-operative analgesic consumed was significantly lower in the study group (p = 0.0001). Sedation scores were similar in the first hour post operatively. The time to home readiness was longer in the midazolam group with a mean difference of 5.37 minutes (39.86 min ± 6.38 min versus 34.49 ± 4.55 min; p = 0.0001). A patient in the bupivacaine-midazolam group had an episode of vomiting; otherwise no other side effect was documented.

Conclusion

This study shows that caudal bupivacaine midazolam injection provide superior quality of analgesia in children undergoing ambulatory groin procedures compared to bupivacaine alone with satisfactory recovery profile.

Keywords: Ambulatory groin surgery, paediatric anaesthesia, caudal analgesia, bupivacaine, midazolam.

Introduction

Postoperative pain remains a major challenge globally despite remarkable advances in anaesthesia and surgery in recent years.[1,2,3] Pain has been identified as the com-

monest complaint among children undergoing ambulatory surgery in Nigeria.[4] Adequate postoperative pain control is an essential component of an ambulatory surgical service; aiding quick return of the patient to normal routines. Unrelieved pain after ambulatory surgery can delay discharge, lead to unanticipated hospital admission and increase cost. Caudal epidural analgesia remains one of the most commonly performed regional blocks in paediatric anaesthesia due to its reliability, safety, and ease of performance.[5] However, short duration of effect is a drawback of single shot caudal analgesia even when long acting local anaesthetics are used.[5] Addition of various adjuvants to local anaesthetics to prolong the duration of analgesia has been explored in recent years. While significant prolongation of analgesia was not achieved with epinephrine, opioids were found to prolong analgesia but their use may be marred by unpleasant side effects including nausea, vomiting, pruritis, urinary retention and delayed respiratory depression.[5,6] Hallucination and potential for toxicity in the event of inadvertent intrathecal injection are limitations to the use of ketamine, and neostigmine is associated with nausea and vomiting though it prolongs duration of analgesia.[6,7] Caudal clonidine has been recommended as an adjuvant to local anaesthetic in children,[8] but it has been associated with bradycardia, hypotension and excessive sedation in adults. These side effects have been reported to be either minimal or absent in children by some clinician.[9,10] Excessive sedation related to caudal clonidine in children appears to be dose-dependent.[5] The gains of an ambulatory surgical service may be eroded by undesirable side effects.

Midazolam, a short acting benzodiazepine with good anxiolytic, amnestic, sedative, hypnotic, anticonvulsant, and skeletal muscle relaxant properties has been demonstrated to possess analgesic property when deposited in the epidural space since its early trials in the 1980s. Its analgesic effect is mediated through the GABA and the benzodiazepine system in the spinal cord.[11] A dose of 50µg/kg co-administered with local anaesthetics has been shown to extend period of analgesia without substantial side effects. However, higher sedation score during the first postoperative hour has been reported.[12] A recent work comparing intrathecal midazolam and low dose clonidine suggested that midazolam provides superior analgesia to clonidine in subarachnoid block with fewer adverse effects.[11] A meta-analysis evaluating the effectiveness and the side effects of intrathecal midazolam among parturient also suggested improved perioperative analgesia and reduced nausea and vomiting during caesarean delivery.[11] Both therapeutic benefits are highly desirable in an ambulatory setting.

Although, concerns with possibility of toxic effects of the epidural use of midazolam particularly in neonates continue to persist, available evidences so far suggest that a small diluted dose of less than 1mg/mL preservative-free intrathecal and epidural midazolam appears free of neurotoxicity.[11,12,13] The use of caudal epidural midazolam has not been previously explored among children undergoing ambulatory surgery; this study was conducted to explore the analgesic benefits of caudal midazolam as an adjuvant to caudal bupivacaine in ambulatory paediatric groin procedures, and to study the recovery and side effect profile of the drug.

Materials and Methods

Ethical approval was obtained from the Hospital's Ethics and Research Committee, and informed consent was obtained from the parents/guardians of the children before recruitment into the study. The sample size was determined by using the Snedecor-Cochran equation for comparing two group means[14] $n = 1+ 2C (s/d)^2$ where: n = sample size; s = standard deviation from a previous study[12]; d = difference in time of recovery to be detected; c = constant dependent on the values of α and β selected. For $\alpha = 0.05$ and $1-\beta = 0.9$, c is 10.51, s = ± 2.7 hours, d = 2 hours, $n = 1+ 2(10.51)(2.7/2)^2$; $n = 1 + 38.3$ i.e. 39 patients in each group. The sample size was increased by 10% to provide for attrition (39 + 4 = 43). Therefore, 43 patients were recruited for each group. Eighty-six ASA I and II patients between the ages of 1

and 6 years scheduled for unilateral groin procedures (herniotomies and orchidopexies) in the Ambulatory theatre of our hospital were recruited into this prospective randomized double blind comparative study, with forty-three patients in each group. Exclusion criteria included; parent`s or guardian`s refusal, in-patients, known allergy to bupivacaine, midazolam, or other benzodiazepines, presence of a neurological disease, lumbosacral deformities or coagulopathy, and regular use of sedative or anticonvulsant for any reason.

On arrival in the theatre, patients were randomly assigned into one of the two groups: bupivacaine only (Group B), and bupivacaine plus preservative free midazolam (Midazolam injection 5mg/ml, Hameln pharmaceuticals Ltd, UK), (Group M) by drawing out of a pool of computer generated codes which were kept in sealed envelopes. Randomization was done by the anaesthetist who also prepared the drugs while drugs administration was done by the lead investigator blinded to patient's group. Another anaesthetist blinded to patients' grouping assessed the children after the block was instituted. The lead investigator and the assessor were blinded to the drugs. Baseline vital signs including pulse rate, systolic blood pressure, respiratory rate and SpO_2 were recorded with a non-invasive multiparameter patient monitor [Mindray; Model PM-5000, Shenzhen Mindray Bio-Medical Electronic Co. Ltd, Shanghai International Holding Corp. GmbH]. Inhalational induction was done with 1 - 2% halothane in 100% oxygen delivered through Jackson Ree's modification of Ayre's T -piece and face mask. Once the patient was asleep, a 20G or 22G intravenous cannula was sited and 4.3% dextrose in 0.18% saline infusion was put up to run at maintenance rate. Following induction of anaesthesia, the patients were placed in left lateral decubitus position with hip and knee flexion. Group B had 1ml/kg of 0.125% bupivacaine and Group M had 1ml/kg of 0.125% bupivacaine with 50µg/kg of midazolam injected into the caudal epidural space using a 22 G hypodermic needle under sterile condition. The patient was then returned to the supine position for the surgery. Surgical procedures were commenced ten to fifteen minutes after administration of caudal block. Anaesthesia was maintained with halothane (0.5% - 1%) in oxygen (2 litres/minute) – air (4 litres/minute) mixture. The blood pressure was cycled every 5 minutes. An intraoperative increase in heart rate or blood pressure by more than 10% above the baseline after 15 minutes of caudal injection was defined as insufficient analgesia and treated with intravenous paracetamol 15mg/kg body weight, and the patient withdrawn from the study.

Halothane was discontinued at the beginning of skin closure. At the end of surgery and upon the achievement of a modified Aldrete score[15] of at least 6, patients were moved to the recovery room, breathing room air. Intraoperative or postoperative decrease in systolic blood pressure or heart rate more than 30% of the baseline values was to be defined as severe hypotension or bradycardia respectively. Severe hypotension and bradycardia were to be treated with ephedrine and atropine respectively. Respiratory depression was defined as a fall in respiratory rate below 15 cycles per minute and it was to be treated with supplemental oxygen and manual ventilation after turning off the inhalational agent. On arrival in the recovery room, systolic blood pressure, heart rate, respiratory rate and SpO_2 were documented every 15 minutes in the first hour and hourly until patient had achieved a modified Aldrete score[15] of ≥ 9. Pain assessment in the postoperative period was done using the objective pain scale[16] (OPS) at 30 minutes, 1 hour and 2 hours. If the OPS score was more than 4 or if the patient was showing obvious signs of pain including restlessness, inconsolable cry, holding on to the site of surgery, intravenous paracetamol 15 $mgkg^{-1}$ was administered. Time to first analgesic requirement from the time of caudal injection was noted. The duration of motor block was assessed by noting the time the patient begins to move his legs after regaining consciousness. Time of first micturition was also noted. Sedation was assessed with the Ramsays Sedation Scores[17] until a score of 2

was achieved. The children were discharged from the ambulatory facility when adjudged home ready (Modified Aldrete Score[15] of ≥ 9) but not earlier than two hours after transfer to recovery room. Parents were instructed on method of pain assessment using modified Objective Pain Score (MOPS).[7,18]

The MOPS which has been validated in parents differs from the OPS by substituting posture assessment (normal = 0; flexed = 1; and holds injury site = 2) for blood pressure. They were instructed to administer the take home analgesic (oral paracetamol) if the MOPS score was more than 4, and requested to note the time of first analgesic and the total number of doses of oral paracetamol administered in the first 24 hours after surgery on a pre- prepared form which was taken home and retrieved at the follow-up clinic.

Parent/Guardian`s satisfaction was measured with a 5-point Likert scale (1. Strongly disagree; 2. Somewhat disagree; 3. Undecided or indifferent; 4. Agree; 5. Strongly agree) during follow-up done via phone contact.

Data was analyzed using the Statistical Package for Social Sciences SPSS version 16 software for windows. Data was presented as mean [±SD], proportions and ratios.

Differences between the groups were analysed using Student's t-test for parametric variables, and Chi-square for non-parametric variables. The difference in time to first analgesia between the two groups was also tested using Mann–Whitney rank sum test.

A confidence interval of 95% [P<0.05] was accepted for the study.

Results

Eighty-six (86) patients between the ages of one and six years, who fulfilled the inclusion criteria, were recruited for the study. There were forty-three patients in each group: the control (B) and the study group (M). All of them were males and of the American Society of Anesthesiologist physical status class I. There was no drop out on account of failed block or withdrawal from the study. The demographic characteristics of both groups were similar as shown on Table I.

The time to first analgesia was statistically longer in the study group compared to the control group (Tables II and III). The pain scores in the first two hours after surgery were essentially similar with 93.0% and 95.3% of patients in the control and the study groups respectively, having a pain score of 1. Two patients (4.7%) in each group had a score of 2, while one patient (2.3%) in the control group had a score of 4 (p =0.603).

	Group B	Group M
Mean Age (months)	34.67 ± 18.99	38.30 ± 20.17
Weight (kg)	13.66 ± 3.31	14.05 ± 3.00
Height (cm)	91.65 ± 11.71	92.87 ± 11.54
BMI (kg/m^2)	16.14 ± 1.62	16.25 ± 1.74
Dose of bupivacaine (mg)	17.07 ± 4.14	17.5 ± 3.71
Duration of anaesthesia (min)	46.65 ± 8.31	49.02 ± 11.67
Duration of surgery in min (Range)	32.98 ± 7.11 (16 to 49)	33.72 ± 11.73 (15 to 86)

Table I. Patient Data in Mean ± SD or Range

	Group M (Mean ± SD)	Group B (Mean ± SD)	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI of the Difference
Time to first Analgesic	477.67 ± 53.79	243.79 ± 44.00	22.164	84	0.0001	234.884	10.598	213.809, 255.958

Table II. Mean Time to first Analgesia in minutes for the Study and Control Groups

	Mean Rank	Sum of Ranks	Mann-Whitney U	Wilcoxon W	Z	Sig. (2-tailed)
Group M	64.09	2756.00	39.00	985.00	-7.696	0.0001
Group B	22.91	985.00				

Table III. Time to first Analgesia - Mann-Whitney U Test

None of the patient in both groups received supplemental analgesic before the third hour after caudal block but 97.7% of patients in the bupivacaine group had received supplemental analgesia within the first six hours as compared to only 6.6% of patients in the bupivacaine-midazolam group. The doses of supplemental oral paracetamol administered to the patients within the first 24 hours post operatively were significantly different

between the groups. No child in the study group had more than two doses of paracetamol in the first 24 hours post operation while 74.4% in the control group had three to four 4 doses of paracetamol during the same period (p – 0.0001) (Figure 1). Three patients (6.9%) in the study group did not require supplemental analgesic during this period.

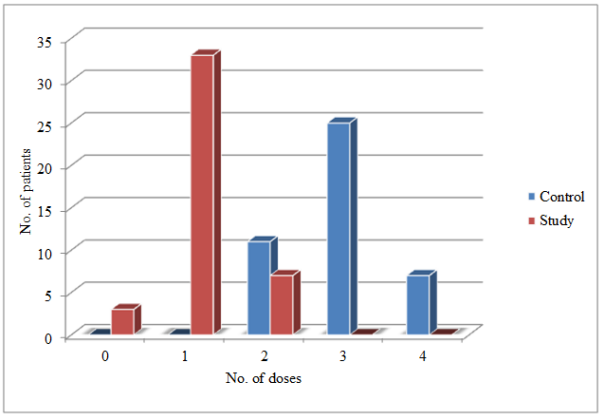

Figure 1. Doses of supplemental oral paracetamol administered within the first 24 hours

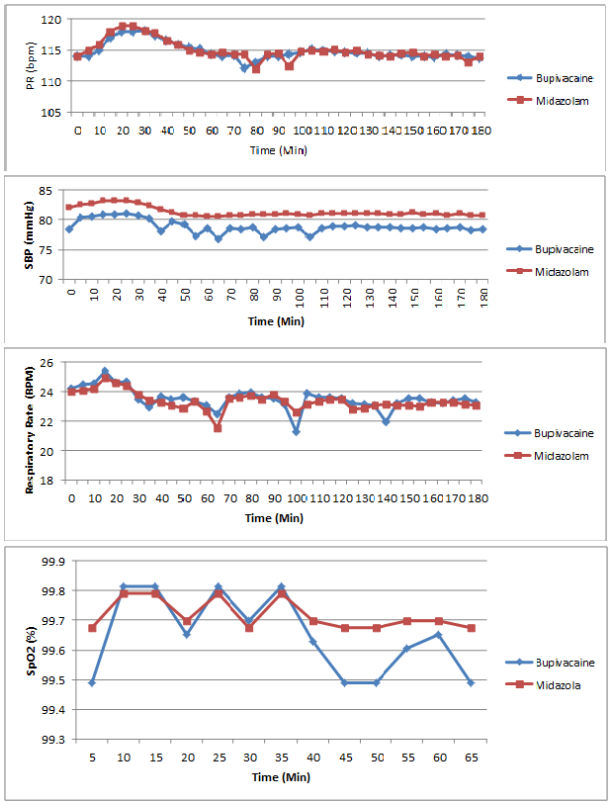

Figure 2. The intraoperative and postoperative haemodynamic and respiratory parameters of the two groups

The time to achieve modified Aldrete score[15] of 6 was similar for the two groups. However, the mean time to home readiness was statistically longer in the study group. The time to void was comparable in the two groups. The recovery profile of the two groups is summarized in Table IV. Sedation scores were also similar in both groups within the first hour postoperatively as shown in Table V.

Recovery Variables (min)	Group M (mean ± SD)	Group B (mean ± SD)	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI of the Difference
Time to achieve MAS 6	10.30 ± 2.10	9.93 ± 2.12	0.818	84	0.416	0.372	0.455	- 0.533, 1.277
Time to achieve MAS ≥ 9	39.86 ± 6.38	34.49 ± 4.55	4.493	84	0.0001	5.372	1.196	2.994, 7.750
Time to void	144.57 ± 27.40	140.75 ± 34.20	0.529	73	0.599	3.821	7.226	- 10.579, 18.222

Table IV. The Recovery Profile for Study and Control Groups
MAS - modified Aldrete score[15]

Time (min)	Group M (mean ± SD)	Group B (mean ± SD)	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI of the Difference
15	4.88 ± 0.324	4.93 ± 0.258	0.736	84	0.464	0.047	0.063	- 0.172, 0.079
30	2.21 ± 0.412	2.14 ± 0.351	0.846	84	0.400	0.070	0.082	- 0.094, 0.234

Table V. Sedation Scores for the Study and Control Groups during the First Postoperative Hour

All the children were fully awake by 35 minutes after transfer to the recovery room. Motor block was not observed in any of the patients. Bradycardia, hypotension and respiratory distress were not observed in any of the patients. A child (2.3%), in the study group had an episode of postoperative vomiting in the recovery room. The baseline haemodynamic parameters were statistically comparable. The intraoperative and postoperative haemodynamic and respiratory parameters of the two groups were also essentially similar (Figure 2). No child desaturated at any time. All the parents/guardians either agreed or strongly agreed that the method of pain relief used was helpful to their wards and were satisfied.

Discussion

This study shows that the addition of midazolam to caudal bupivacaine in children undergoing ambulatory groin surgery results in significant prolongation of analgesia and reduces analgesic consumption in the first 24 hours post operatively. The time to first analgesia was nearly doubled without undue sedation or motor block. There was a short but significant delayed recovery from

anaesthesia. While this study confirms the finding of previous related works[6,12,19,20] on the analgesic efficacy and safety of caudal midazolam in children, it also demonstrates its possible benefits in ambulatory surgery setting.

Himabindu *et al*[20] explored the use of caudal midazolam for postoperative analgesia in children following infra-umbilical surgeries and reported that only 4% of the children who had bupivacaine alone were pain free 6 hours after surgery compared to 72% of children who had bupivacaine with midazolam. However, Naguib *et al*[21] had earlier demonstrated analgesic efficacy and safety of caudal midazolam and the synergistic analgesic effect when co-administered with bupivacaine in their work in 1991. Caudal midazolam administered postoperatively at a dose of 50µg/kg was found to provide equivalent analgesia to 1ml/kg bupivacaine 0.25%. Over 85% of children in the combination group required no supplemental analgesia in the first 24 hours compared to 46.7% in the bupivacaine alone and midazolam alone groups. Their study established the superiority of co-administration of midazolam and bupivacaine as used in this study. It is noteworthy that 26.7% of their patients in both bupivacaine and bupivacaine-midazolam groups were unable to stand at six hours postoperatively due to timing of injection and the dose of bupivacaine used in their study. This side effect was avoided in our patients with the use of 1 ml/kg of 0.125% administered immediately after induction. It is essential that muscle weakness is avoided in ambulatory anaesthesia to ensure early home readiness.

Kumar *et al*[6] in their work comparing paediatric caudal midazolam, ketamine, and neostigmine co-administered with bupivacaine reported over 157% increase in duration of analgesia and time to first analgesic of 16.8 ± 3.9 hrs with addition of 50µg/kg midazolam with 1ml/kg of 0.25% bupivacaine compared to 7.6 ± 5.2 hrs in the bupivacaine alone group. The mean duration of complete analgesia in this study was prolonged by 196% in the midazolam group and over 80% of the children in this group required not more than one dose of supplemental analgesic in the first 24hrs. Their study also showed no statistically significant difference in duration of pain relief between bupivacaine-neostigmine and bupivacaine-midazolam groups although duration of pain relief as well as the incidence of vomiting was greater in the bupivacaine-neostigmine group. The undesirability of postoperative nausea and vomiting in ambulatory anaesthesia service makes neostigmine a poor choice compared to midazolam.

Bano *et al*[12] in their evaluation of peri- and postoperative analgesic effect of 50µg/kg midazolam combined with bupivacaine used 0.75ml/kg of 0.25% bupivacaine compared to 1ml/kg of 0.125% used in this study and reported more than doubled the duration of analgesia in the combination group (21.41 ± 2.7 hours) compared to the bupivacaine alone group (9.97 ± 2.25 hours). While the relatively longer duration of analgesia which is desirable could be attributed to the synergy of higher dose of bupivacaine used in their study with midazolam; cautious use of a lower dose in our study was informed by the desire to avoid muscle weakness which could delay home readiness of the patients.

Anaesthesia for ambulatory surgery must be such that ensures quick and adequate recovery of the patient with early return to normal life. To achieve this, the anaesthetic plan must balance drug effectiveness and side effects profile in achieving a satisfactory outcome. It is noteworthy in this study that midazolam caused a brief but significant delay (mean difference of 5.37 minutes) in time to home readiness. However, both groups achieved satisfactory recovery within one hour and were home ready. Besides the single case of vomiting in the study group noted which was not statistically significant, the commonly reported postoperative complications in ambulatory anaesthesia including nausea, difficulty with walking, and dizziness were not encountered in this study. To the contrary, Naguib *et al*[21] reported one case (6.6%) of postoperative vomiting in the midazolam-bupivacaine group compared to two (13.3%) in

the bupivacaine alone group though this was not statistically significant.

All our patients were fully awake within 35 minutes after transfer to the recovery room. In keeping with our finding, Abodisera *et al*[22] in a study of Egyptian adult population undergoing ambulatory surgery did not observe a significant delay in recovery after caudal administration of ropivacaine-midazolam mixture. The sedation score of all their patients returned to normal after 15 minutes in the recovery room, though the definition of term "normal" was not clear from their report.

Similar to our finding, Baris *et al*[23] reported a statistically significant difference in time to achieve Aldrete score of 10 when they compared 0.75 ml/kg of 0.25% bupivacaine with addition of midazolam (50µg/kg) for caudal block in 75 children undergoing inguinal herniorrhaphy. They also reported a significant difference in sedation scores at 60 and 90 minutes contrary to our findings, and suggested that 0.75ml/kg of 0.25% bupivacaine administered caudally was adequate at controlling the mild to moderate pain associated with inguinal herniotomy. However, the use of a 3-point sedation score in their study could have masked observable differences in the sedation spectrum. Sedative medication used for treating agitation in some of the children postoperatively could have influenced their observation.

As part of limitations to this study, it is noteworthy that the time to void could not be ascertained in some of the patients because they were on diapers immediately after surgery. The ability of the parents/guardians to evaluate pain without emotional bias could not be guaranteed, and could have influenced the time to first analgesia reported. It was also difficult to evaluate the sensory block height achieved, and the occurrence of motor block in the children, more so they were under general anaesthesia when the blocks were instituted.

Another limitation to this study is that the use of midazolam in the ambulatory setting did not allow for routine neurological assessment that would have been possible on in-patients until patients were presented at the follow-up clinic days later. The use of single-shot caudal midazolam has not been associated with neurological damage so far but caution is advised. This study does not provide conclusive safety data on caudal midazolam use in children. Hence, further studies in this regard are required.

Conclusion

This study shows that addition of midazolam to caudal bupivacaine confers longer duration of analgesia and reduced requirement for supplemental analgesia among children undergoing ambulatory infra-umbilical surgeries. There was no significant adverse effect observed with its use in the setting of this study when compared with bupivacaine alone.

Ethics (IRB approval number): *IRB/IEC/0004553; NHREC/27/02/2009a*

Pan African Clinical Trial Registry number: *PACTR201605001626353*

Funding: *The study was funded with departmental resources.*

Disclosure: *There is no conflict of interest among the authors.*

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