

Midazolam for caudal analgesia in children: Comparison with caudal bupivacaine

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Abstract

Background: Caudal analgesia is the most popular and commonly used regional anaesthesia technique for post operative analgesia in children undergoing lower limb, anoperineal and abdominal surgical procedures. It is commonly applied in all the paediatric patients undergoing the above mentioned surgery, as the goal of balanced anaesthesia is not only limited to intraoperative period but also good analgesia in post operative period. Many drugs like morphine, Pethidine, Neostigmine etc have been used as analgesic agent via the caudal route but not without their side effects. So Midazolam was used as an alternative drug as it may not be associated with the side effects encountered with the other drugs.

Aims and objectives: The objective of the study was to see the analgesic efficacy of caudal administration of Midazolam with comparison to Bupivacaine for post operative analgesia, and to observe for side effects if any.

Materials and methods: This was a single blinded prospective observational study in children of age 1 to 6 years of ASA grade I undergoing elective hernia or hydrocoele surgery. The patients were allocated randomly into two groups (n=25) to receive caudal injection of either 0.25% Bupivacaine 1ml/kg (group A) or Midazolam 50µg/kg with normal saline 1ml/kg (group B). In the post operative period heart rate, blood pressure, pain score, recovery to first analgesic time, total number of analgesics required in 24 hours and side effects if any were noted and analysed.

Results: There were no significant differences in quality of pain relief, postoperative behaviour or analgesic requirements between the Midazolam group and the Bupivacaine group. Recovery to first analgesic time though was longer in the Bupivacaine group (9.65 hr) than Midazolam group (7.32 hr); it was statistically not significant (P= 0.9). Any of the side effects such as motor weakness, urinary retention, and respiratory depression were not observed in both the groups. However in both the groups, few of the patients had post operative vomiting.

Conclusion: We conclude that caudal Midazolam in a dose of 50µg/kg provides equivalent analgesia to Bupivacaine 0.25%, when administered in a volume of 1ml/kg for children undergoing unilateral inguinal herniotomy for hernia or high ligation of processus vaginalis for hydrocoele.

Key words: analgesia, caudal, Midazolam, Bupivacaine, paediatric

Caudal analgesia is the most popular and commonly used regional technique for post operative analgesia in children undergoing lower limb, anoperineal and abdominal surgical procedures¹.

Bupivacaine is the most commonly used drug for caudal epidural analgesia at present. The side effects of Bupivacaine include cardiovascular and central nervous system toxicity by unintentional intravascular injection during caudal block placement; common side effects are motor weakness and urinary retention. Even administration of an epidural test dose containing epinephrine for detection of unintentional intravascular canula position does not reliably produce hemodynamic responses in children during inhalational anaesthesia. So Midazolam has been chosen as an alternative analgesic to Bupivacaine for caudal analgesia in children for post-operative analgesia^{2,3,4}.

In order to minimize side effects of local anaesthetics and to maximize analgesia of caudal epidurals many drugs have been administered into epidural space for example Morphine⁵, Clonidine^{6,7}, Tramadol⁸, Ketamine^{9,7}. Several lines of evidence suggest that the nociceptive processing may be modulated at the level of spinal cord by a variety of local receptor systems; including those of opoid, adrenergic and benzodiazepine agonists. Caudal administration of morphine produces a prolonged postoperative analgesia, but is associated with major side effects, in particular the potential of

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delayed respiratory depression⁵. Clonidine, an Alpha 2 adrenergic agonist, has been shown to potentiate postoperative analgesia when used in combination with local anaesthetics. Although the addition of Clonidine to Bupivacaine improved the efficacy of caudal analgesia, it was associated with prolonged sedation in children^{6,7}. Of all the agents used, epidural Midazolam seems to be promising because of the absence of the aforementioned side effects.

Material and methods

Design

This is a single blinded prospective randomized study of 50 male paediatric patients, ASA grade I, of age groups 1 – 6 years, scheduled to undergo unilateral inguinal herniotomy for inguinal hernia or high ligation of processus vaginalis for unilateral hydrocoele.

After the approval from the hospital authority, informed consents were taken from the parents for the study.

Children with age group < 1 year, > 6 year, weight > 20 kg, infection at the site of caudal injection, hypersensitive to local anaesthetics and Midazolam and those who refused to give consent were excluded from the study.

No premedication were given to the patients and all the operations were carried out under general anaesthesia. Anaesthesia was induced with volatile anaesthetic agent halothane, oxygen and nitrous oxide. Intravenous cannulation was done with 22 Gz canula. Intubation was done under direct laryngoscopic view facilitated with Succinylcholine 1.5 mg/kg. Anaesthesia was maintained with halothane, oxygen and nitrous oxide (66%) delivered via Jackson Ree's modification of Ayre's T piece circuit with spontaneous ventilation. The patients were randomly divided in one of the two groups after the patients were settled with the general anaesthesia. Group A received caudal injection of 0.25% Bupivacaine, 1 ml/kg and the patients in Group B received caudal Midazolam 50µg/kg diluted with 0.9% normal saline in same weight related volumes. All the caudal blocks were performed with the patient in left lateral position with 23 Gz butterfly needle under full aseptic measures. Epidural space was identified by characteristic giving away sensation during needle advancement through sacral hiatus, absence of subcutaneous swelling and absence of resistance during drug injection and absence of cerebrospinal fluid on aspiration. Sterile dressing was applied and fixed with leucoplast over the sacral hiatus. Then the patient was turned in supine position and anaesthesia was maintained with oxygen, nitrous oxide and halothane 1%. After 15 minutes of caudal block, surgery was started. The patients did not receive

any other analgesics intraoperatively. Intraoperative pulse, blood pressure, respiratory rate and oxygen saturation were noted. Absence of increase in heart rate and blood pressure more than 20% of the pre incision value after surgical incision was regarded as indication of effectiveness of epidural drug.

Intra operative fluid given was 5% dextrose in normal saline with 4:2:1 formula i.e. 4ml/kg/hr for 1st 10 kg, 2ml/kg/hr for next 10 kg and then 1ml/kg/hr for rest of the body weight for maintenance period as well as for the fasting hour deficit. Third space loss was calculated as 2ml/kg/hour.

After completion of surgery, the patients were extubated and transferred to the recovery room. The patients were observed for 1 hour in the recovery room and heart rate and oxygen saturation were continuously monitored by pulse oximeter. In the recovery room objective pain assessment, heart rate, blood pressure and respiratory rate were recorded by nursing staff every 15 minutes. The patients were transferred to the ward after one hour. In the surgical ward, assessments were done every 15 minutes for first hour, 30 minutes interval for next one hour, hourly for next 4 hours and after 24 hours from recovery from anaesthesia. Pain was scored with reference to six point scale (none/insignificant pain 1 – 2; moderate pain 3 – 4, severe pain 5 – 6) according to the modified pain discomfort scale. The patients were allowed to have clear fluids after two hours of recovery.

The patients received either rectal Paracetamol (if the pain score was ≥ 3 in two subsequent readings within 2 hours in the postoperative period) or oral syrup of Paracetamol on evidence of pain that is if the pain score was ≥ 3 in two subsequent readings. The time at which first analgesia received (recovery to first analgesic time) and total number of analgesics in 24 hours were recorded. Side effects were noted with concern to nausea/vomiting, urinary retention, respiratory depression (respiratory rate <12) and motor weakness (unable to stand unaided after 3 hours from recovery from anaesthesia).

Further assessment was done at 24 hour postoperatively during follow up with records and by inquiring nurses and patients' guardian about the quality of overnight sleep (good/interrupted), behaviour at bed time on the day of surgery (calm and quiet or restless).

Data analyses were done under following sub headings:-

- Age and weight of the patients
- Duration of anaesthesia

- Blood pressure, heart rate, respiratory rate and pain scale of the patients
- Time at which first analgesia was received, that is recovery to first analgesic time and total number of analgesics received
- Total number of patients with complications in both the groups

All the data were analyzed by using t test. The data were analyzed with statistical methods using Pentium III version of computer using statistical package for social science (SPSS).

Results

The results were analysed in relation to age, weight of the patients, duration of anaesthesia in minutes, systolic, diastolic and mean arterial pressure, heart rate, respiratory rate, and pain scale in 24 hours in postoperative period, recovery to first analgesic time and total number of analgesics in 24 hours.

Both the groups were comparable in relation to age and weight without any statistically significant difference (Table 2). Duration of anaesthesia was also similar without any statistically significant difference. (Table 2)

Recovery to first analgesic time was longer in the Bupivacaine group than the Midazolam group; however it was not statistically significant (Table 2).

There was no significant difference in the frequency of analgesia administered in 24 hours in both the groups (Bupivacaine vs. Midazolam group, 1.2 ± 0.87 vs. 1.28 ± 0.79 , $P = 0.38$).

Sixteen percentage of the patients in the Midazolam group did not require any analgesic in 24 hour; whereas in the Bupivacaine group this was 24% (Table 3).

There was no statistically significant difference in systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and level of pain score observed in the 24 hours postoperative period among the two groups. (Figures 1, 2, 3, 4)

Frequency of analgesia administration in 24 hours were 1.20 ± 0.87 vs. 1.28 ± 0.79 ($P = 0.38$) in Bupivacaine and Midazolam group, respectively. Since the calculated value is less than tabulated value at 0.05 level of significance; it is concluded that there is no any significant difference between two types of drugs used.

Post operatively vomiting occurred in 12% and 8% of the patients in the Midazolam and Bupivacaine group respectively. However other complications like urinary retention, motor weakness, respiratory depression, hypotension, and bradycardia were not observed in any of the groups. All the patients in both the groups had uninterrupted overnight sleep.

Table 1: Modification of pain/discomfort scale²³

<i>Observation</i>	<i>Criteria</i>	<i>Points</i>
Crying	Not crying	1
	Crying but responds to tender loving care (TLC)	2
	Crying and does not responds to TLC	3
Posture	No special posture	1
	Flexing legs and thighs	2
	Holding /Covering incision site	3

Table 2: Different variables of the patient

	Bupivacaine group	Midazolam group	P value
	(n=25)	(n=25)	
Age in years	3.28 ± 1.80	3.77 ± 1.81	0.82
Weight in kg	12.76 ± 3.40	13.52 ± 2.93	0.78
Duration of anaesthesia (in minutes)	40.4 ± 8.28	43.6 ± 10.55	1.06
Recovery to 1st analgesic (in hours)	9.65 ± 8.97	7.32 ± 7.09	0.9

Values are mean \pm SD. Significance value is regarded as P value < 0.05

Table 3: Frequency of analgesia administered in 24 hours

Analgesia No. of doses in 24 hours	Bupivacaine group (n=25)	Midazolam group (n=25)
0	6 (24%)	4 (16%)
1	9 (36%)	11 (44%)
2	9 (36%)	9 (36%)
3	1 (4%)	1 (4%)
Total	25 (100%)	25 (100%)

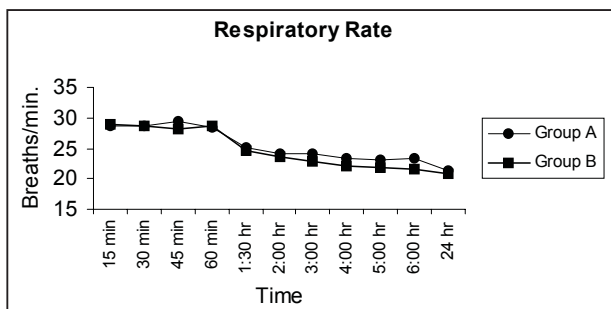


Fig 1: Respiratory rate in 24 hours in post-operative period

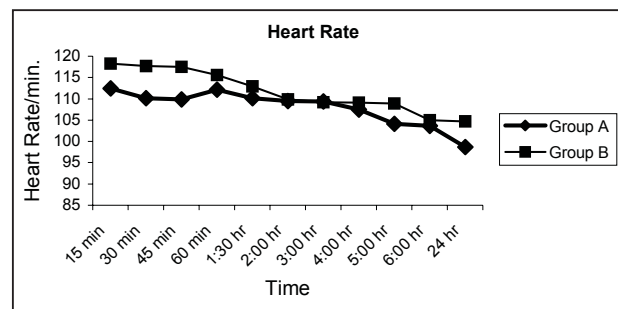


Fig 2: Heart rate in 24 hours in post-operative period

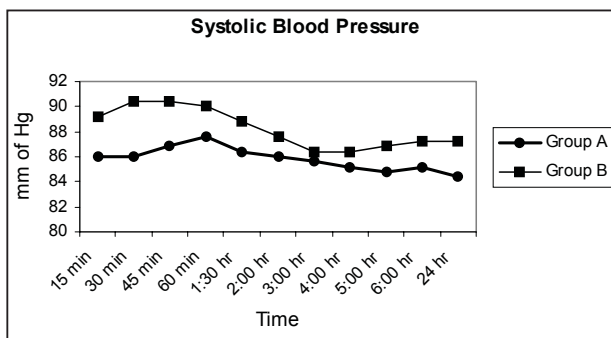


Fig 3: Systolic blood pressure in 24 hours in post-operative period

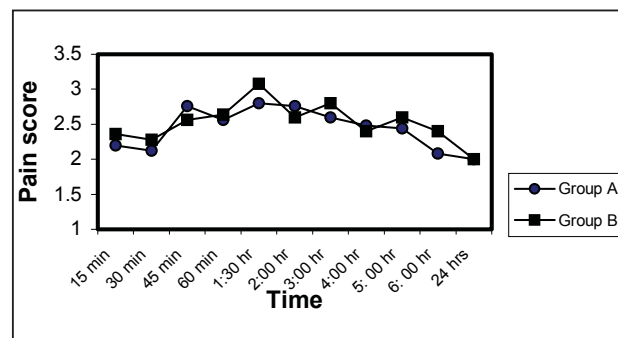


Fig 4: Pain score in 24 hours in post-operative period

Discussion

This study was carried out to compare the post operative analgesic efficacy of the caudal administration of Midazolam (Group B) with the caudal administration of Bupivacaine (Group A) administered after general anaesthesia but, before surgery in the paediatric patients of age group 1 – 6 years undergoing unilateral herniotomy or high ligation of processus vaginalis for hernia or hydrocoele respectively.

An important goal of modern anaesthesia is not only to provide balanced anaesthesia but also to provide

quality control of post operative analgesia. In the last two decades there has been renewed interest in regional analgesia for the paediatric procedures¹⁰. In the prospective study carried out by Elisabeth and Bernard et al it has been showed that central blocks accounted for 62% of all the regional anaesthetics techniques and caudal blocks accounted for 50% of all the regional blocks and 81% of all central blocks. The trend of using regional blocks in the paediatric patients are increasing and the complications associated with them are found to be very minor¹⁰. In one another study carried out in

United Kingdom by JC Sanders, it has been found that 96% of the paediatric anaesthesiologists use caudal block and 91% do not have lower age limit for the block¹¹. However in this study only one anaesthesiologist used Midazolam as an adjunct to local anaesthetics for caudal block.

In this study, caudal administration of Midazolam 50µg/kg in children produced postoperative analgesia comparable with that associated with caudal injection of 0.25% Bupivacaine, 1ml/kg.

Extradural administration of Midazolam to postoperative adult patients and individuals with chronic pain has shown to result in significant analgesia^{12,13}. Nishiyama et al. evaluated four doses (25, 50, 75 and 100 µg/kg) of epidural Midazolam mixed with saline in patients undergoing upper abdominal surgery. 50µg/kg was found to be the optimal dose. Higher doses were associated with prolonged and deep sleep¹².

Epidural administration of Bupivacaine in the dose of 2.5mg/kg is considered to be safe and is used extensively^{9,6,14,7,15}. In one study Veronica et al. have found that lumbar epidural administration of Bupivacaine in children in doses below 3mg/kg also resulted in safe plasma concentration below 3µg/ml¹⁶.

The principal mechanism by which epidural Midazolam provides analgesia is through the GABA (gamma-aminobutyric acid A)-benzodiazepine system in the spinal cord. Binding sites for benzodiazepines have been demonstrated in the spinal cord and endogenous benzodiazepine-like substances have been discovered in the human cerebrospinal fluid. At all levels, the highest density of binding sites was found within lamina II of the dorsal horn, a region which plays a prominent role in the processing of nociceptive information. Based on radioligand binding assays and electrophysiological studies, the benzodiazepine site appears to be linked to the GABA receptor complex. Several investigators have reported that intrathecally or epidurally administered Midazolam produces a dose-dependent modulation of spinal nociceptive processing in both rats and humans without respiratory depression, suggesting that some of the spinal benzodiazepine sites are associated with dorsal horn systems which encode pain-related information. Midazolam has been used in the epidural space and as a spinal anaesthetic and has been shown to have no neurological deficits^{12, 13,15,17,18, 19, 20, 21}.

Although there is controversy related with the treatment of postoperative pain pre emptively, in a study by Woolf CJ et al, it has been mentioned that post operative pain can be treated by pre emptive analgesia which works by preventing the establishment of central sensitization²².

Assessing pain scale in children is difficult as they cannot actually express their feeling. Assessment of pain in children was done by modification of pain/discomfort scale. It is a valid and reliable method of assessing pain in children and has been used by other groups also^{9, 15, 23}.

This study group included patients of age groups 1 – 6 years as caudal block is easier to perform in younger children. In a retrospective study of 750 consecutive caudal blocks in children Dalens and Hasnoui noted a failure rate of only 1% in children less than 7 yrs old, compared with a 14.5% failure rate in older children²⁴.

Duration of recovery to first analgesic time was found to be longer in Bupivacaine group (mean 9.65 hrs) than in Midazolam group (mean 7.32 hrs); however it is not statistically significant (P value 0.9). In different studies caudal block in children with 0.25% Bupivacaine has shown to provide 4 – 8 hours of post operative analgesia which is comparable to this study also^{9, 6, 14}. None of the patient in the Bupivacaine group experienced motor blockade unlike similar study by Naguib and colleagues where it was 26.7%.^{9,15}. Duration of recovery to first analgesic time in Midazolam group was 7.32 hrs (mean) which is longer than in the study carried out by Nishiyama and colleagues with the same dose of epidural Midazolam, where it was 2 hours. It could be due to the type of surgery as Nishiyama and colleagues studied in the patients undergoing upper abdominal surgeries¹².

Twenty four percentages of the patients in Bupivacaine group and 16% of the patients in Midazolam group did not require any additional analgesia in the first 24 hours after surgery. However this does not correlate with the study by the Naguib and colleagues where 46.7% of the patients in both the groups did not require additional analgesia for 24 hours¹⁵.

No other complications except vomiting (Bupivacaine group 8% vs. Midazolam group 12%) like respiratory depression, prolonged sedation, motor weakness, urinary retention were observed in either of the group. However in the similar retrospective study, Naguib and colleagues noted incidence of vomiting in Bupivacaine group as 13.3% and none in Midazolam group¹⁵. Yet in other study, incidence with postoperative vomiting after caudal Bupivacaine was 25%⁹.

In various other studies motor weakness with caudal Bupivacaine has been reported^{9, 25}. In a retrospective study carried by Naguib and colleagues⁹, 10% of the patients postoperatively developed motor weakness, whereas it was 54% in another study carried out by Dalens and Hasnaoui²⁵. In this study there was no

incidence of motor weakness in any patients in any of the groups.

This study has shown that caudal administration of Midazolam is equipotent to Bupivacaine for postoperative analgesia without any added side effects. Hence caudal Midazolam is safe and may be used as an effective alternative to Bupivacaine for postoperative analgesia via caudal route.

Conclusion

We conclude that the caudal administration of Midazolam in a dose of 50µg/kg provides equipotent analgesia to Bupivacaine 0.25%, when administered pre-emptively in a volume of 1 ml/kg to children undergoing unilateral inguinal herniotomy.

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