Section: Anaesthesia

Research

COMPARISON OF MIDAZOLAM AND BUPIVACAINE FOR CAUDAL BLOCK IN CHILDREN FOR POST OPERATIVE ANALGESIA

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Abstract

Background: Regional anaesthesia is used widely in children, mostly in conjunction with general anaesthesia to provide balanced anaesthesia and they significantly improve patient comfort in the post operative period. Caudal blocks are the most common regional technique for postoperative pain relief in children. We compared the analgesic efficacy of caudal administration of Bupivacaine vs Midazolam on 50 children (divided into 2 groups) aged 1 – 12 years in ASA I physical status scheduled to undergo elective infraumbilical surgeries. **Materials and Methods:** 50 children were divided into 2 groups randomly to receive a caudal injection of either 0.25% bupivacaine I ml/Kg or midazolam 50 micrograms/ kg with normal saline 1 ml/kg. **Result:** A standard General anaesthesia technique was used and caudal block was achieved at the end of the surgery. Group I received Midazolam 50 micrograms\kg, in a volume of 1ml\kg and Group II received Bupivacaine 0.25% 1ml\kg. Short acting opioid was used for intra operative analgesia. There was no difference in quality of pain relief, duration of analgesia and analgesic requirements in both the groups. Side effects, such as motor weakness, nausea and vomiting and urinary retention were not observed in Midazolam group. **:**It was concluded that caudal Midazolam 50 micrograms\kg provides equivalent analgesia to Bupivacaine 0.25% when administered postoperatively in a volume of 1 ml\kg for children following infraumbilical surgeries. Lesser side effects were observed in the Midazolam group.

INTRODUCTION

Neuraxial blocks have achieved wide acceptance as the standard for intra and post operative pain control in infants and children.[1] Because of the ease of its performance in children, the block has been recommended for a wide variety of surgical procedures, both as the sole anaesthetic and in combination with light general anaesthesia.

Bupivacaine is the most widely used long-acting local anaesthetic for caudal block in children but has been found to have its own side effects which include motor weakness, urinary retention, cardiovascular system and central nervous system toxicity.[2] The use of midazolam in appropriate doses as an alternative has been found to be effective in providing post operative analgesia and is at the same time devoid of the aforementioned side effects.[2] Several lines of evidence suggest that the respective processing may be modulated at the level of spinal cord by a variety of local receptor systems including those of opioids, adrenergic and benzodiazepines agonists.

Several investigators have reported that intrathecally or epidurally administered Midazolam in optimal doses,[3] provides 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.[4,5]Midazolam has been used in epidural space and as a spinal anaesthetic in humans and has been shown to have no neurological side effects.[6,7]

This study intends to compare the analgesic efficacy of caudal administration of Midazolam with that of Bupivacaine in prevention of pain after infraumbilical surgeries in children.

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MATERIALS AND METHODS

Study was carried out by performing caudal blocks in 50 children (divided into two groups) between Jan 2000 and Feb 2002 in boys and girls between 2 – 12 years of age in ASA I physical status scheduled for elective infra umbilical surgery. Children with history of allergic reaction to local anaesthetics, bleeding diathesis, aspirin ingestion in preceding one week, pre-existing neurological or spinal disease, presence of septic focus on the skin over caudal region and any bony abnormalities of sacrum were excluded from the study.

General anaesthesia was administered to all children as per existing institutional practice. Routine premedication was given for all the children. No analgesics were given in premedication. Induction was achieved with thiopentone i.v / inhalational induction with O2, N2O and Sevoflurane. Injection vecuronium was used for intubation and maintenance of muscle relaxation intra operatively. O2, N2O and Sevoflurane were used for maintenance of anaesthesia. A short acting opioid (Inj fentanyl) was used for maintenance of adequate intra operative analgesia. Caudal block was achieved with patient in left lateral position using 22/23G hypodermic needle under strict aseptic precautions at the end of the surgery and before extubation. Midazolam hydrochloride 50 μg/kg in 0.9% saline at 1 ml/kg was administered in Group I and 0.25% Bupivacaine Hydrochloride at 1 ml/kg was administered in Group II patients.

All the children were reversed with Inj neostigmine and Inj glycopyrrolate. Intra operatively Systolic B.P., SpO2, Heart rate, ECG, EtCO2 were monitored.

Post Operative Assessment of pain was done for 24 hours and pain scoring was done with reference to a six-point scale (a modification of pain / discomfort scale).[2][Table1]

Table 1: Post Operative Pain Scoring

OBSERVATION CRITERIA		POINTS
Crying	Not crying	1
	Crying but responds to tender loving care	2
	Crying and does not respond to tender loving care	3
Posture	No special posture	1
	Flexing legs and thighs	2
	Holding groin	3

None / insignificant pain2 Points
Moderate pain3 – 4 Points
Severe pain5 – 6 Points

1. Demeanour was scored with reference to a three-point scale (cheerful and calm, restless or tense and tearful).
2. Time at which analgesia was at first required (TNA – Time to next analgesia Syp/Tab Ibuprofen 5 – 8 mg/kg).
3. Total number of analgesic doses required in first 24 hours.
4. The patient's ability to stand unaided 6 hours post – operatively.
5. Further assessment at 24 hours post operatively was made as to the child's behaviour at bedtime on the day of operation and on the following morning with respect to analgesia (acceptable / not acceptable) and the quality of overnight sleep (good / interrupted)
6. Side effects / other observations if any.

The results of the above study were analyzed statistically.

RESULTS

The patients for this study were in the age group 2-10 years. The patients in both the groups were comparable in age and weight. The mean age was 76.5 months in midazolam group and 70.75 months in bupivacaine group. The mean weight was 16.41 Kgs in midazolam group and 15.75 Kgs in bupivacaine group. The majority of patients in both the groups were males. [Table 2]

Table 2: Age and Weight Distribution

	MIDAZOLAM GROUP(n=24)	BUPIVACAINE GROUP (n=24)
AGE (MONTHS)	24 -136 (76.5)	24 -134 (70.75)
WEIGHT (KGS)	12 – 20 (16.41)	10 -20 (15.75)

The analgesic requirements in both the groups were similar. 12 patients in midazolam group and 11 patients in bupivacaine group did not require any supplemental analgesics in first 24 hours. 6 patients in both the groups received 1 and 2 supplemental doses each of analgesics in first 24 hours. Only 1 patient in bupivacaine group received 3 supplemental doses of analgesics in the first 24 hours. [Table 3]

Table 3: Requirement of supplemental analgesia

NO. OF ANALGESIC DOSES	MIDAZOLAM GROUP (n=24)	BUPIVACAINE GROUP (n=24)
0	12 (50%)	11 (45.83%)
1	6 (25%)	6 (25%)
2	6 (25%)	6 (25%)
3	0 (0%)	1 (4.17%)
Total	24(100%)	24 (100%)

$\chi^2 = 0.12$, df =2, $p>0.05$ (not significant)

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By the end of 4hrs 4 children in bupivacaine group had moderate to severe pain and were given supplemental analgesics. By the end of 8hrs 6 children in both the groups required supplemental analgesia. At 24 hrs post operatively 12 children in midazolam group and 13 children in bupivacaine group had received supplemental analgesics (table 4). Time to next analgesia was plotted as survival curves. The area under the curves depicts the proportion of patients not requiring analgesia.

Table 4: no of children requiring analgesics

Time(post operative)	Midazolam group(n=24)	bupivacaine group (n=24)
0 - 4 Hours	0 (0%)	4 (16.66%)
5 - 8 Hours	6 (25%)	2 (8.33%)
9 -12 Hours	6 (25%)	7 (29.16%)
At 24 Hours	12 (50%)	13 (54.16%)

$\chi^2 = 0.04$, df =2, p>0.05 (not significant)

Table 5: Complications

	MIDAZOLAM GROUP	BUPIVACAINE GROUP
NAUSEA AND VOMITING	2 (8.33%)	8 (33.33%)
URINARY RETENTION	0 (0%)	4 (16.66%)
PROLONGED SEDATION	0 (0%)	0 (0%)
RESPIRATORY DEPRESSION	0 (0%)	0 (0%)
CVS CHANGES	0 (0%)	0 (0%)
CONVULSIONS	0 (0%)	0 (0%)

In general, the quality of analgesia in the group who received caudal injection of midazolam did not differ from caudal bupivacaine group. All the children in the midazolam group were pain free in the immediate postoperative period as compared to 20 children in the bupivacaine group. At the end of 8 hours 22 children in midazolam group and 24 patients had none or insignificant pain. 4 children in bupivacaine group had moderate pain in first 4 hours post operatively. At the end of 8 hours 2 children in both the groups had moderate pain. None of the children in either group experienced severe pain till 24 hours postoperatively.

Administration of midazolam or bupivacaine caudally was not associated with changes in post operative behaviour. More children in the midazolam group were cheerful and calm in the immediate postoperative period (24 Vs 14 patients). 22 children in bupivacaine group and 20 children in midazolam group were cheerful and calm and the end of 8 hours. 6 children in bupivacaine group were tense or restless in the immediate post operative period compared to none in the midazolam group. At the end of 4 hours none of children in either groups were tense/restless..4 patients in bupivacaine group were tearful in the immediate postoperative period and 2 patients 8 hours postoperatively. In the caudal midazolam group 2 children were tearful 8 hours postoperatively.

The patient's ability to stand unaided was checked 6 hours post operatively. All the patients in the midazolam group could stand unaided 6 hours post operatively whereas 6(25%) patients in bupivacaine group were unable to stand unaided 6 hours post operatively. No patient in midazolam group had any motor weakness postoperatively.

The results from mothers' and nurses' assessment 24 hours postoperatively showed no differences among the two groups with respect to pain, overnight sleep and acceptability.

In this study we could not perform caudal block in two patients (one in each group), thereby having a failure rate of 4%. The reason for failure was mainly, chubby children in whom landmarks were not very well appreciated. These two cases were not included in the study.

8 patients in bupivacaine group had nausea and vomiting compared to 2 patients in midazolam group. 4 patients in the bupivacaine group had urinary retention and two patients had to be catheterized. There were no cases of prolonged sedation in either group. There were no cases of respiratory depression (Breath rate less than 12 bpm), CVS collapse or convulsions. [Table 5]

DISCUSSION

Adequate pain relief is an extremely important aspect of post operative care. This is important not only for the psychological wellbeing of the patient, but also decreases the stress response to surgery and favours a better outcome. Conventionally this has been achieved by the use of narcotic analgesics which are not without hazards particularly in children. The fears associated with their use have resulted in under treatment of pain. Bupivacaine is the most widely used long-acting local anaesthetic for caudal block in children but has been found to have its own side effects which include motor weakness, urinary retention, cardiovascular system and central nervous system toxicity.[2]

The present study was undertaken to clinically evaluate the use of caudal epidural midazolam as an alternative analgesic to caudal epidural bupivacaine for post-operative analgesia and to compare the efficacy of caudal epidural midazolam with that of caudal epidural bupivacaine for relief of post-operative pain in children undergoing infra-umbilical surgeries.

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In this study fifty caudal blocks were performed using midazolam and bupivacaine. The two groups were well matched for age, sex and weight. The assessment of pain was done for 24 hours with pain scoring, time to next analgesia, total number of analgesic doses required in first 24 hours, demeanor, the patient's ability to stand unaided 6 hours post operatively was noted. We closely observed for the occurrence of complications to establish its safety.

All our cases were operated under general anaesthesia. Use of analgesics was avoided in premedication to avoid confusion in evaluation of pain relief. However adequate intra operative analgesia was maintained using short acting intravenous fentanyl and adequate depth of anaesthesia was maintained using inhalational agents.

In this study, caudal blocks were performed at the end of surgery. Based on animal studies it has been suggested that pre-emptive administration of regional administration of regional anaesthesia to patients might reduce postoperative pain to greater extent than postoperative administration. 8 However, several studies have failed to demonstrate any advantages of pre-emptive analgesia. In fact, Holthusen et al. failed to demonstrate any advantages in performing caudal blocks before, compared with after, surgery in children.[9]

The result of the present study confirm and extend previous reports that epidural administration of midazolam exerts modulatory influences on postoperative pain mechanisms. In this study, caudal administration of midazolam 50µg kg¯1 in children produced postoperative analgesia comparable with that associated with caudal injection of 0.25% bupivacaine, 1ml kg¯1. In this study, 50% of patients in the caudal midazolam group required additional analgesia during the first 24 hrs after surgery [Table 4]. These results are similar to those of a previous report on herniotomy, 2 in which 50 – 55% of patients who had caudal block with 0.25% bupivacaine 1ml kg¯1 group required further analgesia. The amount of postoperative analgesics required by the children in bupivacaine and midazolam group were comparable [Table 4]. In addition, the recovery to first analgesic times were similar in both the groups [Figure 1].

Several families of spinal receptors are known to modulate the processing of nociceptive stimuli. Among these are the GABA receptors.[10,11] The benzodiazepine receptor seems to be coupled to both the GABA receptor and the chloride channel complex. The antinociceptive effects of intrathecal benzodiazepine are antagonized by the specific benzodiazepine antagonist (RO15-1788; flumazenil) but not by naloxone.[10] In the dorsal horn of spinal cord, GABA produces a mild depolarization of the primary afferent and thereby can reduce the release of the excitatory transmitter onto second order neurons in the spinal cord and brain stem.[4] Beside the effect of midazolam on the benzodiazepine-GABA ionophore complex; pharmacological properties, other than modulation of the function of GABAA receptor have also been described. These properties provide possible ways of modifying the processing of spinal pain without an interaction with GABA receptor. First midazolam has been shown to inhibit the reuptake of GABA from synaptosomes from brain.[12] Secondly, Hunkeler et al,[13] noted that the binding of the benzodiazepine agonists to the benzodiazepine receptor is enhanced by GABA itself. Thirdly, benzodiazepine receptor agonists in cultured neurons of the spinal cord depolarize the cell and elevate the absolute threshold for the generation of action potentials.[14]

In humans, Midazolam, administered intrathecally before abdominal or leg surgery, partially blocked pain evoked by somatic but not by visceral stimuli.[15] Extradural administration of midazolam to postoperative adult patients. 7 and individuals with chronic pain resulted in significant analgesia. 15 Nishiyama et al,[16] evaluated four doses (3,50,75 and 100 µg kg¯1) of epidural midazolam mixed with saline in patients undergoing upper abdominal surgery. They concluded that midazolam 50µg kg¯1 was the optimal dose for postoperative analgesia. Higher doses were associated with prolonged and deep sleep (patients were not responding to verbal command).

The overall incidence of side effects observed in the bupivacaine groups were more compared to midazolam group. Prolonged sedation was noted following extradural administration of midazolam 75 - 100µg kg¯1. 7,14 This large dose of midazolam have resulted in rostral migration of significant quantities of drug into supraspinal areas. In contrast, in present study, we did not observe any prolonged somnolence or sedation following caudal administration midazolam 50µg kg¯1. Infact, the administration of midazolam caudally was not associated with changes of postoperative behaviour[Figure 4,5,6]. In accordance with other reports.[2]We noted that caudal midazolam was not associated with respiratory depression or motor block and rapid mobilization was possible in that group.

Animal studies demonstrated a lack of deleterious effect on spinal functions or morphologic features after subarachnoid midazolam.[16,17] No sign of toxicity of midazolam on the spinal cord or meninges were found in the rat after constant subarachnoid administration of midazolam (50 µg per day) for 15 days. 1 (21). Similar observations were noted in rabbits (0.3 ml of 0.1%; equivalent to 111 µg kg ¯1) were changes in blood-brain barrier observed.[18] It is well known that even higher concentration of lidocaine are believed to possess neurotoxic effects in humans.[19,20] The safety of neuraxial administration of midazolam in to humans has been demonstrated by several investors.[6,7,15]

The result of above study show that postoperative analgesia, time to next analgesia and requirement of additional analgesia was comparable in both the groups. Postoperative behaviour was also

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comparable in both the groups however children in caudal midazolam group were more cheerful in the immediate postoperative period. There were no incidences of motor weakness and urinary retention in midazolam group and the children could be ambulated earlier than the bupivacaine group. There were lesser incidence of postoperative nausea and vomiting in caudal midazolam group. Our failure rate was 4% and there were no incidence of prolonged sedation, respiratory depression or CVS complications.

CONCLUSION

It is concluded that caudal administration of midazolam in a dose of 50µg/kg provides equivalent analgesia to bupivacine 0.25% administered postoperatively in a volume of 1 ml/kg in children undergoing infra umbilical surgeries with lesser side effects. However this was a small study and a larger study would be required to definitely determine the efficacy and safety of this drug.

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