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Comparison of Midazolam with Lidocaine and Fentanyl for Caudal Analgesia in Children

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To compare postoperative analgesia provided by caudal administration of midazolam and mixture of lidocaine and fentanyl in children, in a randomized, double-blind study, forty children, undergoing hypospadia repair were allocated randomly into two groups (n = 20 in each) to receive a caudal injection of either lidoacaine 4 mg kg^{-1} added with fentanyl 1 μg kg^{-1} and epinephrine 1/200000 or midazolam 50 μg kg^{-1}, each solution diluted with normal saline for reaching a volume of 1 mL kg^{-1}. There were no differences in quality of pain relief, postoperative behaviour or analgesic requirements between the midazolam group and the lidoacaine group. Times to first analgesic administration (paracetamol suppositories) were similar in two groups. Caudal midazolam in a dose of 50 μg kg^{-1} and in a volume of 1 mL kg^{-1} provides equivalent analgesia to 4 mg kg^{-1} lidoacaine added to fentanyl and epinephrine, when administered postoperatively for children following hypospadia repair.

Key words: Caudal block, caudal lidoacaine, caudal midazolam, postoperative analgesia, caudal fentanyl

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INTRODUCTION

Caudal epidural analgesia is one of the most popular and commonly performed regional blocks in pediatric anesthesia. It is a reliable and safe technique that can be used with general anesthesia for intra-and postoperative analgesia in patients undergoing abdominal and lower-limb surgery (Beer and Thomas, 2003). The main disadvantage of caudal anesthesia is the short duration of action after a single injection of local anesthetic solution (Luz *et al*., 2000). Because of the side effects of local anesthetics (especially bupivacaine) which include motor weakness, urinary retention and cardiovascular and central nervous system toxicity, (Maxwell *et al*., 1994) so caudal injection of midazolam have been chosen as an alternative analgesic to local anesthetics for children.

In order to minimize side effects of local anesthetics and to maximize analgesia of caudal epidurals, many Pharmaceuticals have been administered into the epidural space. Several lines of evidence suggest that the nociceptive processing may be modulated at the level of the spinal cord by a variety of local receptor systems, including those of opioid, adrenergic and benzodiazepine agonists (Kumar *et al*., 2005). Caudal administration of some opioids some morphine produces a prolonged postoperative analgesia, but is associated with major side effects, in particular the potential of delayed respiratory depression (Krane, 1988). Clonidine, an alpha2 adrenergic agonist, administered in epidural space has been shown to potentiate postoperative analgesia in adults (Nishina and Mikawa, 2002) and this finding was led to its evaluation in pediatric caudal epidural block. The resulting studies have consistently shown caudal clonidine to increase the duration of postoperative analgesia (Cook, 1995). Although the addition of clonidine to bupivacaine improved the efficacy of caudal analgesia, it was associated with prolonged sedation in children (Lee and Rubin, 1994) and there is also a risk of hypotension in patients. In adult studies, epidural clonidine has been associated with a reduction in heart rate and arterial pressure (Bonnet *et al*., 1989).

Epidural midazolam seems to be a good choice because of the absence of these side effects. The principal mechanism by which epidural midazolam provides analgesia is through the GABA-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 (Kasparov *et al*., 2001; Kim and Lee, 2001).

At all levels, the highest density of binding sites was found within lamina II of the dorsal horn, (Doble and Martin, 1992) 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 (gamma-aminobutyric acid receptor complex (Unnerstall *et al*., 1981; Nistri and Berti, 1984). Several investigators have reported that intrathecally or epidurally administered midazolam produces a dose-dependent modulation of spinal nociceptive processing (Niv *et al*., 1983; Serrao *et al*., 1991). Midazolam has been used in the epidural space and as a spinal anaesthetic in humans, (Yanez *et al*., 1990) and has been shown to have no neurological effects (Auroy *et al*., 1988). Dose-dependent analgesia without respiratory depression following the intrathecal or epidural administration of midazolam has been demonstrated in both animal and adult human studies (Schoeffler *et al*., 1991).

The antinociceptive effects are antagonized by flumazenil and possibly also by naloxone, thereby implying that the mechanism of analgesia may involve activation of opioid receptors (Mahajan *et al*., 2001).

The intrathecal or epidural administration of midazolam in animal studies has not been associated with any adverse neurological effects. Even after a constant subarachnoid infusion of midazolam 50 μg day^{-1} for 15 days, no signs of spinal cord or meningeal toxicity were found in the rat (Schoeffler *et al*., 1991). Only after administration of very large doses of midazolam 0.1% (0.3 mL) intracisternally in rabbits (equivalent to 111 μg kg^{-1}) were changes in the blood-brain barrier observed (Malinovsky *et al*., 1991).

Clinical studies in adults have shown that epidural midazolam provides significant postoperative analgesia. A dose of 50 μg kg^{-1} appears to be optimum in patients undergoing upper abdominal surgery, higher doses (75-100 μg kg^{-1}) being associated with prolonged sedation (Nishiyama *et al*., 1992). The administration of caudal midazolam alone was not associated with prolonged sedation, respiratory depression or motor block. Despite the results of these studies, the caudal administration of midazolam remains controversial (Beer and Thomas, 2003).

In a study Baris *et al*. (2003) reported that caudal block with 0.75 mL kg^{-1} 0.25% bupivacaine and 50 μg kg^{-1} midazolam or 1 μg kg^{-1} fentanyl provides no further analgesic advantages to bupivacaine alone when administered immediately after induction of anaesthesia in children undergoing unilateral inguinal herniorrhaphy.

Kumar *et al*. (2005) also have compared a mixture of bupivacaine-midazolam with bupivacaine alone.

The aim of this double-blind, randomized study was to compare the adverse effects and duration of postoperative analgesia provided by midazolam alone administered to caudal space in children with lidocaine.

We have not choose bupivacaine for caudal analgesia because there is a possibility of cardiac toxicity with its use (Maxwell *et al*., 1994). We have added fentanyl and adrenaline to lidocaine for prolongation of analgesia after hypospadia repair in children.

MATERIALS AND METHODS

The present prospectively designed study was approved by the ethics and clinical studies committee of Zahedan University of medical sciences and informed and signed consent was obtained from the parents of all the patients who were enrolled in the study.

We enrolled forty healthy boys aged 4-8 years, classified as ASA I scheduled for hypospadia repair. Patients who had contraindications to caudal anesthesia or have an anomaly in sacral anatomy were excluded. Participants were randomly allocated equally to two groups. All patients were fasted 6 h before surgery. No premedication was used. Pulse oximetry, ETCO2, non invasive blood pressure and EKG monitoring were used for all patients. Anesthesia was induced with atropine 0.01 mg kg^{-1}, Thiopentone 5 mg kg^{-1}, fentanyl 2 μg kg^{-1}, atracurim 0.5 mg kg^{-1} and meperidine 1 mg kg^{-1} for prevention of shivering. In all patients anesthesia was maintained with controlled ventilation and inhalation of mixture of O_2 50%, N_2O 50% and halothane 1% delivered by a Mapelson D system. Intravenous fentanyl 1 μg kg^{-1} was repeated after 20 min. At the end of surgery, using a 22G needle, the prepared solution was injected to caudal extradural space. The solution consisted of lidocaine 4 mg kg^{-1} added with fentanyl 1 μg kg^{-1} and epinephrine 1/200000 in lidocaine group and midazolam 50 μg kg^{-1} in midazolam group, both solution were diluted with 0.9% saline for reaching a volume of 1 mL kg^{-1}.

All patients were observed for 2 h in the recovery room. When the child was awake in the recovery room, objective pain assessments, respiratory rate, blood pressure and heart rate were recorded by a nurse investigator unaware of patients grouping. Assessment were made at 15 min intervals for the first hour, 30 min intervals for the second hour and intervals of 1 h until 12 h after caudal injection. The observer scored pain on each visit with reference to six-points scale: 1-2: none-insignificant pain; 3-4: Moderate pain; 5-6: Severe pain.

Acetaminophen suppository was administrated for pain score = 3 and the time of first analgesic requirement was recorded.

Motor block was assessed 30 min after awaking of the patients using a modified Bromage scale (0: no paralysis; 1: Unable to raise extended leg; 2: Unable to flex knee; 3: Unable to flex ankle).

Sedation was scored and recorded with reference between 1(calm), 2(easily calmed), 3 (calm-moderately agitated) and 4 (combative), in the recovery room.

Statistical test were performed using SPSS 11 for Windows. Results are reported as absolute value, mean±SD. Continuous variables were analyzed using Student's t-test. Nominal or ordinal variables were analyzed by Chi square test and Fisher exact test or Mann-Whitney U test. $p<0.05$ was considered statistically significant.

RESULTS

The groups were comparable in age and weight and duration of surgery (Table 1).

All patients were judged to have successful postoperative analgesia and mean hourly pain scores in two groups in the recovery room and in the ward were similar (Table 2).

No patient in the recovery room required analgesia. The time of first requiring of additional analgesia did not differ significantly between two groups (4.05 vs 4.12 h) as reported in Table 2.

There were no significantly differences between two groups in mean hourly sedation scores (Table 2).

Nausea and vomiting are not seen in any patients. In general, the quality of postoperative analgesia in both group were similar. There was no difference between the caudal midazolam group and the group in the number of analgesic doses required in the first 12 h.

We found that administration of midazolam caudally alone was not associated with changes in postoperative behavior.

No patient in any group had any sign of motor weakness. No child had a recorded respiratory rate of less than 12 bpm, the episodes of oxygen desaturation or

Table 1: Patients demographic data: midazolam (M) group and lidocaine (L) group

Variables	M group	L group
Age (year)	5.3	5.00
Weight (kg)	15.6	15.57
Surgery duration (min)	45.5	50.00

Table 2: Characteristics of caudal analgesia in midazolam (M) group and lidocaine (L) group

Variables	M group	L group
Analgesic duration (h)	4.05	4.12
VAS at 1 h	1.35	1.50
VAS at 2 h	2.11	2.25
VAS at 3 h	2.40	2.90
Sedation score at 1 h	1.70	2.00
Sedation score at 3 h	2.80	3.20

showed any changes in heart rate and blood pressure in the first 12 h postoperatively. There were no instances of prolonged sedation, hypotension, bradycardia, residual paralysis, or toxic reactions to lidocaine or midazolam during or after administration of caudal blocks.

DISCUSSION

The results of the present study confirm the previous reports that epidural administration of midazolam exerts modulatory influences on postoperative pain mechanisms. In this study, caudal administration of midazolam 50 μg kg^{-1} in children produced postoperative analgesia comparable with that associated with caudal injection of lidocaine 4 mL kg^{-1} added to fentanyl 1 μg kg^{-1} and epinephrine 1/200000.

These results are similar to those of a previous report on herniotomy (Kumar *et al*., 2005; Ivani *et al*., 2000. Mahajan *et al*., 2001) in which the addition of midazolam 50 μg kg^{-1} to 0.25% bupivacaine 1 mL kg^{-1} improved caudal analgesia compared with that provided by bupivacaine alone, without an increase in the incidence of side effects.

Clinical studies in adults have shown that epidural midazolam provides significant postoperative analgesia. A dose of 50 μg kg^{-1} appears to be optimum in patients undergoing upper abdominal surgery, higher doses (75-100 μg kg^{-1}) being associated with prolonged sedation (Nishiyama *et al*., 1992).

In children undergoing inguinal or urogenital surgery, bupivacaine 0.125% (0.75 mL kg^{-1}) combined with midazolam 50 μg kg^{-1} produced a mean duration of analgesia of 21.1 (SD1.2) h compared with 14.5 (1.6) h for bupivacaine 0.125% (0.75 mL kg^{-1}) combined with morphine 50 μg kg^{-1} ($p<0.01$) and 8.1 (1.3) h for plain bupivacaine (Güleç *et al*., 1998). Although sedation scores were higher in the bupivacaine/midazolam and bupivacaine/morphine groups than in the bupivacaine group at 8-12 h after surgery ($p<0.01$), there were no other significant side-effects. In another study, Naguib *et al*. (1995) showed that caudal administration of midazolam 50 μg kg^{-1} produced equivalent analgesia to bupivacaine 0.25% (1 mL kg^{-1}) in children undergoing unilateral inguinal herniotomy. However, the combination of caudal midazolam 50 μg kg^{-1} and bupivacaine 0.25% (1 mL kg^{-1}) significantly increased the duration of analgesia compared with that achieved with either midazolam or bupivacaine alone ($p<0.001$). Furthermore, only 13.3% of patients in the bupivacaine/midazolam group required analgesia during the first 24 h after surgery, compared with 53.3% of those in the bupivacaine or midazolam groups ($p<0.05$).

If caudal opioids are used either alone or in combination with a local anaesthetic, the patient should be monitored after surgery in a high-dependency setting to avoid the major side effects the opioids: The respiratory depression, resulting from rostral spread of opioid to the brainstem with subsequent depression of the medullary respiratory centers.

But no episodes of delayed respiratory depression have been reported following the use of epidural fentanyl (Kawaraguchi *et al*., 2006) and the use of fentanyl 1 μ kg^{-1} seems to be safe.

Several mathematical formulae have been used to calculate the volume of local anaesthetic required for caudal blockade (Busoni and Andreucetti, 1986, Satoyoshi and Karnivama, 1984). These formulae are based on individual variables, including age, weight, length of the spinal column and number of spinal segments to be blocked. Since these formulae require cumbersome calculations that may be subject to error, none has achieved universal clinical acceptance. However, one such formula for effective sensory blockade is lidocaine 0.056 mL kg^{-1} for each segment (Takasaki *et al*., 1977). So the dose of 1 mL kg^{-1} is effective to achieve a sensory block at the level needed for ilio-inguinal surgery.

CONCLUSIONS

The administration of caudal midazolam alone was not associated with prolonged sedation, respiratory depression or motor block.

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