Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies ***NLM ID:*** *101716117*

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Index Copernicus value = 85.10

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Original Research

Comparison of Midazolam and Bupivacaine for Caudal Block in Children for Post- Operative Analgesia, a Randomized Double Blind Study

Col (Dr) Vishal Chaudhary[1], Lt Col (Dr) Anish Adya[2], Col (Dr) Ravi Singhal[3]

[1]Professor, Department of Anaesthesia, AICTS, Pune, India;
[2]Assistant Professor, Department of Anaesthesia, Command Hospital, Chandimandir, Panchkula, Pin – 134107, Haryana, India;
[3]Head, Department of Anaesthesia, Military Hospital Jammu, India

ABSTRACT:
Background: Caudal block is widely in children, mostly in conjunction with general anaesthesia and it significantly improves patient comfort in the post -operative period. Bupivacaine is the most widely used local anaesthetic for caudal block in children but has numerous side effects. Midazolam in appropriate doses has been found to be effective in providing post- operative analgesia and is devoid of side effects. We in our study compared the efficacy of Bupivacaine and Midazolam as analgesics and studied their side effects. **Methods:** This randomized, double blind study was conducted on 56 children scheduled for infra-umbilical surgery in a tertiary care hospital. All the patient were given general anaesthesia as per standard protocol and caudal block was administered postoperatively either using 0.25% bupivacaine 01ml/Kg or midazolam 50 μg Kg^{-1} in 0.9% saline 01 ml/Kg. Post-operative assessment of pain was done for 24 hours and pain scoring was done with reference to a six point modification of pain and discomfort scale. Demeanor was observed as cheerful and calm, restless and tense. Total number of analgesic doses required in first 24 hours were noted. Side effects like nausea, vomiting, urinary retention, respiratory depression, convulsions and any cardiovascular abnormality were looked for and noted. **Results:** The analgesic requirements in both the groups were similar. 13 patients in M group and 11 patients in B group did not require any supplemental analgesics in first 24 hours, 7 patients in both the groups received one supplemental dose of analgesics, 8 patients in M group and 9 in B group received two supplemental doses of analgesics. Only 1 patient in B group received 3 supplemental doses of analgesics. More children in the M group were cheerful and calm in the immediate postoperative period (26 Vs 22). 04 children in B group were tense or restless in the immediate post operative period compared to 02 in the M group. At the end of six hours 02 children in the B group and none of children in M group were tense/restless. 08 patients in B group had nausea and vomiting compared to 02 patients in M group. 04 patients in the B group had urinary retention and 02 patients had to be catheterized. **Conclusion:** Caudal midazolam provides equivalent analgesia to bupivacaine in children undergoing infra umbilical surgeries with lesser side effects.
Keywords: Caudal block, Midazolam, Bupivacaine

Received: 23/04/2020 **Modified:** 14/06/2020 **Accepted:** 16/06/2020

Corresponding Author: Lt Col (Dr) Anish Adya, Assistant Professor, Department of Anaesthesia, Command Hospital, Chandimandir, Panchkula, Pin – 134107, Haryana, India

This article may be cited as: Chaudhary V, Adya A, Singhal R. Comparison of Midazolam and Bupivacaine for Caudal Block in Children for Post- Operative Analgesia, a Randomized Double Blind Study. J Adv Med Dent Scie Res 2020;8(10):147-153.

INTRODUCTION

Regional anaesthesia and nerve blocks are 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. 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] There is evidence to suggest that the pain 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.[6,7,8]

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

MATERIALS & METHODS

Study was conducted in a tertiary care hospital after taking clearance from the institutional ethics committee. A total of 62 children were recruited in the study, 06 children had to be excluded from the study because of not fulfilling the inclusion criteria. Two of them had deranged coagulation profile, one child had sacral deformity, in one child the parental consent could not be obtained and in two children the caudal block could not be administered because the children were obese and the anatomical landmarks could not be felt (Figure 1). 56 eligible children of either sex scheduled for elective infra-umbilical surgery were randomly divided in to two groups. Informed written consent was taken from the parents of all the children who participated in the study. The children were between 2 – 12 years of age in ASA I physical status. 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. Randomization was done with sealed envelope method and the participants were divided in to group bupivacaine (group B) or group midazolam (Group M) to receive bupivacaine or midazolam caudally. The bupivacaine and midazolam preparations were made to appear identical. Medication administration and data collection was done in double blinded manner such that neither the patient nor the health care workers were aware of medication assignment

Standardized general anaesthesia technique was used for all the children. Routine institutional premedication was given to all the children which included inj Ketamine 4 mg/kg with 0.1 mg glycopyrrolate intramuscular in case of no IV access, or 2mg/Kg ketamine and same dose of glycopyrrolate if the child had IV access. Induction of anaesthesia was achieved with intravenous thiopentone or inhalational agents O_2, N_2O and Sevoflurane. Injection vecuronium was used for intubation and maintenance of muscle relaxation intra operatively. O_2, N_2O 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^{-1} in 0.9% saline at 1 mL Kg^{-1} was administered in Group M and 0.25% Bupivacaine Hydrochloride at 1 mL Kg^{-1} was administered in Group B patients. Neuromuscular blockade was reversed in all the children with Inj neostigmine and Inj glycopyrrolate. Intraoperatively noninvasive blood pressure, SpO2, Heart rate, electrocardiogram, end tidal carbon dioxide and depth of neuromuscular block 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 and discomfort scale) (Table1). Demeanor was observed as cheerful and calm, restless and tense. Total number of analgesic doses required in first 24 hours were noted. Observation was made of patient's ability to stand unaided 6 hours post-operatively.

Further assessment post operatively was made of the child's behavior 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). Side effects like nausea, vomiting, urinary retention, respiratory depression, convulsions and any cardiovascular abnormality were looked for and noted.

The results of the above study were analyzed statistically. Data was analysed by using SSPS vers II (Chicago) software. Data was represented as mean and SD and frequency percentages. Average between the two groups in continuous parameters was compared by using t test/ Mann Whitney test. P value less than 0.05 was taken as significant.

RESULTS

The patients for this study were in the age group 2-12 years. The patients in both the groups were comparable in age and weight (table 2). The mean age was 76.5 ±

18.8 months in midazolam (M) group and 74.75 ± 22.2 months in bupivacaine (B) group. The mean weight was 12.6 ± 3.6 Kg in M group and 13.2 ± 4.2 Kg in B group. The majority of patients in both the groups were males. The analgesic requirements in both the groups were similar. 13 patients in M group and 11 patients in B group did not require any supplemental analgesics in first 24 hours. 7 patients in both the groups received one supplemental dose of analgesics in first 24 hours. 8 patients in M group and 9 in B group received two supplemental doses of analgesics. Only 1 patient in B group received 3 supplemental doses of analgesics in the first 24 hours (table 3).

By the end of four hours 05 children in group B and 03 in group M had moderate to severe pain and were given supplemental analgesics. By the end of eight hrs seven children in both the groups required supplemental analgesia. fifteen children in M group and seventeen children in B group had received supplemental analgesics by the end of 24 hours (table 4).

In general, the quality of analgesia in the group who received caudal injection of midazolam did not differ from caudal bupivacaine group. More number of children in the M group were pain free in the immediate postoperative period as compared to children in B group (5 v/s 3). At the end of eight hours 18 children in group M and 16 children in group B had none or insignificant pain. At the end of eight hours 10 children in group M and 12 in group B had moderate pain. None of the children in either groups experienced severe pain till 24 hours postoperatively.

Administration of midazolam or bupivacaine caudally was not associated with changes in post-operative behavior. More children in the M group were cheerful and calm in the immediate postoperative period (26 Vs 22). 04 children in B group were tense or restless in the immediate post - operative period compared to 02 in the M group. At the end of six hours two children in the B group and none of children in M group were tense/restless (Table 5).

The patient's ability to stand unaided was checked six hours post operatively. 22 patients in M group could stand unaided six hours post operatively whereas 08 (28.5%) patients in B group were able to stand unaided 6 hours post operatively. No patient in M group had any motor weakness post- operatively. 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 3.5%. 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. Eight patients in B group had nausea and vomiting compared to two patients in M group. Four patients in the B group had urinary retention and two patients had to be catheterized. There were no cases of prolonged sedation in either groups. There were no cases of respiratory depression (Breath rate less than 12 bpm), CVS collapse or convulsions (Table 6).

Table 1 : Post Operative pain scoring

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

None / insignificant pain 2 Points
Moderate pain 3 – 4 Points
Severe pain 5 – 6 Points

TABLE 2: Age, Weight & Sex Distribution

	Group (M) (n=28)	Group (B) (n=28)	p Value
Age (Months) (Mean ± SD)	76.5 ± 18.8	74.75 ± 22.2	0.82
Weight (Kg) (Mean ± SD)	12.6 ± 3.6	13.2 ± 4.2	0.18
Males	25	27	
Females	03	01	

Table 3 : Requirement of Supplemental Analgesia

No. of Analgesic Doses	Group (M) (n=28)	Group (B) (n=28)
0	13 (46.4%)	11 (39.3%)
1	07 (25%)	07 (25%)
2	08 (28.5%)	09 (32.1%)
3	0 (0%)	01 (3.5%)
	28 (100%)	28 (100%)

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

Table 4 : Time Line and Number of Children Requiring Analgesia

Time (Post operative)	Group (M) (n=28)	Group (B) (n=28)
0 - 4 Hours	03 (10.7%)	05 (17.8%)
5 - 8 Hours	07 (25%)	07 (25%)
9 -12 Hours	08 (28.5%)	10 (35.7%)
12 – 24 Hours	15 (53.5%)	17 (60.7%)

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

TABLE 5 - Postoperative Behaviour

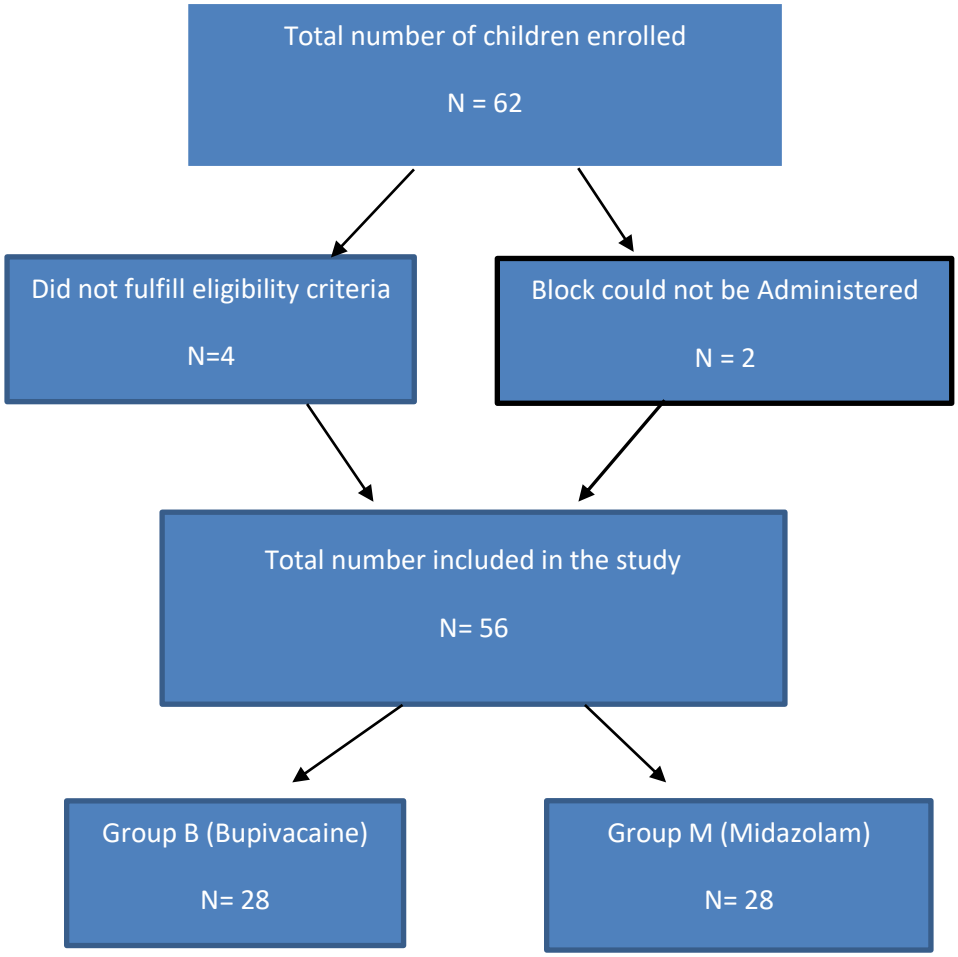
	Group (M) (n =28)	Group (B) (n = 28)	P Value
Cheerful and calm	26	22	0.2
Tense and Restless			
Immediate post op	02	04	0.9
6 hrs post op	00	02	0.1
Ability to stand unaided 6 hrs Post op	22	08	0.01*

Significant p Value * $p < 0.05$

TABLE 6 : Rate of Complications

	Group (M)	Group (B)
Nausea & Vomiting	2 (7.1%)	8 (28.5%)
Urinary retention	0 (0%)	4 (14.2%)
Prolonged Sedation	0 (0%)	0 (0%)
Respiratory Depression	0 (0%)	0 (0%)
CVS Changes	0 (0%)	0 (0%)
Convulsions	0 (0%)	0 (0%)

Fig A - Flow of patients



DISCUSSION

Adequate pain relief is an extremely important aspect of post operative care. This is important not only for the psychological well being of the patient, but also decreases the stress response to surgery and favours a better outcome and early recovery.

The use of narcotic analgesics is not without hazards particularly in children. The fear associated with their side effects has 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.

In our study sixty 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 , total number of analgesic doses required in first 24 hours, demeanour, the patient's ability to stand unaided 6 hours post operatively were noted. We closely observed for the occurrence of complications to establish its safety.

All our cases were operated under general anaesthesia. 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 anaesthesia might reduce postoperative pain to greater extent than postoperative administration.[10] However, several studies have failed to demonstrate any advantages of pre-emptive analgesia. Holthusen et al. failed to demonstrate any advantages in performing

caudal blocks before, compared with after, surgery in children.[11] The results 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 50 μg 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. These results are similar to those of a previous report by Naguib M, on caudal analgesia for herniotomy in which 50 – 55% of patients who had caudal block with 0.25% bupivacaine 1ml kg^{-1} required further analgesia.[2] The amount of postoperative analgesics required by the children in bupivacaine and midazolam group were comparable.

Several families of spinal receptors are known to modulate the processing of nociceptive stimuli, among these are the GABA receptors.[4,5] The benzodiazepine receptors seem to be coupled to both the GABA receptors 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.[4] In the dorsal horn of spinal cord, GABA produces a mild depolarization of the primary afferents and thereby can reduce the release of the excitatory transmitter onto second order neurons in the spinal cord and brain stem. Besides the effect of midazolam on the benzodiazepine-GABA ionophore complex; pharmacological properties other than modulation of the function of GABA receptor have also been described. These properties provide possible ways of modifying the processing of spinal pain without an interaction with GABA receptors. Midazolam has been shown to inhibit the reuptake of GABA from synaptosomes from brain. Hunkeler et al. noted that the binding of the benzodiazepine agonists to the benzodiazepine receptor is enhanced by GABA.[13] 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.[8] Extradural administration of midazolam to postoperative adult patients and individuals with chronic pain resulted in significant analgesia.[8,9] Nishiyama T et al. evaluated four doses (30,50,75 and 100 μg Kg^{-1}) of epidural midazolam mixed with saline in patients undergoing upper abdominal surgery. They concluded that midazolam 50 μg Kg^{-1} was the optimal dose for postoperative analgesia. Higher doses were associated with prolonged and deep sleep resulting in failure by the patients to respond to verbal command.[15]

In our study, 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 – 100 μg Kg^{-1} by Nishiyama T et al and Pullerits J et al.[7,12] These large doses of midazolam possibly resulted in rostral migration of significant quantities of drug into supraspinal areas. In contrast, in our study, we did not observe any prolonged somnolence or sedation following caudal administration of midazolam 50 μg Kg^{-1}, infact, the administration of midazolam caudally was not associated with changes in postoperative behaviour. In accordance with other reports including one by Naguib M [2] caudal midazolam in our study was not associated with respiratory depression or motor block and rapid mobilization was possible in children in group M.

Animal studies demonstrated a lack of deleterious effect on spinal functions or morphologic features after subarachnoid midazolam.[16,17] No signs of toxicity of midazolam on the spinal cord or meninges were found in the rats after constant subarachnoid administration of midazolam (50 μg per day) for 15 days. The safety of neuraxial administration of midazolam in humans has been demonstrated by several investigators.[6,7,8]

The results of our study show that postoperative analgesia and requirement of additional analgesia were comparable in both the groups. Postoperative behaviour was also 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 incidences of postoperative nausea and vomiting in caudal midazolam group. Our failure rate was 3% and there were no incidence of prolonged sedation, respiratory depression or CVS complications.

CONCLUSION

From this study it is concluded that caudal administration of midazolam in a dose of 50 μg Kg^{-1} provides equivalent analgesia to bupivacaine 0.25% administered postoperatively in a volume of 1 $mLKg^{-1}$ 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.

REFERENCES

1. TCK Brown. Local and Regional Anesthesia in children BJA 1999; 83(1): 65 – 77.
2. Naguib M, Midazolam for caudal analgesia in children : Comparison with caudal bupivacaine, CJA 1995 Sep; 42 (9) : 758 – 64.
3. Nishiyama T. Epidural midazolam with saline – optimal dose for post- operative pain Masui 1992 ; 41 : 49 – 54.

4. Niv D, Whitwam JG, Loh L. Depression of Nociceptive Sympathetic Reflexes by the intrathecal administration of midazolam. BJA 1983; 55;541 – 7.
5. Serrao JM, Stubbs SC, Goodchild CS, Gent JP. Intrathecal Midazolam and fentanyl in the rats; evidence for different spinal antinociceptive effects. Anesthesiology 1989; 70; 780 – 6. 6
6. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man – a pilot study BJCP 1987; 23: 279 – 85.
7. Nishiyama T. Odaka Y, Hirasaki A, Seto K. Epidural Midazolam for treatment of postoperative pain. Masui 1991; 40: 1353 – 58.
8. Serrao JM, Goodlchild CS. Intrathecal Midazolam for the treatment of chronic mechanical low back pain: A controlled comparison with epidural steroid in a pilot study. Pain 1992; 48: 5 – 12.
9. Nishiyama T, Epidural administration of midazolam with saline or bupivacaine for postoperative pain, Masui 1991; 40**:** 1523 – 30.
10. Woolf CJ. Recent advances in pathophysiology of acute pain, Br J of Anaesth 1989; 62:139-46.
11. Holthusen H, Eichwede F, Stevens M, Willnow U, Lipfert P. Preemptive analgesia: comparison of preoperative with postoperative caudal block on postoperative pain in children. Br J of Anaesth 1994; 73: 440-42.
12. Pullerits J, Holzman RS. Paediatric neuraxial blockade. J of Clin Anaes *1993*; 5: 342 -54.
13. Hunkeler W, Mohler H, Pieri L, et al. Selective antagonists of benzodiazepines, Nature 1981; 290: 514-16.
14. Haefely W, Polc P. Physiology of GABA enhancement by benzodiazepines and barbiturates. In: Olsen RW, Venter JC (Eds.). Benzodiazepines/GABA Receptors and Chloride Channels: Structural and Functional properties. New York: Liss, 1986: 97-133.
15. Nishiyama T, Hirasaki A, Odaka Y, Mikane T, Kobayashi O, Seto K. Epidural midazolam with bupivacaine--optimal dose for postoperative pain relief; Masui 1992 Jul;41(7):1113-18.
16. Schoeffler P et al.Subarachnoid midazolam histologic study in rats and report of its effects on chronic pain in humans. Reg anesth 1991;16: 329-32.
17. Malinovskyjm, Cozian A, Lepage J-y, Mussini J-M Pinaud M, Sourano R. Ketamine and midazolam neurotixicity in the rabbit. Anaesthesiology 1991; 75:91 – 97.

Source of support: The study was carried out in a government institute and no grant or financial support was taken from any agencies.

Conflict of interest: none declared