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Research Article

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Efficacy of Adding Midazolam to Bupivacaine (0.5%) on the Duration of Spinal Anesthesia in Unilateral Inguinal Hernia Surgery

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ABSTRACT

Introduction: Inguinal hernia is the most common type of abdominal hernia which is 7 times more common in men than women. Surgical treatment is performed under general or local anesthesia (spinal or epidural). Neuraxial anesthesia has a greater advantage than general anesthesia. Today, spinal block anesthetics with local drug anesthetics along with adjuvant drugs is widely used for surgery. Midazolam is one of these adjuvants whose spinal injection, in addition to its appropriate analgesic effect, enhances the effect of local anesthetics.

Aim: The aim of this study was to determine the effect of intrathecal midazolam (1 mg) to bupivacaine (0.5%) on the quality and timing of sensory block, motor block and hemodynamic changes during of inguinal herniation surgery.

Materials and Methods: 64 patients with ASAI / II criteria (30-70 years old) were randomly divided into two groups of 32 patients under spinal anesthesia for inguinal herniation surgery. The anesthesiologist and the patient did not know the status of the studied drugs. Group 1 received 0.5 ml of bupivacaine 0.5% + 0.2 ml of normal saline and group 2 received 3 ml of bupivacaine 0.5% + 0.2 ml of midazolam (1 mg). The return time of sensory block and the return time of motor block, the time of the first request for analgesics, the degree of satisfaction and the hemodynamic status were compared between these group.

Results: The return time of sensory block in group 1 was 124.81 ± 16.15 minutes and in group 2 was 193.18± 34.53 minutes, which was statistically significant and in group 2 the return time of sensory block was longer (001 ≤. <P). reaction block return time: in group 2: (140.43 ± 27.46) minutes, group: 1 (107.78 ± 13.82) minutes were shorter and statistically significant (P≤ .001). The time of the first analgesic request by patients in group 1 was 157.87 ± 16.32 minutes and in group 2, 264.59 ± 50.17 minutes, which was statistically significant (P ≤ .001). Satisfaction index and hemodynamic changes were not significant between groups (P > 0.05).

Conclusion: Addition of 1 mg of midazolam in spinal anesthesia with bupivacaine 0.5% increased of the duration of analgesia and the time of first request for analgesia without changing the hemodynamic status in patients with inguinal herniation surgery.

Keywords: Inguinal Herniation, Midazolam, Bupivacaine and Spinal Anesthesia

Introduction

An inguinal hernia is a protrusion of the contents of the abdomen in the area of the inguinal canal. The main cause of abdominal hernias is a decrease or weakness in the abdominal wall or increased pressure on it in one area. Inguinal hernia is the most common type of abdominal hernia, which is 7 times more common in men than women. Inguinal hernia repair is one of the most common surgeries performed by general surgeons and its repair can be performed under general, typical (spinal) anesthesia or local anesthesia [1]. It is clear that surgeries are not painless and vary in severity and duration of pain depending on the extent of the injury and the area of surgery. Therefore, choosing the right method of anesthesia and pain relief is a characteristic and basic need for any anesthesia technique. Pain management can functionally reduce physiological and psychological mortality, as well as improve hospitalization time and postoperative quality of life [2]. As we know, pain is a very unpleasant feeling and in addition it causes a number of unpleasant side effects such as the release of inflammatory mediators and overactive sympathetic system and its consequences, restlessness and disruption of

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daily and vital activities [3]. Weakening the stress response and reducing pain may facilitate the patient's postoperative recovery. Increased coagulation, which results in deep vein thrombosis, venous occlusion, and myocardial ischemia, which are associated with stress responses [4,5]. Stress-induced hyperglycemia delays wound healing and suppresses the immune system [6]. In addition, stimulation of the sympathetic system due to pain leads to increased oxygen consumption by the myocardium and also delays gastrointestinal motility after surgery and leads to ileus [4,5]. For perineal and lower limb surgeries, various methods of anesthesia are used. Today, the preferred method is the selected method according to the patient's conditions in surgeries such as uterine resection, prostate, bladder tumor, cesarean section, inguinal hernia, spinal anesthesia [7]. In spinal anesthesia, various drugs such as lidocaine, tetracaine and bupivacaine are widely used, but bupivacaine is very popular due to its long duration of action [8]. It is the first known local anesthetic to block pain without major effect on motor fibers. Bupivacaine is an amide local anesthetic with high protein band and slow metabolism and has a duration of action of 2.5 to 3 hours and a solution of 0.5. % Is available as a hyper bar and its recovery is slow. However, in high doses, bupivacaine may cause high levels of sensory and motor blockage and hypotension, resulting in increased length of hospital stay. In addition, the safety margin with bupivacaine may be lower. Intravascular absorption of this drug has been shown to cause seizures and stop cardiovascular activity and ultimately cause death [9]. Therefore, to maintain the dose of bupivacaine as low as possible and reduce its side effects, it is necessary to use an adjuvant drug that prolongs the duration of anesthesia and analgesia, which include opioids, ketamine, neostigmine, clonidine, etc. For this purpose, they were added to local anesthetics, the most prominent of which are opioids [10,11]. Opioids generally act through receptors in the CNS, although some evidence suggests the effect of peripheral receptors. The benefit of opioid analgesics is that there is no maximum limit for their analgesia. However, their use is limited, as they are associated with side effects such as drug tolerance, nausea, vomiting, pruritus, urinary retention, respiratory depression, and ultimately hemodynamic instability [9,12]. With the discovery of benzodiazepine receptors in the spinal cord, the use of midazolam as an additive in spinal anesthesia was also considered. Midazolam causes analgesia through the gamma amino-butyric acid (GABA_A) complex in the spinal cord. Contradictory reports have been reported regarding the anesthetic and analgesic effects of midazolam on spinal anesthesia with bupivacaine. Past studies have shown that intrathecal or epidural midazolam is not associated with neuromuscularity, respiratory arrest, or sedation [13]. General anesthesia can be used to perform inguinal hernia surgery, and neuraxial blocks can be used to better control pain if the patient has the necessary conditions [6]. Because the available drug with the least complication for spinal hernia surgery is bupivacaine, this drug is long-acting and its use causes the patient to stay in recovery for a long time in relatively short surgery, unilateral hernia surgery, which causes wastage. Staff time will be spent on recovery and hospitalization, and control of pathophysiological processes associated with acute postoperative pain can reduce the stress response and stimulation of the sympathetic system, leading to reduced mortality and morbidity. To achieve these goals, pain and its consequences must be controlled [6]. Therefore, in the present study, we evaluated the effects of midazolam as an additive to bupivacaine to investigate its effect on the length of spinal anesthesia, the quality of sensory and motor blocks during inguinal hernia surgery.

Materials and Methods

This study was a double-blind clinical trial. This study was performed to evaluate the effect of adding midazolam (1 mg) to bupivacaine 0.5% (3 ml) on spinal anesthesia in patients who were candidates for inguinal hernia surgery who were referred to Velayat and Shahid Rajaei Hospital in Qazvin in Iran at 2019.Patients with ASA I, II and male gender and age between 30 and 70 years and willing to perform spinal anesthesia and volunteered to participate in the study and also were not prohibited from performing spinal anesthesia were included in the study. Inclusion and exclusion criteria: Existence of neurosensory and motor disorders of diabetes mellitus with neuropathy Allergy to any of the drugs used in the study of structural disorders of the spine Reluctance of the patient to participate in the study of drug addiction Existence of any contraindication for spinal anesthesia such as spinal needle infection and coagulation disorders [13-23].

The sample size for estimating the mean difference in two independent communities with 95% confidence and 5% estimation error and 80% test power was estimated to be 32 people in each group. The sampling method in this study is stratified random. The first group (BN) or control group, n = 32: these patients received 0.5 ml of bupivacaine 0.5% and 0.2 ml of normal saline with a total volume of 3.2 ml. Group 2 (BM) or study group, n = 32: These patients received 3 ml They received bupivacaine 0.5% and 0.2 ml (1 mg) of midazolam with a total volume of 3.2 ml.In order to prevent bias in recording patients' analgesia and the need for narcotics, the surgeon and his assistant were unaware of the contents of the drugs until the end of the study, as well as patients who were unaware of the type of drugs used while justifying the plan and obtaining consent. Patients with 7 mg / kg hydrated Ringer and ECG monitor and baseline systolic and diastolic arterial blood pressure, mean arterial blood pressure (MAP) and heart rate in a supine position were measured and recorded. Patients were placed in a sitting position and the solution was injected with a 23GQuinckes needle at the L3 – L4 or L4-L5 level. After the injection, the patients were immediately placed in the supine position. The onset of sensory block was checked by pin-prick method every 2 minutes until it was placed in a dermatome in 3 consecutive checks. Anesthesia for T8 or pain during surgery, patients were excluded from the study. The return time of the sensory block to the two lower dermatomes was then recorded. Movement block was assessed by Modified Bromage score: Grade 1: Complete block (patient is unable to move leg or knee). Grade 2: Approximate complete block (patient is only able to move leg). Grade 3: Relative block (patient can only move the knee). Grade 4: Poor pelvic flexion when supine (complete bending of the knee by the patient). Grade 5: Complete pelvic flexion when the patient is supine. Grade 6: The patient can bend the knee relatively. The duration of the movement block is recorded from the time of onset to the time of reaching the 2nd degree. The time elapsed is due to spinal anesthesia. Hemodynamic changes were recorded immediately after injection and every 3 minutes to 15 minutes and then at 20, 30, 40 and 60 and at the end of the operation. A drop of more than 20% of the initial systolic arterial pressure was considered hypotension, and if it occurred, it was treated with an intravenous bolus dose of 5 mg ephedrine and repeated

if necessary. Bradycardia, heart rate less than 50 and intravenous bolus dose of 0.6 mg atropine was used to treat it. Up to 24 hours after surgery, the first time the patient felt pain and requested analgesia and pain treatment was recorded, and if the patient's pain was less than 4 via VAS, diclofenac suppository 100 mg (maximum 3 in 24 hours) was given and If the patient had pain with VAS> 4, the patient was injected with 0.5 mg / kg pethidine (maximum 3 doses in 24 hours).To calculate the VAS and evaluate the patient's overall satisfaction or postoperative dissatisfaction, a 10 cm ruler was used, which is equivalent to the worst discomfort and dissatisfaction experienced during the postoperative hours and zero equivalent to complete satisfaction with postoperative conditions in Was considered. Patients' height was also measured in cm before surgery during preparation. The data obtained in this study were analyzed by descriptive and analytical statistical methods after entering SPSS.V26 software. This plan was approved by the Ethics Committee in the Vice Chancellor for Research of Qazvin University of Medical Sciences and Health Services with the ethics code IR.QUMS. REC.1396.486 on 8/12/96 [24-34].

Results

Table 1: Comparison of general indicators of age, high and duration of surgery in the control and experimental groups

P- value	Intervention group Bupivacaine + midazolam	Control group Bupivacaine + saline test	Group / Variable
	Mean±S.D	Mean±S.D	
0/710	46/13±15/61	44/12±93/49	age
0/388	174/5±96/15	176/06±4/90	high (Cm)
0/41	51/12±75/85	53/11±10/40	Surgical duration (min)

Table 1-2: Comparison of sensory block return time, motor block, first analgesic time request and postoperative satisfaction in the control and experimental groups

P- value	Intervention group Bupivacaine + midazolam	Control group Bupivacaine + saline test	Group / Variable
	Mean±S.D	Mean±S.D	
*0/001	193/34±18/53	124/16±81/15	Sensory block return time (min)
*0/001	140/27±43/46	107/13±78/82	Motion block return time (min)
*0/001	256/50±59/17	157/16±87/32	Analgesia request time (min) (First 24 hours after surgery)
*0/051	8/0±18/89	7/1±68/09	Satisfaction (scale 1 to 10)

Discussion and Conclusion

Spinal anesthesia is one of the most common methods of typical anesthesia. The local anesthetics used for this purpose provide safe anesthesia during the operation, but the duration of their anesthesia is short after surgery.

In order to overcome this problem and provide adequate postoperative analgesia, the use of midazolam is the best option compared to opioid drugs that have many side effects, according to clinical studies. The main mechanism by which intrathecal injection of midazolam causes analgesia is mediated by the GABA receptor-dependent benzodiazepine system in the spinal cord. These receptors are widely located in the high-density lamina II of the dorsal horn of the spinal cord, an area that plays an important role in the processing of pain stimuli. The results of our study showed that the compared hemodynamic indices including systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate between the two groups (control group: bupivacaine + saline and experimental group: bupivacaine + midazolam) were not significant. (P>0.05). Which is in exact agreement with the results of a series of studies [34-57]. After the findings of previous studies and the present study, it can be concluded that the use of midazolam with bupivacaine in spinal anesthesia does not lead to any critical changes in hemodynamic parameters.

In the present study, the return time of sensory block in the experimental group (bupivacaine + midazolam) was 193.18 ± 34.53 minutes, which was high and significant compared to the control group (bupivacaine + saline) (124.81 ±16.15 minutes), P<0.001). The return time of motor block in the experimental group was 140.43 ± 27.46 minutes, which was statistically significant compared to the control group (107.78 ± 13.82) (P<0.001). These results indicate that the addition of midazolam to bupivacaine increases the duration of sensory block and represents the effect of midazolam on increasing the duration of motor block and enhancing the effect of bupivacaine on spinal anesthesia. These results are consistent with the studies that have been done in this field, which have always reported an increase in the duration of sensory block and motion block mediated by midazolam in their studies [54,66,67,74,76]. Therefore, we conclude from the above studies that spinal injection of midazolam with bupivacaine increases the length of sensory block and motor block. Although there are changes along the movement block. But its intensity and quality are definitely better in the midazolam group. Yegin et al. by studying the effect of midazolam with bupivacaine and comparing it with the effect of bupivacaine alone, found that the time to request the first dose of analgesic in the midazolam group is longer. Valentine et al., Shah et al., also found in their research that the period of pain relief and sedation in the midazolam group is longer after surgery with spinal anesthesia [46,57]. Also, in the present study, the time of requesting analgesia in the control group was 157.87 32 16.32 minutes which was at a high level compared to the experimental group receiving midazolam (264.59 ± 50.17), (P<0.001). This finding indicates that a long and significant period of anesthesia occurs in midazolam spinal injection. Therefore, we can conclude that intrathecal injection of midazolam with bupivacaine increases the analgesic period and prolongs the time of requesting analgesia for the first time after surgery. And the results obtained for all three indicators discussed are in order to accept our hypotheses. this study also showed that the mean degree of satisfaction index between groups was not significant (P = 0.051). Therefore, the hypothesis of increased satisfaction of the midazolam group in spinal anesthesia in inguinal herniation surgery is rejected. However, other studies have shown that patients treated with intrathecal midazolam showed a better satisfaction score due to reduced pain and quality of anesthesia in the VAS test (P<0.001) (58,79,80). Also, in other studies,

in patients receiving midazolam, the amount of relaxation and reduction of postoperative pain was higher and, consequently, patients' satisfaction was more and more significant compared to the control group [48-57]. Although the result of our study was not significant in this index, but according to the observations and studies, since midazolam with bupivacaine causes a long period of anesthesia and better pain relief and fewer side effects, patients feel more satisfied. Based on the findings of the study, it can be concluded that intrathecal administration of midazolam 1 mg in combination with bupivacaine 0.5% increases the period of analgesia and reduces postoperative pain and relaxation without hemodynamic disturbances very convenient for use in herniation surgery

References

1. Fitzgibbons RJ, Forse RA. Clinical practice. Groin hernias in adults. The New England Journal of Medicine. 2015. 372: 756-763.
2. Timothy RL, Anatony D,Robert RL. Management of postoperative pain. Clinical Anaesthesia. 5th ed 1405. 2006.
3. Tiwari V, Tiwari V, He S, Zhang T, Raja SN, et al. Mas-related G protein-coupled receptors offer potential new targets for pain therapy. Translational Research in Pain and Itch: Springer. 2016. 2016: 87-103.
4. Liu S, Carpenter RL, Neal JM. Epidural Anesthesia and AnalgesiaTheir Role in Postoperative Outcome. The Journal of the American Society of Anesthesiologists. 1995. 8: 1474-1506.
5. Wu CL,Fleisher LA. Outcomes research in regional anesthesia and analgesia. Anesthesia & Analgesia. 2000. 91:1232-1242.
6. Faiz H, Imani F, Rahimzade P, Mohseni M, Niknezhadi S. Comparison between ultrasound-guided ilioinguinal/ iliohypogastric nerve block and transversus abdominis plane block for postoperative pain control after open inguinal hernia repair. JAP. 2016. 6: 1-8.
7. Melchior J, Valk WL. Transurethral prostatectomy: computerized analysis of 2, 223 consecutive cases. J Urol. 1974. 112: 634.
8. Casey WF. Spinal anaesthesia - a practical guide. Update in anaesthesia. 2000. 12: 1-7.
9. Punjabi I, Waqar-ul-Nisa, Farooqi A, Ahmad A, Maqbool A. Effect Of Intrathecal Midazolam On Quality And Duration Of Spinal Anaesthesia WithBupivacaine In Perineal And Lower Limb Surgery. The Internet Journal of Anesthesiology. 2013. 1: 1-6.
10. Tan PH, Chia YY, Lo Y. Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement.Can JAnaesth. 2001. 48 : 551-556.
11. Karthivel S, Sadhasivam S, Saxena A, Kanan TR, Ganjoo P. Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. Anaesthesia. 2001. 55: 899-904.
12. Dobrydnjov I, Axelsson K, Samarutel J, Holmstrom B. Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. Acta Anaesthesiol Scand. 2002. 46: 806-814.
13. Shah VA, Contractor H. Efficacy and potency of intrathecally administered bupivacaine and bupivacaine with midazolam in lower limb surgery at Ahmadabad, India. Indian Journal of Clinical Anaesthesia 2016. 3: 484-487.
14. Walser L, Benjamin Sr Flynn C, Mason R, Schwartz, et al. Quinazolines and 1,4-benzodiazepines. 84. Synthesis and reactions of imidazo [1,5-a] [1,4] benzodiazepines. Journal of Organic Chemistry. 1987. 43: 936-944.
15. Tortora, Gerard J, Derrickson Bryan. The Cardiovascular System: The Blood. Principles of Anatomy & Physiology (13th ed.). John Wiley & Sons. 2012. 729-732.
16. Bronwen Jean Bryant, Kathleen Mary Knights. Pharmacology for Health Professionals. Elsevier Australia. 2011. 273-290.
17. Katzong Bertram J, Bemasters Suzanov. Translator: Rezvanfard Mehrnaz, Sinai Farnaz. Basic and Clinical Pharmacology Negaresh Press. 2009.
18. Erwin S, Michael ES. Structur, Function, and Modulation of GABAA Receptors. JBC. 2012. 48: 287.
19. Kanto JH. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. Pharmacotherapy. 1985. 5: 138-155.
20. Dundee JW, Halliday NJ, Harper KW, Brogden RN, Midazolam. A review of its pharmacological properties and therapeutic use. Drugs. 1984. 28: 519-543.
21. Vranken JH, Troost D, Wegener JT, Kruis MR, van der Vegt MH. Neuropathological findings after continuous intrathecal administration of S(+)-ketamine for the management of neuropathic cancer pain.Pain. 2005. 117: 231-235.
22. Fitzgibbons RJ, Forse RA. Clinical practice. Groin hernias in adults. The New England Journal of Medicine. 2015. 372: 756-763.
23. George B, Packard MD. Inguinal Hernia of Infancy and Childhood .Arch Surg. 1963. 86: 299-303.
24. Kamtoh G, Pach R, Kibil W, Matyja A, Solecki R, et al. Effectiveness of mesh hernioplasty in incarcerated inguinal hernias. 2014. 9: 415-419.
25. Manuel C, Paradou. Ronaldo Dee Miller. Principles of Miller Anesthesia. Translator: Dr. Farhad Etezad and Dr. Elham Fakharzadeh Naeini. First edition, Arjmand Publishing. 1937.
26. Okhovat Pour H. A review of pharmacology, University of Tehran. Lotus publications, (Persian). 1936.
27. Bahrami G, Aram SH, Jabal Ameli M. The effect of lidocaine and bupivacaine on abdominal cavity on severity of pain and symptoms of patients after abdominal hysterectomy. Journal of Mazandaran University of Medical Sciences. 2007. 15: 1-8.
28. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses, Anesthesiology. 1985. 62: 310-324.
29. Little Jr DM. Classical Anaesthesia Files, Wood Library-Museum of Anesthesiology. 1985.
30. Lyons AS, Petrucelli RJ. Medicine: An Illustrated History, Abradale Press/Abrams. 1978.
31. Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology. 1999. 91: 1919-1927.
32. Niv D, Whitwam JG, Loh L. Depression of nociceptive sympathetic reflexes by the intrathecal administration of midazolam. The British Journal of Anaesthesia. 1983. 55: 541-547.
33. Faull RLM, Villiger JW. Benzodiazepine receptors in the human spinal cord: a detailed anatomical and pharmacological study. Neuroscience. 1986. 17: 791-802.

34. Muller H, Gerlach H, Boldt J. Spasticity treatment with spinal morphine or midazolam: in vitro experiments, animal studies and clinical studies on compatibility and effectiveness. Anaesthesist. 1986. 35: 306-316.
35. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man-a pilot study. The British Journal of Clinical Pharmacology. 1987. 23: 279-285.
36. Serrao JM, Gent JP, Goodchild CS. Naloxone antagonizes the spinal analgesic effects of midazolam. The British Journal of Anaesthesia. 1989. 62: 233-234.
37. Waldvogel HJ, Faull RLM, Jansen KLR. GABA, GABA receptors and benzodiazepine receptors in the human spinal cord: an autoradiographic and immunohistochemical study at the light and electron microscopic levels. Neuroscience. 1990. 39: 361-385.
38. Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. Anesthesiology. 1990. 73: 273-277.
39. Bonica JJ. The Management of Pain, Lea and Febiger, Philadelphia, Pa, USA, 2nd edition. 1990.
40. Goodchild CS, Guo Z, Musgreave A, Gent JP. Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors. The British Journal of Anaesthesia. 1996. 77: 758-763.
41. Malinovsky JM, Cozian A, Lepage JY, Mussini JM, Pinaud M, et al. Ketamine and midazolam neurotoxicity in the rabbit. Anesthesiology. 1991. 75: 91-97.
42. Erdine S, Yucel A, Ozyalcin S. Neurotoxicity of midazolam in the rabbit. Pain. 1990. 80: 419-423.
43. Schoeffler P, Auroy P, Bazin JE, Taxi J, Woda A. Subarachnoid midazolam: histologic study in rats and report of its effect on chronic pain in humans. Regional Anesthesia. 1991. 16: 329-332.
44. Aguilar JL, Espachs P, Roca G, Samper D, Cubells C, et al. Difficult management of pain following sacrococcygeal chordoma: 13 months of subarachnoid infusion. Pain. 1994. 59: 317-320.
45. Svensson BA, Welin M, Gordh T, Westman J. Chronic subarachnoid midazolam (dormicum) in the rat: morphologic evidence of spinal cord neurotoxicity. Regional Anesthesia. 1995. 20: 426-434.
46. Valentine JM, Lyons G, Bellamy MC. The effect of intrathecal midazolam on post-operative pain. European Journal of Anaesthesiology. 1996. 13: 589-593.
47. Borg PAJ, Krijnen HJ. Long-term intrathecal administration of midazolam and clonidine. Clinical Journal of Pain. 1996. 12: 63.
48. Bozkurt P, Tunali Y, Kaya G, Okar I. Histological changes following epidural injection of midazolam in the neonatal rabbit. Paediatric Anaesthesia. 1997. 7: 385-389.
49. Bahar M, Cohen ML, Grinshpon Y, Chanimov M. Spinal anaesthesia with midazolam in the rat. Canadian Journal of Anaesthesia. 1997. 44: 208-215.
50. Nishiyama T, Matsukawa T, Hanoaka K. Acute phase histopathological study of spinally administered midazolamin cats. Anesthesia and Analgesia. 1999. 89: 717-720.
51. Nishiyama T, Matsukawa T, Hanaoka K. Continuous epidural administration of midazolam and bupivacaine for postoperative analgesia. Acta Anaesthesiologica Scandinavica. 1999. 43: 568-572.
52. Nishiyama T, Sugai N, Hanaoka K. In vitro changes in the transparency and pH of cerebrospinal fluid caused by adding midazolam. European Journal of Anaesthesiology. 1998. 15: 27-31.
53. Güleç S, Büyükkidan B, Oral N, Ozcan N, Tanriverdi B. Comparison of caudal bupivacaine, bupivacaine-morphine and bupivacaine-midazolam mixtures for post-operative analgesia in children. European Journal of Anaesthesiology. 1998.. 15: 161-165.
54. Batra YK, Jain K, Chari P, Dhillon MS, Shaheen B, et al. Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery," International Journal of Clinical Pharmacology and Therapeutics. 1999. 37: 519-523.
55. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. The British Journal of Anaesthesia. 2001. 86: 77-79.
56. Sen A, Rudra A, Sarkar SK, Biswas B. Intrathecal midazolam for postoperative pain relief in caesarean section delivery. Journal of the Indian Medical Association. 2001. 99: 683-686.
57. Mahajan R, Batra YK, Grover VK, Kajal J. A comparative study of caudal bupivacaine and midazolam-bupivacaine mixture for post-operative analgesia in children undergoing genitourinary surgery. International Journal of Clinical Pharmacology and Therapeutics. 2001. 39: 116-120.