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Effects of Combination of Intrathecal Lidocaine and Two Doses of Intrathecal Midazolam on Post-operative Pain in Patients Undergoing Herniorrhaphy: A Randomized Controlled Trial

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Abstract: Assessment of the effect of combination of intratechal midazolam and lidocaine on postoperative pain was the aim of this study. This randomized controlled trial was performed during 2007 in a teaching hospital of Arak University of Medical Sciences. Forty five male patients who were candidates for elective inguinal herniorrhaphy entered the study and randomly divided into three groups of control (lidocaine 5% plus normal saline), M 0.5 (lidocaine 5% and midazolam 0.5 mg) and M 1.0 (lidocaine 5% and midazolam 1 mg) according intrathecal solution injected for spinal anesthesia. Mean arterial blood pressure, heart rate, post-operative pain, narcotic requirements and complications (nausea, vomiting, pruritis, headache, hypotension and bradycardia) were recorded. The severity of post-operative pain was lowest in M 1.0 group in all postoperative measurements except at 2 h after operation. With regard of complications, only there was significant difference in vomiting between three groups which had the highest frequency in M 0.5 group. No severe hypotension was seen; though, bradycardia occurred in one patient in M 0.5 group which needed treatment. Present findings suggest that administration of intrathecal midazolam (especially 1 mg) together with lidocaine is effective in reducing post-operative pain in patients undergoing open inguinal herniorrhaphy and is not associated with adverse effect.

Key words: Intrathecal, midazolam, lidocaine, spinal anesthesia, postoperative pain, inguinal herniorrhaphy

INTRODUCTION

An inguinal hernia is defined as protrusion of abdominal contents through the inguinal canal. They are very common and inguinal hernioplasty is among the most frequently performed surgical procedures by general surgeons (Abrazhda *et al*., 2010). Hernia repair can be performed using general, regional (spinal or epidural), or local anesthesia (Antadze *et al*., 2008).

Reducing postoperative pain, many adjuvant drugs have been tried with intrathecal anesthesia to prolong postoperative analgesia; however, many of these drug combinations produce significant side effects. For instance, opioids are used widely for relieving post-operative pain as both intrathecal and epidural routes. Although they prolong the duration of spinal anesthesia without delaying recovery to ambulation, these agents are associated with some adverse effects such as nausea and emesis, tolerance, pruritus, urinary retention and respiratory depression (Baig *et al*., 2006; Rathmell *et al*., 2005).

An available option for reducing post-operative pain and so opioids requirement is using adjunct drugs such as intrathecal midazolam. Niv *et al*. (1983) showed that administration of intrathecal midazolam depresses nociceptive sympathetic reflexes. Similarly, several experimental and clinical studies have shown other effects of intrathecal midazolam (Bahar *et al*., 1997; Goodchild and Serrao, 1987; Kim and Lee, 2001; Tucker *et al*., 2004a, b). One to 2 mg intrathecal midazolam was safely and effectively used in several studies (Batra *et al*., 1999; Kim and Lee, 2001; Yegin *et al*., 2004). Most of previous studies have focused on combination of bupivacaine and midazolam (Bharti *et al*., 2003; Kim and Lee, 2001; Prakash *et al*., 2006) and to the best of our knowledge, there is no investigation about combination of intrathecal lidocaine and midazolam in the literature. The only survey in this regard is the effects of supplementing epidural lidocaine with midazolam.

This study was designed to evaluate the effects of intrathecal midazolam in combination with intrathecal lidocaine on multiple perioperative parameters especially post-operative pain.

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MATERIALS AND METHODS

This study was conducted at Valiasr Hospital, Arak University of Medical Sciences, during a one year period (2007). Ethical committee of human research of the university approved the protocol of the study and all subjects signed an informed consent before entering the study. During this time period all male patients who were candidated for elective ipsilateral open inguinal herniorrhaphy under spinal anesthesia and had other inclusion criteria were enrolled into the study. These criteria included age between 45 to 65 years, ASA class I and II, operations shorter than 60 min, absence of history of drug abuse and mental and psychological disorders and the sensory loss at the below T_6 level. Patients with contraindication for spinal anesthesia (patient's refusal, infection at the site of puncture, anatomical difficulties that might make the administration of anesthesia difficult and presence of neurological disease), history of alcohol consumption, needing to further sedatives, analgesics and narcotics than routine requirement (prolongation of the operation than durability of spinal anesthesia and incomplete analgesia), patients with level of sensory loss above T_6 or below T_8 and allergy to the studied drugs were excluded.

Then patients with these characteristics randomly were divided into three groups utilizing table of randomization:

- Intrathecal preservative free hyperbaric lidocaine 5% (Lidocard®; Orion Pharma, Finland) (75 mg) plus 1 mL of 0.5% midazolam (5 mg mL^{-1}; Exir, Iran) (M 0.5 group)
- Intrathecal preservative free hyperbaric lidocaine 5% (75 mg) plus 1 mL of 1% midazolam (M 1.0 group)
- Control group in which the patients received intrathecal preservative free hyperbaric lidocaine 5% (75 mg) and 1 mL normal saline

Also an attempt was made all solution have the same color, appearance and viscosity. Then, standard monitoring (electrocardiogram, pulse oxymetry, noninvasive arterial blood pressure and heart rate) was established.

The patients were premedicated with diazepam 5 mg orally, 60 min before coming to the operation room. After preloading patients with 500 mL of intravenous 0.9% saline, spinal anesthesia was performed with the patient in the sitting position under aseptic condition by an anesthesiologist who was blinded to the contents of solutions. Using midline approach, a 24-gauge Whitacare spinal needle (Dr. Japan Co Ltd., Tokyo, Japan) was entered in L_{4-5} interspace. The needle placement in dural space was confirmed by free flow of CSF from the needle. The needle bevel was oriented cephalad while the drugs were injected. The patients were placed supine after drug injection.

The severity of post-operative pain, complications (nausea, emesis, pruritus, headache and sedation), in addition to mean arterial blood pressure (MAP) and Heart Rate (HR) were recorded. Severity of pain was obtained using visual analogue score (0 cm = no pain, 10 cm = the most severe pain) at 1, 2, 3, 4, 6, 8, 10 and 12 h after operation by a trained nurse who was blinded to the group of patients. MAP and HR were recorded during 60 min after initiation of operation every 5 min and then at 75th min, when the patients were transferred to the recovery. Hypotension defined as 20% decrease in systolic blood pressure from the baseline values and was treated with intravenous fluids and 6 mg ephedrine every 2 min until normotension was achieved (Vosoughian *et al*., 2007). Bradycardia (pulse rate <60 min^{-1}) was treated with intravenous atropine sulphate (0.5 mg).

Sample size and power were estimated by determining the duration of analgesia after operation. We assume that like pervious study of Bharti *et al.* (2003) adding midazolam to lidocaine will prolong the duration of sensory block near 53 min. Accordingly, number of patients required to show the significant difference between lidocaine and lidocaine with midazolam in post-operative pain were determined 14 patients in each group. A total of 42 patients would be required to show a statistically significant difference between the two arms using an α of 0.05 and power of 80%. We enrolled one extra patient in each arm in the event that a patient dropped out of the study.

All the variables have been presented as Mean±SD. Statistical analysis was performed using SPSS version 15 (SPSS Inc., Chicago IL.). Kruscal wallis, Mann-Whitney, chi square and Fisher's Exact (if necessary) tests were used to analyze data. p-value <0.05 was considered statistically significant.

RESULTS

A total of 45 patients (15 subjects in each group) were enrolled into the study. There were no significant differences regarding age, weight and ASA status of the patients between these groups (Table 1).

Table 1: Baseline characteristics of the patients in different groups

Characteristics	Control	M 0.5	M 1	p-value
Age (year)	53.87±11.56	60.5±4.18	50.73±14.12	0.064
Weight (kg)	63.63±6.11	65.57±8.22	63.14±5.82	0.610
ASA (I/II)	50%/50%	54%/46%	57%/53%	0.942

M 0.5: Midazolam 0.5 mg, M 1.0: Midazolam 1 mg

Table 2: Frequency of complications occurred in each group. Emesis occurred just in midazolam 0.5 mg ($p<0.05$)

Groups	Control	M 0.5	M 1	p-value
Nausea	8 (80%)	10 (77%)	13 (93%)	0.139
Emesis	0	5 (38%)	0	0.004
Vomiting require treatment	0	2 (15%)	0	0.123
Pruritus	0	0	0	-
Headache	8 (80%)	8 (62%)	7 (50%)	0.915
Hypotension	0	0	0	-
Bradycardia	0	1 (8%)	0	0.360

M 0.5: Midazolam 0.5 mg, M 1.0: Midazolam 1 mg

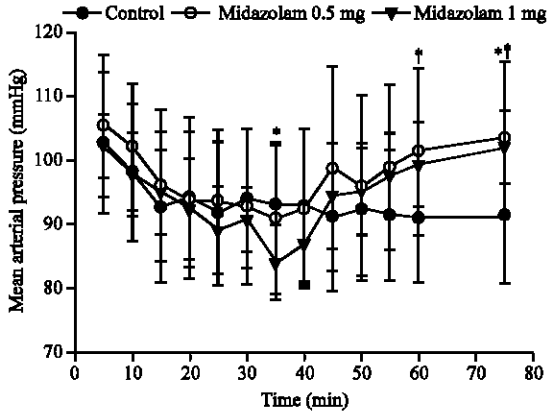

Fig. 1: Mean arterial blood pressure in different post-operative times in three groups. *: Significant differences between Midazolam 1 mg and control group, †: Significant differences between Midazolam 0.5 mg and control group

Regarding the observed complications (nausea, vomiting, pruritus, headache, hypotension and bradycardia), only there was significant difference in vomiting between three groups which had the highest frequency in M 0.5 group (Table 2).

Comparison of MAP in different groups has been shown in Fig. 1. Present findings showed significant differences at 35 and 75 min between M1 group and Control group and between M 0.5 group and Control group at 60 and 75 min ($p<0.05$).

Regarding HR, there our results showed significant differences at 5, 10, 40 and 75 between M 1 group and Control group and at 15 and 25 between M 0.5 group and Control group and at 20 and 30 min between both Midazolam groups with control group ($p<0.05$). The details have been shown in Fig. 2.

The severity of post-operative pain was lower in M 1 group compared with M 0.5 group and Control groups in most of times. The difference was statistically significant except at 2 h after operation; however, M 0.5 group did not show significant reduction in post-operative pain in comparison to Control group at most of times (Fig. 3).

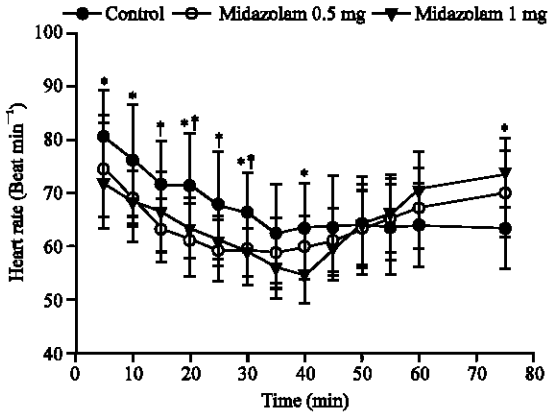

Fig. 2: Heart rate in different post-operative times in three groups. *: Significant differences between Midazolam 1 mg and control group. †: Significant differences between Midazolam 0.5 mg and control group

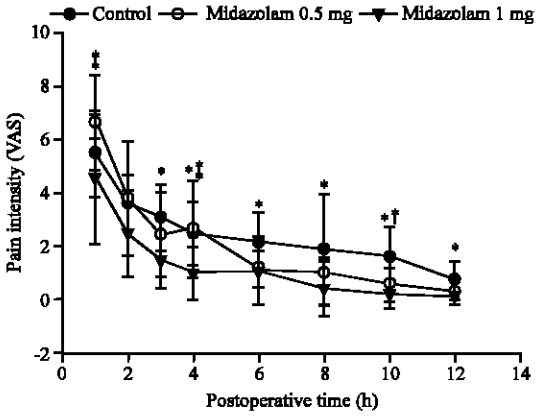

Fig. 3: Pain intensity in different post-operative times in three groups, *: Significant differences between Midazolam 1 mg and control group. †: Significant differences between Midazolam 0.5 mg and control group. ‡: Significant differences between Midazolam 0.5 mg and Midazolam 1 mg

Also the prescribed dose of narcotics was significantly lower in M 1 group than two other groups (20.67±19.72 mg vs. 37.33±19.81 mg and 55.33±17.97 mg in M 0.5 and control groups successively, $p = 0.001$).

DISCUSSION

Present results, for the first time, showed combination of intrathecal midazolam and lidocaine has also antinociceptive effects. Furthermore, while it has been revealed intrathecal administration of 1 mg midazolam resulted in significant reduction in post-

operative pain score in comparison to control group at most of times, 0.5 mg midazolam did not.

Similarly, in a study conducted by Prakash *et al.* (2006), higher dose of intrathecal midazolam (2 mg rather than 1 mg) provided a moderate prolongation of postoperative analgesia when used as an adjunctive drug to bupivacaine in patients underwent cesarean delivery.

The suggested mechanism for antinociceptive effect of intrathecal midazolam is acting on GABA receptors (Valentine *et al.*, 1996). Gamma-aminobutyric acid (GABA) (A) receptors has an important role in antinociception in the spinal cord (Nishiyama *et al.*, 2002; Nishiyama, 2009a,b). In other words, intrathecally injected midazolam, a water soluble benzodiazepine, binds with presynaptic GABA-A receptors in the spinal cord, as the main site of benzodiazepine action, leading to an analgesic effect (Dureja *et al.*, 2010; Ho and Ismail, 2008; Kohno *et al.*, 2000). In that way, midazolam reduces excitatory synaptic transmission which results in decreased excitability of spinal dorsal horn neurons (Kohno *et al.*, 2006).

However, intrathecal midazolam was not associated with an increased risk of neurologic symptoms (Tucker *et al.*, 2004a) and no neurotoxicity from long-term (>5 years) intrathecal infusion of midazolam in humans has been reported (Canavero *et al.*, 2006), neurotoxic effect of midazolam remained a concern. Several clinical studies have shown that midazolam can be safely added to intrathecal local anesthetics with minimal side effects (Batra *et al.*, 1999; Bharti *et al.*, 2003; Kim and Lee, 2001; Sen *et al.*, 2001; Tucker *et al.*, 2004b; Valentine *et al.*, 1996). In this regard, in a meta-analysis the effect of intrathecal midazolam on perioperative and peripartum analgesia was assessed. The results concluded that intrathecal midazolam improves perioperative analgesia. Although the incidence of neurological symptoms after intrathecal midazolam was uncommon (1.8%) and did not differ from placebo, they suggested current data are limited and a multicentre registry or large randomized controlled study with a prolonged follow-up period would be useful to confirm the clinical safety of intrathecal midazolam (Ho and Ismail, 2008).

While it has been shown that benzodiazepines, including midazolam, are effective in reducing post-chemotherapy vomiting as well as in treatment of persistent post-operative nausea and vomiting (Edwards *et al.*, 1990; Ho and Ismail, 2008) there is no consensus in this regard in the literature and different results have been reported regarding the effect of intrathecal midazolam on post-operative emesis (Prakash *et al.*, 2006; Tarhan *et al.*, 2007). Present results not only did not showed a reduction in post-operative vomiting in midazolam groups compare with controls, but also significantly more patients in midazolam 0.5 mg group complicated by post-operative vomiting. Present findings are in contrast with the report by Prakash and associates (Prakash *et al.*, 2006) who found intrathecal midazolam, 1 and 2 mg, decreased postoperative nausea and vomiting. Conversely, in another study by Nishiyama (1995) it has suggested that administration of epidural midazolam adds emesis effect on spinal anesthesia.

Regarding hemodynamic effects of intrathecal midazolam, previous studies have shown no significant differences between combination of intrathecal bupivacaine and midazolam and bupivacaine alone (Bahar *et al.*, 1997; Batra *et al.*, 1999; Kim and Lee, 2001). Yet, in the present study we found significant differences between intrathecal midazolam/lidocaine and lidocaine alone. We cannot find any convincing reason of this phenomenon; though, it does not seem to be related to different local analgesic were used (lidocaine vs. bupivacaine). A study conducted by Kyokong *et al.* (2001) failed to show significant differences regarding hamodynamic parameters in intrathecal lidocaine and bupivacaine.

Small number of patients in each group may be considered as a limitation of our study; however, present results showed it was enough to detect the differences between groups regarding post-operative pain.

In conclusion, present results showed administration of intrathecal midazolam (especially 1 mg) together with lidocaine is effective in reducing post-operative pain in patients undergoing open inguinal herniorrhaphy and is not associated with severe adverse effects.

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