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The Effects of Adding Intrathecal Midazolam to Bupivacaine in Spinal Anesthesia

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Authors' contributions

This work was carried out in collaboration between three authors. Author KI was responsible for analysis and interpretation of data, drafting the article are making critical revisions related to important intellectual content of the manuscript, final approval of the version of the article to be published. Author ME was responsible for substantial contributions to conception and design of the study, acquisition of data, drafting the article are making critical revisions related to important intellectual content of the manuscript, final approval of the version of the article to be published. Author ZA was responsible for substantial contributions to conception and design of the study, drafting the article are making critical revisions related to important intellectual content of the manuscript, final approval of the version of the article to be published.

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ABSTRACT

Aim: To study of intrathecal bupivacaine with and without midazolam to assess its effect on the onset, duration of sensory and motor block in lower limb surgery.
Place and Duration of Study: Fatemi Hospital, Ardebil University of Medical sciences, Iran. From March until September 2014.
Methodology: Eighty patients were randomly allocated to two groups: 40 patients in the control group received 3 ml of 0.5% bupivacaine plus 0.4 ml of 0.9% saline intrathecally; 40 patients in the

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midazolam group received 3 ml of 0.5% bupivacaine plus 0.4 ml (2 mg) midazolam. The onset, duration of sensory/motor block, side effects, sedation score and time for request for first rescue analgesia were noted in two groups. Data collected by questionnaires and the data were extracted and analyzed by SPSS software with Ch-square and T-tests.

Results: The deference in onset of sensory and motor block between groups was not significant ($p>0.05$). The duration of sensory and motor block was prolonged in the midazolam group significantly (p-value =0.005, p-value = 0.014 respectively). There were no episodes of hypotension, bradycardia, pruritus, vomiting and urinary retention in any patients. Incidence of nausea and sedation score was comparable in the two groups. Sedation score in the Midazolam group (3 patient had grade 1 sedation, 35 patients had grade 2 sedation and 2 patients had grade 3) was slightly higher than control group (1 patient had grade 1 sedation, 32 patients had grade 2 sedation and 7 patients had grade 3) (p=0.05). Request time for first rescue analgesia (Diclofenac) was longer in patients who received midazolam (147.38 versus 215.88, p-value<0.001).

Conclusion: Intrathecal midazolam increased the duration of sensory and motor block without increasing side effects.

Keywords: Analgesia; bupivacaine; intrathecal midazolam; sensory block.

1. INTRODUCTION

Compared to general anesthesia, regional anesthesia offers numerous opportunities for better pain control and patient satisfaction. Modern regional anesthesia offers low morbidity and mortality rates [1]. Regional Anesthesia techniques have had great advances such as the reduction of the likelihood of complications; these techniques also lead to less bleeding than the surgery under GA. Although there are several different techniques for RA, spinal anesthesia is the easiest and the most economical compared to other methods [2].

Inadequate control of postoperative pain has adverse effects on the physiological, metabolic, and psychological status of individual [3,4].

To reduce side effects of the technique and increase the duration of analgesia as well as its faster onset, various additives are used in spinal anesthesia [3,4]. Bupivacaine 0.5% is one of the local anesthetics that are used in regional anesthesia [5]. For improvement of the rapid onset; maximize the duration and quality of spinal anesthesia many adjuvants such as adrenaline, clonidine, midazolam, neostigmine, ketamine and opiates have been tried [6].

Although adding opiates to local anesthetics improved intraoperative and postoperative analgesia provided by 0.5% bupivacaine, it has some complications such as delayed respiratory depression, nausea, vomiting, urinary retention and pruritus [6,7]. Midazolam is a rather short-acting benzodiazepine, with anxiolytic, sedative, anticonvulsant and muscle relaxant effects, influencing GABA receptor and influence on neurons by entering chloride into them. Midazolam is metabolized in the liver and excreted in the urine [8,9].

The effects of midazolam are studied in some studies, for example in one study adding midazolam at various doses only provides faster sensory-motor block than bupivacaine [1] and in other study the effects of adding midazolam to bupivacaine on postoperative pain reduction in spinal anesthesia provided more desirable and advisable control pain [7]. Another study showed that in spinal anesthesia adding midazolam significantly increases duration of analgesia (320 minutes compared to 220 minutes) as well as motor block (255 minutes compared to 195 minutes) and decreases postoperative nausea and vomiting (PONV) [10].

In this triple blind clinical trial study we evaluated the effects of adding midazolam to bupivacaine on the duration of sensory and motor block in patients undergoing lower limb orthopedic surgery by spinal anesthesia and compare the side effects of intrathecal midazolam plus bupivacaine and bupivacaine alone.

2. MATERIALS AND METHODS

A triple-blind prospective randomized clinical trial (registered at Iranian Registry of Clinical Trials; registration code: IRCT2014021716612N1) was planned from March until September 2014 on patients scheduled for hip fracture surgery under spinal anesthesia at Fatemi Hospital, Ardebil, Iran. After obtaining approval from the Ethics Committee of Ardebil University of Medical Sciences, 80 adult patients, aged 15–80 yr, ASA I–II, undergoing lower limb orthopedic surgery,

were recruited in this study. Written informed consents were obtained from all study participants, after describing all aspects of the study. Exclusion criteria were loss of consciousness, patients with contraindications to regional anesthesia, or sensitivity to study drugs. Based on existing studies and articles, and in particular with regards to the results obtained from the study of Shadangi and colleagues, [6] 40 samples of each group were determined considering α = 0.05, p =%80.

Patients were randomly allocated into two groups in a triple-blinded manner using a sealed envelope. Control group (n = 40) received 3 mL 0.5% bupivacaine with 0.4 mL saline, while case group (n = 40) received 3 mL 0.5% bupivacaine and 0.4 mL (2 mg) midazolam (5 mg/mL, preservative-free) mixture.

For ensuring blinding, randomly allocated coded syringes of drugs were prepared by an anesthesiologist who did not perform subarachnoid block or record the outcome intraoperative and postoperative period. Neither the participants, nor the anesthesiologist responsible for following the participants, and investigators collecting data and assessing the outcomes were aware of the intervention assignments.

After hydration all patients with Ringer's solution, spinal anesthesia was performed intrathecally in the sitting position using a 25- gauge needle at L4-L5 or L3-L4 in midline approach, under aseptic condition.

In case of creating inadequate level of anesthesia and anesthesia for surgery, the patient was excluded, another patient enrolled in the study and another vial was received from anesthetic technician of the same group number.

Hemodynamic changes such as pulse oximetry, heart rate, respiratory rate, blood pressure and cardiac monitoring (ECG) were monitored continuously.

These parameters were assessed in this study: pain intensity (via the Verbal Numerical Rating, zero to 10 scoring method), sedation. Onset of sensory block (with the sense of touch and sense of pain tests by sterile needle), onset of motor block, duration of sensory block, duration of motor block. Diclofenac sodium 75 IM was used as a rescue analgesic if patient complained of pain and requested for analgesia.

The level of sedation of the patients was assessed by the Ramsay sedation score (1: anxious, agitated and restlessness, 2: oriented and cooperative, 3: responds to command only, 4: brisk response to loud voice and light glabellar tap, 5: sluggish to no response to light glabellar tap or loud auditory stimulus, 6: no response even to pain).

The level of sensory block was assessed by pin-prick testing bilaterally along the mid-clavicular line. The assessment was performed at 5, 10 and 15 min after intrathecal injection and then every 15 min until regression to the S2 segment. Motor block was assessed using a 6-point modified Bromage scale (MBS) [11]. These measurements were performed at 5, 10 and 15 min after intrathecal injection and then every 15min after surgery until no motor blockade could be detected

Pruritus, dizziness, nausea, vomiting, urinary retention were observed duration of operation and in the postoperative period. The request time for the first painkiller drug or the patient's pain complaint was recorded on the checklist.

The data was expressed as mean (SD), numbers with percentage. Quantitative variables were analyzed using Student's independed *t*-test. Categorical data was analyzed using Chi-square and Fischer exact test. The Mann-Whitney 'U' test was used wherever appropriate. Value of $P<0.05$ is considered statistically significant and value of $P<0.01$ is considered high statistically significant. An SPSS V.16 package was used for statistical analysis.

3. RESULTS AND DISCUSSION

Patient groups did not show differences in age, gender, body weight and duration of surgery (Table 1).

The onsets of sensory and motor block were comparable between the two groups. The duration of sensory blockade was prolonged in the midazolam group (p=0.005) and the duration of motor blockade also was prolonged in this group (Table 2).

There were no episodes of hypotension, bradycardia, pruritus, vomiting and urinary retention in any patients, but the incidence of nausea was comparable between two groups (Table 3).

Table 1. Demographic profiles of the two groups

Demographic	Mean ± SD		P-value
	Control group (n=40)	Midazolam group (n=40)	
Age (yrs)	49.43±12.59	46.95±20.46	0.517
Gender (M:F)	27:13	27:13	1
Weight (Kg)	70.37±7.7	68.77±9.9	0.42
Height (cm)	167.06±18.44	168.72±10.34	0.65
Duration of surgery (min)	53.88±7.8	53.45±11.5	0.84

SD: standerd deviation; M: male; F: female

Table 2. Onset and duration of sensory and motor block in tow groups

Parameter (min)	Mean ± SD		P-Value
	Control group (n=40)	Midazolam group (n=40)	
Onset of sensory block	2.9±0.5	3.3±1.5	0.5
Onset of motor block	4.7±0.6	5.1±1.9	0.94
Duration of sensory block	95.13±17.7	106.25±28.8	0.005*
Duration of motor block	85.1±14.9	92.05±25.5	0.014

**High statistically significant*

Table 3. Complications/adverse effects in the two groups

Parameter (min)	No (%)		P-Value
	Control group (n=40)	Midazolam group (n=40)	
Bradycardia	0(0)	0(0)	
Pruritus	0(0)	0(0)	
Hypotension	0(0)	0(0)	
Nausea	3(7.5)	8(20)	0.193
Vomiting	0(0)	0(0)	
Urinary Retention	0(0)	0(0)	
Sedation			

Sedation score in the Midazolam group (3 patient had grade 1 sedation, 35 patients had grade 2 sedation and 2 patients had grade 3) was slightly higher than control group (1 patient had grade 1 sedation, 32 patients had grade 2 sedation and 7 patients had grade 3) (p=0.05).

Comparing the two group's patients receiving Diclofenac, the time was longer for Midazolam group (147.38±31.112 vs. 215.88±49.106), which was high statistically significant (p<0.001).

3.1 Discussion

In this study, the effects of adding Midazolam to Bupivacaine were investigated based on age, sex, weight, and the duration of surgery and in none of the four mentioned criteria, the difference in the two groups was statistically significant.

In an article by Gupta and colleagues, the effects of adding Intrathecal Midazolam to hyperbaric Bupivacaine on postoperative pain after orthopedic surgery of the lower limbs has been studied. At the time of onset of sensory block, there was no statistically significant difference (p>0.05). The value of p=0.943 for motor block onset time was statistically insignificant between the two groups [12].

In a study conducted by Malarica Kulkarni and his colleagues, discussing the role of intrathecal midazolam as an additive to bupivacaine in postoperative pain control at the surgery of lower abdomen and lower extremities, there was no significant differences in assessing the onset time of sensory block and the time to reach the maximum sensory block (p>0.05) [13].

In another study conducted by Dr. Indrajit and colleagues, analgesic effects of adding intrathecal Midazolam to Bupivacaine in the surgical resection of the prostate has been studied. In this study, there was no obvious differences between the two groups in terms of sensory block onset (2.37 ± 0.15 minutes in group B compared with 2.29 ± 0.12 minutes in group BM), It was also shown that there was no

significant differences between the two groups in terms of the onset time of motor block (p>0.05) [14]. Our study also, according to the obtained results indicated that there was no significant difference between the experimental and the control group (p>0.05) in terms of the onset time of both sensory and motor block after administration of anesthetic drug (Table 2).

In a research by Boussofora M et al. [15] the effects of intrathecal Midazolam on postoperative analgesia when added to a combination of clonidine-bupivacaine was evaluated. The results showed that the duration of both sensory and motor block was significantly higher in the Midazolam group (P>0.05).

In another study by N Bhrati and colleagues, the effects of adding Midazolam to Bupivacaine to reduce postoperative pain and enhance the quality of anesthesia after lower abdominal surgery were compared and the results showed that the duration of sensory block was longer in experimental (intervention) group than the control group (218 minutes compared with 165 minutes and p>0.001. Moreover, the duration of the motor block was higher in the experimental (intervention) group than the control group (p>0.01) [16].

In a study conducted by Dr. Indrajit and colleagues, the duration of sensory block was significantly higher in BM group (p<0.001).

Additionally, the study by Malarica Kulkarni and his colleagues as well as other similar studies indicated that the duration of sensory block was significantly higher in the experimental (intervention) group (B) than the control group's (A) (266.36 ± 22.56 minutes in group B compared to 187.8 ± 22.92 minutes in group A) [13].

In our study, the duration of sensory block in the Midazolam group has also been longer and the difference in the two groups was statistically significant (106.25± 28.643 minutes in the Midazolam group compared to 95.13 ± 17.746 in the saline group and p=0.005). In addition, the difference between the two groups was statistically significant in terms of the duration of motor block (92.05 ± 25.579 minutes in Midazolam group compared to 85.10 ± 14.999 minutes in saline group and p=0.014).

In a study by Anirban Chattopadhyay and colleagues, "the analgesic effects of Bupivacaine by itself as well as its combination with Midazolam on lower abdominal surgery" were compared and it was found that there was no significant difference between the two groups in terms of the comparison of intraoperative events (hypotension, bradycardia, nausea, vomiting and respiratory depression) (p>0.05).

Regarding the comparison of postoperative events (PONV and respiratory depression), we found that the p-value for PONV was equal to 0.025, which was statistically significant (9 out of 45 patients in group B, and 2 out of 45 patients in BM group had nausea). However, there was no significant difference between the two groups in terms of respiratory depression (p<0.05) [10]. In a study performed by Dr. Indrajit and his colleagues there was no significant difference between the two groups in terms of hemodynamic changes (Sat O2, Bp, PR) (p>0.05) [14]. In a study by N Bhrati and colleagues, there was no significant difference between the two groups in terms of neurological and other complications [16]. In addition, in another study by Jeshnv Prakash Tople and colleagues the effects of adding intrathecal Midazolam to Bupivacaine on postoperative pain in patients undergoing lower limb orthopedic surgery were evaluated. The study results proved that there was no significant difference between the two groups in terms of side effects such as nausea and vomiting, Desaturation, neurological complications and urinary retention and also in terms of hemodynamic variables (p>0.05) [17].

In our study, although the rate of nausea incidence (Table 3) was more in the Midazolam group than in the control group, but there was no significant difference between the two groups (p=0.193). Other side effects such as bradycardia, pruritus, dizziness, hypotension, urinary retention were not seen in none of the control and intervention group.

Anirban Chattopadhyay and colleagues compared Intraoperative Sedation Score between the two groups, and the obtained result (p=0.017) was statistically significant [10].

The Ramsy Sedation Score between the two groups in our study was equal to p=0.05 and although this difference was not significant, the Sedation Score (drowsiness) of the intervention group was slightly higher than that of the control group (2.15 ± 0.427 in Midazolam group compared with 1.98 ± 0.357 in the saline group).

On the other hand, this insignificant difference may be due to small sample size of the study case and if increasing the sample size, perhaps more significant differences was observed. Boassofora M and others has shown in their study that there was a significant difference between the two groups in terms of the time needed to get sedatives after surgery and the time is longer in the intervention (experimental) group ($p<0.05$) [15]. In our own study, the time of receiving the first analgesic (Diclofenac) after surgery was $p<0.001$. It was statistically significant, and this time was longer in the intervention group than that of the control group.

4. CONCLUSION

The present study found that adding Midazolam to Bupivacaine in spinal anesthesia is effective on increasing the duration of sensory block and therefore it increases the duration of analgesia, duration of motor block, Ramsy Sedation Score (the drowsiness) and also elongates the time required to ask for sedatives after surgical operations.

Like most of the studies, this study had also some limitations including the duration of the patients' follow-up. If the duration of follow-up were longer, results that are more accurate would be obtained. Since Midazolam has very few undesirable side effects and even in its administration by itself, just leads to the least respiratory and cardiovascular weakness, it is considered relatively safe drug even at high doses. Thus, it is recommended in patients who are candidates for surgery under prolonged spinal anesthesia. Midazolam is offered as an additive to the main anesthetic, for intrathecal use.

CONSENT

All authors declare that written informed consent was obtained from all patients.

ETHICAL APPROVAL

This trial registered at Iranian Registry of Clinical Trials; registration code: IRCT2014021716612N1, after obtaining approval from the Ethics Committee of Ardebil University of Medical Sciences.

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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