

The Effect of Intravenous Midazolam on Duration of Spinal Anesthesia

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Background: A variety of systemic and intrathecal adjuvants to local anesthetics have been found to expand the duration and improve the quality of spinal block and decrease pain after surgeries.

Objectives: The aim of this study was to evaluate the effect of the addition of midazolam to lidocaine for spinal anesthesia in lower abdomen and lower limb surgeries.

Patients and Methods: In a prospective, randomized, double blind study, 36 patients aged 20 to 60 years, and American Society of Anesthesiologists (ASA) I or II, were randomly allocated to receive either intravenous midazolam (30 µg/kg) or placebo in spinal anesthesia. Level of sensory block, time to achieve maximum motor and sensory block, duration of sensory and motor block, recovery time, side effects, heart rate, blood pressure, arterial oxygen saturation and sedation score were measured and analyzed using the SPSS software version 15 by t-test and ANOVA. Data were considered significant at 0.05.

Results: The motor block duration in midazolam and control group was 82.9 ± 27.3 and 59.1 ± 26.5, respectively (P = 0.01). However the duration of sensory block was not different between the two groups (P = 0.07). The median of sensory block level was at T8 and T10 in midazolam and control group (P = 0.02). Recovery time was more prolonged in the midazolam group (P = 0.002). Hemodynamic indices did not show any significant differences between the two groups.

Conclusions: Addition of 30 µg/kg midazolam to lidocaine for spinal anesthesia improved duration of motor block and increased intraoperative sedation score without causing side effects in patients' requiring lower abdomen and lower limb surgery.

Keywords: Anesthesia, Spinal; Midazolam; Intravenous Injection

1. Background

Spinal anesthesia using local anesthetics has been broadly applied especially for ambulatory surgery. A variety of systemic and intrathecal adjuvants to local anesthetics have been found to expand the duration and improve the quality of spinal block and decrease pain after surgeries (1).

Intrathecal opioids like lipophilic fentanyl and sufentanil, hydrophilic morphine, adrenergic agonists, such as adrenaline and phenylephrine, and clonidine and dexmedetomidine are the most frequently used, which enhance and prolong sensory block, while nausea/vomiting, pruritus, urinary retention, hypotension and respiratory depression are possible side effects (2-4).

Other intrathecal adjuvants, such as midazolam, ketamine and neostigmine, may also improve the quality of block and prolong analgesia, yet are not popular because of their adverse effects. Several drugs may also affect the spinal block characteristics after systemic administration. Opioids, alpha-2 agonists, ketamine, magnesium sulfate, nitrous oxide and nimodipine reduce postoperative analgesic consumption and may prolong the block. However, applying these agents are limited owing to adverse effects such as respiratory depression, hemodynamic instability, pruritus, urinary retention, nys-

tagmus, and severe nausea and vomiting (4, 5). It is well known that intrathecal midazolam creates analgesic and sedative effects and also potentiates the effect of the local anesthetic without having remarkable side effects (6).

Although a large number of adjuvants are now used for regional anesthesia (RA), clinical evidence of the efficacy of these newer drugs such as midazolam and tramadol is still lacking, and additional studies are indubitably required.

2. Objectives

The aim of this study was to evaluate the effect of the addition of 30 µg/kg midazolam to lidocaine for spinal anesthesia in patients requiring lower abdomen and lower limb surgery.

3. Patients and Methods

This double blind clinical trial (IRCT registration number: IRCT2014090716415N5) included 36 patients aged 20 to 60 years with American Society of Anesthesiologists (ASA) class I or II, who were scheduled for elective lower abdomen and lower limb surgery. After obtaining the approval of the ethics committee of the Isfahan Medical University, the study protocol was explained for patients and

written informed consent was taken from all patients. The participants were randomized into two groups of 18 patients each by randomization software. Patients, who had used benzodiazepine before the surgery, had a history of alcohol or other substance abuse, benzodiazepine hypersensitivity reaction, and any regional anesthesia contraindication, were excluded from the study. The participants were allowed to leave the study whenever they wished.

In the operating room, after routine monitors including non-invasive blood pressure monitor, electrocardiogram, and pulse oximeter were attached to the patients, baseline vital signs were recorded. All patients received 10 cc/kg of Ringer's lactate serum. Spinal anesthesia was performed by 2 mL of 5% lidocaine in sitting position at L3 - L4 or L4 - L5 levels using a 23 G Quincke type needle.

The subjects in the first group received 0.03 mg/kg of midazolam and 1 µg/kg of fentanyl, five minutes after midazolam, intravenously. The second group was considered as control and received normal saline (2 cc) plus 1 µg/kg fentanyl, five minutes after normal saline injection. An anesthesiologist not involved in the study prepared the study solutions so both patient and investigators were blinded to the patient group assignment.

After completion of spinal anesthetic drug administration, level of sensory block was assessed by pinprick testing, every two minutes, until the highest dermatomal level of sensory blockade was achieved. Time to achieve maximum motor and sensory block, duration of sensory and motor block, any side effect (regarding hypotension, nausea and vomiting) and recovery duration were recorded by another anesthesiologist not involved in the study.

Heart rate, systolic and diastolic blood pressure, arterial oxygen saturation (SaO₂) and sedation score were monitored five minutes before surgery and every five minutes during the surgery. Assuming a 5% significance level ($\alpha = 0.05$) and power of 80% ($\beta = 0.20$), to detect seven minutes sedation time differences in two groups, a sample size of 18 patients per group was required. Data were analyzed using the SPSS software version 15. Student's t-test and repeated measure ANOVA (RMA) was used for compar-

ing the two groups' quantitative variable, while the chi-square test was used to evaluate categorical data. P value of < 0.05 was considered statistically significant.

4. Results

We studied a total of 36 patients, 18 in each group with a mean age of 45.9 ± 14.4 years and mean weight of 70.1 ± 9.3 kg. All patients had successful spinal anesthesia and no one was excluded because of technical failure. Twenty-six participants (72.2%) were male and ten were female (27.8%). Demographic and baseline data were similar between the two groups Table 1.

As assessed by Student's t-test, the motor block duration was 82.9 ± 27.3 and 59.1 ± 26.5 minutes for the midazolam and control group, respectively ($P = 0.01$). However, the duration of sensory block was not different between the two groups ($P = 0.07$). The median of sensory block level was at T8 for the midazolam group and at T10 for the control group ($P = 0.02$). Our results showed that the duration of recovery was more prolonged in the midazolam group compared with the control group ($P = 0.002$).

Based on the participants' vital signs, as shown in Table 1, systolic and diastolic blood pressure and heart rate did not show any significant changes within or among the groups. The mean of SaO₂ change was not significantly different between and within groups although in measurements at 25 and 30 minutes after inducing spinal anesthesia, the midazolam group had lower saturation level compared with the control group. There was a trend for progressively higher sedation scores over time in the midazolam group ($P < 0.001$). In addition, postoperative sedation score values were significantly higher in the midazolam group compared with the control group ($P = 0.04$). One patient in the midazolam group and two in the control group required opioid for postoperative pain ($P = 0.99$).

No adverse effect was seen throughout the study period in either group; only three patients had nausea that required antiemetic treatment, among which two were from the midazolam group ($P = 0.04$). None of the patients from either group had vomiting or respiratory distress.

Table 1. Demographic Data, Vital Sign and Physiologic Variables of Participants^{a, b}

Variables	Midazolam Group	Control Group	P Value
Age, y	46.6 ± 15.7	45.3 ± 13.4	0.76
Weight, kg	72.8 ± 6.4	67.3 ± 11	0.08
Gender			0.46
Male	14 (77.8%)	12 (66.7%)	
Female	4 (22.2%)	6 (33.3%)	
Sensory block duration, min	75.1 ± 28	58.8 ± 23.3	0.07
Motor block duration, min	82.9 ± 27.3	59.1 ± 26.5	0.01
Recovery duration, min	116.1 ± 29.6	87.8 ± 21.4	0.002
Systolic blood pressure, mmHg	125.9 ± 17.6	126.1 ± 16.7	0.97
Diastolic blood pressure, mmHg	72.6 ± 10.6	71.5 ± 14.4	0.77
Heart rate, beat/min	81.9 ± 15.9	86.7 ± 17.6	0.36
SaO ₂	97.4 ± 2.3	97.9 ± 1.8	0.21
Sedation score	1.17 ± 0.05	0.46 ± 0.05	< 0.001

^a No. = 18.

^b Data are presented as Mean ± SD.

5. Discussion

This study indicated that the addition of 30 µg/kg midazolam to lidocaine for spinal anesthesia in patients requiring lower abdomen and lower limb surgery, improved duration of motor block and increased intraoperative sedation score without causing side effects.

There are diverse explanations for sedation or analgesia/sedation in regional anesthesia. First, since it is useful to have a cooperative patient during placement of the block, needle puncture and electric stimulation, using continuous infusion or an initial bolus can be helpful. Moreover, sedation reduces postoperative recall and increases global tolerance and acceptance of a regional block (7). In addition, continuous sedation can improve comfort, particularly during uncomfortable positioning and time-consuming surgery (8). Sedatives can lessen the need of opioid analgesics and consequently reduce the prevalence of postoperative nausea and vomiting (9). Lastly, it has been suggested that sedation allows the selection of a shorter duration anesthetic method that improves recovery time and discharge (10-12).

The best sedative agent should also have the least adverse-effects, such as hemodynamic impairment and respiratory depression, which may previously be caused by a spinal block. At present, among the available benzodiazepines, midazolam is the drug chosen for sedation due to its good sedation, excellent amnesia and rapid on- and off-set time (13-16). Midazolam was more effective than metoclopramide for the prevention of nausea and vomiting in patients undergoing caesarean section under spinal anesthesia (17).

Nuotto's study compared clinical sedation and psychomotor function after intravenous injection of midazolam, diazepam, or placebo (saline), and showed that midazolam (0.15 mg/kg) produced the highest scores of sedation and most impairment of psychomotor performance (18). Heart rate and systolic and diastolic blood pressure did not differ amongst the two groups and did not change during the study, as reported by previous studies (6, 19). Nishiyama showed that adding midazolam to a continuous epidural infusion of bupivacaine in patients undergoing laparotomy, improved sedation and amnesia, and provided better analgesia than bupivacaine alone without any side effects (19). In a previous study that evaluated the potential pain reducing effect of IV midazolam in patients undergoing oral surgery, patients in the midazolam group had significantly lower pain intensity scores, significantly longer time to first analgesic, less analgesic consumption and better global assessment than those in the control group (20). Systemically administered midazolam had antinociceptive effects on acute thermal, acute mechanical, and acute inflammatory-induced nociception in mice (21).

Ghai assessed the effect of adding midazolam to continuous epidural infusion of bupivacaine for postoperative analgesia in children and concluded that the number

of patients requiring rescue analgesia during infusion was significantly lower in Group BM (bupivacaine plus midazolam). Time to first rescue analgesia was significantly prolonged in Group BM compared with Group B, and greater sedation scores were noted in Group BM. Frequency of rescue analgesia administration was significantly less in Group BM and median pain scores were significantly lower in Group BM than Group B, at all-time intervals (22).

Midazolam produces neuraxial analgesia by affecting gamma-aminobutyric acid (GABA) receptors and causing antinociception by reducing spinal cord hyperexcitability (23). Some clinical studies have discussed the efficacy of midazolam in producing analgesia, when administered intrathecally and epidurally for labor and postoperative pain (24, 25). In the present study, we evaluated the effect of midazolam in combination with lidocaine. We observed that adding 30 µg/kg of midazolam to lidocaine for spinal anesthesia improved duration of motor block and increased intraoperative sedation score without causing side effects in patients' requiring lower abdomen and lower limb surgery.

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Authors' Contributions

Study concept and design: Reihanak Talakoub, Mehran Rezvani, Ameneh Alikhani and Mohammad Golparvar. Acquisition of data: Reihanak Talakoub, Ameneh Alikhani, Mohammad Golparvar and Zahra Amini. Analysis and interpretation of data and statistical analysis: Mohammad Golparvar, Mitra Jabalameli and Zahra Amini. Drafting of the manuscript: Reihanak Talakoub, Mehran Rezvani, Mohammad Golparvar and Zahra Amini. Critical revision of the manuscript for important intellectual content: Reihanak Talakoub, Mohammad Golparvar and Zahra Amini. Study supervision: Reihanak Talakoub.

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