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Dose-finding study of intravenous midazolam for sedation and amnesia during spinal anesthesia in patients premedicated with intramuscular midazolam

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Abstract

Purpose. We investigated the effective and safe dose of intravenous midazolam for sedation and amnesia during spinal anesthesia in patients premedicated with intramuscular midazolam.

Methods. One hundred and eighty patients aged 20–50 years scheduled for spinal anesthesia received midazolam 0.06 mg·kg^{-1} and atropine 0.01 mg·kg^{-1} intramuscularly 15 min before entering the operating room. Spinal anesthesia was performed with 0.5% hyperbaric tetracaine. Five minutes after starting surgery, midazolam 0 (control group), 0.01, 0.02, 0.03, 0.04, or 0.05 mg·kg^{-1} was intravenously administered (30 patients each). Blood pressure, heart rate, respiratory rate, percutaneous oxygen saturation ($S_{P_{O_2}}$), verbal response, eyelash reflex, and involuntary body movement were measured every 5 min for 30 min. Memory during surgery was also investigated.

Results. The number of the patients with loss of verbal response, with loss of eyelash reflex, and with no memory during surgery were significantly larger in the groups receiving midazolam ≥0.03 mg·kg^{-1}, ≥0.04 mg·kg^{-1}, and ≥0.02 mg·kg^{-1}, respectively. The decrease in blood pressure or increase in respiratory rate with decrease in $S_{P_{O_2}}$ was significantly larger in the groups receiving midazolam ≥0.03 mg·kg^{-1} or 0.05 mg·kg^{-1}, respectively.

Conclusion. For sedation and amnesia of the patients aged 20–50 years in spinal anesthesia with about 1 h duration receiving intramuscular midazolam 0.06 mg·kg^{-1} as a premedication, intravenous midazolam 0.02 mg·kg^{-1} might be effective and safe.

Key words Spinal anesthesia · Sedation · Midazolam · Intravenous · Intramuscular

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Introduction

During surgery under spinal anesthesia, many patients prefer to be sedated. For this purpose, bolus administration of midazolam is reported to give enough sedation during spinal anesthesia [1,2]. Patients would be comfortable, with freedom from anxiety, if they do not have the memory of surgery [3]. In the previous study [1], intravenous midazolam 0.05 mg·kg^{-1} was judged as adequate for sedation and amnesia of patients aged 30–70 years under spinal anesthesia. In that study, intramuscular hydroxyzine was used as a premedication. The drugs administered as a premedication would have interactions with intravenous sedatives used during surgery. In the present study, we investigated the effective and safe dose of intravenous midazolam for sedation and amnesia during spinal anesthesia in patients premedicated with intramuscular midazolam.

Patients and methods

After the approval of the research committee of the hospital and informed consent from the patients, 180 patients aged 20–50 years scheduled for spinal anesthesia with ASA physical status I were divided into six groups according to the intravenous dose of midazolam using a random number table. Those patients who had cardiovascular, respiratory, neurological, psychological, hepatic, renal, or spinal disease, and those who had taken any drugs influencing liver metabolism or mental state, were not included in the study.

As a premedication, midazolam 0.06 mg·kg^{-1} with atropine 0.01 mg·kg^{-1} (maximum, 0.5 mg) was administered intramuscularly 15 min before entering the operating room in the ward as a standard procedure. Spinal anesthesia was performed at the L4–L5 interspinal space with 0.5% hyperbaric tetracaine. The dose and speed of injection of tetracaine were judged by the

Table 1. Patient characteristics ($n = 180$)

Midazolam iv dose ($mg \cdot kg^{-1}$)	0 (control)	0.01	0.02	0.03	0.04	0.05
Age (years)	37 ± 8	40 ± 6	42 ± 7	38 ± 6	39 ± 7	41 ± 6
Sex (Male/female)	11/19	13/17	12/18	14/16	12/18	13/17
Body weight (kg)	53 ± 7	51 ± 7	52 ± 8	49 ± 7	51 ± 8	53 ± 8
Surgery						
Lower abdomen	18	16	17	15	19	16
Lower extremities	12	14	13	15	11	14
Duration of surgery (min)	53 ± 11	58 ± 10	59 ± 13	52 ± 10	56 ± 11	54 ± 10
Interval between premedication and intravenous midazolam (start of the study) (min)	65 ± 17	60 ± 14	64 ± 18	66 ± 17	62 ± 13	62 ± 15
Dose of tetracaine (mg)	11 ± 2	10 ± 3	12 ± 2	11 ± 3	10 ± 3	11 ± 3
Maximum anesthesia level[a]	Th6 (Th4–Th10)	Th7 (Th4–Th11)	Th6 (Th4–Th9)	Th6 (Th4–Th11)	Th5 (Th4–Th7)	Th6 (Th4–Th9)

Data are mean ± standard deviation or number of patients
Th, thoracic segment
[a] Median (range)

anesthesiologist in each case. Anesthesia level was checked with a cold sensation. After fixing the anesthesia level, surgery started. Five minutes after starting surgery, midazolam 0 (nothing was administered, control), 0.01, 0.02, 0.03, 0.04, or 0.05 $mg \cdot kg^{-1}$ was intravenously administered as a bolus (30 patients each). Lactated Ringer's solution was infused at a rate of 4 $ml \cdot kg^{-1} \cdot h^{-1}$ using an infusion pump from the start of anesthesia. Oxygen 2 $l \cdot min^{-1}$ was administered nasally. Those with failed spinal anesthesia and with anesthesia level more than Th4 were excluded from the study and other patients were enrolled until each group had 30 patients.

Noninvasive blood pressure, heart rate, respiratory rate, percutaneous arterial oxygen saturation (Sp_{O_2}), verbal response against calling the name of the patient, and eyelash reflex were monitored every 5 min for 30 min after intravenous midazolam was administered (5 min from the start of surgery in the control group). At the end of surgery, all the parameters were measured again. Body movement was also checked. Involuntary movement was judged as having moved. Memory of the verbal contact (calling the name of the patient) during the study was checked on the next morning.

Data are expressed as mean ± standard deviation. Statistical analysis was performed with the chi-square test for gender, and the number of patients with loss of verbal response, eyelash reflex, and movement, factorial analysis of variance (ANOVA) for other demographic data, and repeated-measures ANOVA followed by the Student–Newman–Keuls method as a post hoc test if applicable for blood pressure and heart rate. Respiratory rate and Sp_{O_2} were analyzed by the Kruskal–Wallis test and Friedman test. A $P < 0.05$ was considered statistically significant. A post hoc power analysis was performed with the G Power Version 2.1.2 (Trieter University, Trieter, Germany).

Results

No patients failed spinal anesthesia. One patient in the control group (midazolam 0 $mg \cdot kg^{-1}$) had anesthesia level with Th3; therefore, this patient was excluded from the study and one more patient was added into the study at the end. Patient background and anesthesia level were not different among the six groups (Table 1). The power of this study was 0.7212.

No patients lost verbal response or eyelash reflex before intravenous midazolam. The number of the patients with loss of verbal response was significantly larger in the 0.03, 0.04, and 0.05 $mg \cdot kg^{-1}$ groups than the control group (0 $mg \cdot kg^{-1}$) (Table 2). The number of the patients with loss of eyelash reflex was significantly larger in the 0.04 and 0.05 $mg \cdot kg^{-1}$ groups than the control group (0 $mg \cdot kg^{-1}$). Body movement was observed in the 0.01, 0.02, 0.03, and 0.04 $mg \cdot kg^{-1}$ groups, but the number of the patients with body movement was not different among the groups. At the end of surgery, all the patients were alert and calm. The number of the patients with no memory during surgery was significantly larger in the 0.02, 0.03, 0.04, and 0.05 $mg \cdot kg^{-1}$ groups than the control group (0 $mg \cdot kg^{-1}$).

Blood pressure decreased significantly at 5, 10, and 15 min compared to the control value (time 0) in the 0.03, 0.04, and 0.05 $mg \cdot kg^{-1}$ groups (Fig. 1). However, no treatment was necessary. Heart rate did not change significantly during the study in all groups. Respiratory rate increased and Sp_{O_2} decreased significantly at 5, 10, and 15 min in the 0.05 $mg \cdot kg^{-1}$ group. No changes were observed in the other groups (Table 3).

Table 2. Verbal response, eyelash reflex, body movement, and memory

Midazolam iv dose ($mg \cdot kg^{-1}$)		0 (control)	0.01	0.02	0.03	0.04	0.05
	Time (min)						
Loss of verbal response	0	0	0	0	0	0	0
	5	0	3	7	9	10	20
	10	2	4	7	11	15	20
	15	3	4	7	11	15	18
	20	2	3	6	8	9	12
	25	2	2	4	5	5	8
	30	0	0	1	2	3	4
	At the end of surgery	0	0	0	0	0	0
	Total	3	4	7	11*,**	15*,**,***	20*,**,***,****
Loss of eyelash reflex	0	0	0	0	0	0	0
	5	0	1	2	3	8	14
	10	0	1	3	3	9	14
	15	0	0	2	2	8	10
	20	0	0	1	1	5	8
	25	0	0	1	1	2	5
	30	0	0	0	0	1	2
	At the end of surgery	0	0	0	0	0	0
	Total	0	1	3	3	9*,**	14*,**,***,****
Body movement	0	0	0	0	0	0	0
	5	0	1	0	0	0	0
	10	0	0	1	1	0	0
	15	0	2	1	2	1	0
	20	0	2	2	1	1	0
	25	0	1	1	0	0	0
	30	0	0	0	0	0	0
	At the end of surgery	0	0	0	0	0	
	Total	0	3	3	2	1	0
Loss of memory		9	14	19*	23*,**	27*,**,***	30*,**,***,****

Number of patients is shown; total number of patients in each dose tested is 30
* $P < 0.05$ vs. the control (midazolam $0\,mg \cdot kg^{-1}$); ** $P < 0.05$ vs. $0.01\,mg \cdot kg^{-1}$; *** $P < 0.05$ vs. $0.02\,mg \cdot kg^{-1}$; **** $P < 0.05$ vs. $0.03\,mg \cdot kg^{-1}$

Table 3. Respiratory rate and oxygen saturation

Midazolam iv dose ($mg \cdot kg^{-1}$)	0 (control)	0.01	0.02	0.03	0.04	0.05
Respiratory rate						
Time (min)						
0	14 (12–16)	13 (10–16)	15 (12–17)	14 (11–16)	13 (11–15)	14 (11–17)
5	15 (13–17)	14 (11–16)	16 (13–18)	15 (13–17)	16 (15–17)	18 (16–20)*
10	16 (13–19)	14 (12–16)	14 (12–16)	16 (14–17)	15 (13–17)	18 (14–22)*
15	14 (11–17)	14 (12–16)	15 (12–18)	15 (13–17)	14 (13–15)	17 (14–19)*
20	14 (12–16)	13 (10–16)	14 (12–16)	15 (13–17)	15 (13–17)	15 (14–17)
30	15 (12–18)	14 (11–16)	13 (10–17)	14 (13–15)	14 (11–17)	14 (12–16)
S_{PO_2}						
Time (min)						
0	98 (97–100)	97 (96–98)	97 (96–98)	97 (98–99)	98 (97–100)	98 (97–100)
5	97 (96–100)	97 (96–100)	97 (96–99)	96 (95–97)	96 (95–98)	95 (94–97)*
10	98 (97–99)	98 (97–99)	96 (95–97)	97 (95–98)	96 (95–97)	95 (94–96)*
15	99 (98–100)	98 (96–99)	97 (96–99)	98 (97–99)	97 (96–98)	96 (95–97)
20	98 (97–99)	97 (96–98)	97 (96–98)	97 (96–98)	98 (97–99)	97 (96–98)
30	98 (97–100)	98 (97–99)	98 (97–99)	97 (96–99)	97 (96–98)	97 (96–99)

Median (range) is shown
S_{PO_2}, percutaneous arterial oxygen saturation
* $P < 0.05$ vs. the value at time 0

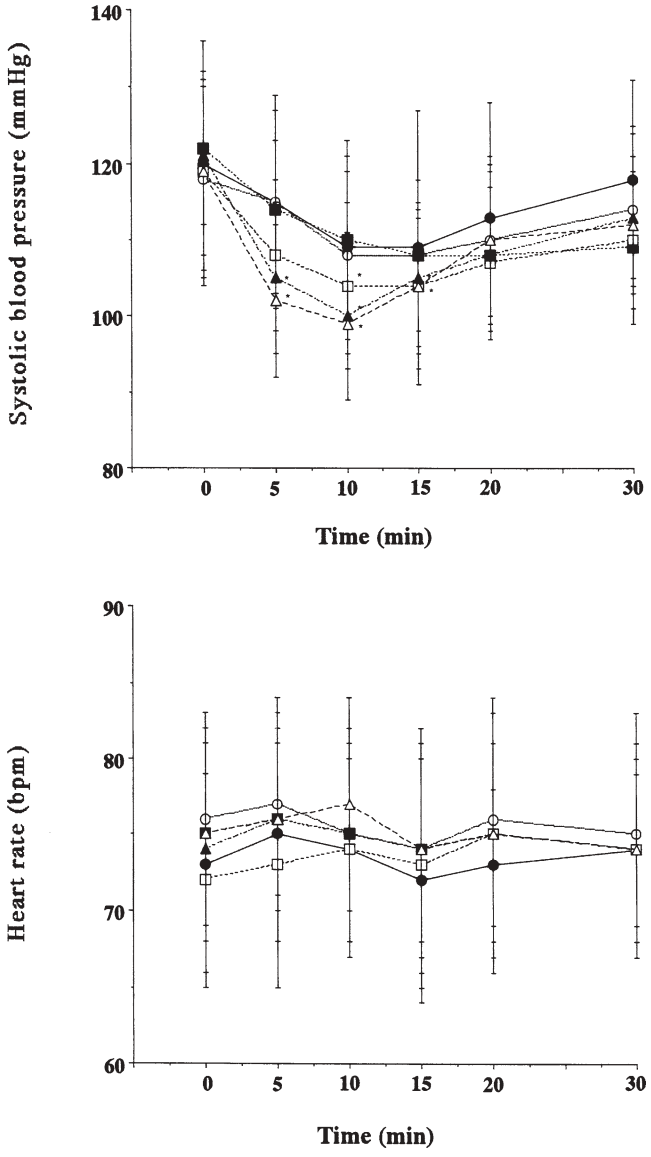

Fig. 1. Blood pressure (*upper*) and heart rate (*lower*): mean ± standard deviation. *Closed circles*, control (0 mg·kg^{-1}); *open circles*, 0.01 mg·kg^{-1}; *closed squares*, 0.02 mg·kg^{-1}; *open squares*, 0.03 mg·kg^{-1}; *closed triangles*, 0.04 mg·kg^{-1}; *open triangles*, 0.05 mg·kg^{-1}. *$P < 0.05$ vs. the control value (the value at time 0 in each dose)

Discussion

As a premedication, intramuscular midazolam combined with atropine would have the benefit of inducing amnesia, avoiding harmful reflex, and decreasing salivary excretion. Therefore, we used midazolam with atropine as our routine premedication. The optimal administration time of intramuscular midazolam was 15 min before entering the operating room, judged by amnesic and sedative effects as well as hemodynamic and respiratory adverse effects [4]. This is also confirmed by its pharmacological aspect, in that a peak blood concentration is obtained 20–45 min after injection [5]. The optimal dose of intramuscular midazolam premedication was 0.08 mg·kg^{-1} and 0.06 mg·kg^{-1} in patients aged 20–39 years and 40–59 years, respectively, in the previous study [6]. In the present study, therefore, midazolam 0.06 mg·kg^{-1} was administered 15 min before entering the operating room.

Intramuscular midazolam premedication was reported to reduce the loading and infusion dose of propofol for sedation about 17% and also reduced the incidence of intraoperative memory [7]. When hydroxyzine was used as a premedication [1], intravenous midazolam 0.05 mg·kg^{-1} was the optimal dose for sedation and amnesia during spinal anesthesia, whereas in the present study using midazolam as a premedication, 0.02 mg·kg^{-1} of intravenous midazolam was sufficient. Midazolam premedication could decrease the dose of intravenous midazolam for sedation and amnesia compared to hydroxyzine premedication. During spinal anesthesia, decreased neuronal input induces sedative tendency to increase sensitivity to hypnotics [8]. Therefore, loss of verbal response observed even in the control group might be caused by the additive effects of midazolam premedication and spinal anesthesia.

Dose-dependent decrease in blood pressure was observed with significant decreases at 0.03 to 0.05 mg·kg^{-1} of midazolam, whereas no patients required treatment. Therefore, clinically these changes are not important, although 0.02 mg·kg^{-1} or less might be safer than the higher doses. Regarding respiration, midazolam is reported to decrease tidal volume and increase respiratory rate [9]. In the present study, respiratory rate increased and S_{pO_2} decreased significantly only with midazolam 0.05 mg·kg^{-1}. Therefore, less than 0.04 mg·kg^{-1} of midazolam would not have any harmful effects on respiration.

The amnesic effect of midazolam [3] makes it useful as a premedicant and/or an intraoperative sedative. Amnesic effect had no relation with sedative effect [10]. During spinal anesthesia that lasted for 40–60 min, intravenous midazolam 0.05 mg·kg^{-1} was enough to give adequate sedation with complete amnesia after hydroxyzine 50 mg intramuscular premedication [1]. Even when an additional dose was required, 1 mg was enough to maintain amnesia [2]. In the present study, after intramuscular midazolam 0.06 mg·kg^{-1} as a premedication, intravenous 0.02 mg·kg^{-1} midazolam could induce significant amnesia during approximately 1 h of surgery. For longer surgery, we need further studies to investigate whether additional midazolam is necessary and, if necessary, how much is an adequate dose.

In conclusion, it is suggested that intravenous midazolam 0.02 mg·kg^{-1} might be enough for sedation and intraoperative amnesia of patients aged 20–50 years

receiving spinal anesthesia with approximately 1 h duration after premedication with intramuscular midazolam 0.06 mg·kg^{-1}.

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