Influence of Intravenous Sedation with Midazolam on Respiratory Function and Muscle Activity in Elderly and Young Patients

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Abstract

Objective: *The purpose of this study was to investigate the optimal dosage of intravenous midazolam for sedation in elderly patients and compare the amount of depression of respiratory function and skeletal muscle activity after obtaining similar sedation levels in younger patients.*

Patients and Methods: *Fifteen elderly patients older than 65 years (group E) and 15 patients younger than 55 years (group Y) underwent oral surgery or dental treatment with or without local anaesthesia after intravenous administration of midazolam.*

Results: *The optimal dose for the elderly patients was 62% that for the younger patients. The duration of depression of arterial oxygen saturation and vital capacity was more prolonged among patients in group E than in those in group Y. The number of patients whose grip strength value recovered 15 and 30 minutes after administration of midazolam was significantly smaller for group E than for group Y.*

Conclusion: *These results suggest that elderly people should be carefully treated with attention to the decrease in skeletal muscle activity, including respiratory and upper airway muscles, when receiving intravenous sedation with midazolam.*

Key Words: Aged, Sedative, nonbarbiturate, Respiratory muscles, Hand strength

Introduction

Intravenous sedation is sometimes given to elderly patients to decrease surgical stress and accidental complications during oral surgery.[1,2] Excessive sedation, airway obstruction, and respiratory failure may occur in elderly patients when the same dose of benzodiazepine sedatives as that needed for younger patients is administered, because the pharmacodynamics and/or pharmacokinetics of these drugs are different for elderly and younger persons.[3-8] The purpose of this study was to investigate the optimal dosage of intravenous midazolam for sedation of elderly patients, and compare the amount of depression of respiratory function and skeletal muscle activity after obtaining similar sedation levels in younger patients.

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Patients and Methods

Fifteen elderly patients older than 65 years (group E) and 15 patients younger than 55 years (group Y) were enrolled in the study after obtaining Hokkaido University Graduate School of Dental Medicine Review Board approval and informed consent. The patients underwent oral surgery or dental treatment with or without local anaesthesia after intravenous administration of midazolam. Long-term benzodiazepine users and those who suffered from liver, renal, or neuromuscular disorders were excluded from the study.

Midazolam was carefully titrated for 4 to 5 minutes until the optimal sedation level was obtained. This was defined as ptosis of the eyelid, slow response to verbal commands, or slight slurring of speech. No incremental dose was given after the optimal sedation level was achieved. The parameters studied were

arterial oxygen saturation (SpO_2) measured perioperatively with a pulse-oxymeter, grip strength at baseline, and 5, 15, 30, and 45 minutes after midazolam administration, and spirogram at baseline, and 60 and 90 minutes after midazolam administration.

The value measured at each time point was compared with the baseline value and compared between the 2 groups. When there were already significant differences in the baseline values between the groups, a comparison of values at each time was not calculated. For the parameters other than SpO_2, comparison of the rate of patients in whom the value at each time recovered to more than 90% of the baseline value was also done between the groups.

Statistical analyses were performed using repeated-measures analysis of variance (ANOVA), Mann-Whitney U test, and Fisher's exact probability test using statistics programs (StatView and Super ANOVA, ABACUS Concepts Inc., Berkeley, USA). The level of significance was 5%. All data are presented as mean values ± the standard deviation.

It was confirmed that there were no significant differences in any parameters between the 2 groups 5 minutes after administration of midazolam (Figure 1), supporting the hypothesis that any decrease and recovery of function from similar sedation levels could be compared between the 2 groups.

Results

The patients' characteristics are summarised in Table 1. There were no significant differences between the 2 groups except for age. Two patients had pre-existing pulmonary disease in group E, and none had pulmonary disease in group Y. Six patients were smokers in both groups. Eleven patients in group E underwent oral surgery such as removal of cysts or benign tumours, and tooth extraction, and 4 underwent dental treatment. Twelve patients in group Y received oral surgery as described above and 3 had dental treatment. Fourteen patients received local anaesthesia in each group.

	Elderly patients (n = 15)	Younger patients (n = 15)	
Age (years)	72.1 ± 4.9 (range, 66-82)	34.7 ± 12.7 (range, 18-54)	$p < 0.0001$
Male/female	9/6	8/7	
Height (cm)	156.9 ± 10.6	162.0 ± 8.5	Not significant
Weight (kg)	58.8 ± 10.1	58.4 ± 10.6	Not significant
Body mass index (kg/m^2)	23.7 ± 2.7	22.2 ± 3.9	Not significant

Table 1. Patients' characteristics.

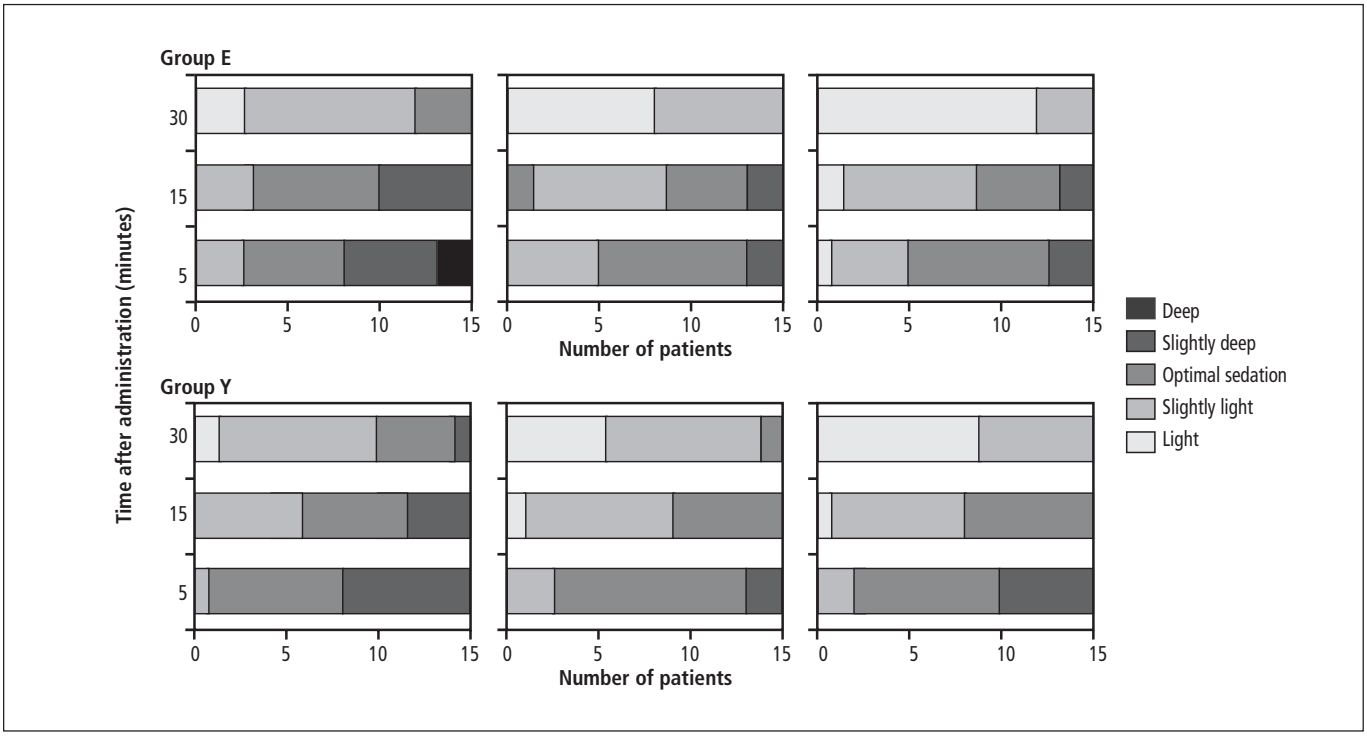

Figure 1. Degree of sedation after administration of midazolam.

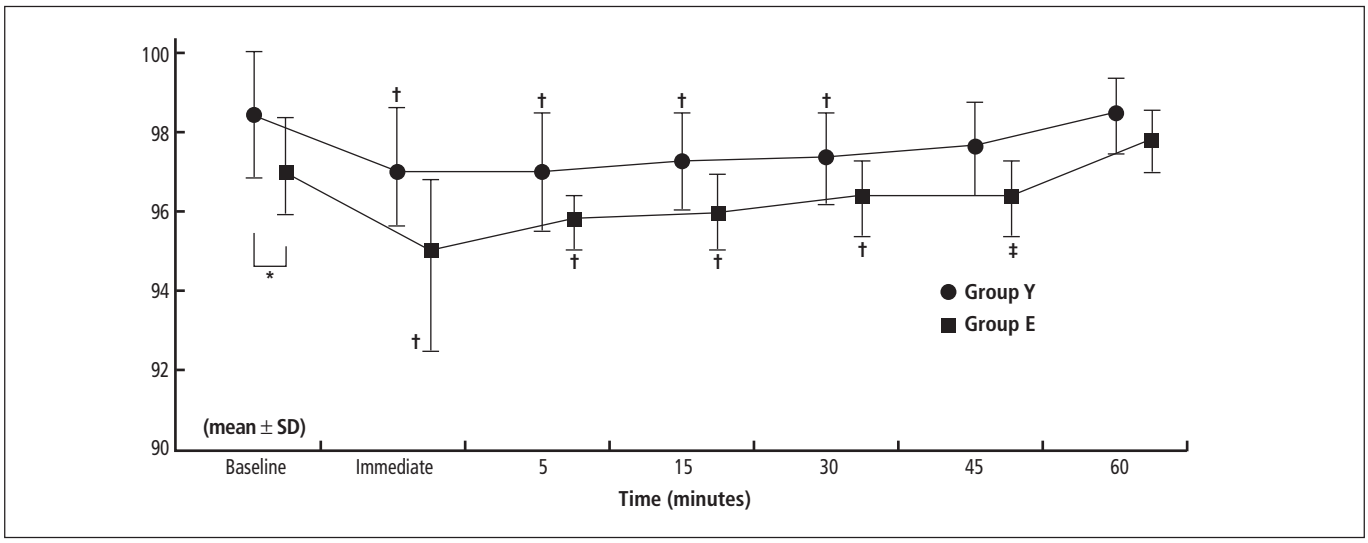

Figure 2. Time course of SpO_2 after administration of midazolam. * p < 0.05 (between the groups); † p < 0.01 (vs baseline); ‡ p < 0.05.

There were no significant differences for the duration of the operation between the 2 groups (group E, 29.7 ± 17.2 minutes; group Y, 38.7 ± 19.3 minutes). The mean dose of midazolam administered was 2.60 ± 0.57 mg (0.045 ± 0 .012 mg/kg) for group E. This was significantly less than for group Y (4.20 ± 1.18 mg; 0.074 ± 0.026 mg/kg; $p < 0.001$). The dosage for the elderly patients was 62% of that needed for the younger patients. The duration of the SpO_2-depression effect of midazolam in group E was more prolonged than in group Y (45 to 60 minutes vs 30 to 45 minutes; Figure 2). The 3 patients older than 75 years old showed a decrease in SpO_2 below 93% and were administered nasal oxygen during surgery.

The grip strength level significantly decreased until 30 minutes after administration of midazolam compared with the baseline values in both groups (Figure 3a). However, the rate of recovered patients in group E was significantly smaller than that of group Y 15 and 30 minutes after the administration (7% vs 47% and 40% vs 87%, respectively; $p < 0.05$; Figure 3b). Vital capacity among patients in group E significantly decreased 60 minutes after the administration of midazolam compared with the baseline value (Figure 4). There were no significant changes in forced expiratory ventilation$_{1.0}$ ($FEV_{1.0}$) in either group. All patients were safely treated without complications, including respiratory problems.

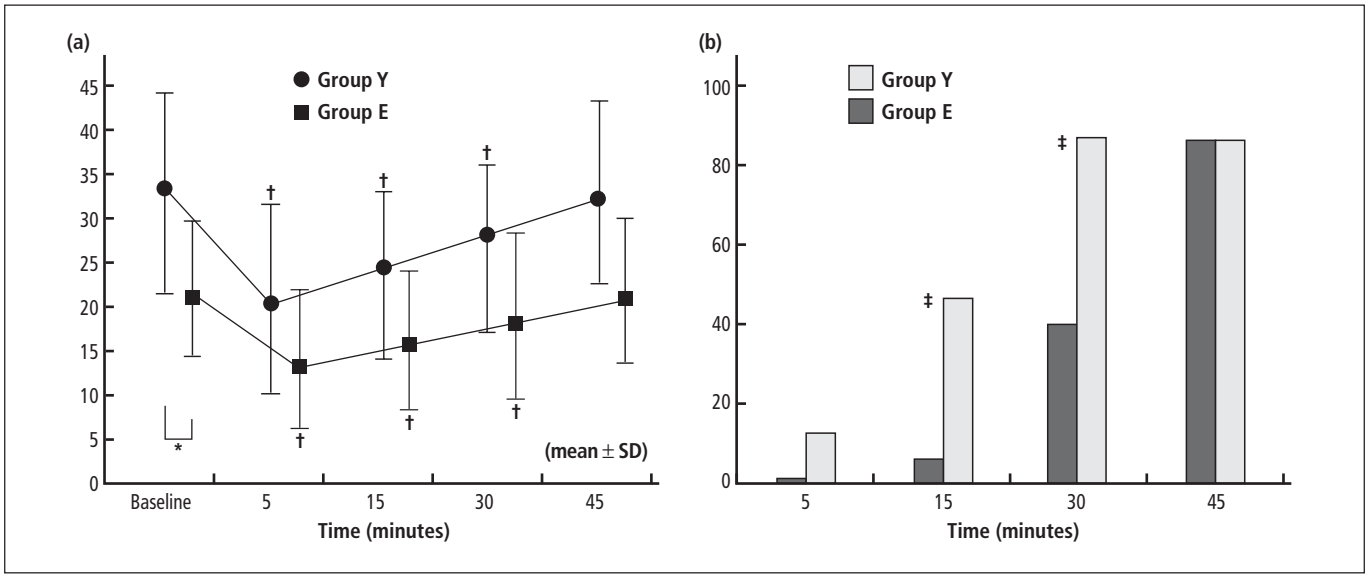

Figure 3. Grip strength. (a) Time course of grip strength; and (b) number of patients whose grip strength recovered to more than 90% of the baseline value. * p < 0.01 (between the groups); † p < 0.01 (vs baseline); ‡ p < 0.05 (between the groups).

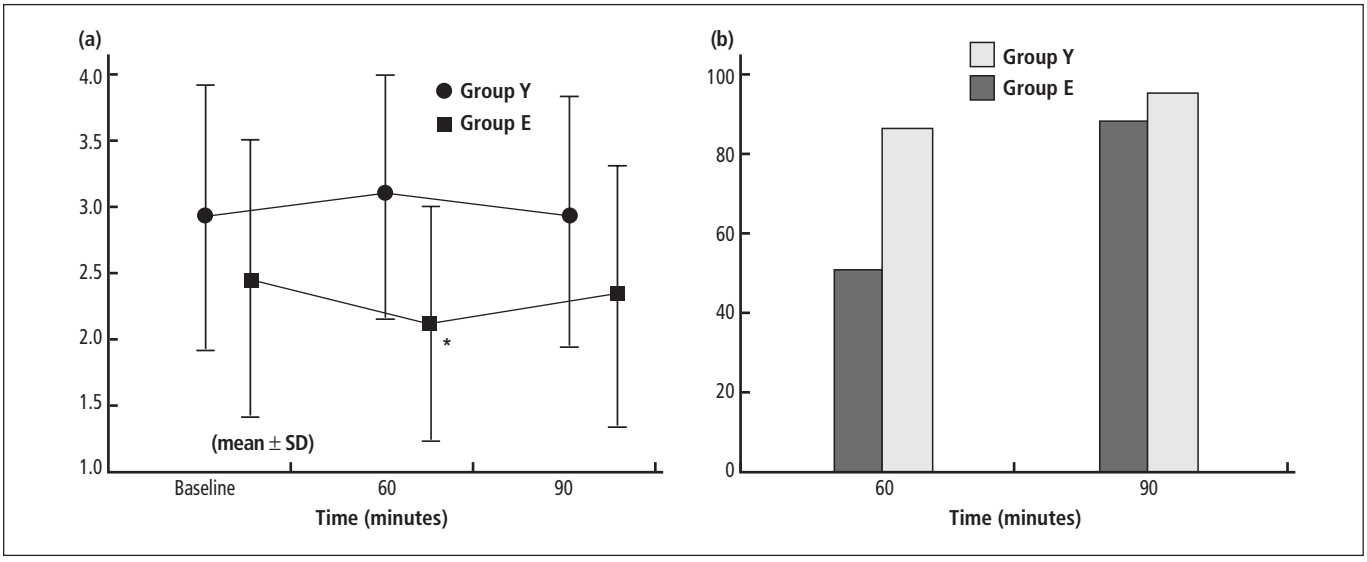

Figure 4. Vital capacity. (a) Time course of vital capacity; (b) number of patients whose vital capacity recovered to more than 90% of the baseline value. * p < 0.05 (vs baseline).

Discussion

There have been reports about optimal doses of minor tranquillisers for intravenous sedation for the elderly.[2,9,10] Reidenberg et al reported that the required dosage of diazepam for intravenous sedation of the elderly (aged 75 years or older) was 50% of that for those in their 20s.[9] Kitagawa et al reported that the required dosages of diazepam and flunitrazepam for optimal sedation of patients in their 60s, 70s, and 80s were 75%, 40% to 60%, and 30% to 45%, respectively, of those for young and middle-aged patients.[2] Bell et al reported that the required dosage for intravenous sedation with midazolam, which is the drug used in the present study, for fiberoptic examination of the stomach in the elderly (older than 65 years) was less than 60% of that for those in their 20s.[10] As expected, in the present study, the required dosage of midazolam for elderly patients was 62% that of younger patients.

This study clarified that the duration of SpO_2 depression induced by midazolam in group E was more than 45 minutes. Midazolam is often used for operations taking approximately 30 minutes. Therefore, postoperative monitoring of SpO_2 should be continued until 1 hour after the administration of midazolam for elderly patients, even after they enter the recovery room. Haines et al reported that mean oxygen saturation had not returned to pre-sedative values by 2 hours after the procedure, when midazolam (mean 3 mg) was intravenously administered to elderly patients undergoing upper gastrointestinal endoscopy.[11] The difference in these durations is probably because the patients in their study were very elderly (mean, 79 years; range, 63 to 91 years). These authors reported that SpO_2 values of 5 of 30 patients fell below 85% during the procedure. Likewise, in the present study, all 3 patients aged older than 75 years showed a decrease in SpO_2. In general, hypoxia is accompanied with hypercapnia when breathing room air. Although hypoxia can easily be corrected with nasal oxygen, leaving severe hypercapnia uncorrected may lead to respiratory arrest.[12] Therefore, careful attention should be paid to the management of the elderly, especially those aged more than 75 years.

No studies have been done on decrease in grip strength after intravenous sedation for the elderly. In the present study, the reason for the significant decrease in grasping power 5 and 15 minutes after the administration of midazolam compared with control values seem to be derived from central nervous system depression as well as decreased grasping power. However, since the sedation level decreased for many patients 30 minutes after administration, decreased grasping power 30 minutes after administration seemed to be due to a decrease in muscle power. Moreover, the baseline values of the elderly patients was two-thirds that of younger patients. The rate for recovered elderly patients was also smaller than that of younger patients 30 minutes

after the administration, suggesting that elderly patients should refrain from supporting their own weight such as when gargling during treatment or moving after surgery within 30 minutes after the administration of midazolam.

It has been reported that a sedative dose of midazolam depresses respiratory and pharyngeal muscle activity in adults.[13-15] Drummond reported that the activity of the muscles of the tongue, anterior neck, and scalene group decreased significantly after 0.08 mg/kg intravenous midazolam administration.[13] Molliex et al also reported that diaphragm activity was reduced and upper airway obstruction was seen after a sedative dose of midazolam.[14] Moreover, Montravers et al reported that a 6-fold increase in upper airway resistance was observed due to the impaired activity of the upper airway muscles such as the genioglossus muscle after 0.1 mg/kg of intravenous midazolam administration in healthy volunteers.[15] These results suggest that the decrease in the activity of these muscles induced by midazolam is one of the main reasons for the SpO_2 depression.

Benzodiazepines are presumed to exert muscle-relaxation effects via benzodiazepine$_2$ (BZD_2) receptors on $GABA_A$ receptors in the spinal cord.[16-18] Date et al reported that a sedative dose of benzodiazepine produced central muscle relaxation by inhibiting polysynaptic pathways in the spinal cord in decerebrated cats.[16] Griebel et al also reported that BZD_2 receptors play an important role in the muscle relaxation effects of benzodiazepine ligands, whereas activity at BZD_1 receptors is associated with anxiolytic and sedative effects.[17] Since the receptor and action sites of the muscle-relaxation by benzodiazepine are different from those of its sedative effects (BZD_2 vs BZD_1, spinal cord vs cerebral cortex),[18] one should consider that the recovery of one action does not always mean the recovery of other actions. In the present study, there was a difference in the degree of recovery of grasping power between the 2 groups. Although the reason is not clear, it may derive from the enhanced affinity or sensitivity of midazolam to receptors in the elderly as well as muscle atrophy. If a partial BZD agonist, which produces a potent anxiolytic effect with weak muscle-relaxant and respiratory-depressant effect, becomes commercially available for intravenous administration, the management of intravenous sedation should be safer.

It has been reported that vital capacity recovered to 90% of the baseline value 2 hours after the end of surgery using spinal anaesthesia and intravenous midazolam for elderly patients.[19] However, this result was obtained after several incremental doses during surgery. In the present study, a significant delay in recovery from decreased vital capacity was seen for elderly patients and the duration of the depression effect seemed to be 60 to 90 minutes. Although vital capacity is one of the indices of respiratory reservation, it is measured under non-physiological respiration. Therefore, a decrease in vital capacity may not be important for safe management of intravenous sedation unless it is severe. However, the present study revealed that respiratory muscle activity in the elderly was not perfectly recovered, even 60 minutes after the administration of midazolam when significant reduction of SpO_2 had improved.

It is appreciated that ageing increases sensitivity to the sedative effects of midazolam and prolongs the duration of its action.[3-8] The increasing pharmacodynamic sensitivity due to ageing has been explained by electroencephalography data,[3] the dose for disappearance of reaction to verbal commands,[4] and psychometric tests.[5] The elimination half-life was significantly prolonged and total clearance was significantly reduced,[6,7] whereas no significant differences were seen in the distribution phase half-life and volume of distribution between young and elderly patients.[4,8] In the present study, similar sedation levels were obtained in the elderly with 62% of the midazolam dosage needed for younger patients, probably because of pharmacodynamic effects. Although the midazolam dose administered was initially smaller for the elderly patients, the depression effect on SpO_2 and vital capacity was prolonged, probably because of the pharmacokinetic factors described above. These results were obtained in the study of midazolam administration just prior to surgery. In the case of the incremental injection during surgery, a prolonged depression effect may be enhanced for the elderly in relation to distribution, metabolism, and elimination.

Conclusion

When the optimal dose was administered, elderly patients could be safely treated using intravenous sedation with midazolam, as could younger patients. However, elderly patients should be carefully managed with attention to the decrease in skeletal muscle activity, including respiratory and upper airway muscles, even when the administered dose is smaller than for younger patients.

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