Risk factor analysis of additional administration of sedative agent and patient dissatisfaction in intravenous conscious sedation using midazolam for third molar extraction

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Abstract (J Korean Assoc Oral Maxillofac Surg 2017;43:229-238)

Objectives: The primary purpose of this study was to investigate the factors related with additional administration of sedative agent during intravenous conscious sedation (IVS) using midazolam (MDZ). The secondary purpose was to analyze the factors affecting patient satisfaction.
Materials and Methods: Clinical data for 124 patients who had undergone surgical extraction of mandibular third molar under IVS using MDZ were retrospectively investigated in this case-control study. The initial dose of MDZ was determined by body mass index (BMI) and weight. In the case of insufficient sedation at the beginning of surgery, additional doses were injected. During surgery, peripheral oxygen saturation, bispectral index score (BIS), heart rate, and blood pressure were monitored and recorded. The predictor variables were sex, age, BMI, sleeping time ratio, dental anxiety, Pederson scale, and initial dose of MDZ. The outcome variables were additional administration of MDZ, observer's assessment of alertness/sedation, intraoperative amnesia, and patient satisfaction. Descriptive statistics were computed, and the *P*-value was set at 0.05.
Results: Most patients had an adequate level of sedation with only the initial dose of MDZ and were satisfied with the treatment under sedation; however, 19 patients needed additional administration, and 13 patients were unsatisfied. In multivariable logistic analysis, lower age (odds ratio [OR], 0.825; *P*=0.005) and higher dental anxiety (OR, 5.744; *P*=0.003) were related to additional administration; lower intraoperative amnesia (OR, 0.228; *P*=0.002) and higher BIS right before MDZ administration (OR, 1.379; *P*=0.029) had relevance to patient dissatisfaction.
Conclusion: The preoperative consideration of age and dental anxiety is necessary for appropriate dose determination of MDZ in the minor oral surgery under IVS. The amnesia about the procedure affects patient satisfaction positively.

Key words: Midazolam, Conscious sedation, Drug dosage calculation, Patient satisfaction, Third molar

[paper submitted 2017. 3. 24 / revised 2017. 5. 10 / accepted 2017. 5. 26]

I. Introduction

The fear about dental treatment is relatively high, and minor oral surgeries such as surgical extraction of third molar give much anxiety and stress to patients. To solve this problem, a variety of stress reduction protocols and intravenous conscious sedation (IVS) methods have been developed[1,2]. Among these, IVS using midazolam (MDZ) has been used widely in medical areas, including the dental department, because MDZ affects the vital signs minimally, easily imparts the adequate calming effect, causes intraoperative amnesia, and provides quick recovery time due to the short half-life of this medicine[3,4].

Although MDZ is a relatively safe medication, side effects such as respiratory depression can occur and recovery time after surgery may increase when overdose is injected[5,6]. Therefore, the clinic, in which the surgeon is responsible for the whole process of sedation because the anesthesiolo-

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gist is not resident, may prefer to inject a relatively low dose only once for safety. However, if the degree of sedation is insufficient, the operation cannot be performed normally, and additional medication needs to be administered during the operation. This causes increase of total operation time and dissatisfaction of both operator and patient. However, to date, there is a lack of research on the factors involved in the administration of additional medications due to insufficient sedation after initial dose, and what contributes to patient satisfaction.

In this study, we revealed factors related to additional administration of MDZ in the cases of insufficient sedation after initial dose. In addition, factors related to patient satisfaction were also analyzed. The ultimate goal of this study was to provide the guideline for adequate sedation with the minimum dose of MDZ.

II. Materials and Methods

This study was approved by the Institutional Review Board of SMG-SNU Boramae Medical Center, Seoul, Korea (IRB No. 26-2014-139), and followed the Declaration of Helsinki on medical protocol and ethics. This is a case-control study that compared the case group with insufficient sedation to the control group with adequate sedation after infusion of only the initial dose of MDZ, and that compared the case group with dissatisfaction to the control group with satisfaction with the treatment under conscious sedation. The inclusion criteria were patients with American Society of Anesthesiology (ASA) physical status I, who have received surgical extraction of both lower third molars with or without simple extraction of upper third molars under IVS using MDZ in SMG-SNU Boramae Medical Center from August 2013 through July 2016. The exclusion criteria were patients with systemic diseases of ASA physical status II to V, renal or hepatic diseases that can affect the metabolism of MDZ, medications having the effect on cytochrome P 450 enzymes or gamma-aminobutyric acid receptors, histories of the recent use of sedatives, no presence of pericoronitis around the impacted third molar, or surgical cases with a total time of more than one hour.

1. Sedation protocol and clinical setting

The crystalloid solution (Plasma Solution A; CJ Health Care, Seoul, Korea) was administered through an 18-gauge intravenous line at a speed of 100 mL/h. After the confirma-

tion of no allergic response through a skin test, a 1 g prophylactic antibiotics (Yamatetan Injection; Jeil Pharmaceutical, Seoul, Korea) was injected. Each patient's peripheral oxygen saturation (SpO_2), bispectral index score (BIS), heart rate, and noninvasive blood pressure (NIBP) were monitored during the whole sedation procedure. A 30 mg opioid analgesic (Pethidine HCl Injection; Bio & Chemical R&D, Seoul, Korea) was given for 30 seconds. The main sedative agent MDZ (Midazolam Injection; Bukwang Pharmaceutical, Seoul, Korea) was administered at the speed of 200 mg/h using an infusion pump (Syramed uSP 6000 syringe pump; Arcomed AG, Regensdorf, Switzerland) intravenously after the dose was determined according to body mass index (BMI) and weight. On the basis of BMI, patients were categorized as underweight (BMI <18.00 kg/m^2), normal weight (BMI 18.00-24.99 kg/m^2), or overweight (BMI ≥25.00 kg/m^2); according to this categorization, MDZ of 0.05 mg/kg was administered for underweight patient, 0.06 mg/kg for normal weight patient, or 0.07 mg/kg for overweight patient. Five minutes after the MDZ administration, the surgeon verified the slurred speech and drooping eyes of the patient, and performed the routine surgical aseptic draping. The surgery began 5 minutes after the injection of the local anesthetic agent (Lidocaine HCl 2% injection 1:100,000 epinephrine; Huons, Seoul, Korea). If the patient responded readily to his or her name being spoken in a normal tone and complained of great anxiety around the beginning of surgery, these signs were regarded as insufficient sedation, and an additional dose of 1 mg MDZ was administered at the same speed of the initial dosage. If the sedation was still insufficient 5 minutes after additional administration, the second additional administration of MDZ was carried out. If it was still insufficient, the same procedure was repeated, with the maximum number of additional administrations limited to four. On the contrary, if SpO_2 decreased below 95 and the patient did not respond after mild prodding or shaking, these signs were regarded as excessive sedation, and the surgeon awakened the patient by giving painful trapezius squeeze. In case this procedure had no effect, a 0.2 mg flumazenil (Flunil Injection; Bukwang Pharmaceutical) was administered for 15 seconds. If there was no effect after 1 minute, an additional 0.1 mg of flumazenil was administered. If this also did not work, the cardiovascular resuscitation procedure was initiated. The patient was discharged after the confirmation of having 9 points of the Aldrete post-anesthesia recovery score[7]. The whole sedation protocol was controlled by one operating team, and all surgeries were performed randomly by one of the two surgeons

with at least five years of clinical experience as specialists in oral and maxillofacial surgery.

2. Variables

The predictor variables were sex, age, BMI, sleeping time ratio, dental anxiety score (DAS), Pederson scale[8], and initial dose of MDZ. BMI was calculated in weight (kg) divided by the square of the height (m). The information about sleeping time was acquired by asking the patient. The sleeping time ratio was defined as the ratio of the amount of sleep the night before the operation to the average amount of sleep in patient's daily life. DAS was collected by a questionnaire[9]. DAS was categorized into one of two groups: lower dental anxiety, 4 to 12 points; higher dental anxiety, over 12 points. Pederson scale was calculated in panoramic radiograph by one independent investigator, and the average of both mandibular third molars was used as the final value.

The outcome variables were whether the additional MDZ was administered, observer's assessment of alertness/sedation scale (OAA/S)[10], the level of amnesia with the operation, patient satisfaction, SpO$_2$, BIS, heart rate, systolic and diastolic NIBP. OAA/S was recorded in the range of 0 to 5 points on the moment 20 minutes after local anesthesia. For information of amnesia, the patient was asked about whether the patient remembered three moments within the whole sedation procedure; injection of local anesthesia, a certain point in the operation itself, and the comment of the operator signaling the start of suturing. If the patient remembered each moment, each amnesia point was recorded as 0, and if not, the point was recorded as 1. The total amnesia score was the sum of each point. Immediately after being asked about amnesia, the patient was also asked about the degree of satisfaction; very dissatisfied, dissatisfied, moderate, satisfied, or very satisfied. Each rating was converted to a point, from 1 to 5. This scale was categorized into one of the two groups; dissatisfaction (from 1 to 3 points) or satisfaction (4 or more points). BIS was recorded with an electroencephalographic sensor (BIS Quatro Sensor; Covidien, Mansfield, MA, USA) attached to the forehead of the patient using an electroencephalographic monitoring system (BIS Vista Monitoring System; Aspect Medical Systems, Norwood, MA, USA). SpO$_2$, BIS, heart rate, systolic and diastolic NIBP were monitored continuously during the operation, and the records of five moments of each procedure were extracted and used for statistical analysis; the moment right before MDZ administration (T0), the moment 5 minutes after MDZ administration (T1), the time

of injection of the local anesthetic agent (T2), the moment 20 minutes after local anesthesia (T3), and the time of the first stitch (T4).

3. Statistical analysis

Pearson's chi-square tests or Fisher's exact tests for categorical variables and Student's t-tests for continuous variables were conducted. Multivariable logistic regression tests were performed to identify factors related to additional administration of MDZ and patient satisfaction. A goodness-of-fit test and model selection were executed using the Hosmer-Lemeshow goodness-of-fit test and the Akaike information criterion. All statistical analyses were performed using the IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA), and probabilities less than 0.05 were considered to be statistically significant.

III. Results

1. General characteristics

One hundred and twenty four patients were enrolled and analyzed. Among these, 19 patients (15.3%) had additional administration of MDZ. Of these 19 patients, 10 patients (8.1%) were medicated with additional administration once, 7 patients (5.6%) twice, and 2 patients (1.6%) three times. Thirteen patients (10.5%) were unsatisfied with the treatment under sedation. Two patients (0.8%) were very dissatisfied or dissatisfied with the operation under sedation, and 11 patients (8.9%) was neither dissatisfied nor satisfied.

The general characteristics of no addition group and addition group are summarized in Table 1, Fig. 1, and Fig. 2. There were 75 men (60.5%) and 49 women (39.5%). The youngest patients were 13-year-old boy and girl, and the oldest was a 72-year-old man, with the mean age of 26.8±10.6 years. The mean height of patients was 1.68±0.09 m (range, 1.52-1.86 m), and the mean weight was 66.1±15.7 kg (range, 39.0-140.0 kg). The mean BMI was 23.2±4.5 kg/m^2 (range, 15.8-42.7 kg/m^2). The mean sleep ratio was 0.9±0.3 (range, 0.3-2.0). The mean DAS was 11.2±2.8 (range, 5-20), and twenty-nine patients (23.4%) had the higher dental anxiety. The mean Pederson scale was 4.9±1.3 (range, 3-9). The mean initial dose was 4.2±1.3 mg (range, 1.0-9.8 mg). The mean OAA/S was 4.1±0.9 (range, 2-5). The mean intraoperative amnesia score was 1.6±1.1 (range, 0-3); amnesia regarding the injection of local anesthesia was recorded in

Table 1. Description of factors in cases stratified by the necessity of additional administration of midazolam during surgical extraction of third molars

Factors	Total (n=124)	No addition group (n=105)	Addition group (n=19)	*P*-value
Sex, male (n)	75 (60.5)	65 (61.9)	10 (52.6)	0.447[2]
Age (yr)[1]	26.8±10.6	27.8±11.2	21.4±3.5	0.000[3,]*
Body mass index (kg/m^2)	23.2±4.5	23.1±4.6	23.9±4.1	0.475[3]
Sleeping time ratio	0.9±0.3	0.9±0.3	0.8±0.2	0.265[3]
Higher dental anxiety[1] (n)	29 (23.4)	20 (19.0)	9 (47.4)	0.015[4,]*
Pederson scale	4.9±1.3	4.8±1.3	4.9±1.6	0.888[3]
Initial dose (mg)	4.2±1.3	4.1±1.3	4.4±1.3	0.456[3]
OAA/S	4.1±0.9	4.0±0.9	4.2±0.7	0.256[3]
Amnesia	1.6±1.1	1.7±1.1	1.5±1.1	0.474[3]
Satisfaction (n)	111 (89.5)	96 (91.4)	15 (78.9)	0.114[4]
Bispectral index score				
T0	93.2±5.3	93.0±5.4	94.5±4.6	0.272[3]
T1	78.0±5.2	77.6±4.9	80.1±6.2	0.059[3]
T2	82.4±5.2	82.2±5.2	83.5±4.8	0.335[3]
T3	82.8±4.4	82.7±4.3	83.2±4.5	0.683[3]
T4	86.4±5.2	86.2±5.2	87.2±5.7	0.500[3]
Heart rate (bits per minute)				
T0	73.0±13.9	72.9±14.0	74.0±13.0	0.753[3]
T1	72.8±14.4	72.8±14.9	73.0±11.7	0.958[3]
T2	80.6±17.6	79.7±18.3	85.4±12.2	0.190[3]
T3	87.8±22.5	87.2±22.0	91.1±25.7	0.487[3]
T4	87.2±19.2	87.5±18.0	85.1±25.2	0.607[3]
Systolic NIBP (mmHg)				
T0	134.8±19.7	134.0±19.2	139.0±22.6	0.318[3]
T1	131.1±20.3	131.3±20.6	130.0±19.0	0.785[3]
T2	139.4±21.6	139.3±21.9	139.7±20.6	0.951[3]
T3	138.7±29.9	139.5±28.1	134.2±38.8	0.481[3]
T4	137.3±27.1	139.4±24.6	129.5±37.8	0.140[3]
Diastolic NIBP (mmHg)				
T0	74.6±10.5	74.6±10.5	74.5±10.9	0.989[3]
T1	69.7±10.0	70.1±10.1	67.5±9.1	0.289[3]
T2	72.9±13.3	73.4±13.1	70.2±13.9	0.343[3]
T3	68.5±16.6	68.8±15.6	66.9±21.7	0.654[3]
T4	72.2±16.3	73.1±15.5	67.2±20.0	0.153[3]

(OAA/S: observer's assessment of alertness/sedation, T0: the moment right before midazolam administration, T1: the moment 5 minutes after midazolam administration, T2: the time of injection of the local anesthetic agent, T3: the moment 20 minutes after local anesthesia, T4: the time of the first stitch, NIBP: noninvasive blood pressure)
[1]Post-hoc power analysis: Age, 0.997; Higher dental anxiety, 0.729. [2]Chi-square test, [3]Student's t-test, [4]Fisher's exact test.
*$P<0.05$.
Values are presented as number (%) or mean±standard deviation.
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75 patients (60.5%), a certain point of operation itself in 64 patients (51.6%), and the signal of the start of suturing in 57 patients (46.0%). SpO$_2$ levels of all patients were maintained over 96% during the whole procedure, and there were no patients with respiratory complications. The mean BIS values were 93.2±5.3 on T0 (range, 77-99), 78.0±5.2 on T1 (range, 66-97), 82.4±5.2 on T2 (range, 66-95), 82.8±4.4 on T3 (range, 73-95), and 86.4±5.2 on T4 (range, 75-97). The patient with a BIS of 97 on T1 had been treated with three additional MDZ doses for sufficient sedation. The mean heart rate was 73.0±13.9, 72.8±14.4, 80.6±17.6, 87.8±22.5, and 87.2±19.2 bits per minutes on each moment from T0 to T4, respectively. The mean systolic NIBP was 134.8±19.7,

131.1±20.3, 139.4±21.6, 138.7±29.9, and 137.3±27.1 mmHg on each moment. The mean diastolic NIBP was 74.6±10.5, 69.7±10.0, 72.9±13.3, 68.5±16.6, and 72.2±16.3 on each moment. Of 124 total patients, no patients needed flumazenil administration or cardiopulmonary resuscitation in cases of over-sedation. The factors related with patient satisfaction are summarized in Table 2.

2. Factors related with additional administration and patient dissatisfaction

Lower age and higher dental anxiety were related with additional administration of MDZ in multivariable logistic
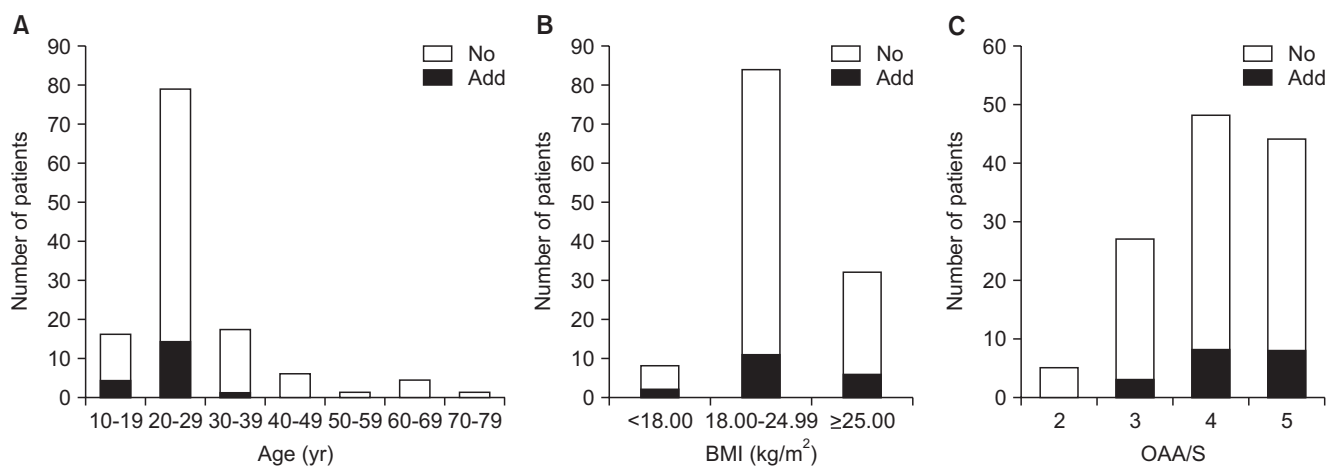
Fig. 1. Comparison of several variables in cases stratified by the necessity of addition administration of midazolam during surgical extraction of third molars. A. Comparison according to the age. B. Comparison according to body mass index (BMI). C. Comparison according to observer's assessment of alertness/sedation (OAA/S). (No: no addition group, Add: addition group)

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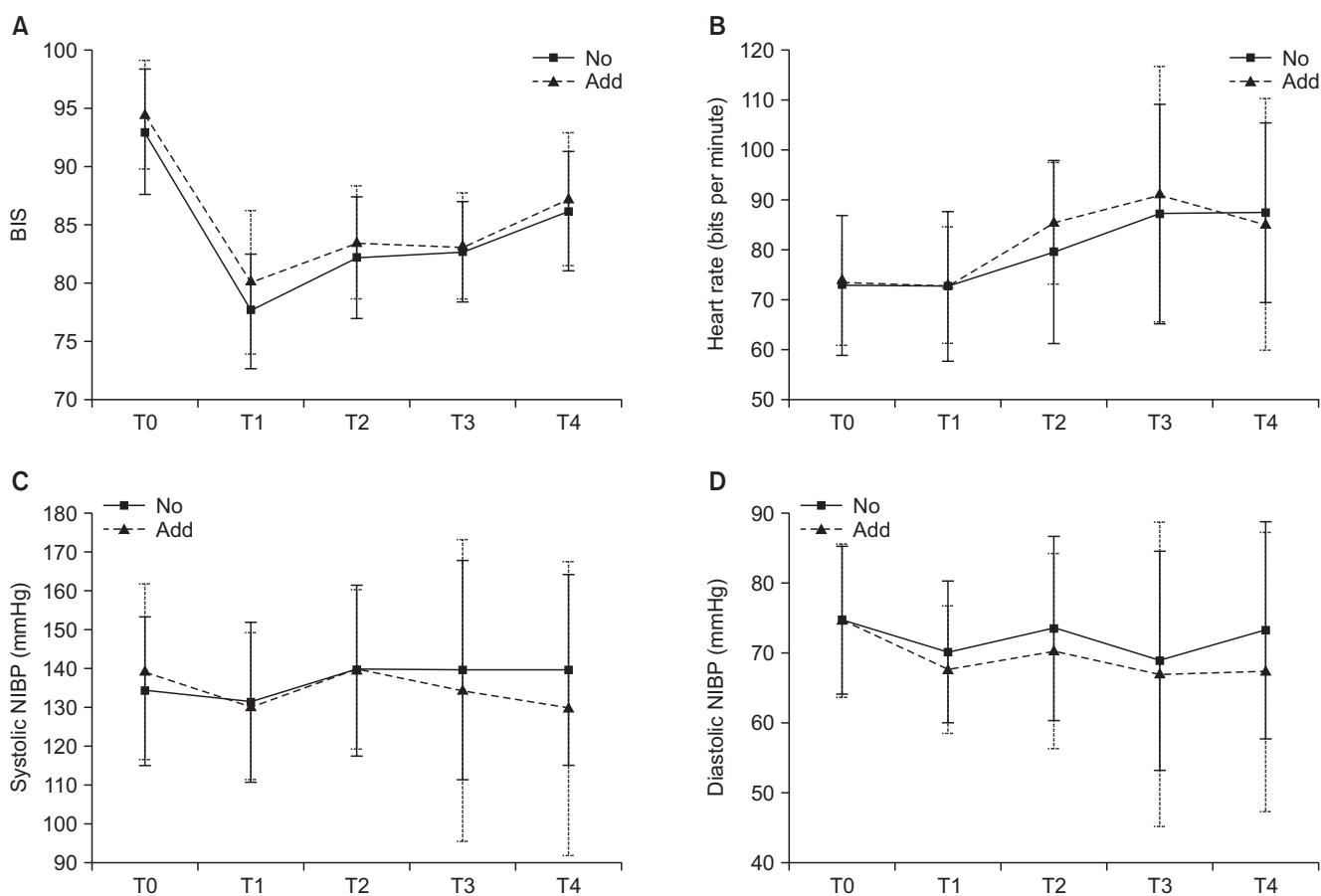

Fig. 2. Comparison of BIS and vital signs in cases stratified by the necessity of addition administration of midazolam during surgical extraction of third molars. Values are presented as mean±standard deviation. A. Comparison according to the mean bispectral index score (BIS). B. Comparison according to the mean heart rate. C. Comparison according to the mean systolic NIBP. D. Comparison according to the mean diastolic noninvasive blood pressure (NIBP). (T0: the moment right before midazolam administration, T1: the moment 5 minutes after midazolam administration, T2: the time of injection of the local anesthetic agent, T3: the moment 20 minutes after local anesthesia, T4: the time of the first stitch, No: no addition group, Add: addition group)

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Table 2. Description of factors in cases stratified by the satisfaction or dissatisfaction during surgical extraction of third molars

Factors	Total (n=124)	Satisfaction group (n=111)	Dissatisfaction group (n=13)	P-value
Sex, male (n)	75 (60.5)	68 (61.3)	7 (53.8)	0.605[2]
Age (yr)	26.8±10.6	27.0±10.8	25.4±9.2	0.608[3]
Body mass index (kg/m^2)	23.2±4.5	23.3±4.6	22.6±4.3	0.616[3]
Sleeping time ratio	0.9±0.3	0.9±0.3	0.8±0.2	0.202[3]
Higher dental anxiety (n)	29 (23.4)	23 (20.7)	6 (46.2)	0.076[4]
Pederson scale	4.9±1.3	4.9±1.3	4.8±1.5	0.807[3]
Initial dose (mg)	4.2±1.3	4.2±1.3	3.9±1.3	0.455[3]
Additional administration (n)	19 (15.3)	15 (13.5)	4 (30.8)	0.114[4]
OAA/S	4.1±0.9	4.0±0.8	4.5±0.9	0.053[3]
Amnesia[1]	1.6±1.1	1.8±1.0	0.4±0.9	0.000[3],*
Bispectral index score				
T0[1]	93.2±5.3	92.9±5.4	96.1±2.2	0.000[3],*
T1[1]	78.0±5.2	77.6±4.9	81.2±6.4	0.016[3],*
T2	82.4±5.2	82.3±5.2	83.6±4.7	0.374[3]
T3	82.8±4.4	82.9±4.3	82.0±5.3	0.556[3]
T4	86.4±5.2	86.4±5.2	86.5±5.9	0.963[3]
Heart rate (bits per minute)				
T0	73.0±13.9	73.0±14.1	73.0±11.4	0.995[3]
T1	72.8±14.4	72.6±14.9	74.9±10.0	0.584[3]
T2	80.6±17.6	80.1±18.1	84.3±12.4	0.417[3]
T3	87.8±22.5	90.0±18.1	69.5±41.7	0.107[3]
T4	87.2±19.2	88.8±15.8	73.2±35.0	0.136[3]
Systolic NIBP (mmHg)				
T0	134.8±19.7	134.5±19.4	137.0±22.9	0.669[3]
T1	131.1±20.3	130.5±20.4	136.4±18.9	0.324[3]
T2	139.4±21.6	139.6±21.2	138.2±25.8	0.827[3]
T3	138.7±29.9	141.5±20.3	114.6±68.0	0.180[3]
T4	137.3±27.1	140.5±20.3	116.9±56.1	0.150[3]
Diastolic NIBP (mmHg)				
T0	74.6±10.5	74.4±10.6	76.2±10.1	0.547[3]
T1	69.7±10.0	69.6±10.2	70.7±7.9	0.712[3]
T2	72.9±13.3	72.6±13.0	75.0±15.6	0.544[3]
T3	68.5±16.6	69.9±12.7	56.4±33.9	0.178[3]
T4	72.2±16.3	73.4±13.9	61.3±28.6	0.157[3]

(OAA/S: observer's assessment of alertness/sedation, T0: the moment right before midazolam administration, T1: the moment 5 minutes after midazolam administration, T2: the time of injection of the local anesthetic agent, T3: the moment 20 minutes after local anesthesia, T4: the time of the first stitch, NIBP: noninvasive blood pressure)
[1]Post-hoc power analysis: Amnesia, 0.998; Bispectral index score T0, 0.974; Bispectral index score T1, 0.446. [2]Chi-square test, [3]Student's t-test, [4]Fisher's exact test.
*P<0.05.
Values are presented as number (%) or mean±standard deviation.
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Table 3. Results of multivariable logistic regression analysis for factors affecting the necessity of additional administration of midazolam during surgical extraction of third molars[1]

Risk factors	OR (95% CI)	P-value
Age	0.825 (0.722-0.943)	0.005*
Higher dental anxiety	5.744 (1.812-18.208)	0.003*

(OR: odds ratio, CI: confidence interval)
[1]Hosmer-Lemeshow goodness-of-fit test: P=0.606, Akaike information criterion=92.451.
*P<0.05.
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regression analysis.(Table 3) On the basis of odds ratio, the need for additional doses decreased by 1.21 times as the age of patient increased by 1 year (P=0.005). In the presence of higher dental anxiety, the need for addition increased 5.74 times over lower dental anxiety (P=0.003).

To further elucidate the relationship of age and additional administration, we performed statistical analysis of all variables for younger and older age groups. The cut-off-value for age was 22.5 years.(Fig. 3. A) Four variables showed a significant difference between groups; the younger age group had more additional administration, higher BIS on T2, lower diastolic NIBP on T0 and T1.(Table 4)

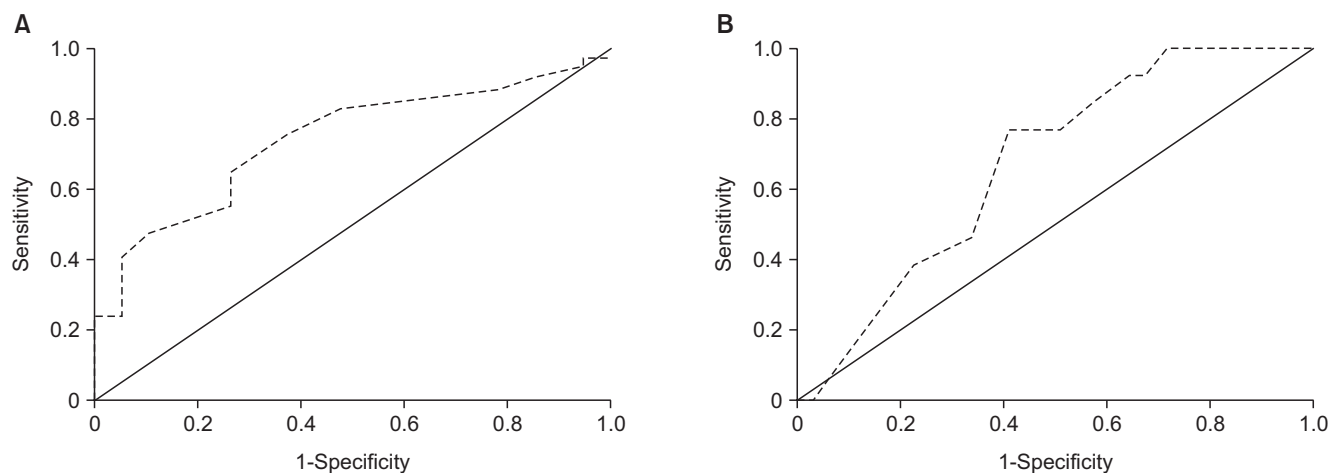Lower intraoperative amnesia and Higher BIS on T0 were

A

B

Fig. 3. Receiver operating characteristics curve obtained by multivariable logistic regression. A. The cut-off-value for age was 22.5 years with an area-under-curve of 0.741 (*P*=0.001). It was determined according to the Youden index with sensitivity of 64.8% and specificity of 73.7%. B. The cut-off-value for bispectral index score on T0 was 95.5 with an area-under-curve of 0.673 (*P*=0.043). It was determined according to the Youden index with sensitivity of 76.9% and specificity of 59.2%. (T0: the moment right before midazolam administration)
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Table 4. Factors showing statistically significant differences between younger and older age groups during surgical extraction of third molars

Factors	Total (n=124)	Younger age group (<22.5 yr)[1] (n=51)	Older age group (≥22.5 yr)[1] (n=73)	*P*-value
Additional administration (n)	19 (15.3)	14 (27.5)	5 (6.8)	0.002[2],*
Bispectral index score				
T2	82.4±5.2	83.8±5.8	81.5±4.5	0.020[3],*
Diastolic NIBP (mmHg)				
T0	74.6±10.5	71.6±9.6	76.6±10.7	0.009[3],*
T1	69.7±10.0	66.4±8.8	72.0±10.2	0.002[3],*

(T0: the moment right before midazolam administration, T1: the moment 5 minutes after midazolam administration, T2: the time of injection of the local anesthetic agent, NIBP: noninvasive blood pressure)
[1]Cut-off-value was determined according to the Youden index (sensitivity 64.8%, specificity 73.7%). [2]Chi-square test, [3]Student's t-test.
P<0.05.
Values are presented as number (%) or mean±standard deviation.
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related with dissatisfaction of patient in the multivariable logistic regression analysis.(Table 5) On the basis of odds ratio, dissatisfaction decreased by 4.39 times as the degree of amnesia increased by 1 point (*P*=0.002). In addition, dissatisfaction increased by 1.38 times as BIS on T0 increased by 1 (*P*=0.029). The cut-off-value for BIS on T0 was 95.5.(Fig. 3. B)

IV. Discussion

IVS using MDZ helps patients have comfortable treatment and surgeons concentrate on the operations. However, there are occasionally cases that require additional dosing of sedative during surgery due to the lack of sedation. In an

Table 5. Results of multivariable logistic regression analysis for factors affecting the dissatisfaction during surgical extraction of third molars[1]

Risk factors	OR (95% CI)	*P*-value
Amnesia	0.228 (0.088-0.589)	0.002*
Bispectral index score		
T0	1.379 (1.033-1.840)	0.029*

(OR: odds ratio, CI: confidence interval, T0: the moment right before midazolam administration)
[1]Hosmer-Lemeshow goodness-of-fit test: *P*=0.060, Akaike information criterion=55.725.
P<0.05.
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outpatient setting where an anesthesiologist does not reside, additional dosing puts a lot of pressure on surgeons because it might increase the complication of sedative itself and recovery time after sedation treatment. Therefore, from the surgeon's point of view, it is helpful to identify factors related to the need for extra doses before initiation of treatment. Ultimately, one of the major purposes of sedation is to satisfy the patient with the whole process of treatment. Thus, from the patient's point of view, it is helpful to identify factors related to patient satisfaction with the sedation treatment. In this study, several factors affecting addition of sedative dose and satisfaction of patient were analyzed. These factors have not been studied previously in the areas of oral and maxillofacial surgery.

In the previous studies, the initial doses of MDZ varied from 0.03 to 0.1 mg/kg, and the methods of sedation were also diverse, for example, titration until the emergency of signs like ptosis or slurred speech, continuous administration of small doses after initial doses, or dose control by patients themselves[11-14]. In this study, the authors have designed the sedation protocol as the initial slow administration of the customized dose combined by an additional dose as necessary under the surgeon's decision. In most previous studies, the initial doses were adjusted by the body weight only; however, several other factors were also related to the adequate doses. Among these, higher BMI cases needed more doses of sedative agents and showed shorter recovery time than lower BMI cases[15,16]. Moreover, in overweight patients, the blood concentrations of sedatives were lower than in normal or underweight patients because of the high central and peripheral volumes of distribution; therefore, a longer time for sedatives to reach the blood concentration was needed for sufficient sedations[17]. On the basis of these studies, the authors designed the sedation protocol that determined the initial dose according to three ranges of BMI[18]. In the cases of severe overweight patients with concomitant systemic diseases like fatty liver, the clearances of MDZ could be affected and the dose reduction was essential[19]. Therefore, the patients with these kinds of systemic diseases were excluded in this study.

The adequate levels of sedation were observed in most patients of this study; however, 19 patients (15.3%) had additional administration of MDZ because of insufficient sedation. Among them, 9 patients had the additional administration more than once. Additional administration was related with the lower age; in other words, decreasing age needed more dosages. This could be a result of increased metabolism or decreased sensitivity to the sedatives in the younger pa-

tient. Czwornog and Austin[20] also reported that patients with low age and female gender needed a greater dose of MDZ for adequate sedation. Although there were no direct relationship between sex and additional administration of MDZ in the present study, OAA/S of women was larger than men (4.3±0.7 vs. 3.9±0.9; *P*=0.028), which proved the relation between sex and the level of consciousness. Higher dental anxiety was related to additional administration. Seto et al.[21] also reported that the dose of sedative agents increased with increasing fear of the dental treatment. In addition, women showed higher dental anxiety than men in this study (36.7% vs. 14.7%; *P*=0.005). Taken together these factors, for sedation of young women patient with higher dental anxiety, increasing the initial dose or early administration of additional dose may help reduce the delay of operation due to waiting time for onset of effect of additional sedatives. Furthermore, with decreasing age, BIS on T2 increased in this study. The time of additional administration was around the start of operation after the injection of the local anesthesia, therefore, BIS during local anesthesia may be an indirect reference for determining whether to administer additional doses.

The subjective factors, such as the postoperative satisfaction, are also important for evaluating the adequacy of sedation. In this study, the average satisfaction score was 4.5±0.8 on a five-point scale, and 89.5% of patients were very satisfied or satisfied with the treatment under sedation. Amnesia during the operation and BIS on T0 affected satisfaction significantly. High level of amnesia resulted in high satisfaction of patients. Intraoperative amnesia is the marked characteristics of MDZ compared with other sedatives[12]. In the present study the mean amnesia point was 1.6±1.1 on a three-point scale. Zacharias et al.[14] reported that 70% of patients experienced amnesia using the continuous infusion of MDZ. Meanwhile, Levitzky et al.[22] reported that old age was related with high satisfaction; however, there was no significant relationship between these two factors in this study. High BIS on T0 may reflect the high nervousness about the surgery. It implies that preoperative relaxation therapy is as important as sedation procedure itself[23].

There have been several methods measuring the state of consciousness during sedation. Among these, BIS based on electroencephalogram has been used frequently[24,25]. The state of consciousness reading BIS under 60 is regarded as the general anesthesia, from 61 to 70 as deep or moderate sedation, and from 71 to 90 as light or moderate sedation[26-28]. In this study, BIS was also used to evaluate the level of consciousness. Bower et al.[29] reported that 82 of BIS value was

adequate for the endoscopy. Therefore, the authors set the target value of BIS as 80, and actually values of BIS maintained around 80 through all operational procedures. Other than the objective methods like BIS, subjective methods like OAA/S or Ramsay score based on observation of operators have been used[10]. Chisholm et al.[26] reported that the OAA/S and Ramsay scores showed a similar tendency and had the positive relationship with BIS. In this study, the target value of OAA/S was 4, and this goal was achieved in most patients.

This case-control study had several limitations. First, there may have been performance bias. Although the sedation protocol and clinical setting have been established, not all extraction procedures of the two surgeons could be fully standardized. Second, confounding bias may have influenced the results. Although the data were controlled via multivariable logistic regression analysis after data collection, there may be other confounding factors that were not collected, such as exact total operation time, the presence of temporomandibular joint disorder, the amount of maximum mouth opening, elasticity of facial skin. Third, there may have been information bias. In this study, only previous medical records were used. Thus, errors that occurred at the time these records were made could not be detected. Fourth, there may have been over-interpretation. Since this study was a case-control study, the odds ratio was presented instead of the relative risk. In addition, the rate of additional administration of MDZ was 15.3%, and dissatisfaction rate was 10.5%, which was comparatively high. Thus, this study provides a weaker basis for causality than a cohort study does. Consequently, the odds ratio calculated in this study was predicted to be higher than the actual relative risk. Fifth, for more accurate respiratory monitoring, measurement of end tidal pressure of carbon dioxide using capnography was required rather than SpO_2, although there were no patients with respiratory depression in this study. Further research using capnography is needed. Finally, the operation using an electric drill or saw, such as block bone graft, might need higher intensity of sedation and larger additional dose than surgical tooth extraction. Further research is needed on the sedation treatment of more aggressive surgery.

V. Conclusion

Multivariable logistic regression analysis showed that lower age and higher dental anxiety were meaningfully associated with additional administration of MDZ, and that higher intraoperative amnesia and lower BIS on T0 were meaning-

fully associated with patient satisfaction. For the sufficient sedation of young or anxious patients, surgeons should consider the possibility of using an additional dosage of MDZ or modifying the methods to determine the adequate initial dose. Drugs that induce amnesia, such as MDZ, help improve patient satisfaction with treatment; therefore surgeons can consider these drugs when choosing a sedative agent.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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