

Independent Factors Affecting Recovery Time After Sedation in Patients with Intellectual Disabilities

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Abstract: *Purpose:* The purpose of this study was to identify independent factors associated with prolonged recovery time after intravenous sedation for dental treatment in patients with intellectual disabilities. *Methods:* This study was designed as a prospective cohort study. Participants were patients with intellectual disabilities, for whom sedation for dental treatment was planned in Okayama University Hospital. The outcome variable was recovery time. The predictor variables were patient background, antiepileptic and psychotropic drugs, and anesthesia-related variables. Factors affecting the outcome were examined with multiple regression analysis. *Results:* We enrolled 260 cases in this study. Oral midazolam was a strong independent determinant in prolonged recovery time. Teeth extraction, short treatment time and lower body mass index were significant independent predictors of prolonged recovery time. *Conclusion:* Oral midazolam is a clear independent determinant of prolonged recovery time after sedation, while psychotropic drugs and antiepileptic drugs were not independent determinants in this study.

Keywords: Anesthesia recovery period, intellectual disability, midazolam, propofol.

INTRODUCTION

Sedation is used for minor oral surgery and dental treatment in persons with severe intellectual disabilities [1, 2]. Patients with intellectual disabilities have a high rate of significant co-morbid conditions, such as epilepsy and mental disorders, which require daily medication that may influence the clinical effect of anesthetics used in sedation.

At present, propofol and midazolam are the primary agents used for sedation for dental treatment in patients with intellectual disabilities because of their short half-life and amnesic effects [3, 4]. However, because a significant number of these patients require a longer recovery time after sedation, it is thought that the interaction of factors such as concomitant medication and anesthetic choice may influence their recovery time. The pharmacokinetics of anesthetics are affected by drug-drug interactions [5-7], and the interactions are mainly mediated by cytochrome P450 (CYP) isoenzymes, so the anesthetics used in sedation are thought to be affected by antiepileptic and psychotropic drugs. Thus, the purpose of our study was to identify independent factors for prolonged recovery time after sedation using prospective multivariate analysis.

MATERIALS AND METHODOLOGY

Study Design/Sample

The investigators designed and implemented a prospective cohort study. The study population was composed of all

patients presenting for evaluation and management of dental treatment under intravenous sedation in the clinic for Special Needs Dentistry in Okayama University Hospital from January 2011 to December 2011.

Variables

The outcome variable was recovery time, which was defined as the interval from termination of treatment until permission for discharge. We judged the patient's state of recovery using a post-anesthetic discharge scoring system [8] to estimate activity, vital signs, water intake, pain, and bleeding. Patients were permitted to be discharged when these factors had recovered to the same level as on admission. The subjects' recovery was evaluated by at least two dentists.

Predictor variables were age, gender, body mass index (BMI), daily use of representative antiepileptic or psychotropic drugs (carbamazepine, valproate, phenytoin, risperidone, haloperidol, and quetiapine), oral (PO) midazolam, amount of intravenous (IV) midazolam ($\mu\text{g}/\text{kg}$ BW), propofol rate ($\mu\text{g}/\text{kg}$ BW/min), tooth extraction and treatment time (min).

Anesthetic Procedure and Data Collection Methods

As the patients had intellectual disabilities, written informed consent was obtained from parents or family members. Fasting times were 6 h for food and 2 h for clear water. Medicines in daily use were taken as usual. Intravenous sedation was started with insertion of an intravenous line, followed by injection of midazolam, and continuous injection of propofol was started in a target-controlled infusion (TCI) manner. The initial TCI value was set at 1.0-2.0 $\mu\text{g}/\text{ml}$. When patients could not cooperate with the insertion because of their intellectual disabilities, 0.3-0.5 mg/kg of oral midazolam was administered.

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zolam was given. After adequate sedation was obtained, an intravenous line was placed, followed by a continuous infusion of propofol as described above. In patients under 16 years of age, the propofol infusion was started at 5 mg/kg/h (83.5 µg/kg/min) because TCI could not be used owing to the basic settings of the infusion pump.

Patients were continuously monitored with electrocardiograph, and for blood pressure and SpO₂. During treatment, the sedation level was maintained at a score of 1–2 on the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) [9] by adjusting the target concentration of propofol. A score of 1 denotes "Does not respond to mild prodding or shaking" and a score of 2 denotes "Responds only after mild prodding or shaking". During treatment, local anesthetic containing 2% lidocaine and 1:80,000 adrenalin was used if it was considered necessary. After treatment was completed, the infusion of propofol was terminated. Patients were permitted to be discharged according to the standards outlined above.

The sedation was managed by dentists certified by the Japanese Dental Society of Anesthesiology. All data were collected by a person not in charge of anesthetic management. Patient information was de-identified and stored appropriately. This study was approved by the Ethics Committee, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (No.433), registered in the UMIN clinical trial registry (No. UMIN000006262), and conducted according to the Helsinki Declaration.

Data Analysis

Data were analyzed using JMP 9.0.0 (SAS Institute Inc., Cary, NC). Student's t-test was used between the primary outcome variable (recovery time) and the nominal variables, while a linear regression was applied to examine the bivariate regression between the outcome variable and continuous variables. To extract independent variables affecting the primary outcome, possible predictive variables were selected with stepwise regression, for which the cut-off was a p value < 0.20, followed by multiple regression analysis. The difference in the amount of IV midazolam used with oral midazolam and the amount used without oral midazolam was analyzed by Student's t-test.

RESULTS

Two hundred and sixty subjects (165 males and 95 females) were enrolled in this study. No patient was hospitalized after intravenous sedation and no major complications occurred. The average age of the subjects was 32.5 years. Recovery time was 62.8 ± 25.8 min (average ± SD). Carbamazepine, valproate, phenytoin, risperidone, haloperidol and quetiapine were used in 86, 80, 38, 21, 86 and 17 patients, respectively. As a premedication for sedation, oral midazolam was used in 38 cases, in which the amount of oral midazolam was 297 ± 121 µg/kg (average ± SD). Tooth extraction was performed in 30 cases (Table 1). Among these variables, oral midazolam was significantly correlated with recovery time, but there was no significant difference between recovery time and other variables, such as antiepileptic or psychotropic drugs.

Table 1. Differences in time to recovery from the sedation by nominal variables.

Variables (No. of patients)	Recovery time (min)		
	Average	SD	p value
Gender			0.928
male (165)	63.1	27.6	
female (95)	62.8	24.8	
Carbamazepine			0.672
yes (86)	61.9	25.8	
no (174)	63.3	25.9	
Valproate			0.550
yes (80)	64.3	27.4	
no (180)	62.2	25.1	
Phenytoin			0.235
yes (38)	58.3	19.8	
no (222)	63.6	26.7	
Risperidone			0.527
yes (48)	60.7	21.8	
no (172)	63.3	26.7	
Haloperidol			0.199
yes (21)	69.8	32.8	
no (239)	62.3	25.1	
Quetiapine			0.166
yes (17)	54.5	8.8	
no (243)	63.4	26.5	
Oral Midazolam			<0.001
yes (38)	88.8	37.5	
no (222)	58.4	20.2	
Extraction			0.099
yes (30)	70.2	30.8	
no (230)	61.9	25.0	

The average amount of IV midazolam and the propofol rate were 29.3 µg/kg and 43.1 µg/kg/min, respectively. Treatment time was 43.1 ± 12.5 min (average ± SD). Among the five continuous variables analyzed in this study, only the amount of IV midazolam was significantly and negatively correlated with recovery time (Table 2).

Using stepwise regression, haloperidol, oral midazolam, extraction, BMI, amount of IV midazolam, propofol rate and treatment time were selected for a standard least squares calculation, in which oral midazolam was shown to be strongly associated with prolonged recovery time. Lower BMI, tooth extraction, and shorter treatment time were also

Table 2. Continuous variables and their relationship to time to recovery from the sedation.

Variables	Average	SD	Correlation with Time to Recovery			
			5% Upper 95%	Age (yrs) 32.4 11.6	-0.018	
				Lower 95%	Upper 95%	
Age (yrs)	32.4	11.6	-0.018	-0.139	0.104	0.775
BMI (kg/m ²)	21.4	4.6	-0.042	-0.163	0.080	0.498
Amount of IV midazolam (µg/kg)	29.3	17.8	-0.289	-0.397	-0.173	<0.001
Propofol rate (µg/kg/min)	98.2	31.8	-0.005	-0.157	0.231	0.930
Treatment time (min)	43.1	12.5	-0.111	-0.170	0.219	0.072

Table 3. Stepwise logistic regression model for time to recovery from intravenous sedation.

Variable	Estimate	SE	t value	p value (Prob> t)
Intercept	124.337	12.454	9.98	<0.001*
Haloperidol (yes or no)	3.460	2.644	1.31	0.192
Oral Midazolam (yes or no)	14.235	2.644	5.38	<0.001*
Extraction (yes or no)	6.120	2.237	2.74	0.007*
BMI (kg/m ²)	-0.920	0.335	-2.74	0.007*
Amount of IV midazolam (mg/kg)	-0.156	0.111	-1.41	0.161
Propofol rate (µg/kg/min)	-0.068	0.046	-1.48	0.141
Treatment time (min)	-0.299	0.115	-2.59	0.010*

R²=0.238, *Significant parameter.

shown to be independent determinants of prolonged recovery time (Table 3). However, antiepileptic and/or psychotropic drugs were not independent predictor variables of recovery time.

The amount of IV midazolam used was significantly less in subjects who did not take oral midazolam (Table 4).

Table 4. Differences in amount of IV midazolam by Oral midazolam (yes or no).

Variables (No. of patients)	Amount of IV Midazolam (µg/kg)		
	Mean	SD	p value
Oral Midazolam (yes or no)			<0.0001
yes (38)	1.9	6.8	
no (222)	34.0	14.6	

DISCUSSION

The results of this study show that oral midazolam is a clear independent predictor of prolonged recovery time after sedation. The average amount of oral midazolam in partici-

pants who used oral midazolam as a premedication was 297 ± 121 µg/kg, which is almost 10 times higher than the average amount of IV midazolam (29.3 ± 17.8 µg/kg). In a previous report, 2 mg of IV midazolam brought about the same level of plasma concentration as 7.5 mg of oral midazolam [10], suggesting that 10 times the amount of oral midazolam directly contributes to prolonged recovery time after sedation. Antiepileptic and psychotropic drugs, the amount of IV midazolam, and the propofol rate were not independent determinants. Although the amount of IV midazolam was negatively correlated with recovery time in bivariate regression, it is considered to be a confounding factor because there was a significant difference in the amount of IV midazolam used, depending on whether oral midazolam was used.

Participants used a variety of antiepileptic and antipsychotic drugs. Although common side effects of these drugs are sleepiness and/or drowsiness, the drugs were not independent factors for prolonged recovery time after sedation. In this study, oral or IV midazolam were used for all participants. This may have masked the effect of the antiepileptic and antipsychotic drugs after sedation, and these drugs were not shown to be independent factors for prolonged recovery time.

Shorter treatment time was shown to be another independent predictor of prolonged recovery time. This may be the result of residual midazolam effects. Oral midazolam was used as a premedication, and IV midazolam was administered at the beginning of the sedation. As the half-life of midazolam is longer than that of propofol [11], shorter treatment time would mean more prominent midazolam effects at the beginning of the recovery time, requiring a longer duration for metabolic clearance.

BMI was negatively correlated with recovery time in this study. Although the person responsible for the sedation kept the anesthesia level at class 1–2 in the MOAA/S scale, the upper airway of an obese person is more easily obstructed than that of a non-obese person at the same level of sedation, as described previously by Wani *et al.* [12]. Accordingly, to maintain the airway safely, the sedation level in an obese person might be lighter than that in a non-obese person. This might explain the negative correlation of BMI with recovery time. Tooth extraction was another independent predictor of prolonged recovery time. This is considered to be a reflection of a delay in discharge permission to comply with the post-anesthetic discharge scoring system, in which achieving hemostasis was a requirement. Because bleeding is specific in tooth extraction, this was considered to cause tooth extraction to be an independent factor for prolonged recovery time.

In this study, oral midazolam was a strong predictor for prolonged recovery time after sedation, but interactions between anesthetics and antiepileptic and/or psychotropic drugs were not observed. In a clinical situation, the interaction of these medications may be ignored when assessing recovery from sedation. To detect further interactions, it would be necessary to measure plasma concentrations of the anesthetics or instigate a more sophisticated research design.

CONCLUSION

Oral midazolam is a clear independent determinant of prolonged recovery time after sedation for dental treatment in patients with intellectual disabilities, while psychotropic drugs and antiepileptic drugs were not independent determinants in this study.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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