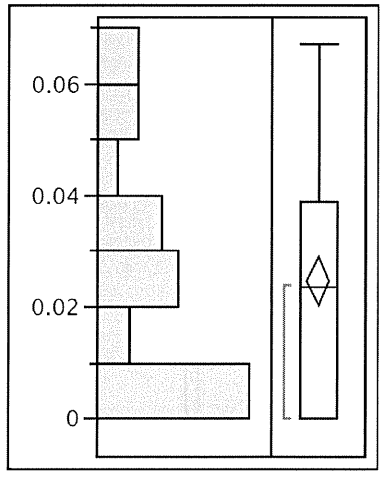
図５．ミダゾラム静脈内投与量 (mg/kg)



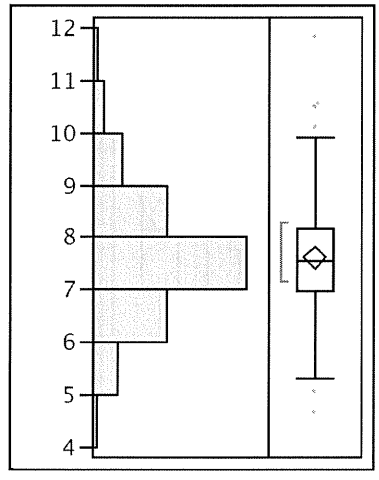
分位点

100.0%	最大値	0.06696
99.5%		0.06696
97.5%		0.06534
90.0%		0.0595
75.0%	4分位点	0.03895
50.0%	中央値	0.02367
25.0%	4分位点	0
10.0%		0
2.5%		0
0.5%		0
0.0%	最小値	0

モーメント

平均	0.0247569
標準偏差	0.0223657
平均の標準誤差	0.0021723
平均の上側95%信頼限界	0.0290642
平均の下側95%信頼限界	0.0204495
N	106

図６．プロポフォール平均当予測後 (mg/kg/hr)



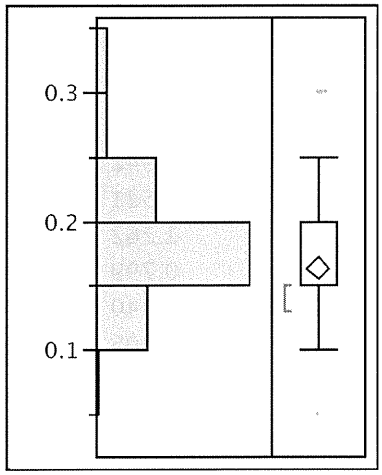
分位点

100.0%	最大値	11.82
99.5%		11.82
97.5%		10.511
90.0%		9.038
75.0%	4分位点	8.18
50.0%	中央値	7.57
25.0%	4分位点	6.96
10.0%		6.25
2.5%		5.229
0.5%		4.66
0.0%	最小値	4.66

モーメント

平均	7.6175238
標準偏差	1.1656442
平均の標準誤差	0.1137552
平均の上側95%信頼限界	7.8431047
平均の下側95%信頼限界	7.3919429
N	105

図７．レミフェンタニル
投与速度の最頻値(μg/kg/min)



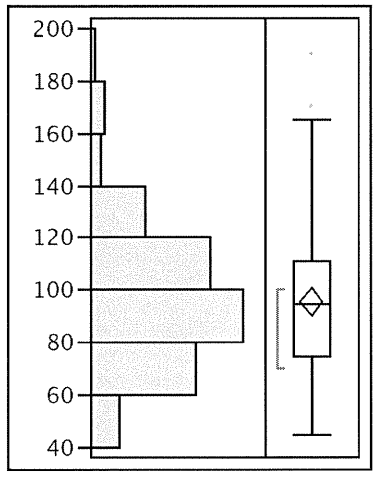
分位点

100.0%	最大値	0.3
99.5%		0.3
97.5%		0.3
90.0%		0.2
75.0%	4分位点	0.2
50.0%	中央値	0.15
25.0%	4分位点	0.15
10.0%		0.12
2.5%		0.1
0.5%		0.05
0.0%	最小値	0.05

モーメント

平均	0.1637736
標準偏差	0.0436535
平均の標準誤差	0.00424
平均の上側95%信頼限界	0.1721807
平均の下側95%信頼限界	0.1553665
N	106

図８．回復時間



分位点

100.0%	最大値	190
99.5%		190
97.5%		166.625
90.0%		130
75.0%	4分位点	111.25
50.0%	中央値	95
25.0%	4分位点	75
10.0%		65
2.5%		55
0.5%		45
0.0%	最小値	45

モーメント

平均	95.688679
標準偏差	26.57975
平均の標準誤差	2.5816535
平均の上側95%信頼限界	100.80762
平均の下側95%信頼限界	90.569737
N	106

表３．回復時間と関連する要因のステップワイズ回帰

追加	パラメータ	推定値	自由度	平方和	"F値"	"p値(Prob>F)"
☑	切片	103.348498	1	0	0.000	1
☑	年齢	-0.4930503	1	1674.788	2.533	0.11462
☐	性別{女-男}	0	1	3.99798	0.006	0.93848
☐	BMI	0	1	26.39016	0.040	0.8428
☐	脳性麻痺の有無{1-2}	0	1	108.9964	0.163	0.68683
☐	自閉有無{1-2}	0	1	597.4709	0.903	0.34434
☐	てんかん有無{1-2}	0	1	101.8098	0.153	0.69681
☐	抗精神病薬{1-2}	0	1	694.5244	1.051	0.30777
☐	治療時間 （分）	0	1	623.0529	0.942	0.33416
☑	導入方法{点滴-吸入&内服&内服＋吸入}	-6.8763332	1	2328.147	3.521	0.06348
☐	導入方法{吸入&内服-内服＋吸入}	0	1	832.1067	1.262	0.26401
☐	導入方法{吸入-内服}	0	2	1060.96	0.799	0.45261
☑	静注ﾐﾀﾞｿﾞﾗﾑ mg/kg	295.728695	1	3199.876	4.840	0.03009
☐	ﾌﾟﾛﾎﾟﾌｫｰﾙ mg/hr/kg	0	1	794.8793	1.205	0.27504
☐	ﾚﾐﾌｪﾝﾀﾆﾙ最頻値	0	1	134.9795	0.203	0.65366
☐	歯科治療{その他抜歯-歯科治療&智歯抜歯}	0	1	584.6074	0.883	0.34961
☐	歯科治療{歯科治療-智歯抜歯}	0	2	1898.668	1.449	0.23985

表４．回復時間と関連する要因の多変量解析

項	推定値	標準誤差	t値	p値(Prob>|t|)
切片	103.69719	7.576708	13.69	<.0001*
年齢	-0.507028	0.306064	-1.66	0.1007
導入方法{点滴-吸入&内服&内服＋吸入}	-6.790302	3.641176	-1.86	0.0651
静注ﾐﾀﾞｿﾞﾗﾑ mg/kg	289.93628	132.9014	2.18	0.0314*

表５．回復時間が120分以上となった症例と関連する要因のステップワイズ回帰

追加 パラメータ	推定値	自由度	Wald/スコアカイ2乗	"有意確率"
切片[2]	5.58019384	1	0	1
年齢	0	1	0.549656	0.45846
性別{女-男}	0.9885285	1	3.092388	0.07866
BMI	0	1	0.041913	0.83779
脳性麻痺の有無{1-2}	0	1	0.693505	0.40497
自閉有無{2-1}	0	1	0.349983	0.55412
てんかん有無{1-2}	0	1	0.42869	0.51263
抗精神病薬{1-2}	-0.6820123	1	3.954495	0.04675
治療時間 （分）	0	1	0.451586	0.50158
治療時間<100{1-2}	0.78351045	1	5.882658	0.01529
導入方法{点滴-吸入&内服&内服＋吸入}	1.254684	1	7.456796	0.00632
導入方法{吸入&内服-内服＋吸入}	0	1	1.204512	0.27242
導入方法{吸入-内服}	0	2	3.104514	0.21177
静注ﾐﾀﾞｿﾞﾗﾑ mg/kg	-40.963571	1	4.427169	0.03537
ﾌﾟﾛﾎﾟﾌｫｰﾙ mg/hr/kg	-0.4010352	1	2.579567	0.10825
ﾚﾐﾌｪﾝﾀﾆﾙ最頻値	0	1	0.976371	0.3231
歯科治療{その他抜歯&智歯抜歯-歯科治療}	0	1	0.814193	0.36688
歯科治療{その他抜歯-智歯抜歯}	0	2	0.871219	0.64687

表６．回復時間が120分以上となった症例と関連する要因の多変量解析

項	推定値	標準誤差	カイ2乗	p値(Prob>ChiSq)
切片[1]	5.68169201	2.2045943	6.64	0.0100*
性別[女]	0.9885285	0.5621371	3.09	0.0787
抗精神病薬[2-1]	1.36402456	0.685925	3.95	0.0467*
治療時間<100[2-1]	-1.5670209	0.6460825	5.88	0.0153*
導入方法{点滴-吸入&内服&内服＋吸入}	1.254684	0.4594711	7.46	0.0063*
静注ﾐﾀﾞｿﾞﾗﾑ mg/kg	-40.963571	19.468602	4.43	0.0354*
ﾌﾟﾛﾎﾟﾌｫｰﾙ mg/hr/kg	-0.4010352	0.2496946	2.58	0.1083

表７．治療後の興奮状態と関連する要因のステップワイズ回帰

追加 パラメータ	推定値	自由度	Wald/スコアカイ2乗	"有意確率"
☑ 切片[2]	0.07465922	1	0	1
☑ 年齢	-0.06442	1	2.84684	0.09155
☐ 性別{男-女}	0	1	0.480231	0.48832
☐ BMI	0	1	0.000386	0.98432
☐ 脳性麻痺の有無{2-1}	0	1	2.230858	0.13528
☐ 自閉有無{1-2}	0	1	1.513151	0.21866
☑ てんかん有無{2-1}	0.52284037	1	2.497511	0.11403
☐ 抗精神病薬{1-2}	0	1	1.402662	0.23628
☐ 治療時間 （分）	0	1	0.55462	0.45644
☑ 導入方法{点滴&吸入-内服&内服＋吸入}	-1.1289497	2	8.136889	0.0171
☑ 導入方法{点滴-吸入}	-0.5604698	1	1.460223	0.22689
☐ 導入方法{内服-内服＋吸入}	0	1	0.607504	0.43573
☑ 静注ﾐﾀﾞｿﾞﾗﾑ mg/kg	22.6747066	1	1.720042	0.18969
☐ ﾌﾟﾛﾎﾟﾌｫｰﾙ mg/hr/kg	0	1	0.053516	0.81706
☐ ﾚﾐﾌｪﾝﾀﾆﾙ最頻値	0	1	0.011591	0.91426
☐ 歯科治療{その他抜歯&歯科治療-智歯抜歯}	0	1	0.027875	0.8674
☐ 歯科治療{その他抜歯-歯科治療}	0	2	0.028024	0.98609

表８．治療後の興奮状態と関連する要因の多変量解析

項	推定値	標準誤差	カイ2乗	p値(Prob>ChiSq)
切片[1]	0.11301336	0.8155712	0.02	0.8898
年齢	-0.0663199	0.0380796	3.03	0.0816
てんかん有無[1]	-0.516793	0.3310415	2.44	0.1185
導入方法{点滴&吸入-内服&内服＋吸入}	-1.1263281	0.4114152	7.49	0.0062*
導入方法{点滴-吸入}	-0.5560789	0.4637452	1.44	0.2305
静注ﾐﾀﾞｿﾞﾗﾑ mg/kg	22.2945015	17.296775	1.66	0.1974

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分担研究報告書

静脈内鎮静法からの回復に影響を与える因子について

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研究要旨

静脈内鎮静法は重度の知的障害を持つ患者の歯科治療をするために，有用である。全身疾患や，そのための治療薬，および麻酔薬の選択によって，静脈内鎮静法で用いられる薬剤の効果は影響を受けると考えられるため，鎮静法からの回復に影響を与える因子を同定することを本研究の目的とした。

本研究は前向きコホート研究である。参加者は岡山大学病院スペシャルニーズ歯科において静脈内鎮静法での歯科治療を受ける知的障害者とした。説明変数は患者背景，麻酔関連の変数，および歯科治療の内容とした。従属変数は治療終了から帰宅可能と判断されるまでの回復時間とした。回復時間に影響を与える因子を多変量解析によって調べた。

研究の対象は260ケースであった。平均年齢は32.4歳であった。鎮静法に関して重篤な合併症は認められなかった。前投薬として用いた内服ミダゾラムは，回復の遅れと有意に関連していた。他に，治療時間が短いこと，抜歯を行ったこと，BMI (body mass index)が小さいことが回復の遅れの予測因子であった。本研究を実施する前には，抗けいれん薬や抗精神病薬によって回復が遅れることを予想していたが，そのような因子は回復時間に影響を与えていないことが示された。

A．研究目的

Persons with severe intellectual disabilities (IDs) have a disadvantage in the management of their dental care. First, it may be difficult for them to understand instructions for preventing dental caries and periodontal disease. Second, they may not be able to cooperate adequately with dental treatment. To solve the first problem, family members and facility staff are expected to manage their oral health for them. To cope with the second problem, intravenous

sedation (IS) and general anesthesia (GA) have been used (Cillo, 1999; Maeda et al., 2005; McQuaid and Laine, 2008; Sakaguchi et al., 2011).

GA is useful for an intensive dental treatment including tooth extraction, caries treatment and tooth preparation but requires special facilities at higher cost. On the other hand, no special facility is needed for IS and the cost is much lower. In addition, IS does not entail the complications associated with GA, such as sore throat and postoperative nausea and vomiting. Thus, IS is often sufficient to meet the requirements of patients with IDs for limited dental treatments and periodic maintenance of oral hygiene.

Patients with IDs have a high rate of significant co-morbid conditions, such as epilepsy, mental disorders, cerebral palsy, and so on. They often require daily medications to control these illnesses. These diagnoses and medications might influence the clinical effect of anesthetics used in IS. At present, propofol and midazolam are the primary agents used for IS because of their short half-lives and amnesic effects (Kucukyavuz and Cambazoglu, 2004; Padmanabhan et al., 2009; Sandler et al., 2001). However, since usage of these anesthetics varies widely depending on the clinical features of each patient, standard doses of both anesthetics remain unclear. Since the interactions of several factors such as co-morbid conditions, concomitant medications and anesthetic choice influence recovery from anesthesia, the purpose of our study was to identify any independent factors for this outcome.

We hypothesized that there would be one or more variables associated with the outcome of delayed recovery and we aimed to measure these variables of interest using prospective multivariate analysis of dental treatments given to patients with ID under IS.

B. 研究方法

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 IS in the clinic of Special Needs Dentistry in Okayama University Hospital from January 2011 to December 2011.

Variables

Predictor variables were divided into three groups as follows: Patient-specific (age, gender, body mass index (BMI), cerebral palsy (yes or no), autism (yes or no), epilepsy (yes or no), and mental disorders (yes or no)); Anesthetic Technique (induction procedure, amount of midazolam peroral (PO) (per body weight), amount of intravenous (IV) midazolam (per body

weight), and average rate of propofol infusion (per body weight)); and Surgical/Dental Treatment (duration of treatment and tooth extraction (yes or no)). A mental disorder was defined by patient use of psychotropic drugs.

The primary outcome variable was time to recovery. Recovery time was defined as the interval from termination of treatment until permission for discharge. We judged the recovery state of patients using a post-anesthetic discharge scoring system (Chung et al., 1995) to estimate activity, vital signs, intake, pain, and bleeding. Patients were permitted to be discharged when these factors had recovered to the same levels as on admission.

Anesthetic procedure and Data collection methods

Since the patients had IDs, a written informed consent was obtained from parents or family members. Fasting times were 6 h and 2 h for food and clear water, respectively. Medicines in daily use were taken as usual. IS was started with insertion of an intravenous line, followed by injection of 0.5–3.0 mg of midazolam, and continuous injection of propofol was started in a target-controlled infusion (TCI) manner. The TCI value was set at 1.0–2.0 μg/ml at the beginning. When patients could not initially lie down at a dental unit because of inability to cooperate from their ID, 0.3–0.5 mg/kg of midazolam was given peroral (PO). After adequate sedation was obtained, an intravenous line was placed, followed by a continuous infusion of propofol as described above. If patients resisted vigorously on the dental unit even after the oral midazolam, 5% of sevoflurane was administered by inhalation and then, after obtaining loss of consciousness, an intravenous line was placed, followed by continuous infusion of propofol. In young patients under 16 years of age, the propofol infusion was started at 5 mg/kg/hr (83.5 μg/kg/min) because TCI cannot be used due to the basic settings of the infusion pump.

Patients were continuously monitored with ECG, blood pressure, and SpO_2 (noninvasive oxygen saturation of hemoglobin in arterial blood). During treatment, sedation level was maintained at a score of 1–2 on the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) (Cohen et al., 2007) (1: Does not respond to mild prodding or shaking; 2: Responds only after mild prodding or shaking) by adjusting the target concentration of propofol. During treatment, local anesthetic containing 2% lidocaine and 1:80,000 adrenalin was used if considered necessary. After treatment was completed, the infusion of propofol was terminated. Patients were permitted to be discharged, according to the standards given above.

IS 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. This study accorded with the STROBE guidelines for reporting cohort studies.

Data analysis

Data were analyzed using JMP 9.0.0 (SAS Institute Inc., Cary, NC). A linear regression was applied to examine the bivariate regression between the primary outcome variable (time to recovery) and all continuous study variables, while Student's t-test was used between the primary outcome variable and the nominal study variables. In order 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 a multiple regression (standard least squares).

C. 結果

Two hundred and sixty subjects were enrolled in this study. Their backgrounds and summaries of anesthetic data are shown in Table 1. In 60.8% of participants, anti-epileptic medicine was used. Psychotropic drugs were used in 33.8 % of subjects. IS was started with an intravenous line in 86.8%, while oral midazolam was used in 13.2% of subjects, who took 0.300 ± 0.121 (mean±SD) mg/kg of midazolam PO. In cases without PO midazolam, 0.034 ± 0.015 (mean±SD) mg/kg of midazolam was injected IV. Treatment time was 43.1 ± 12.5 (mean±SD) min, and time to recovery was 62.9 ± 25.8 (mean±SD) min. No case was hospitalized after IS and major complications did not occur.

With a bivariate regression (Table 2), no relationship was observed between time to recovery and Patient-specific variables. On the other hand, a significant relationship of time to recovery was observed with the use of midazolam PO in the induction procedure, the amount of midazolam PO, and the amount of midazolam IV. While the amount of midazolam PO was positively associated with prolongation of time to recovery, the amount of midazolam IV was negatively correlated with recovery time.

Prior to standard least squares, using stepwise regression, BMI, mental disorder, induction procedure, midazolam IV amount, treatment time, and tooth extraction were selected. In a standard least squares calculation, midazolam PO was significantly associated with prolonged recovery time. In

addition, lower BMI, shorter treatment time, and tooth extraction were also shown to be independent determinants of prolonged time to recovery (Table 3). On the other hand, parameters related to disabilities, such as cerebral palsy, autism, epilepsy and mental disorder, were not variables predictive of recovery time.

In order to clarify confounding factors, pairwise correlations were analyzed for the continuous variables (Table 4). Midazolam PO was negatively correlated with age and midazolam IV, and positively correlated with propofol rate. Midazolam IV had clear negative correlations with BMI and midazolam PO. Because we suspected that tooth extraction might be correlated with anesthetic dose, the relationships between tooth extraction (yes or no) and the anesthetic parameters were explored. We found that the amount of midazolam IV (mg/kg) in IS for tooth extraction was significantly higher than the amount for dental treatment without tooth extraction (t-test; p=0.0496).

D. 考察

The purpose of this study was to determine the factors affecting recovery time from IS with a prospective multiple regression analysis in patients with IDs. Before this study, we expected that both disabilities and medicines for epilepsy and/or mental disorders might affect recovery from IS, but such parameters were not found to be independent determinants.

The results show that using midazolam PO in the induction is a clear independent predictor of delayed recovery. The aim of midazolam PO is to make an uncooperative patient sleepy enough to be carried to a dental chair while the aim of midazolam IV is to support the effect of propofol during treatment. As a result, the amount of midazolam PO (0.300 ± 0.121 mg/kg) is almost 9 times higher than that given intravenously (0.034 ± 0.015 mg/kg). In a previous report, 2 mg midazolam IV brought about the same level of plasma concentration as 7.5 mg midazolam PO (Link et al., 2008). Based on this report, a two-fold or higher level of plasma midazolam might occur after midazolam PO in our study compared with midazolam IV. This difference in plasma midazolam level is likely to have contributed to delayed recovery.

In bivariate regression, midazolam IV (mg/kg) was negatively correlated with recovery time. That is because the amount of midazolam IV was less in patients given midazolam PO. This is supported by the significant and negative correlation between midazolam PO and midazolam IV. Thus, midazolam IV is a confounding factor for midazolam PO. Shorter treatment time is also shown to be another independent predictor of delayed time to recovery. This may be the

result of residual midazolam effects. Midazolam was used PO or IV at the beginning of IS. Since the half-life of midazolam is longer than that of propofol (Dundee et al., 1984; Langley and Heel, 1988), shorter treatment time would mean more prominent midazolam effects at the beginning of the recovery time, requiring longer duration for metabolic clearance.

It was unexpected that BMI was negatively correlated with time to recovery since obesity has been associated with a prolonged elimination half-life of midazolam (Adams and Murphy, 2000). In this study, the person in charge of IS kept the anesthesia level at class 1-2 in the OAA/S. 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 (Wani et al., 2011). 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 time to recovery. Tooth extraction was another independent predictor of delayed recovery, consistent with higher amounts of midazolam IV being used for teeth extraction. This is considered to be a reflection of a subjective decision of the person in charge of IS, to assist in coping with the stress of tooth extraction, again resulting in a longer recovery time.

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E. 結論

本研究は，知的障害者を対象とした歯科治療のための静脈内鎮静法において，回復時間に影響を与える因子を調べた初めての研究である。前投薬として用いた内服ミダゾラムは，回復の遅れと有意に関連していた。他に，治療時間が短いこと，抜歯を行ったこと，BMI が小さいことが回復の遅れの予測因子であった。本研究を実施する前には，抗けいれん薬や抗精神病薬によって回復が遅れることを

予想していたが，そのような因子は回復時間に影響を与えていないことが示された。

F．健康危険情報

該当なし。

G．研究発表

1．友安弓子，前田　茂，森　貴幸，江草正彦，宮脇卓也．静脈内鎮静法下歯科治療に関する合併症と回復時間に関わる要因について　障害者歯科専門外来患者を対象として．障害者歯科 32(3)；487，2011.

2．前田　茂，友安弓子，森　貴幸，江草正彦，宮脇卓也．外来全身麻酔下歯科治療に関する合併症と回復時間に関わる要因について　知的障害者を対象とした多変量解析．障害者歯科 32(3)；486，2011.

3．Maeda S, Tomoyasu Y, Higuchi H, Mori T, Egusa M, Miyawaki T. Midazolam is associated with delay in recovery and agitation after ambulatory general anesthesia for dental treatment in patients with disabilities: a retrospective cohort study. J Oral Maxillofac Surg (in press).

H．知的財産権の出願・登録状況

該当なし。

Table 1. Patient background and summary of anesthetic data.

Category	Variables	(Average ± SD)
Patients	male/female (%)	63.5/ 36.5
	Age (yrs)	(32.4 ± 11.6)
	Body mass index	(21.4 ± 4.63)
	Autism (%)	37.7
	Cerebral palsy (%)	11.2
	Epilepsy (%)	60.8
	Mental disorder (%)	33.8
Anesthetic	Induction procedure (%)	
	IV (intravenous line)	86.8
	PO (per oral midazolam)	13.2
	Midazolam PO (mg/kg)	(0.043 ± 0.114)
	Midazolam IV (mg/kg)	(0.029 ± 0.018)
	Propofol rate (mg/kg/h)	(5.89 ± 1.90)
	[Propofol rate (μg/kg/min)]	([98.2 ± 31.7])
Surgical/Dental treatment	Treatment time (min)	(43.1 ± 12.5)
	Teeth extraction (%)	11.5
Outcomes	Time to recovery (min)	(62.9 ± 25.8)

Continuous variables were given as mean ± SD, and descriptive variables were given as %.

Table 2. All study variables versus the primary outcome variable (time to recovery) (Bivariate regression)

	Correlation	Confidence interval lower 95%	Confidence interval upper 95%	P value
Age [1)]	-0.018	-0.139	0.104	0.775
Gender [2)]	-	-	-	0.928
BMI [1)]	-0.042	-0.163	0.080	0.498
Cerebral palsy [2)]	-	-	-	0.642
Autism [2)]	-	-	-	0.731
Epilepsy [2)]	-	-	-	0.226
Mental Disorder [2)]	-	-	-	0.363
Induction procedure [2)] (PO vs without PO)	-	-	-	<0.0001
Midazolam PO (mg/kg) [1)]	0.396	0.288	0.493	<0.0001
Midazolam IV (mg/kg) [1)]	-0.289	-0.397	-0.173	<0.0001
Propofol rate (mg/kg/h) [1)]	-0.005	-0.127	0.116	0.930
Treatment time (min) [1)]	-0.113	-0.230	0.011	0.073
Wisdom tooth extraction [2)]	-	-	-	0.530

[1)]Linear regression was used for analysis of continuous variables. Pearson correlation coefficients, confidence intervals and p values are shown. [2)]For nominal variables, t-test was used to compare groups.

Table 3. Results of a multivariate regression (standard least squares) with the primary outcome variable (time to recovery) as an independent variable.

parameter	Estimate	SE	t value	P value (Prob>|t|)
Intercept	107.86	10.72	10.05	<0.0001*
BMI	-0.71	0.34	-2.08	0.038*
Mental disorder	-2.76	1.55	-1.78	0.076
Induction procedure (PO vs without PO)	14.40	2.63	5.47	<0.0001*
Midazolam IV (mg/kg)	-157.44	110.82	-1.42	0.157
Treatment time (min)	-0.27	0.12	-2.33	0.020*
Tooth extraction	5.73	2.23	2.57	0.011*

R^2=0.238, *p-value<0.05.

Table 4. Pairwise correlations (A) and probability (B) in continuous variables.

A. Correlations

parameter	Age	BMI	Midazolam PO	Midazolam IV	Propofol
Age	1	0.147	-0.266	0.062	-0.363
BMI	0.147	1	0.079	-0.355	-0.100
Midazolam PO (mg/kg)	-0.266	0.078	1	-0.584	0.185
Midazolam IV (mg/kg)	0.062	-0.355	-0.584	1	-0.007
Propofol rate (mg/kg/hr)	-0.363	-0.100	0.185	-0.007	1

B. Probability

parameter	Age	BMI	Midazolam PO	Midazolam IV	Propofol
Age	-	0.018*	<0.001*	0.320	<0.001*
BMI	0.018*	-	0.208	<0.001*	0.109
Midazolam PO (mg/kg)	<0.001*	0.208	-	<0.001*	0.003*
Midazolam IV (mg/kg)	0.320	<0.001*	<0.001*	-	0.912
Propofol rate (mg/kg/hr)	<0.001*	0.109	0.003*	0.912	-

Linear regression was used for analysis of continuous variables. Pearson correlation coefficients (A) and p values (B) are shown. *p-value<0.05

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分担研究報告書

日帰り全身麻酔後の覚醒と回復に影響を与える因子について

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研究要旨

日帰り全身麻酔は知的障害者の歯科治療のために，有効である。われわれは早期回復と合併症が少ないことを理由として，基本的に完全静脈麻酔を行っている。しかし，あまりにも早い回復を求めると，術中覚醒のリスクが増す。今回の前向き観察研究では，日帰り全身麻酔後の覚醒と回復に関わる要因を見つけ出すことを試みた。

対象は知的障害を持った歯科患者であった。全身麻酔では気管内挿管を行い，プロポフォールとレミフェンタニルで維持した。BIS 値が 40-50 になるよう，麻酔薬の投与速度を調節した。アウトカムは覚醒までの時間と，帰宅許可がでるまでの回復時間とした。前向きステップワイズ多変量解析により，アウトカムに独立して影響を与える因子を求めた。

対象症例数は 102 症例で，そのうち 13 例が治療終了から 10 分以内に覚醒した。また 15 例は帰宅許可が出るまで 120 分以上を要した。統計学的にはてんかん，男性および若年者が回復の遅れに関して重要な因子であった。女性であることと，てんかんがないことは，早期覚醒のリスクファクターであった。

今回の麻酔管理方法は，全般的にほぼ満足できるものであった。てんかん，男性および若年は，知的障害者の外来全身麻酔下歯科治療において，回復遅延のリスクファクターであった。女性であることと，てんかんがないことは，術中覚醒のリスクとなるかもしれないと思われた。

A．研究目的

General anaesthesia is useful for patient with intellectual disability since intellectual disability keeps patient away from dental management [1]. It is performed as an outpatient in most cases because it is hard for them to stay in hospital, unfamiliar and uncomfortable circumstance [2, 3]. We basically perform total intravenous

anesthesia consisting of propofol and remifentanil. Advantage of propofol is strong antiemetic effect [4-6], which leads to comfortable recovery. Remifentanil is metabolized by non-specific cholinesterase in plasma [7, 8], meaning it can be metabolized quickly in any conditions a patient is with.

In our previous retrospective study, midazolam was shown to be a strong independent factor for delay in recovery [9]. And since midazolam basically does not have analgesia [10], it is not effective to control vessel pain caused by propofol. Therefore, we limited the use of midazolam as a premedication only for patients with extremely severe difficulty in cooperation. In this study, participants were patients without need of midazolam as a premedication. A longer recovery time is the primary outcome, and secondary outcome is a shorter emergence time since a risk of intraoperative awareness increases if quick recovery is sought excessively [11].

B．研究方法

The study was conducted according to the revised Declaration of Helsinki and approved by Ethics Committee, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (approval no: 433 and 530). Written informed consent procedure was waived as no interventions were conducted and the design was entirely observational. The study was registered to UMIN Clinical Trial Registry (intellectual disability: UMIN000006262).

Study setting

To address the research purpose, 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 ambulatory general anaesthesia in the clinic of Special Needs Dentistry in Okayama University Hospital from January 2011 to September 2012. To be included in the study sample, general anaesthesia with tracheal intubation had to be maintained with total intravenous anaesthesia consisting of remifentanil and propofol. Patients were excluded as study subjects if hospitalization and/or midazolam use was planned.

Variables

Predictor variables were divided into three groups as follows: patient's variables (gender, age, gender, body mass index (BMI), autism, epilepsy,

valproate, mental disorders and cerebral palsy); anesthetic variables (sevoflurane use, propofol dose (μg/kg/min), and remifentanil dose (μg/kg/hr)); and treatment variables (tooth extraction, treatment time). A mental disorder was defined by patient use of psychotropic drugs.

The primary outcome variable was delay of recovery (>120 min). The secondary outcome variable was delay of emergence (>20 min). Recovery time was defined as the duration from termination of treatment until permission for discharge. We judged the recovery state of patients using a post anesthetic discharge scoring system [12], with which activity, vital signs, intake, pain, and bleeding were estimated. Patients were permitted to be discharged when these factors had recovered to the same levels as on admission. Emergence time was from the termination of treatment to extubation of tracheal tube, which was just after eye opening.

Anaesthetic procedure

Fasting times were 6 hrs and 2 hrs for food and clear water, respectively. Medicines in daily use were taken as usual. General anaesthesia was started with insertion of an intravenous line. When it was difficult to place, sevoflurane was inhaled as induction for general anaesthesia, followed by insertion of an intravenous line. Remifentanil was started at 0.25 μg/kg/min and propofol was started in a target-controlled infusion (TCI) manner and the target concentration was initially set at 4.0 μg/ml. In obese patients, standard weight is calculated as a body mass index (BMI) of 22. Based on standard weight, the infusion rate of remifentanil was determined. In young patients under 16 years old, propofol was infused at 10 mg/kg/hr (167 μg/kg/min) because TCI cannot be used due to the basic settings of the infusion pump. After loss of consciousness, rocuronium was injected to obtain muscle relaxation, and an endotracheal tube was inserted, usually through the nose.

Patients were continuously monitored with ECG, blood pressure, SpO_2 (non invasive oxygen saturation of hemoglobin in arterial blood), bispectral index (BIS) monitoring, and partial pressure of CO_2 in an anaesthetic circuit. Body temperature was measured every 30 min. After intubation, the infusion rate of remifentanil was reduced to 0.10-0.15 μg/kg/min and the target concentration of propofol was set at 3.0 μg/ml. During

treatment, the BIS value was maintained between 40 and 50 by adjusting the target concentration of propofol [13]. Systemic blood pressure was maintained at no less than 80 mmHg. During treatment, local anaesthetic containing 2% lidocaine and 1:80,000 adrenaline was used if considered necessary. Intravenous or suppository non-steroidal anti-inflammatory drugs (NSAIDs) were used after tooth extraction. After treatment, infusion of both remifentanil and propofol was terminated and the effect of the muscle relaxant was reversed with sgammadex. The tracheal tube was removed when eye opened and spontaneous breathing recovered. Patients were permitted to be discharged, according to the standards given above.

Data analysis

Data were analyzed using JMP 9.0.0 (SAS Institute Inc., Cary, NC). Fisher's exact test was used between the outcome variables and nominal variables. A logistic regression was used to test the relationship between the outcome variables and continuous variables. Probabilities of less than 0.05 were accepted as significant.

Forward stepwise multivariate logistic regression analysis was then used to control for potential confounding variables and to calculate the odds ratios (OR) and 95% CI for potential independent predictors of outcome. Relevant variables that had probabilities of less than 0.25 in the initial analyses were entered into the logistic regression model as independent variables.

C. 結果

The study group comprised 102 cases (69 male and 33 female) ranging in age from 6 to 63 years (mean (SD) 27(14) years). Emergence time ranged from 2 to 51 min (mean (SD) 19.2(9.1)). In 13 cases of the total number, it took less than 10 min until emergence. Recovery time ranged from 46 to 147 min (maen (SD) 94.4(23.0)). And in 15 cases, it took more than 120 min until recovery.

Distributions among patients of the variables studied and their relation to outcome are shown in Tables 1-5. Two variables were significantly associated with early emergence: male ($p=0.03$) and epilepsy ($p=0.013$) (Table 1). Epilepsy was significantly associated with delay of recovery ($p=0.02$) (Table 1). There were no significant correlation between the outcomes and either anaesthetic variables or treatment variables (Table 3-5). Patients with epilepsy