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

were significantly correlated with valproate use, and doses of both propofol and remifentanil were significantly lower in male than female.

Multivariate logistic regression analysis (Table 6A) resulted in that female and non-epilepsy are clear independent predictors in early emergence. Female and non-epilepsy had 6.5 times ($p=0.007$) and 11.3 times ($p<0.001$) the risk of early emergence, respectively. In delay of recovery, it confirmed the importance of "younger than 20 years", epilepsy, and male as independent predictors (Table 6B). "Younger than 20 years, epilepsy and male had 12.2 times ($p=0.004$), 11.5 times ($p=0.007$) and 7.1 times ($p=0.032$) the risk of delay of recovery.

D. 考察

Overall performance of this procedure is considered almost satisfactory from a fact that all participants were aroused and fulfilled the criteria of recovery within permissive range. In this prospective cohort study, we made an effort to unify the anaesthetic procedure; initial administration speeds of both propofol and remifentanil were defined, and a depth of general anaesthesia was strictly maintained according to BIS value between 40-50 by adjusting administration speeds of both anaesthetics. Then, as a result, independent predictors for delay of recovery from general anaesthesia are "younger than 20 years", epilepsy and male, suggesting these patients have a risk for delay of recovery from total intravenous anaesthesia. On the other hand, female and non-epilepsy are likely to be possible risk factors of intraoperative awareness.

After general anaesthesia maintained with propofol, the emergence time was reported to be significantly shorter in female than male [14, 15]. From pharmacokinetic analysis, the plasma concentrations at the termination of the propofol infusion were statistically significantly lower in female than male after similar continuous infusions, leading to consideration that difference in emergence time is a result of pharmacokinetic differences between male and female [16, 17]. In our results, male was the risk factor in delay of recovery, despite of that lower doses of both propofol and remifentanil were used in male than female. The depth of anaesthesia was

defined according to BIS value, and administration speeds of both anaesthetics were adjusted. Lower doses in male are considered to reflect lower BIS value. In spite of the effort to maintain BIS value by adjusting doses, male was shown to be the risk factor in delay of recovery. Although we did not measure plasma concentration of the anaesthetics, pharmacokinetics of both anaesthetics seemed different between male and female.

On the other hand, it is reported that female is one of risk factors for intraoperative awareness from systematic review made from 271 cases of awareness with 19504 patients who did not suffer it [18]. Besides, faster emergence in female was reported after general anaesthesia also through inhalation but not propofol [19]. Thus, other factors from pharmacokinetics of propofol are likely to be involved with the gender difference in clinical effect of anaesthetics. And intraoperative awareness can happen if fast emergence and/or recovery are sought. In this meaning, it is suggested that female and non-epilepsy can be a risk for intraoperative awareness.

Epilepsy was a clear independent predictor in delay of recovery. In this study, patient with epilepsy was defined as a patient taking anti-epileptic drugs, such as barbiturate, carbamazepine, phenytoin and benzodiazepine. Action mechanism of anti-epileptic drugs is mainly to stabilize voltage-gated sodium channel and/or stimulate GABA receptor [20, 21]. Pharmacological effect of propofol is reported to be mediated with GABA receptor [22 23] and activating transient potential receptors [24]. These mechanisms lead to decrease membrane potential and have possibility to interact with anti-epileptic drugs. In clinical study, patient without epilepsy needed significant much amount of propofol to maintain same level sedation for dental treatment compared with patient taking balproate [25]. In our study, patient with epilepsy used valproate in significant higher rate, suggesting valproate is a confounding factor of epilepsy. Besides, since valproate inhibits a propofol metabolizing enzyme CYP2C9 [26], this may be another reason to interact of propofol and anti-epileptic drugs.

"Younger than 20 years" was shown to be other risk for delay of recovery. Most common complication related with general anaesthesia in children and adolescent is an emergence agitation [27],

and a mechanism of the emergence agitation remains unknown [28]. Reaction of child to anesthetics is different from adult, such as the emergence agitation and propofol syndrome. Our result may reflect one of characteristic reaction of child to anesthetics like these through unclear mechanism.

When the depth of general anaesthesia maintained with both propofol and remifentanil was determined according to BIS value, which has been established to be useful in prevention of intraoperative awareness [29 11 30 31], the risk factors raised in this study should be minded. Male, epilepsy and young age are risks for delay of recovery while female and non-epilepsy may have higher risk for intraoperative awareness. Thinking of significance of intraoperative awareness, seeking for fast recovery in female or non-epilepsy patient does mean less advantage and much risk of intraoperative awareness.

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E．結論

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。

F．健康危険情報

該当なし。

G．研究発表

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H．知的財産権の出願・登録状況

該当なし。

Patients' variables and their relation to emergence and recovery time

Variables	Total (n=102)	Emergence time <10 min (n=13)		Recovery time from GA >120 min (n=15)	
	No(%)	No	p-Value	No	p-Value
Sex					
Male	69 (68)	5	0.03	13	0.13
Female	33 (32)	8		2	
Age					
<20yrs	44 (43)	8	0.23	10	0.05
>20yrs	58 (57)	5		5	
BMI					
>25	30 (29)	2	0.34	6	0.36
<25	72 (71)	11		9	
Autism					
Yes	61 (60)	9	0.55	9	1.00
No	41 (40)	4		6	
Epilepsy					
Yes	59 (58)	3	0.013	13	0.02
No	43 (42)	10		2	
Valproate					
Yes	27 (27)	1	0.18	7	0.07
No	75 (74)	12		8	
Mental disorder					
Yes	17 (17)	2	1.00	2	1.00
No	85 (83)	11		13	
Cerebral palsy					
Yes	11 (11)	2	0.63	1	1.00
No	91 (89)	11		14	

Anesthetic variable (sevoflurane) and its relation to emergence and recovery time

(a)

Variables		Emergence time		Recovery time from GA	
	Total (n=102)	<10 min (n=13)		>120 min (n=15)	
	No(%)	No	p-Value	No	p-Value
Sevoflurane					
Use	37 (36)	8	0.063	5	1.00
Non use	65 (64)	5		10	

Anesthetic variables and their relation toemergence and recovery time

(b)

Variables		Emergence time from GA			Recovery time from GA		
	Total (n=102)	<10 min (n=13)	>20 min (n=89)	p-Value	>120 min (n=15)	<120 min (n=87)	p-Value
Propofol dose (μg/kg/min)							
Mean	119	122	119	0.629	119	119	0.941
SD	26	17	27		23	27	
Range	76-216	101-157	76-216		91-175	76-216	
Remifentanill dose (μg/kg/hr)							
Mean	9.7	9.7	9.7	0.97	9.4	9.7	0.725
SD	2.8	3.7	2.6		1.3	2.9	
Range	4.9-19.4	4.9-17.1	6.0-19.4		7.3-12.2	4.9-19.4	

Treatment variable (tooth extraction) and its relation to emergence and recovery time

(a)

Variables		Emergence time		Recovery time from GA	
	Total (n=102)	<10 min (n=13)		>120 min (n=15)	
	No(%)	No	p-Value	No	p-Value
Tooth extraction					
Yes	38 (37)	5	1	8	0.25
No	64 (63)	8		7	

Treatment variable (treatment time) and its relation to emergence and recovery time

(b)

Variables		Emergence time from GA			Recovery time from GA		
	Total (n=102)	<10 min (n=13)	>10 min (n=89)	p-Value	>120 min (n=15)	<120 min (n=87)	p-Value
Treatment time (min)							
Mean	96	93	97	0.49	97	96	0.812
SD	20	22	20		21	20	
Range	27-141	49-126	27-141		62-140	27-141	

A. Stepwise logistic regression model for fast emergence from GA (<10 min)

Variable	Regression coefficient	p-Value	Odds ratio	Confidence interval for odds ratio
Intercept	-2.153			
Female	0.937	0.007	6.517	1.635-31.631
Autism	0.469	0.208	2.554	0604-13.331
non-epilepsy	1.213	<0.001	11.321	2.575-70.640
Sevoflurane	0.522	0.127	2.840	0744-12.005

B. Stepwise logistic regression model for delay of recovery from GA (>120 min)

Variable	Regression coefficient	p-Value	Odds ratio	Confidence interval for odds ratio
Intercept	-2.949			
Age<20	1.251	0.004	12.207	2.543-79.961
Male	0.980	0.032	7.093	1.430-57.780
Epilepsy	1.220	0.007	11.487	2.367-94.741
Sevoflurane	-0.471	0.231	0.390	0.077-1.740
Extraction	0.683	0.054	3.918	1.028-17.684

別紙４

研究成果の刊行に関する一覧表レイアウト（参考）

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
該当なし					