Original Article

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Delayed awakening time from general anesthesia for dental treatment of patients with disabilities

Junglim Choi[1], Seungoh Kim[2]

[1]Department of Advanced General Dentistry, School of Dentistry, Dankook University, Cheonan, Republic of Korea
[2]Department of Dental Anesthesiology, School of dentistry, Dankook University, Chenonan, Republic of Korea

Background: Patients with disabilities often require general anesthesia for dental treatment because of their cooperative or physical problems. Since most patients with disabilities take central nervous system drugs, the management of recovery status is important because of drug interactions with anesthetics.
Methods: The anesthesia records of patients under general anesthesia for dental treatment were reviewed, and data were collected. Healthy patients under general anesthesia for dental phobia or severe gagging reflex were designated as the control group. Patients with disabilities were divided into two groups: those not taking any medication and those taking antiepileptic medications. The awakening time was evaluated in 354 patients who underwent dental treatment under general anesthesia (92 healthy patients, 183 patients with disabilities, and 79 patients with disabilities taking an antiepileptic drug). Based on the data recorded in anesthesia records, the awakening time was calculated, and statistical processes were used to determine the factors affecting awakening time.
Results: Significant differences in awakening time were found among the three groups. The awakening time from anesthesia in patients with disabilities (13.09 ± 5.83 min) ($P < 0.0001$) and patients taking antiepileptic drugs (18.18 ± 7.81 min) ($P < 0.0001$) were significantly longer than in healthy patients (10.29 ± 4.87 min).
Conclusion: The awakening time from general anesthesia is affected by the disability status and use of antiepileptic drugs.

Keywords: Awakening Time; Dental Care for Disabled; General Anesthesia.

INTRODUCTION

Ambulatory general anesthesia (GA) is useful when providing safe and readily available dental treatment for patients with cooperative or physical problems. However, it may cause difficulty or delay in emergency care if complications of anesthesia or side effects of anesthetics occur after returning home, especially in persons with disabilities; it is difficult to determine the recovery state when they wake up [1-4]. In addition, most patients with disabilities take psychotic or antiepileptic drugs to relieve their behavioral symptoms and treat their medical condition [4,5]. Moreover, for uncooperative patients, premedication, commonly benzodiazepines, is often used to reduce anxiety and facilitate the application of anesthesia [3,6,7]. Therefore, the management of the recovery state is important for patients with disabilities after GA because of interactions between anesthetics and central nervous system (CNS) drugs [8].

Recovery from anesthesia could be defined as a condition of consciousness when an individual is awake and “aware of surroundings and identity,” resulting in the elimination of anesthetic agents from the brain [9,10].

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Corresponding Author: Seungoh Kim, Department of Dental Anesthesiology, School of Dentistry, Dankook University, 119 Dandae-ro, Dongnam-gu, Cheonan-si, Chungcheongnam-do, 31116, Republic of Korea
Tel: +82-41-550-1863 Fax: +82-41-550-1863 E-mail: ksomd@naver.com

According to previous studies, awakening time from anesthesia depends on several factors, including patient age, sex, body mass index (BMI), operating time, and medication administration [10,11]. In addition, the type of anesthetic also affects the awakening time. For example, anesthetics, such as propofol, sevoflurane, and desflurane, generally cause postoperative patients to wake up quickly [10,11].

Patients with disabilities under GA for dental treatment need more sedatives to obtain the proper level of anesthesia and spend a longer time awake from anesthesia. In addition, since patients with neurological disorders often take anticonvulsant drugs, the awakening time is likely to increase. This might be due to the interaction between anesthetics and antiepileptics [8,10-12]. However, Maeda et al. concluded in their study that antiepileptic drugs do not act as independent factors of prolonged awakening time in patients with intellectual disabilities [13].

As previous articles present conflicting opinions on the factors of delayed awakening time in patients with disabilities, it is difficult to determine which factors affect awakening time. Therefore, this study aimed to investigate the independent factors for delayed awakening from GA for dental treatment in patients with disabilities by analyzing the difference in awakening time in three patient groups: healthy patients, patients with disability, and patients with disability taking antiepileptic drugs. We hypothesized that antiepileptic drugs might extend the awakening time, but the factor of disability would not influence the awakening time.

METHODS

This was a retrospective observational study and reviewed the anesthesia records of patients who underwent GA for dental treatment at the Dankook University Dental Hospital in Cheonan, Korea, from November 2018 to October 2020 (IRB No. DKU 2021-03-046). Data on gender, age, weight, height, underlying medical condition, medication taken, anesthesia time, and treatment time were collected from the anesthesia records. The anesthesia time was from the beginning of anesthesia induction to arrival in the recovery room. The treatment time was from the time the dentist started dental treatment until the end of the treatment. The “awakening time” was calculated by subtracting the time that the anesthesia ended from the time that the treatment was over.

1. Anesthesia procedure

Anesthesia was performed by an anesthesiologist. The anesthesia procedure was started after the patient sat in the dental chair and allowed for mask induction. The inhalation sequence contained a mixture of 50% nitrous oxide, 50% oxygen, and a high concentration of sevoflurane. Standard monitors were placed, and an intravenous catheter was inserted. After confirming the loss of consciousness and following sufficient manual ventilation, rocuronium (0.6 mg/kg) was injected before nasotracheal intubation. Anesthesia depth was maintained using 2 vol% sevoflurane and a mixture of 50% nitrous oxide and 50% oxygen gas. Vital signs and entropy were monitored.

After finishing the dental procedure, sevoflurane and nitrous oxide were turned off, 100% oxygen gas was used, and sugammadex (2 mg/kg) was administered as a neuromuscular blocking reversal agent. Extubation was performed when the patient was able to breathe spontaneously and open the eyes. When 100% oxygen was provided, vital signs were monitored, and when the vitals were confirmed to be stable, they were taken to the recovery room.

2. Data collection

In the past 2 years, 952 patients were treated under GA at our clinic. In this study, the subjects were limited to patients over 19-year-old because the response to anesthetics in children or adolescents might differ from that of adults, which may be another factor affecting the awakening time. There were 464 patients aged over 19

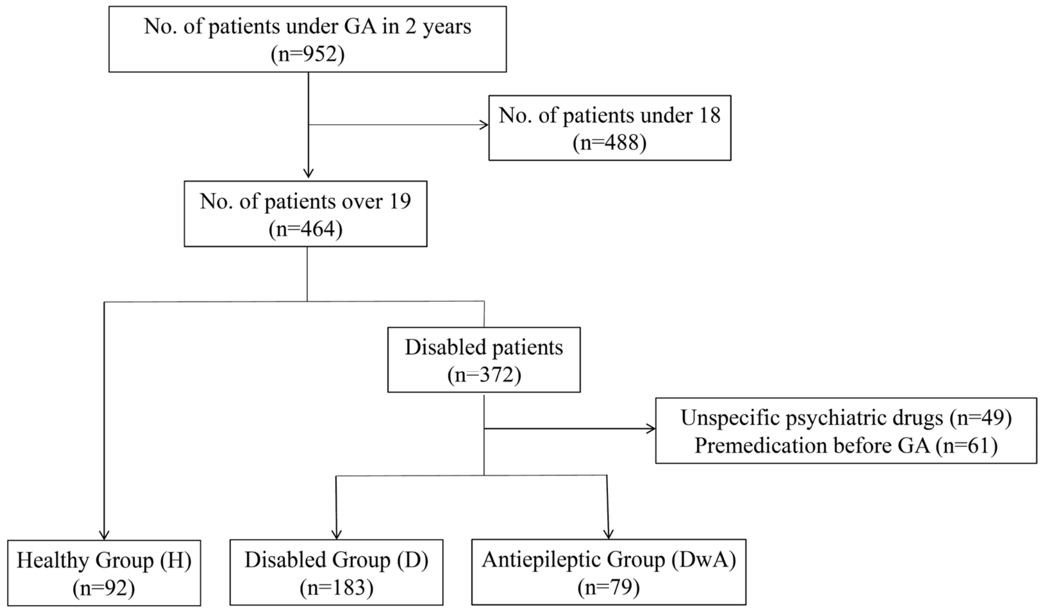

Fig. 1. A flowchart presents an overview of data selection. GA, general anesthesia.

Table 1. Demographic data according to group

	H	D	DwA
No. of patients	92	183	79
M	54 (58.7%)	104 (56.8%)	40 (50.6%)
F	38 (41.3%)	79 (43.2%)	39 (49.4%)
Age (y)	37.15 ± 13.09	33.00 ± 10.62	28.80 ± 10.87
BMI (kg/m^2)	24.29 ± 4.29	22.54 ± 5.53	21.49 ± 4.72
Treatment time (min.)	76.50 ± 53.05	119.64 ± 56.67	129.15 ± 59.66
Anesthesia time (min.)	100.0 ± 56.15	142.49 ± 58.82	163.29 ± 61.76

H, Healthy group; D, Patients with disabilities; DwA, Patients with disabilities taking antiepileptic drugs.

years, 92 of whom were healthy, and 372 had disabilities. Healthy patients who underwent GA due to severe gagging reflex or dental phobia were designated as the control group. Some disabled patients were required to receive a midazolam injection or administer valium to reduce their anxiety before anesthesia. To avoid uncontrolled factors that might have affected the results, 61 patients who received premedication were excluded. In addition, 49 patients receiving non-specific psychiatric drugs were excluded for the same reason. After the selection process, 262 persons with disabilities were included. They were divided into two groups, one group taking anticonvulsant drugs and the other group not taking any medication. Patients with disabilities who did not take any medication were designated as the "D" group and those who took medications as the "DwA" group. Detailed overview of the data selection processes is shown in Fig. 1.

A total of 354 patients (198 males and 156 females) were categorized into three groups: healthy persons (H; n = 92), patients with disabilities (D; n = 183), or patients with disabilities taking antiepileptic medication (DwA; n = 79), and data were collected (Table 1). Patients with disabilities consisted of intellectual disabilities, Down syndrome, autism, brain disorders including cerebral palsy, mental disability, and multi-disabilities. Table 2 shows the demographics of the disabled patients according to the type of disability.

Table 2. Number of patients according to the type of disability

	D	DwA
Intellectual disability	94	41
Down's syndrome	14	0
Autism	12	8
Brain disorder	26	9
Physical disability	17	3
Mental disability	1	3
Multi-disabilities	19	15
Total	183	79

D, Patients with disabilities; DwA, Patients with disabilities taking antiepileptic drugs.

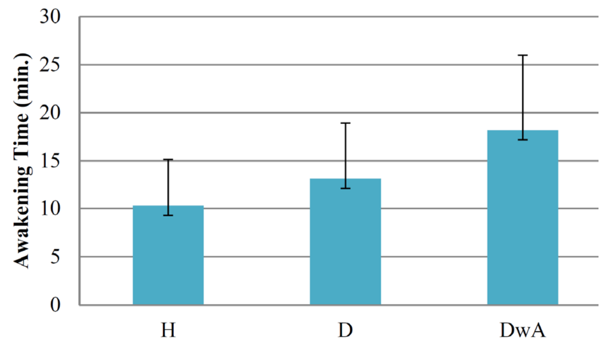

Fig. 2. A bar graph shows the general anesthesia awakening time in the three groups of patients. H, Healthy group; D, Patients with disabilities; DwA, Patients with disabilities taking antiepileptic drugs.

Table 3. Results of one-way analysis of variance for the awakening time of each patient group

		N	Mean	SD	F	P value	Scheffe
Emerge Time	H	92	10.29	4.860	36.289***	<0.001	H < D < DwA
	D	183	13.09	5.827			
	DwA	79	18.18	7.807			

H, Healthy group; D, Patients with disabilities; DwA, Patients with disabilities taking antiepileptic drugs.
*P < 0.05, **P < 0.01, ***P < 0.001

Table 4. The relationship of variables to general anesthesia awakening time

	Average	SD	Correlation	P value
Gender			-0.034	0.527
Age (y)	33.14	11.70	-0.082	0.124
BMI (kg/m^2)	22.76	5.14	-0.173**	0.001
Treatment time (min)	110.55	59.92	0.269***	<0.001
Anesthesia time (min)	136.09	62.98	0.392***	<0.001

*P < 0.05, **P < 0.01, ***P < 0.001

3. Statistical analysis

Data were analyzed using SPSS Statistics version 21 (IBM Corp., USA). For all analyses, the results are expressed as mean ± standard deviation (SD), and a P value of less than 0.05 was considered statistically significant. For comparison of differences in emergence time between the three groups, a one-way analysis of variance (ANOVA) was used, and for post hoc analysis, Scheffe was performed. In addition, Pearson's correlation analysis was used to identify variables that correlated with awakening time. Finally, to determine if the factors were an independent predictor of delayed awakening time, multiple linear regression analysis was performed by statistically controlling each factor, which had been shown to affect the awake time based on previous studies.

RESULTS

The results of the one-way ANOVA showed significant differences in the awakening time from anesthesia between the three groups (Fig. 2). The awakening time in patients with disabilities (13.09 ± 5.83 min) (P < 0.0001) and patients taking antiepileptic drugs (18.18 ± 7.81 min) (P < 0.0001) were significantly longer than in the healthy patients (10.29 ± 4.87 min) (Table 3).

Pearson's correlation analysis showed that gender and age were not related to awakening time, while treatment time showed a positive correlation, and BMI showed a negative correlation (Table 4). According to the correlation coefficient value, the BMI showed a weak relationship, while the treatment time and anesthesia time

Table 5. Multiple regression models for the awakening time from general anesthesia

	B	SE	β	t	P value	VIF
(Constant)	11.892	1.728		6.883***	0.000	
BMI	-0.126	0.063	-0.097	-1.991*	0.047	1.040
Treatment time	0.019	0.006	0.171	3.367**	0.001	1.135
Group (Healthy (H) = ref.)						
D	1.750	0.810	0.131	2.161*	0.031	1.617
DwA	6.526	0.980	0.407	6.659***	<0.001	1.644

F = 22.806 ($P < 0.001$), R^2 = 0.207, adjR^2 = 0.198, Durbin-Watson = 1.86
D, Patients with disabilities; DwA, Patients with disabilities taking antiepileptic drugs.
*P < 0.05, **P < 0.01, ***P < 0.001

were moderately related to awakening time.

Multiple linear regression analysis showed that the use of antiepileptic drugs, disability, treatment time, and BMI were statistically significant factors affecting the awakening time from anesthesia (Table 5). The anesthesia and operative time could not be applied together to multiple regression analysis models because of the high similarity between them, negatively affecting data analysis. Therefore, the operative time was selected to analyze the regression model. After deleting anesthesia time, the variance inflation factor (VIF) was less than 10, so it can be determined that there were no multicollinearity problems. As the adjusted R^2 is 0.198, the independent variables showed 19.8%. The regression model showed that having a disability and the use of antiepileptic medication were significantly independently related to awakening time after adjusting for the relationship between BMI and treatment time. Comparing the constant of the standardization coefficients, it has been verified that the use of antiepileptic medication strongly affects the delayed awakening time, followed by treatment time, disability, and BMI, respectively.

DISCUSSION

The results of our data suggest that the use of antiepileptic medications may influence the awakening time more than any other factor. The maximum awakening time in the healthy group was recorded at 25 min, while it was extended by up to 50 min in the DwA group. The delayed time to open eyes after anesthesia has been shown in previous studies, and this result might be due to the pharmacokinetic and pharmacodynamic factors of antiepileptic drugs [12,14]. Antiepileptic drugs are used to prevent and control seizures and convulsions. It suppresses excessive activation of the brain by blocking sodium or calcium ion channels or by increasing the activity of gamma-aminobutyric acid (GABA) [14-16]. In addition, antiepileptic drugs are metabolized by the liver, catalyzed by cytochrome P450 and uridine diphosphate glucosyltransferase enzymes [14,17]. As the mechanism of anticonvulsants is mediated by activation of the GABA receptor, resulting in neuronal inhibition, antiepileptics have a sedative effect. Since the mechanism of anesthetics may be similar to that of antiepileptic drugs affecting the brain, the antiepileptic makes an extended time to open the eyes.

A previous article claimed that anticonvulsant drugs affect the awake time, but neurological disorders do not influence it [12]. However, our results indicate that not only patients who use antiepileptic drugs but also patients with disabilities not taking any CNS medication take a longer time to return from unconsciousness than healthy patients. The reason for the significantly delayed awakening time for patients with disabilities is unclear [18]. However, according to previous studies, it is possible to assume that they take a longer time to awake from anesthesia. Some articles have shown delayed awakening time in patients with Down syndrome, intellectual impairment, and especially cerebral palsy due to an increased risk of hypoxia [10,11]. Alzheimer's disease, a cognitive disorder, is associated with the loss of cholinergic neurons [19-21]. Developmental disorders, such as autism, have an abnormal cholinergic system [22]. According to several studies, some disabled persons with intellectual disabilities are related to cholinergic dysfunction [22-25]. Kimura et al. found that cholinergic function is an important factor in recovery from GA; the delayed recovery time might be associated with cholinergic dysfunction [26]. Therefore, the claim of previous studies that patients with disabilities are correlated with neurotransmitter dysfunction might explain the reason for extending awakening time.

Another assumption is that the sensitivity to anesthetic agents might be different from that of healthy patients. Miyawaki et al. reported that patients with intellectual impairment needed a higher dose of anesthetics to achieve an appropriate level of anesthesia [18]. Because of the decrease in GABAA receptor binding in patients with cerebral palsy, the required dose of anesthetic agents might be higher to attain an adequate level of sedation [27]. Similarly, since an autistic patient has abnormal GABAA receptors, a higher dose of propofol for anesthesia is needed than in patients with intellectual disability [28]. Therefore, the use of higher doses of anesthetic in patients could lead to longer awakening times, as more time is required to remove anesthetic agents [29]. The prolonged awakening time in patients with disabilities might be caused by the pharmacokinetic and pharmacodynamic factors of anesthetic drugs.

In this study, treatment time, anesthesia time, and BMI were also relevant to the emergence time, while gender and age were not. Treatment time and anesthesia time were moderately correlated with delayed wakening time. As more time is spent on treatment, the dose of anesthetic increases, resulting in longer awakening times [10]. Moreover, the results of this study reveal that BMI is slightly but significantly negatively correlated with awakening time. Some studies suggest that persons with a high-fat mass tend to slow awakening after propofol anesthesia and need more drugs [10,11]. Meanwhile, Maeda et al. found that a person with a higher BMI presented a shorter awakening time and asserted that to keep the airway safe, the level of sedation of overweight patients could be lighter than that of patients with normal weight since obese patients are more likely to have their upper airway obstructed [13]. Similarly, the results of this study show a negative correlation between BMI and awakening time for the same reason.

This study design has some limitations in explaining why patients with disabilities show delayed awakening time. Although significant differences in awakening time were observed between patients with disabilities and healthy persons, different types of disabilities did not affect the results of the study. This might be because most of the patients had intellectual disability (56%) and the number of patients with other types of disabilities was small. Moreover, the underlying medical condition in which the disability occurred was not considered. This may be an important factor to prove our assumption that the response to anesthetics in patients with a disability might be different from that in healthy patients. The definite medical condition of individuals might provide a clear reason for the results of this study.

In addition, this study was designed only by considering whether the anticonvulsant was administered and not considering the dose and type of anticonvulsants. The awakening times of two patients in the DwA group were far from the SD of awakening time (41 and 50 min). This result is likely due to different types or higher doses of antiepileptic drugs since the delayed awakening time is correlated with the pharmacokinetic and pharmacodynamic factors of medication. Therefore, further studies are needed on the effect of awakening time on different dosage or types of antiepileptic drugs. Despite these limitations, this study still provides good data for further research on anesthesia in patients with disabilities, as it could be concluded that disability is one of the main determinants related to awakening time.

In conclusion, the longest awakening time was shown in patients using antiepileptic drugs, and patients with disabilities without using CNS drugs also had a longer awakening time than healthy patients. The use of antiepileptics is an independent determinant that has the greatest impact on awakening time. Having a disability is also independently affected to delay the awakening time from anesthesia. Therefore, to plan ambulatory GA for dental treatment in patients with disabilities, especially those taking anticonvulsants, the awakening time should consider and require meticulous monitoring during the recovery period.

AUTHOR ORCIDs

Junglim Choi: https://orcid.org/0000-0002-8157-8044
Seungoh Kim: https://orcid.org/0000-0001-7288-8457

AUTHOR CONTRIBUTIONS

Junglim Choi: Writing - original draft, Data curation
Seungoh Kim: Conceptualization, Investigation

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