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Original Article

Effect of dexmedetomidine sedation on swallowing reflex: A pilot study

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KEYWORDS
Airway reflex;
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Abstract *Background/purpose:* Swallowing reflex depression during dental treatment or oral surgery may cause water to enter the lower respiratory tract, leading to coughing, thus hindering these procedures. Based on the hypothesis that dexmedetomidine (DEX) sedation may depress swallowing reflex, we aimed to characterize its effects on swallowing reflex and elucidate the affected functions.
Materials and methods: Swallowing reflex was induced in 9 young healthy male volunteers using a 5 mL-distilled water bolus injection over 3 s through a polyethylene catheter 3 times, both under wakefulness and DEX sedation. Swallowing EMG burst duration, pre-swallow EMG activity value, swallowing EMG burst peak value, latency time, and swallowing reflex timing in relation to the respiratory cycle were analyzed.
Results: The EMG burst duration was significantly prolonged with DEX sedation [206.9 ± 90.3% (1.20 ± 0.98 s)] compared to that with wakefulness [100 ± 00% (0.53 ± 0.28 s), $P = 0.007$]. No significant differences in the pre-swallow EMG activity value ($P = 0.343$), swallowing EMG burst peak value ($P = 0.218$), and latency times were apparent between wakefulness and DEX sedation ($P = 0.793$). Distributions of timing of the swallows in relation to the respiratory cycle did not significantly differ between the two conditions ($P = 0.860$).
Conclusion: Our data demonstrate that DEX sedation carries a potential risk of aspiration due to swallowing reflex depression during elevation of the larynx; therefore, suctioning of water and saliva should be rigorously performed. However, peripheral muscle contraction of the submental muscle complex, neural organization function, and timing of the swallowing reflex in relation to the respiratory cycle are not affected.

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Introduction

Most patients experience some anxiety during dental treatment or oral surgeries.[1–3] Pharmacological sedation is one of the most effective ways of management of severe anxiety.[3] However, a majority of the sedative agents depress physiological functions and reflexes, including the swallowing reflex.[4–8] During dental treatment or oral surgeries, a large amount of water is used in the oral cavity, which is a part of the airway. During these procedures, the swallowing reflex acts as a protective airway reflex mechanism to prevent influx of water and saliva into the trachea.[9] Therefore, depression of the swallowing reflex during dental treatment or oral surgery may cause the entry of water in the lower respiratory tract, and cause coughing, resulting in a hindrance to these procedures.[9,10] The swallowing reflex involves a smooth coordinated process of complex functions such as recognition of foreign body, neural organization, contraction of the muscles involved in swallowing, and coordination with the respiratory phase, thereby preventing aspiration.[11] There is a potential risk of aspiration even if one of these functions is depressed.

Dexmedetomidine (DEX), a sedative agent, acts via the alpha-2 adrenoreceptor. Although DEX has several unique clinical characteristics, its most distinctive feature is the absence of a respiratory depressant effect;[12] this renders the sedation safe during the procedures, and is advantageous, particularly in dental procedures and oral surgeries, wherein, the airway and operative field are shared. Therefore, DEX use is gaining popularity for procedural sedation in dental settings.[13] Since it is devoid of respiratory depressant effects, DEX maintains the physiological functions and reflexes in a relatively stable manner. Therefore, there is the possibility that the swallowing reflex is also maintained during sedation with DEX. Moreover, we have not observed cough due to depression of the swallowing reflex during sedation with DEX in clinical practice, although we presume that the incidence may be lower than with other sedative agents.

Therefore, we hypothesized that sedation with DEX may depress swallowing reflex. The aim of this crossover study on healthy volunteers was to characterize the effects of sedation with DEX on swallowing reflex and elucidate the functions of swallowing reflex affected thereby. To the best of our knowledge, there are no studies so far that have examined the effect of sedation with DEX on the swallowing reflex.

Materials and methods

The study was approved by the ethics committee of Nagasaki University [No.1395 (Revision 1)], and the study protocol was based on a previous study.[14] Written informed consent was obtained from all subjects.

Subjects

Nine young healthy male volunteers were recruited for this crossover study. The subjects had no history of dysphagia or oral and neck diseases that could cause dysphagia, drug allergies, or cardiac or respiratory diseases. As per sedation guidelines of the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists,[15] oral intake of clear fluids and solid foods were stopped 2 h and 8 h, respectively, before the study.

Equipment and techniques

Two surface electrodes were attached to the subject's skin in the submental region for electromyography (EMG). A nasal mask connected to a pneumotachometer for measurement of airflow (Model 3830, Hans Rudolph, Kansas, MO, USA) and nasal pressure (Model 1100, Hans Rudolph, Kansas, MO, USA) was fitted over the nose. The distal tip of an 8 Fr flexible polyethylene catheter was placed on the retromolar gingiva for administration of water and fixed using surgical tape. The subject's mouth was then closed using flexible surgical tape for preventing air leak. A 22-gauge intravenous catheter was inserted into a vein on the dorsum of the hand, and lactated Ringer's solution was administered intravenously. Subjects were placed in the supine position on a horizontal operating table, and their heads were positioned such that their Frankfort plane was angled at 70° to the operating table, which is a position without head extension or flexion. Further, sedation depth monitoring using the bispectral index (BIS) monitor (Aspect Medical Systems, Newton, MA, USA), standard hemodynamic monitoring (blood pressure and pulse rate), and respiratory (oxygen saturation) monitoring were carried out.

Experimental protocol

Fig. 1 shows the experimental protocol. After 5 min of resting, swallowing reflex was induced by administration of a bolus injection of 5 mL of distilled water over 3 s through a polyethylene catheter 3 times with the subjects awake, in the supine position. An interval of 1 min was maintained after each bolus administration of distilled water. Following this, DEX was administered for sedation and the swallowing reflex was induced in the same manner under sedation (Fig. 1).

Sedation techniques

Sedation with DEX (Maruishi, PRECEDEX®, Osaka, Japan) was induced with a loading dose of 6 μg/kg/h for 10 min followed by maintenance infusion. Maintenance infusion was adjusted using dosages ranging from 0.2 to 0.7 μg/kg/h to maintain the sedation level [moderate sedation, modified observer's assessment of alertness/sedation scale: 3 (Responds only after name is called loudly and/or repeatedly),[16] BIS index: 60–80].

Data analysis

The digital signal (sampling rate: 200 Hz) of the submental EMG activity, airflow, and nasal pressure were recorded on a laptop computer using a data acquisition system (Embla S7000 with Somnologica, Medcare, Broomfield, CO, USA). The submental EMG data was low-pass filtered with cut-off at 30 Hz.

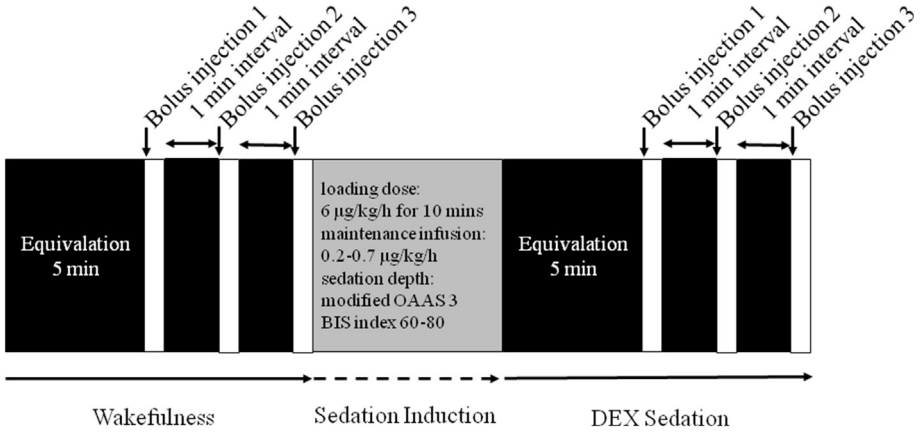

Figure 1 Experimental protocol. BIS: Bispectral index; DEX: Dexmedetomidine; OAAS: Observer's Assessment of Alertness/Sedation Scale.

The primary outcome measured was the duration of the swallowing EMG burst. It was defined as the time from the onset of the EMG burst of swallow induced by the bolus injection to the end of the EMG burst (Fig. 2). The occurrence of swallowing was verified by swallowing apnea, which was determined from the tracings of airflow and nasal pressure (Fig. 2) and visual observation. The value of submental EMG activity immediately before swallowing (pre-swallow EMG activity) and the peak value of the swallowing EMG burst were measured as secondary outcomes (Fig. 2).

The latency time of the swallowing reflex after bolus injection was also measured. It was defined as the time from the start of the bolus injection to the onset of the EMG burst (Fig. 2).[14] If swallowing did not occur within 30 s from the start of the bolus injection or cough occurred due to aspiration, the latency time was described as 30 s. The mean value of 3 latency times was considered as the representative value.

The distribution of the timing of swallowing in relation to the respiratory cycle was also measured. The respiratory cycle (inspiratory and expiratory phases) was determined from the airflow and nasal pressure. Swallows occurring during the inspiratory and expiratory phases and at the inspiratory-expiratory and expiratory—inspiratory transitions were designated as I, E, I-E, and E-I swallows, respectively (Fig. 3).[17]

The subject's demographic data (age, sex, height, weight, body mass index) and values of the BIS index, respiratory rate, and SpO_2 immediately before the first bolus injection under each condition were collected.

Sample size analysis

Sample size estimation was calculated from the data of a preliminary study. The difference in the values of the duration of swallowing EMG bursts between wakefulness

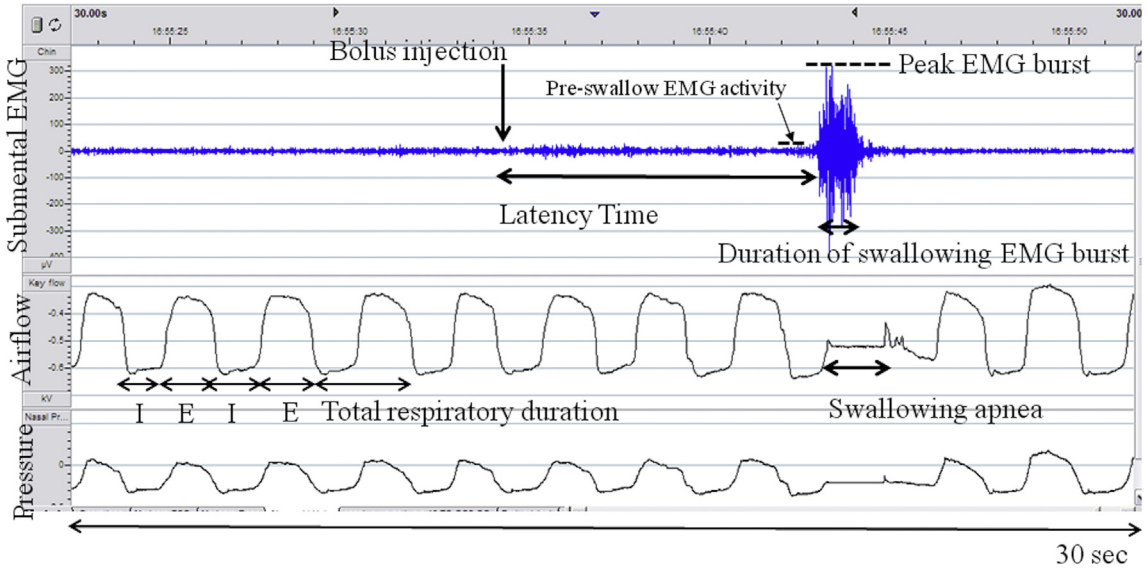

Figure 2 Representative tracing of the experimental recording. Top channel is submental electromyography (EMG) activity. Second channel from the top is the inspiratory airflow. Third channel is the nasal pressure. I represents the inspiratory phase and E represents the expiratory phase.

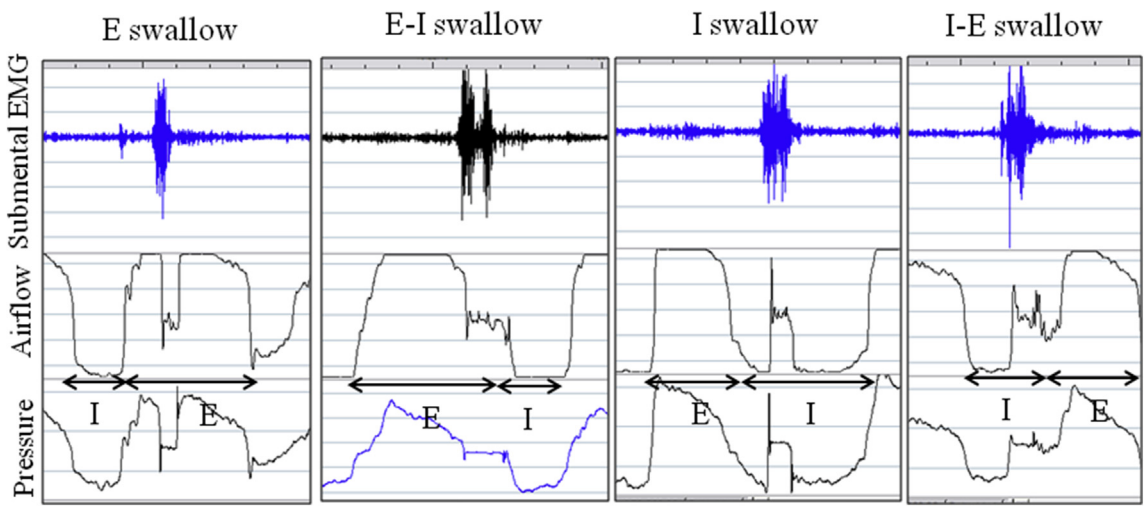

Figure 3 Timing of the swallowing reflex in relation to the respiratory cycle. I represents the inspiratory phase and E represents the expiratory phase. Swallows occurring during the inspiratory and expiratory phases, and at inspiratory-expiratory and expiratory—inspiratory transition were designated I, E, I-E, and E-I swallows, respectively.[17]

and DEX sedation was 71.2%. The standard deviation was set for 45%. We estimated that a sample size of 6 subjects would have a power of 0.8 using the paired t-test with a type I error of 0.05. In consideration of the possibility of withdrawal from study, total 9 of young healthy subjects were enrolled in this study.

Statistical analysis

EMG activity and latency time were expressed as their relative values with respect to the value at wakefulness, because individual differences were large. Continuous data were represented as mean ± standard deviation and analyzed using the paired t-test. Descriptive data were expressed as a number and analyzed using the Yates-corrected-chi square test. Values of $P < 0.05$ were considered significant.

Results

All 9 subjects completed the study without withdrawing. Table 1 shows the subject's demographic data. Table 2 shows the respiratory parameters and the BIS index. There were no significant differences between wakefulness and DEX sedation with regard to respiratory rate (wakefulness vs DEX sedation; 16.1 ± 1.4 breaths/min vs 16.0 ± 1.0 breaths/min, $P = 0.111$) and SpO_2 (98.4 ± 0.6% vs 98.1 ± 0.6%, $P = 0.350$) (Table 2). During DEX sedation, upper airway obstruction was not observed in all subjects. However, in one subject, one of the three bolus injections could not induce a swallow and the subject coughed due to aspiration.

The duration of the EMG burst was significantly prolonged with DEX sedation compared to that with wakefulness [100 ± 00% (593 ± 286 ms) vs 206.9 ± 90.3% (1202 ± 986 ms), $P = 0.007$, Fig. 4]. No significant differences in the value of pre-swallow EMG activity [100 ± 00% (6.8 ± 5.8 μV) vs 90.6 ± 28.0% (6.3 ± 5.6 μV), $P = 0.343$] and the peak value of swallowing EMG burst were apparent between wakefulness and DEX sedation [100 ± 00% (76.7 ± 40.5 μV) vs 92.0 ± 18.0% (69.1 ± 39.7 μV), $P = 0.218$)] (Table 3).

There were no significant differences in the latency times between wakefulness and DEX sedation [100 ± 00% (13.9 ± 2.5 s) vs 96.3% (13.4 ± 6.4 s), $P = 0.793$, Table 3].

During wakefulness, 88.9% of swallows were E swallows, 3.7% were E-I swallows, 7.4% were I-E swallows, and swallow did not occur at I (Table 4). During DEX sedation, 84.6% of swallows were E swallows, 7.7% were I swallows, 7.7% were I-E swallows, and there were no E-I swallows (Table 4). The distribution of timing of the swallows in relation to the respiratory cycle did not differ significantly between the two conditions ($P = 0.860$).

Table 1 Demographic data of the subjects.

Sex (M:F)	9:0
Age (years)	28.8 ± 5.0
Height (cm)	170.8 ± 4.2
Weight (kg)	68.8 ± 5.8
Body mass index (kg/m^2)	23.6 ± 2.1

Values represent mean ± standard deviation or number.

Table 2 Respiratory parameters and BIS index during wakefulness and DEX sedation.

	Wakefulness	DEX sedation	*P* value
Respiratory rate (breaths/min)	16.1 ± 1.4	16.0 ± 1.0	0.111
SpO_2 (%)	98.4 ± 0.4	98.1 ± 0.6	0.350
BIS index	97.0 ± 3.3	65.4 ± 6.8	<0.001

Values represent mean ± standard deviation.
BIS: Bispectral index; DEX: Dexmedetomidine.

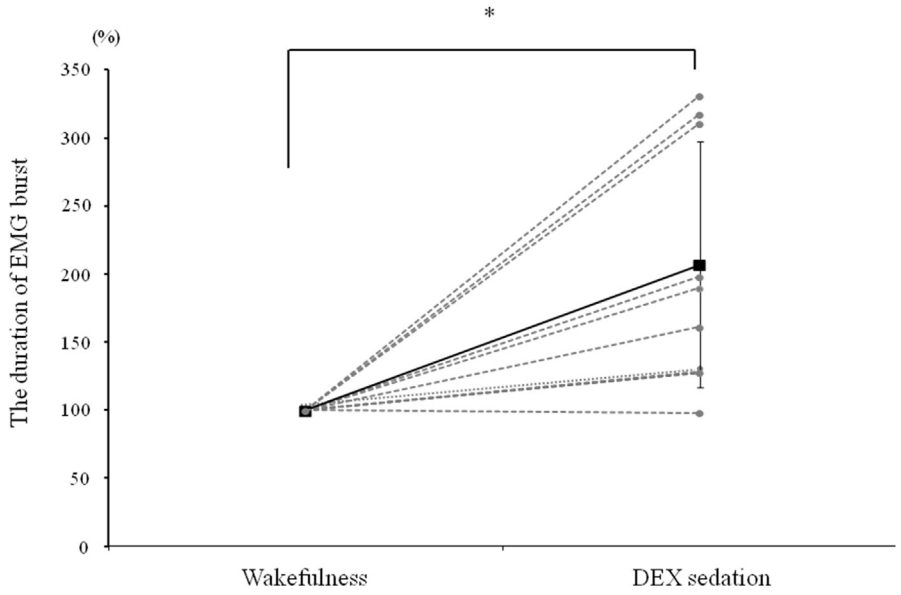

Figure 4 Individual and mean (±standard deviation) data for the relative values of the duration of EMG bursts during the swallowing reflex. *$P < 0.05$ vs. wakefulness. DEX: Dexmedetomidine.

Table 3 Submental EMG activity and latency time.

	Wakefulness	DEX sedation	*P* value
Pre-swallow EMG activity [% (μV)]	100 ± 00 (6.8 ± 5.8)	90.6 ± 28.0 (6.3 ± 5.6)	0.343
Peak value of EMG activity [% (μV)]	100 ± 00 (76.7 ± 40.5)	92.0 ± 18.0 (69.1 ± 39.7)	0.218
Latency time [% (sec)]	100 ± 00 (13.9 ± 2.5)	96.3 ± 40.9 (13.4 ± 6.4)	0.793

Values represent mean ± standard deviation.
DEX: Dexmedetomidine; EMG: Electromyography.

Table 4 Total number of swallows and the distribution of swallows in relation to the phase of respiration.

	Total number of swallows n (%)	E swallow	E-I swallow	I swallow	I-E swallow
	n (%)	n (%)	n (%)	n (%)	n (%)
Wakefulness	27 (100)	24 (88.9)	1 (3.7)	0 (0)	2 (7.4)
DEX sedation	26 (100)	22 (84.6)	0 (0)	2 (7.7)	2 (7.7)

DEX: Dexmedetomidine.

Discussion

This is the first study to describe the effect of DEX sedation on swallowing reflex. Major findings of the present study were as follows: i) the duration of EMG burst during swallowing reflex was significantly prolonged with DEX sedation compared to that with wakefulness, ii) no significant differences in pre-swallow EMG activity value and swallowing EMG burst peak value were apparent between wakefulness and DEX sedation, iii) there were no significant differences in the latency times between wakefulness and DEX sedation, iv) the distribution of timing of the swallows in relation to the respiratory cycle did not differ significantly between wakefulness and DEX sedation. These findings suggest that DEX sedation may be associated with a potential risk of aspiration due to depression of the swallowing reflex during elevation of the larynx. Therefore, strict suctioning of water and saliva should be performed during dental treatment or oral surgery when DEX is used for sedation. However, it appears that DEX sedation does not affect the functions of neural organization, peripheral muscle contraction of the submental muscle complex, and timing of the swallowing reflex in relation to the respiratory cycle. Therefore, the degree of depression of the swallowing reflex induced by DEX might be lesser compared to other sedative agents. To determine this, further research to directly compare DEX with other agents is needed in future.

The submental EMG activity represents contraction of the submental muscle complex, which includes the mylohyoid, geniohyoid, and anterior digastric muscles.[11,18] The submental muscle complex plays the role of laryngeal

elevators.[17] Contraction of the submental muscles pulls up the hyoid bone into an anterosuperior position and elevates the larynx.[18] Elevation of the larynx is a movement of cardinal importance for the passage of material (water or food) from the oral cavity to the pharyngoesophageal segment without aspiration.[18] Therefore, prolongation of this movement is one of the risk factors of aspiration.[19] We observed that the duration of the EMG burst during DEX sedation was prolonged more than twice (206.9 ± 90.3%) compared to that during wakefulness. Our results indicate that DEX may depress elevation of the larynx during the swallowing reflex, resulting in a potential risk for aspiration. In the present study, we also observed that the value of pre-swallow EMG activity and the peak value of the swallowing EMG burst were not significantly changed between the two conditions. These results suggest that prolonged duration of the EMG burst is not due to depression of peripheral muscle contraction of the submental muscle complex. The peripheral muscular relaxant effect of DEX has never been reported before. Thus, the results of the pre-swallow and peak value of swallowing EMG burst seem rational. We speculate that the prolonged duration of the EMG burst (elevation of the larynx) during DEX sedation is caused by a decrease in the central motor function resulting from a decreased level of consciousness.

The latency time is interpreted as the time to onset of the swallowing reflex from the time of recognition of a foreign object/substance. In other words, it can be considered as an index of the function of the neural organization (from peripheral inputs, through afferent pathways, higher center, efferent pathway, to activating the motor neuron).[11] In the present study, there was no significant difference in the latency time between wakefulness and DEX sedation. Therefore, it can be considered that DEX may not affect this neural organization in the swallowing reflex. In general, administration of sedative drugs extends the latency time. This physiological phenomenon was first observed by Nishino et al. in 1987.[4] The study reported that sedation by inhalation of 50% nitrous oxide extends the latency time of the swallowing reflex.[4] Since then, a number of studies investigating the effect of sedative agents on the swallowing reflex were performed using the latency time. D'Honneur et al. showed that midazolam prolonged the latency time even at 2 h after administration despite recovery of consciousness.[6] However, in our study, no significant difference in the latency times was observed between wakefulness and DEX sedation. This might be related to the unique pharmacological and clinical characteristics of DEX. DEX is a highly selective and potent $\alpha 2$ adrenergic receptor agonist. $\alpha 2$ adrenergic receptors are located in the locus coeruleus, and are responsible for sedation and anxiolysis.[12,19] It is well known that the effects of DEX do not cause impairment or disinhibition of cognitive function because DEX acts on noncortical and subcortical structures.[12,20] These unique pharmacological and clinical characteristics of DEX are in contrast with those of propofol or benzodiazepines, which are mediated through the GABA receptors.[12,20] Subjects receiving DEX sedation can rapidly revert to the baseline level of consciousness when stimulated.[12] Therefore, sedation with DEX is called "cooperative sedation," and is now used in awake craniotomy, that is, brain surgeries that require patients to respond or reply to stimulations or questions during surgery.[21,22] The mechanism of the unchanged latency time observed in the present study is unclear; however, we speculate that this may be because of maintenance of cognitive function due to the unique pharmacological and clinical characteristics of DEX.

The majority of swallows during wakefulness are normally caused during the expiration phase.[11,17,23] Swallows occurring in the I and E–I transition periods carry a potential risk of aspiration.[11] Therefore, maintaining the distribution of swallows in relation to the phase of respiration is important for preventing aspiration during both wakefulness and sedation. Hårdemark et al. reported that sedation with midazolam increases swallows in the inspiratory phase.[7] The partial pressure of arterial carbon oxide ($PaCo_2$) levels are an important factor in the distribution of swallows in relation to the phase of respiration.[11,17,23] It is reported that hypercapnia decreases the E swallow and increases the I and E–I transition swallows in awake subjects.[23] A majority of the sedative agents cause depression of respiratory functions resulting in increased levels of $PaCo_2$. Therefore, abnormal distribution of swallows during sedation may be caused by both, a decreased level of consciousness and retention of $PaCo_2$. In the present study, we observed that the distributions of the timing of swallows in relation to the respiratory cycle did not significantly differ between wakefulness and DEX sedation. DEX provides stable sedation without respiratory depression and apnea.[12,13,20] Although we did not evaluate the level of $PaCo_2$ directly, we believe that retention of $PaCo_2$ had no or a very minor role in the present study because upper airway obstructions were not observed during DEX sedation and the values of SpO_2 and respiratory rates between wakefulness and DEX sedation did not change significantly. Therefore, we speculate that the reason why the distribution of timing of the swallows in relation to the respiratory cycle did not significantly differ between wakefulness and DEX sedation is because of respiratory depressant effects of DEX.

The present study has some limitations. First, the targeted sedation level in our study was moderate (modified observer's assessment of alertness/sedation scale 3, Responds only after name is called loudly and/or repeatedly, BIS 60–80), based on conscious sedation for dental treatment or minor oral surgery. Second, sedation was induced by a single agent (DEX). Third, swallows were generated by boluses of 5 mL distilled water. Fourth, all 9 subjects were young healthy males. The results of our study may not be relevant for other conditions (different sedation levels, or sedation using multiple drugs or methods to generate swallows) or other subject populations.

In conclusion, our data demonstrate that DEX sedation is associated with a potential risk of aspiration due to depression of the swallowing reflex during elevation of the larynx. Therefore, suctioning of water and saliva should be rigorously performed during dental treatment or oral surgery conducted under sedation with DEX. However, it appears that DEX sedation does not affect the functions of neural organization, peripheral muscle contraction of the submental muscle complex, and timing of the swallowing reflex in relation to the respiratory cycle. Therefore, the

degree of depression of the swallowing reflex induced by DEX might be lower compared to other sedative agents. To determine this, further research to directly compare DEX with other agents is needed in future.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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