Muscle power during intravenous sedation

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Received 22 April 2016; received in revised form 31 January 2017; accepted 4 February 2017

Summary Intravenous sedation is effective to reduce fear and anxiety in dental treatment. It also has been used for behavior modification technique in dental patients with special needs. Midazolam and propofol are commonly used for intravenous sedation. Although there have been many researches on the effects of midazolam and propofol on vital function and the recovery profile, little is known about muscle power. This review discusses the effects of intravenous sedation using midazolam and propofol on both grip strength and bite force. During light propofol sedation, grip strength increases slightly and bite force increases in a dose-dependent manner. Grip strength decreases while bite force increases during light midazolam sedation, and also during light sedation using a combination of midazolam and propofol. Flumazenil did not antagonise the increase in bite force by midazolam. These results may suggest following possibilities; (1) Activation of peripheral benzodiazepine receptors located within the temporomandibular joint region and masticatory muscles may be the cause of increasing bite force. (2) Propofol limited the long-latency exteroceptive suppression (ES2) period during jaw-opening reflex. Thus, control of masticatory muscle contraction, which is thought to have a negative feedback effect on excessive bite force, may be depressed by propofol.

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KEYWORDS
Bite force; Conscious sedation; Muscle power; Midazolam; Propofol

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http://dx.doi.org/10.1016/j.jdsr.2017.02.001
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1. Introduction

Intravenous sedation is useful for reducing anxiety and fear in patients undergoing dental treatment. It is used in patients with dental phobia, gag reflex and for behavior modification in special needs patients undergoing dental treatment [1—3]. Midazolam and propofol are most commonly used for intravenous sedation today. Midazolam has sedative, anxiolytic and amnesic effects and may be useful for reducing fear and anxiety [4]. Propofol has sedative and antiemetic effects [5] and has a short context-sensitive half-time that allows for rapid awakening and recovery of consciousness [6]. In recent years, intravenous sedation by a combination of midazolam and propofol has become more common in the clinical setting, because a reliable sedative effect can be achieved at lower doses of propofol when used with midazolam than that of propofol alone [7—10] and patients recover from sedation faster.

Patients with dental phobia occasionally clench their teeth with extreme force during relatively light sedation with midazolam or propofol. As a result, dentists sometimes experience difficulties in opening their mouth. Patients with intellectual disabilities or autistic spectrum disorder occasionally show unintended body movements during dental treatment under intravenous sedation. As a result, dentists sometimes suffer from control behavioural management of patients. There have been a number of detailed studies on central nervous system (CNS) effects, circulatory and respiratory effects, and wakening with intravenous sedation by midazolam or propofol [11—18], however, only few studies assessing physical movement or muscle power during sedation [19,20],

This article reviews the effect of intravenous sedation with midazolam and propofol on muscle power (bite force, grip strength) in healthy adult volunteers, and discusses its clinical significance.

2. Gamma (γ)-aminobutyric acid (GABA) receptors and intravenous sedatives

GABA receptors, which are activated by the CNS inhibitory neurotransmitter GABA, can be classified into three types: GABA$_A$, GABA$_B$, and GABA$_C$ receptors. GABA$_A$ receptors are inhibitory ligand-gated ion channels widely present in the CNS. GABA$_A$ receptors consist of a pentameric ion-channel receptor comprising any five of the 19 types of subunit: α1-6, β1-3, γ1-3, δ, ε, π, and ϑ1-3. At least 85% of GABA$_A$ consists a combination of α1β2γ2, α2β3γ2, or α3β1-3γ2 [21,22] (Fig. 1).

Intravenous sedatives, both midazolam and propofol act on the GABA$_A$ receptor to allow selective permeation of chloride ions, resulting in hyperpolarization of the synaptic membrane and inhibition of nerve transmission. Different combinations of subunits in the GABA$_A$ receptors result in different drug sensitivities. Benzodiazepines bind to the benzodiazepine site (benzodiazepine receptor) located on the border between the α1, 2, 3, 5 subunits and the γ subunit [23], producing sedative, amnestic, and anticonvulsive effects at α1; anxiolytic and muscle relaxant effects at α2; and muscle relaxant effects at α3 and α5 [24] (Table 1). Intravenous anesthetics including propofol, the binding site
Muscle subunits produce body muscle movements. Figure 2 BIS and OAA/S score decreased after propofol administration dose-dependent manner. Grip strength slightly increased at the predicted effect site propofol concentration of 1.2 µg/mL or less, and bite force dose-dependently increased. Bite force reached the maximum (50% increase from the baseline) at the predicted effect site propofol concentration of 1.6 µg/mL. At the predicted effect site propofol concentration of 2.0 µg/mL, both muscle powers began to decrease. Data are presented as mean ± standard deviation (n = 14). *P < 0.05 versus before propofol administration. Modified from reference number 27.

| Table 1 | Effects of each alpha subunit of the GABA<sub>A</sub> receptor. |
|---------|---------------------------------------------------------------|
| Subunit | Effects                        | Adverse effects          |
| α<sub>1</sub> | Sedative, Amnestic, Anticonvulsive | Amnestic, Addiction |
| α<sub>2</sub> | Anxiolytic, Muscle relaxant |                                |
| α<sub>3</sub> | Muscle relaxant        |                                |
| α<sub>4</sub>, α<sub>6</sub> | Enhancement of benzodiazepine |                                |
| α<sub>5</sub> | Muscle relaxant, Amnestic, Tolerance |                                |

of which spans the α1 and β2 subunits, act on this site to produce hypnotic effects [25]. Previous study has now shown that propofol binds and acts on transmembrane (TM) site TM2 and TM3 of the β subunits but does not affect the α subunits [26]. This suggests that benzodiazepines suppress muscle power whereas propofol does not; however, in the clinical setting during light intravenous sedation, dentists often experience tension in the masseter muscles and body movements that are difficult to control.

3. Sthenometry researches during intravenous sedation

3.1. Muscle power measured during propofol sedation [27]

Twenty healthy right-handed male volunteers (mean age: 27.3 ± 2.0 years, mean height: 171.2 ± 4.9 cm, and mean body weight 65.3 ± 9.2 kg) classified in American Society of Anesthesiologists (ASA) physical status 1 participated in this study. The subjects who had any history of neurologic, cardiac, pulmonary, hepatic or renal diseases, mental disorders, or drug addiction were excluded. Each subject underwent 2 experiments with at least a 1-week interval in a randomized crossover manner. Sample size was based on data for grip strength and bite force obtained from a pilot study. A power analysis (α = 0.05, β = 0.20) before the pilot study suggested that each group of at least 16 subjects would be required to detect a 15% difference in the mean bite force. Therefore, 20 subjects were recruited to allow for a 10% dropout rate. Participants were asked to sit on a dental chair with the Frankfurt horizontal plane parallel to the floor surface. One percent propofol solution was administered by target-controlled infusion (TCI). Predicted effect-site propofol concentrations were set at 0.4, 0.8, 1.2, 1.6, and 2.0 µg/mL. Measurements prior to propofol administration were defined as baseline values. After each concentration was maintained for 15 min, the bispectral index (BIS) and the observer’s assessment of alertness/sedation scale (OAA/S) were used to evaluate the level of sedation, while grip strength and bite force were measured to evaluate muscle power. For intragroup comparison, repeated measures ANOVA was used for grip strength and bite force as parametric variables and followed by Dunnnett’s post-hoc test. Friedman’s χ² test was used for OAA/S, BIS nonparametric variables. For intergroup comparisons, Student t test for paired samples was used. A P value less than 0.05 was considered statistically significant. Significant dose-dependent reductions relative to baseline measurements were observed in both the BIS and OAA/S score (Fig. 2). Grip strength was observed to increase up to a predicted effect-site concentration of 0.8 µg/mL, but declined at higher concentrations. Bite force was observed to increase up to a
predicted effect-site concentration of 1.6 μg/mL, and then declined at 2.0 μg/mL, though the value was higher than at baseline (Fig. 2). The results suggested that under light sedation using propofol, grip strength increases slightly and bite force increases in a dose-dependent manner. There are weak correlations between BIS value and grip strength/bite force were observed (Fig. 3).

3.2. Muscle power measured during midazolam sedation [28]

This investigation examined the effect of mild intravenous sedation with midazolam on muscle power and the change in muscle power due to administration of the antagonist flumazenil. Twenty healthy right-handed male volunteers (mean age: 27.7 ± 2.3 years, mean height: 170.5 ± 5 cm, and mean body weight 66.6 ± 10 kg) classified in American Society of Anesthesiologists (ASA) physical status 1 participated in this study. The subjects who had any history of neurologic, cardiac, pulmonary, hepatic, or renal disease, mental disorders or drug addiction, and dysfunction of the upper limbs were excluded. Each volunteer underwent 2 experiments with at least a 1-week interval in a randomized crossover manner. Sample size was based on data for grip strength and bite force obtained from a pilot study. A power analysis (α = 0.05, β = 0.20) before the pilot study suggested that each group of at least 16 subjects would be required to detect a 15% difference in the mean bite force. Therefore, 20 subjects were recruited to allow for a 10% dropout rate. Participants were asked to sit on a dental chair with the Frankfurt horizontal plane parallel to the floor surface. Measurements prior to midazolam administration were defined as baseline values. The BIS, OAA/S score, grip strength, and bite force were measured at 2, 5, 10, 20, and 30 min after intravenous bolus administration of 0.05 mg/kg midazolam. Subsequently, 0.5 mg flumazenil was administered 30 min after midazolam administration and the same measurements were observed 5, 10, and 20 min later. For intragroup comparison, repeated measures ANOVA was used for grip strength and bite force as parametric variables and followed by Dunnett’s post-hoc test. Friedman’s χ² test was used for OAA/S, BIS nonparametric variables. For intergroup comparisons, Student t test for paired samples was used. A P value less than 0.05 was considered statistically significant. A slight reduction in both the BIS and OAA/S score was observed after midazolam administration, with the maximum decrease observed at 5 min after midazolam administration. There was a gradual recovery thereafter and a rapid recovery to baseline levels after flumazenil administration (Fig. 4). Grip strength was observed to decrease after midazolam administration, with the maximum reduction observed at 5 min after midazolam administration (a reduction of approximately 20%). Grip strength rapidly recovered to the baseline level after flumazenil administration. Bite force increased after midazolam administration, with the maximum increase also observed at 5 min after midazolam administration (an increase of approximately 40%). Bite force gradually decreased after flumazenil administration, but remained significantly increased compared with baseline at 20 min after flumazenil administration (Fig. 4). With intravenous sedation by midazolam, grip strength decreased immediately after midazolam administration whereas bite force increased. The results also suggested that the increased bite force is maintained and not antagonized after flumazenil administration.

3.3. Muscle power measured during combination use of midazolam and propofol for sedation [29]

Twenty healthy right-handed male volunteers (mean age: 27.5 ± 1.8 years, mean height: 170.6 ± 5.2 cm, and mean body weight 66.9 ± 9.4 kg) classified in American Society of Anesthesiologists (ASA) physical status 1 participated in this study. Subjects were not studied if they had a history of respiratory or circulatory disease or any disturbance of upper-limb mobility. Each volunteer underwent 2 experiments with at least a 1-week interval in a randomized crossover manner. Sample size was based on data for grip strength and bite force obtained from a pilot study. Sample size was based on data for grip strength and bite force obtained from a pilot study. A power analysis (α = 0.05, β = 0.20) before the pilot study suggested that each group
Figure 4  BIS and OAA/S score decreased after midazolam administration. BIS and OAA/S score gradually and quickly recovered, respectively after flumazenil administration. R5, 5 min after reversal with flumazenil administration; R10, 10 min after reversal with flumazenil administration; R20, 20 min after reversal with flumazenil administration. Grip strength decreased after midazolam administration and recovered after flumazenil administration. Bite force increased after midazolam administration and remained increased even after flumazenil administration. R5, 5 min after reversal with flumazenil administration; R10, 10 min after reversal with flumazenil administration; R20, 20 min after reversal with flumazenil administration. Data are presented as mean ± standard deviation (n = 20). *P < 0.05 versus midazolam administration. Modified from reference number 28.

Figure 5  BIS and OAA/S score significantly decreased during sedation but recovered to baseline levels after flumazenil administration. R5, 5 min after reversal with flumazenil administration; R10, 10 min after reversal with flumazenil administration; R20, 20 min after reversal with flumazenil administration; R30, 30 min after reversal with flumazenil administration. Grip strength decreased by approximately 25% during sedation and returned to baseline level after flumazenil administration. Bite force increased by approximately 84% during sedation. Although bite force reduced after flumazenil administration, it remained above baseline throughout the experimental period. R5, 5 min after reversal with flumazenil administration; R10, 10 min after reversal with flumazenil administration; R20, 20 min after reversal with flumazenil administration; R30, 30 min after reversal with flumazenil administration. Data are presented as mean ± standard deviation (n = 20). *P < 0.05 versus baseline; †P < 0.05 versus control. Modified from reference number 29.
of at least 16 subjects would be required to detect a 15% difference in the mean bite force. Therefore, 20 subjects were recruited to allow for a 10% dropout rate. Participants were asked to sit on a dental chair with the Frankfurt horizontal plane parallel to the floor surface. A bolus of 0.02 mg/kg midazolam was administered intravenously and thereafter 1% propofol solution was administered by using TCI so that the predicted effect-site concentration was kept at 1.0 μg/mL. The administration was maintained for 30 min. Subsequently, 0.5 mg flumazenil was given to antagonize the effect of midazolam. In the control group, only physiological saline solution was administered. Measurements prior to administration were defined as baseline and control values. The BIS, OAA/S score, grip strength, and bite force were measured at 5, 10, 15, 20, and 30 min after midazolam administration as well as at 5, 10, 20, and 30 min after propofol administration was stopped and flumazenil was administered; and in the control group before administration and at 5, 10, 15, 20, 30, 35, 40, 50, and 60 min after administration of physiological saline solution. Significant reductions in both the BIS and OAA/S score were observed under sedation and a rapid recovery was observed after flumazenil administration (Fig. 5). Friedman’s Friedman’s x² test was used for OAA/S, BIS, and grip strength and bite force. For intergroup comparisons, the Wilcoxon signed-rank test with Bonferroni correction was used. A p value of less than 0.05 was considered statistically significant.

Grip strength decreased by up to approximately 30% under sedation and rapidly recovered to the same level as baseline after flumazenil administration. Bite force increased by up to approximately 80% under sedation. However, only bite force decreased gradually after flumazenil administration and remained significantly elevated compared with baseline (Fig. 5). The results suggested that during intravenous sedation by combined use of midazolam and propofol, grip strength decreases in the same manner as for midazolam alone, whereas bite force increases in an additive fashion compared with that during sedation by either midazolam or propofol alone.

3.4. Limitation of research

There are several limitations to these studies. First, because this study enrolled healthy young volunteers, there are some limitations to extrapolate the results of this study to the patients. Second, the studies were not completely blinded because the subjects in the control group received saline solution instead of midazolam, propofol, and flumazenil. However, in the propofol group, the infusion pump was placed in the blind side of the subject and the intravenous line was placed in the blinded side of the subject, and other conditions were set in the same way between each group. Third, subjects in the control group received acetated Ringer’s solution and placebo was not used in this study because it compared several variables under sedative conditions or non-sedative conditions. In addition, because side effects such as agitation may occur following administration of flumazenil, the Clinical Research Ethics Committee did not approve the administration of flumazenil to the control group.

4. Discussion of the effects of intravenous sedatives on muscle power

4.1. Effect of propofol on skeletal muscles

Tsai et al. [27] reported that grip strength slightly increased at the predicted effect site propofol concentration of 1.2 μg/mL or less. A previous study has reported that propofol blocks sarclemmaal sodium channels on skeletal muscle at clinically relevant concentrations while maintaining potentials close to the physiological resting potential [30] and this mechanism may contribute to the decrease in muscle excitability. It is suggested that low-dose propofol (light sedation level) may not be enough to block sodium channel. However, there is no study on the increase in muscle power by propofol, while propofol at induction doses reduce muscle tone [31,32].

4.2. Effect of midazolam on skeletal muscles

Huang et al. [28] reported that grip strength decreased immediately after administration of midazolam, while it recovered rapidly with the administration of flumazenil. The benzodiazepine such as midazolam acts on the α2 subunit of the GABA<sub>A</sub> receptor, producing a centrally acting muscle relaxant effect in the skeletal muscles [24,33—35]. This may be partly involved in the reduction in grip strength during sedation. The sedative effects of midazolam last for 20—30 min, with the maximum effect occurring at 2—5 min after administration [36]. Tomita et al. [29] reported that the muscle relaxant effects produced by midazolam sedation offset the increase in grip strength caused by propofol sedation and that this effect was maintained throughout sedation. If the muscle relaxant and sedative effects of midazolam exhibit similar pharmacological changes, there should have been a gradual recovery in the grip strength that had decreased in patients sedated with combined use of midazolam and propofol. In other words, this suggests that the sedative effects of midazolam mediated via the α1 subunit and its muscle relaxant effects mediate via the α2 subunit differ pharmacodynamically, even if both are mediated via the GABA<sub>A</sub> receptor.

4.3. Hypothesis of bite force increase after midazolam or propofol administration

4.3.1. Increased bite force during non-anxious (relaxed) state

Bite force increased when patients underwent mild intravenous sedation using propofol and midazolam [27—29]. One possibility is that the relaxed state produced by mild intravenous sedation increased the power of the masticatory muscles. However, a previous study on enhancement of physical function by drugs showed that alcohol intake reduces anxiety but does not enhance motor function [37]. Furthermore, in a study on benzodiazepine intake and physical capabilities [38], a comparison of individuals taking temazepam and placebo showed no significant difference in muscle power. Therefore, the increased bite force is
not adequately explained by the hypothesis that relaxation enhances muscle power.

4.3.2. Sedation may inhibit the controls of occlusion
A previous study [39] has shown that peripheral GABA<sub>A</sub> receptors present in the temporomandibular joint (TMJ) region in rats inhibit nociceptive signals in the masticatory muscles, suggesting that peripheral GABA<sub>A</sub> receptors may be involved in the increased bite force in humans as well. Both midazolam and propofol act on peripheral GABA<sub>A</sub> receptors and could inhibit nociceptive signals in the TMJ, thereby alleviate excessive bite forces. However, as far as bite forces are concerned, nociceptive reflexes to noxious stimuli are present in areas other than the TMJ, such as in the periodontal membrane and masticatory muscles; currently, it is unclear how these reflexes are involved. Furthermore, because the increased bite force under sedation remained elevated after flumazenil administration and did not recover to the pre-sedation level, the increase in bite force is not adequately explained by nociceptive inhibition alone.

4.3.3. Involvement of peripheral benzodiazepine receptors
Benzodiazepine receptors, which together with GABA<sub>A</sub> receptors form ion-channel complexes, can be categorized into central or peripheral benzodiazepine receptors. The central benzodiazepine receptors are distributed in areas such as the cerebral cortex, cerebellum, and hypothalamus, whereas the peripheral benzodiazepine receptors are mostly distributed in the musculature and peripheral organs such as the liver and kidneys, although they are also found in the CNS [40]. The role of the peripheral benzodiazepine receptors is less clear, but it seems that they are connected with more slowly appearing drug actions, such as modulation of cell proliferation [41]. In a study using mouse diaphragm and diaphragm nerves, activation of peripheral benzodiazepine receptors by ligands was reported to enhance diaphragm contraction [42]. Midazolam acts on both central and peripheral benzodiazepine receptors, while the antagonist flumazenil mainly exhibits an affinity for central benzodiazepine receptors [43]. Moreover, one study has shown that although administration of 0.5–1.0 mg flumazenil can antagonize the sedative effects of midazolam, it cannot completely antagonize the disturbance of the equilibrium function induced by midazolam [44]. This suggests that midazolam enhances bite force by acting on the peripheral benzodiazepine receptors present around the jaw muscles. However, flumazenil does not antagonize this effect. These results are consistent with those of Huang et al. [28] and Tomita et al. [29], and could partly explain the increase in bite force during midazolam sedation and the maintenance of this effect even after flumazenil administration (Table 2).

4.3.4. Suppression of the jaw-opening reflex by propofol
Electrical stimulation of the trigeminal nerve suppresses voluntary contraction of the masseter muscle and temporalis muscle [45]. These responses are referred to as exteroceptive suppression (ES) reflexes. The ES, which is a mechanism for nociception defensive reflexes in the masticatory muscles, is involved in the jaw-opening reflex that a brainstem reflex mediated via the trigeminal nerve. The short-latency ES component is termed ES1 and the long-latency component is termed ES2 [45]. Midazolam does not suppress ES reflexes mediated by the upper CNS, while propofol has been reported to inhibit ES2, which controls masseter muscle contraction in the brainstem [45]. This suggests that propofol may have increased bite force by suppressing the mechanism that inhibits jaw-closing muscle contraction, which presumably has a negative feedback effect against excessive bite force during hard biting.

In the clinical setting, dental anesthesiologists have thus far managed patients incapable of controlling their body movements during intravenous sedation (especially patients with dental phobia or special needs) by increasing sedative doses and ensuring patients are more heavily sedated. However, this may be an inadequate approach to manage enhanced bite force. Furthermore, the use of deep sedation also increases the risks of airway management and other issues. For patients who are difficult to manage under standard intravenous sedation, general anesthesia may be a better choice.

5. Conclusion
(1) Grip strength increased after administration of midazolam during light sedation. According to the effects of α2 subunit of the GABA<sub>A</sub> receptor, midazolam produces centrally acting muscle-relaxant effect in the skeletal muscles.
(2) Bite force increases despite the muscle-relaxant effect of midazolam during light sedation. Peripheral GABA<sub>A</sub> receptors located within the temporomandibular joint region and the peripheral benzodiazepine receptors in the masseter muscle may be partly involved in this increase.
Grip strength decreased whilst bite force increased under light sedation using a combination of midazolam and propofol. Activation of peripheral benzodiazepine receptors in the masticatory muscles may be the cause of this sustained increase. Propofol limited ES2 during jaw-opening reflex. Thus, control of masticatory muscle contraction, which is thought to have a negative feedback effect on excessive bite force, may be depressed by propofol.

This review has yet to fully clarify the detailed mechanism of how midazolam and propofol increase bite force. Further studies, including animal studies, are needed to examine the mechanism of how intravenous sedatives enhance muscle power.

Conflict of interest statement

The author declares no conflict of interest associated with this review.

Ethical approval

This study was conducted after approval from the Clinical Research Ethics Committee at Tokyo Dental College (Research No. 227, 257 and 270) and the written informed consent were obtained from all participants.

Acknowledgements

The author would like to thank Prof. Tatsuya Ichinohe (Department of Dental Anesthesiology, Tokyo Dental College) for valuable advice and helpful discussion, and Dr. Pung-Fei Tsai, Ming-Yu Huang, Satoko Ide (Department of Dental Anesthesiology, Tokyo Dental College) for their contributions in the research results in this review.

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