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Characteristics and selection of the sedative agents and clinical strategies of intravenous moderate sedation during dental treatment

Abstract. As reported in the previous review, midazolam, propofol and their combination are common choices for intravenous moderate sedation of dental outpatients in Japan. In the "Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018", midazolam and dexmedetomidine are recommended for "sedative/analgesic medications not intended for general anesthesia", that is moderate sedation. **The aim** of this review is to introduce modern view of the sedative agents' characteristics and to present the clinical strategies of intravenous moderate sedation during dental treatment. Practitioners should select the sedative agent or its combination depending on the patient's condition and coexisting diseases. Suppression of hemodynamic fluctuation is important in the dental treatment of medically compromised patients such as patients with cardiovascular diseases including hypertension and/or ischemic heart disease. Intravenous moderate sedation has stronger sedative effects than inhalation sedation with nitrous oxide (Minimal sedation: Anxiolysis). Both midazolam and propofol are commonly used in phobic and medically compromised patients. In contrast, propofol is a good candidate for patients with gag reflex and receiving prolonged treatment. Patients with acute closed angle glaucoma and myasthenia gravis, and taking HIV protease inhibitor are contraindications of benzodiazepines including midazolam. Systemic condition of the patient should be evaluated before sedation. Practitioners should consult the family doctor and obtain medical information including laboratory data and regular medications. During sedation basic monitoring items include consciousness, oxygenation, ventilation and circulation such as heart rate and blood pressure. In addition, electrocardiography, capnography and bispectra index monitoring may be appended in some patients with coexisting cardiorespiratory diseases or during deep sedation. Airway protective reflex may be to some degree suppressed during moderate sedation. Airway protective reflex may be to some degree suppressed during moderate sedation. **Conclusion.** Intravenous moderate sedation has wide range of indications and practitioners can propose safe and comfortable dentistry to the patients.

Key words: dentistry, anesthesia, sedation, intravenous controlled sedation, combination of sedatives

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Токийский стоматологический колледж

Характеристика и выбор седативных средств и клинических стратегий внутривенной умеренной седации при лечении зубов

Реферат. Как сообщалось в предыдущем обзоре, мидазолам, пропофол и их комбинация являются обычным выбором для внутривенной управляемой седации у стоматологических пациентов в Японии при амбулаторном лечении. В Практических рекомендациях по управляемой седации и анальгезии — 2018 мидазолам и дексмедетомидин рекомендуются в качестве «седативных/анальгетических препаратов, не предназначенных для общей анестезии», из-за их умеренного седативного эффекта. **Цель** этого обзора — познакомить читателей с современным взглядом на характеристики седативных средств и представить клинические стратегии управляемой внутривенной седации во время стоматологического лечения. Практикующие врачи должны выбирать седативное средство или его комбинацию в зависимости от функционального состояния пациента и с учетом сопутствующих заболеваний. Нормализация гемодинамики является важной составляющей безопасности при стоматологическом лечении у пациентов с сопутствующей патологией, а именно с сердечно-сосудистыми заболеваниями, включая гипертоническую болезнь и/или ишемическую болезнь сердца. Внутривенная управляемая седация оказывает более выраженное седативное действие, чем ингаляционная седация закисью азота, при котором достигается состояние минимальной седации — анксиолиз. И мидазолам, и пропофол обычно используются у пациентов с фобиями и у пациентов с компрометированным общим статусом здоровья. Напротив, пропофол является препаратом выбора для пациентов с повышенным рвотным рефлексом, которым предстоит длительное стоматологическое лечение. Пациентам с закрытоугольной глаукомой и миастенией, принимающим ингибиторы протеаз, противопоказаны бензодиазепины, включая мидазолам. Перед седацией необходимо оценить функциональное состояние пациента. Практикующие врачи должны всегда консультироваться с семейным (лечащим) врачом пациента и получить медицинскую информацию, включая лабораторные данные и сведения о препаратах, которые пациент принимает

на регулярной основе. Во время седации основные параметры мониторинга включают контроль сознания, оксигенации, частоты сердечных сокращений и показатели артериального давления. Кроме того, у некоторых пациентов с сопутствующими сердечно-сосудистыми и бронхолегочными заболеваниями во время глубокой седации могут быть добавлены электрокардиография, капнография и мониторинг биспектрального индекса. Защитный рефлекс дыхательных путей до некоторой может степени подавляться при управляемой седации, а защитный рефлекс дыхательных путей при умеренной седации. **Заключение.** Управляемая внутривенная седация имеет широкий спектр показаний, и практикующие врачи могут предложить пациентам безопасное и удобное лечение.

Ключевые слова: стоматология, обезболивание, седация, внутривенная управляемая седация, комбинация седативных средств

ДЛЯ ЦИТИРОВАНИЯ:

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INTRODUCTION

In the previous review in this journal, the author introduced clinical practices and education of intravenous moderate/deep sedation in Japan [1]. In this second review, the author will focus on the characteristics and selection of the sedative agents and clinical strategies of intravenous moderate sedation during dental treatment mainly based on the researches that had been conducted in our department and the "Practice Guidelines for Intravenous Conscious Sedation in Dentistry" established by the Japanese Dental Society of Anesthesiology in 2017 [2].

THE SEDATIVE AGENTS

As reported in the previous review, midazolam, propofol and their combination are common choices for intravenous moderate sedation of dental outpatients in Japan.

In the "Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018", midazolam and dexmedetomidine are recommended for "sedative/analgesic medications not intended for general anesthesia", that is moderate sedation [3]. However, dexmedetomidine is not commonly used for dental outpatients in Japan because it requires long recovery period. In the guidelines, it is reported that analgesics administered with sedatives include opioids such as fentanyl and remifentanil. However, opioid easily induces respiratory depression and sometimes apnea. In addition, opioids are treated as narcotics and strictly controlled for physicians and dentists to use in Japan. Thus, midazolam has been one of the most common agents for moderate sedation during dental treatment.

Another choice for moderate sedation is propofol. Propofol is classified in "sedative/analgesic medications intended for general anesthesia". These include propofol, ketamine and etomidate. In "Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018" [3], task force members strongly agree with the recommendations to 1) provide care consistent with that required for general anesthesia when moderate sedation with sedative/analgesic medications intended for general anesthesia by any route is intended, and 2) assure that practitioners administering sedative/analgesic medications intended for general anesthesia are able to reliably identify and rescue patients from unintended deep sedation or general anesthesia. Small dose propofol induces moderate sedation, while large dose propofol induces deep sedation and general anesthesia (table 1). Thus, sedation level of the patient depends on the infusion rate of propofol and practitioners must realize the potential risk of unintended loss of consciousness produced by propofol. Fortunately, most Japanese dentists who give propofol for intravenous moderate sedation are certified as the Board Certified Dental Anesthesiology Specialist (BCDAS) or Japanese Board of Dental Anesthesiology (JBDA). They have enough skills and knowledge for general anesthesia and deep sedation as well as intravenous moderate sedation.

1. Midazolam

Midazolam is a benzodiazepine derivative. The standard dose for moderate sedation is 0.05—0.075 mg/kg [2]. Midazolam has four major effects. These include 1) sedative/anxiolytic, 2) amnesic, 3) anticonvulsive, and 4) muscle relaxant effects. Midazolam has stronger anxiolytic and amnesic effects than propofol during moderate sedation. In addition, midazolam

Table 1. Continuum of depth of sedation definition of general anesthesia, and levels of sedation/analgesia

	Minimal (anxiolysis)	Moderate (analgesia/conscious sedation)	Deep (analgesia)	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

has stronger inhibitory effects on sympathetic nervous activities during simulated anxious stress [4, 5]. Thus, midazolam reduces hemodynamic fluctuations during dental treatment, especially in phobic dental patients. Interestingly, midazolam increases bite force, while reduces grip strength during moderate sedation [6]. Therefore, some patients with intellectual disability might clench by unexpected severe force during insufficient sedation. Anticonvulsive and muscle relaxant effects are effective for moderate sedation of patients with strong muscle tone and/or involuntary movement such as cerebral palsy and epilepsy. Midazolam produces respiratory depression. However, desaturation during moderate sedation with midazolam is prevented by inhalation of 50% oxygen [7].

Estimated maximal plasma concentration of midazolam depends on the injection rate (fig. 1). In a simulation analysis, estimated plasma concentration of midazolam exceeds 100 ng/mL (unconscious level) for 4 minutes after bolus injection of 0.05 mg/kg midazolam. If the same dose of midazolam is administered in 2 minutes, estimated plasma concentration of midazolam exceeds 100 ng/mL for 2.5 minutes. Likewise, if administered in 5 minutes, it exceeds for only 1 minute. Thus, the injection rate is quite important to prevent unintended deep sedation. Practitioners should titrate the dose of midazolam according to patient's symptoms [2].

2. Propofol

Propofol is an intravenous anesthetic and given commonly in an infusion technique. As describe earlier, small dose propofol induces moderate sedation, while large dose propofol induces deep sedation and general anesthesia. The standard dose and infusion rate of propofol for moderate sedation is 6—8 mg/kg/hr for 2 minutes and thereafter 2 mg/kg/hr (or 0.2—0.4 mg/kg bolus injection followed by 2 mg/kg/hr infusion) [2]. To precisely control the effect-site concentration of propofol, the target controlled infusion technique is commonly used in Japan and Europe. For moderate sedation, estimated effect-site concentration of propofol is about 1 μg/mL. However, it may be about 1.5 μg/mL or more in some young patients. Because propofol is commonly administered with an infusion technique, sedation level can be easily controlled and accordingly emergence from sedation is rapid and clear.

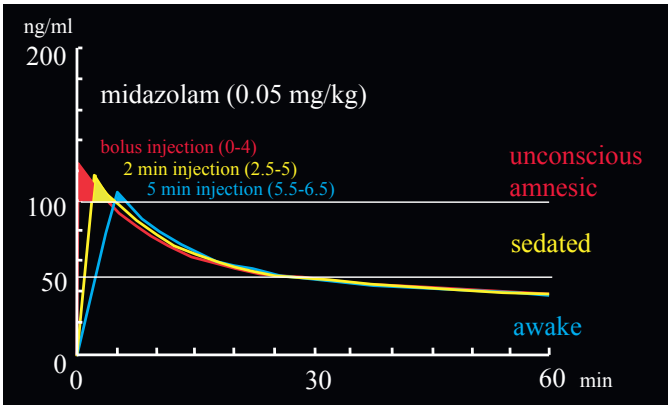


Fig. 1. Midazolam concentration in plasma after various rate of midazolam injection

Propofol has less anxiolytic and amnesic effects than midazolam during moderate sedation. In addition, propofol has less inhibitory effects on sympathetic nervous activities during simulated anxious stress [4, 5]. In contrast, propofol strongly inhibits gag reflex [8]. In a comparative cross-over study of propofol and midazolam in patients with gag reflex, propofol effectively inhibited gag reflex during moderate sedation. This means that the patients were conscious. In contrast, 75% of the patients required to be unconscious to inhibit gag reflex during midazolam sedation. Propofol also increases bite force during moderate sedation like midazolam [9]. Because propofol has moderate to severe pain on injection, the practitioners should administer propofol slowly [10].

3. Midazolam-propofol combination

Intravenous moderate sedation with a combination of smaller doses of midazolam and propofol is widely used in Japan. This method has several advantages. By using smaller doses of midazolam and propofol, the patient can obtain anxiolysis and amnesia produced by midazolam, and stable sedative level and rapid and clear emergence produced by propofol. Meanwhile, side effects can be reduced because of smaller doses of the sedatives.

Sympathetic nervous activations caused by simulated pain sensation was smaller during midazolam-propofol combination compared with propofol alone [11]. Respiratory depression was smaller during midazolam-propofol combination compared with propofol alone [12]. Midazolam-propofol combination increases bite force about twice as much as that before sedation [13].

INDICATIONS AND CONTRAINDICATIONS OF INTRAVENOUS MODERATE SEDATION

Intravenous moderate sedation has stronger sedative effects than inhalation sedation with nitrous oxide (Minimal sedation: Anxiolysis). Indications of intravenous moderate sedation are as follows.

1. Invasive and prolonged treatments
2. Phobic dental patients
3. Medically compromised patients
4. Hyperventilative patients
5. Intellectually disabled patients
6. Patients with strong muscle tone and/or involuntary movement (Cerebral palsy etc.)
7. Epileptic patients
8. Patients with gag reflex

Both midazolam and propofol are commonly used in phobic and medically compromised patients. In addition, midazolam is a good candidate for patients with hyperventilation, strong muscle tone and/or involuntary movement, and epilepsy. In contrast, propofol is a good candidate for patients with gag reflex and receiving prolonged treatment.

Contraindications of intravenous moderate sedation are as follows:

1. Pregnant patients
2. Non-cooperative patients (moderate sedation)
3. Patients with acute closed angle glaucoma

4. Patients with myasthenia gravis
5. Patients taking HIV protease inhibitor

Patients with acute closed angle glaucoma and myasthenia gravis, and taking HIV protease inhibitor are contraindications of benzodiazepines including midazolam.

SELECTION OF THE SEDATIVE AGENTS

Practitioners should select the sedative agent or its combination depending on the patient's condition and coexisting diseases (fig. 2) [14]. Suppression of hemodynamic fluctuation is important in the dental treatment of medically compromised patients such as patients with cardiovascular diseases including hypertension and/or ischemic heart disease. Midazolam is effective for these patients because of its sympatholytic effects. Control of body movement is important for patients with intellectually disability and/or cerebral palsy. Both midazolam and propofol are effective for these patients and are used according to its severity. Mitigation of fear/anxiety is important for phobic dental patients. Midazolam is also effective for these patients because of its strong anxiolytic effects. In patients with gag reflex, propofol is a good choice. Thus, midazolam, propofol or midazolam/propofol combination is used according to patient's condition. Fundamentally, the target level of intravenous sedation is moderate. However, sometimes deep sedation is required especially in patients with intellectually disability, severe fear/anxiety or severe gaging reflex. Some of these patients may undergo general anesthesia instead of intravenous sedation.

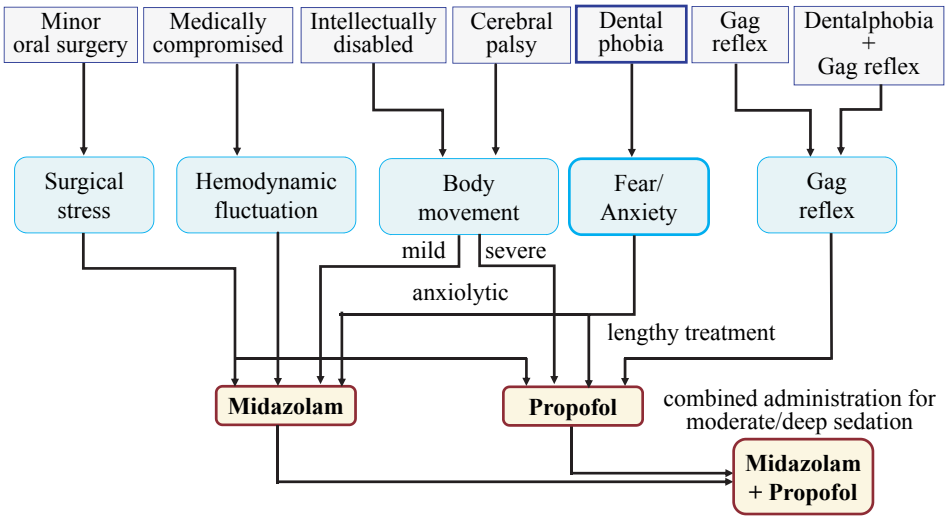


Fig. 2. The schema of drug selection for Intravenous sedation

CLINICAL STRATEGIES OF INTRAVENOUS MODERATE SEDATION [2]

1. Before sedation

Systemic condition of the patient should be evaluated before sedation. Practitioners should consult the family doctor and obtain medical information including laboratory data and regular medications. Sometimes this information may confine the use of sedative agents.

Restriction of oral intake should be considered for moderate sedation and is mandatory for deep sedation. Patients should be fasting for 2 hours to drink clear liquids and for 8 hours or more to eat routine meals (table 2).

2. During sedation

A person or persons responsible for giving sedatives should be independent from the operator. This person must continuously monitor the patient. Basic monitoring items include consciousness, oxygenation, ventilation and circulation such as heart rate and blood pressure. In addition, electrocardiography, capnography and bispectral index monitoring may be appended in some patients with coexisting cardiorespiratory diseases or during deep sedation. To evaluate the sedation level, Ramsay sedation scale (RSS) is useful (table 3). The target level for moderate sedation is 3 and 4. In this state, the patient shows blepharoptosis (Verrill sign; table 4). Although RSS 2 (anxiolysis) is also acceptable for moderate sedation, this level may be sometimes inadequate for severe phobic patients. Practitioners should realize that oxygenation and ventilation is different monitoring items. Oxygenation can be evaluated by pulse oximetry. Inhalation of oxygen via a nasal cannula is useful. Ventilation should be evaluated by observing the thoracic movement or capnography. If the patient is given oxygen and becomes apneic during sedation, high SpO_2 level may interfere with early detection of respiratory arrest.

Airway protective reflex may be to some degree suppressed during moderate sedation. Thus, aspiration may

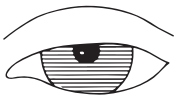
Table 2. Restriction of oral intake (minimum fasting period, hours)

Intake	Period, hours
Clear liquids	2
Nonhuman milk	4
Light meal	6
Fried foods, fatty foods or meat	8 or more

Table 3. Ramsay sedation scale

Effect	Level
1. Anxious and agitated or restless or both	—
2. Cooperative, oriented, and tranquil	Minimal (anxiolysis)
3. Responsive to commands only	Moderate
4. Brisk response to light glabellar tap or loud auditory stimulus	
5. Sluggish response to light glabellar tap or loud auditory stimulus	Deep
6. No response to light glabellar tap or loud auditory stimulus	

Table 4. Sedation symptoms

Level	Subjective symptoms	Objective symptoms	
Minimal	Relaxed	Talkative, rapid response	
Moderate	No anxiety, relaxed, sleepy	Relaxed, slurring, blepharoptosis (Verrill sign), complying to verbal command	
Deep	Asleep, indifferent	Eye closing, slurring, drowsy response	

occur during dental treatment. Attentions should be paid especially when water is accumulated in the patient's mouth. Rubber dam techniques may be effective to prevent aspiration. During deep sedation, airway protective reflex is considerably suppressed and spontaneous breathing may be inadequate. Thus, equipment for artificial ventilation including anesthesia machine and tracheal intubation should be prepared.

3. After sedation

After finishing dental treatment, the patient emerges from sedation. Practitioners should evaluate street fitness of the patient. Subjectively, the patient does not feel lightheadedness. Objectively, practitioners should confirm the recovery of psychomotor and cardiorespiratory functions. These include 1) recovery from sedative feeling, 2) recovery of ambulatory ability, and 3) cardiorespiratory stability. It is recommended that the patient returns home with being accompanied by a caretaker. When sedative effect of midazolam is prolonged, flumazenil can be administered to antagonize midazolam. However, practitioners should realize that flumazenil antagonizes the sedative effect of midazolam, while it cannot antagonize disturbance of equilibrium function.

CONCLUSION

The author has introduced the characteristics and selection of the sedative agents and clinical strategies of intravenous moderate sedation during dental treatment. Intravenous moderate sedation has wide range of indications and practitioners can propose safe and comfortable dentistry to the patients. However, to securely perform intravenous sedation, practitioners must learn skills and knowledge of general anesthesia. The author would expect the development of education and training on systemic management of dental patients including intravenous sedation and general anesthesia in Russia. The author would hope to be involved in this development as a good case of Japanese-Russian dental collaboration.

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