A Comparison of Dexmedetomidine Sedation With and Without Midazolam for Dental Implant Surgery

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Dexmedetomidine (DEX) has a minimal respiratory depressive effect, which is beneficial for dentistry; however, it has the disadvantage of permitting an intraoperative arousal response such that the patient appears to be suddenly no longer sedated, and it has a variable amnesic effect. Since midazolam (MDZ) in an appropriate dose has a profound amnesic effect, we investigated whether additional MDZ compensates for the disadvantage of DEX and enables a better quality of sedation. Forty-three subjects were randomly divided into 4 groups. In group 1, MDZ (0.02 mg/kg) was administered intravenously, followed by a dose of 0.01 mg/kg every 45 minutes. After the first dose of MDZ, preloading with DEX (2 µg/kg/h for 10 minutes) was started and maintained with a dosage of 0.5 µg/kg/h. In group 2, MDZ was infused in the same manner as in group 1, followed by preloading with DEX (1 µg/kg/h for 10 minutes) and maintenance (0.3 µg/kg/h). In group 3, MDZ was infused 0.03 mg/kg, and a dose of 0.01 mg/kg was given every 30 minutes; DEX was administered at the same as in group 2. In group 4, DEX was infused using the same method as in group 1 without MDZ. The sedation levels, amnesia, and patient satisfaction were also investigated. Group 2 had a lower sedation level and a poor evaluation during the first half of the operation. Group 4 did not exhibit an amnesic effect at the beginning of the operation. An evaluation of the degree of patient satisfaction did not reveal any differences among the groups. Optimal sedation was achieved through the combined use of MDZ (0.02 mg/kg with the addition of 0.01 mg/kg every 45 minutes) and DEX (2 µg/kg/h for 10 minutes followed by 0.5 µg/kg/h).

Key Words: Dexmedetomidine; Midazolam; Sedation; Dental treatment; Implant; Amnesia.

Appropriate sedation for dental treatment is useful as a means of mitigating stress in medically compromised patients and patients with fear and anxiety. In the field of dentistry and oral surgery, where the surgical field includes the airway, it is necessary to choose a sedation method that causes minimal respiratory depression. Midazolam (MDZ) and propofol are commonly used but sometimes produce deeper levels of sedation with accompanying respiratory depression and upper airway obstruction, potentially leading to serious com-

plications. Moreover, some patients are unable to respond during sedation. In recent years, dexmedetomidine (DEX), a newly developed drug, has been used clinically for sedation in intensive care units. This agent is said to have a less respiratory depressive effect compared to other existing sedative drugs.^{1,2} The most distinctive characteristic of DEX is the high quality of its hypnotic action. Specifically, unlike existing sedatives, it has been described as inducing a state that is close to physiologic sleep, but allowing full awakening with stimulation.³ The use of DEX for sedation during oral surgery and dentistry has already been assessed.⁴ However, sudden arousal in response to stimulation, especially sound, may be a disadvantage of the drug

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Table 1. Administration Protocols of Dexmedetomidine and Midazolam

	Midazolam (Initial Bolus)	Midazolam (Additional Bolus)	Dexmedetomidine (Initial 10-minute Preload)	Dexmedetomidine (After 10 Minutes)
Group 1 (n = 11)	0.02 mg/kg	0.01 mg/kg, every 45 min	2 µg/kg/h	0.5 µg/kg/h
Group 2 (n = 10)	0.02 mg/kg	0.01 mg/kg, every 45 min	1 µg/kg/h	0.3 µg/kg/h
Group 3 (n = 12)	0.03 mg/kg	0.01 mg/kg, every 30 min	1 µg/kg/h	0.3 µg/kg/h
Group 4 (n = 10)			2 µg/kg/h	0.5 µg/kg/h

for dentistry applications. Its amnestic effect in sedative doses is unfortunately variable.

In dentistry, MDZ is commonly used for intravenous sedation and is known to have a potent amnesic effect in addition to its sedative effect.⁵ Therefore, to obtain high-quality sedation and amnesia using an intravenous sedation method during dental practice, the addition of MDZ to DEX may be an appropriate combination. The purpose of the present study was to clarify the quality of the sedative effect of various doses of DEX and MDZ in dentistry.

SUBJECTS AND METHODS

We conducted this study after obtaining the approval of the Ethics Committee of the Faculty of Dentistry, Tokyo Medical and Dental University. The subjects included in this study were healthy patients between 20 and 65 years of age who were scheduled to undergo 1 or 2 primary dental implants in the alveolar bone. Informed consent was obtained from each patient after he/she had received a thorough explanation of the research methods. Patients who might be allergic to the drugs used and patients who had a history of dental treatment phobia, an abnormal gag reflex, or unpleasant feelings during dental treatment were excluded from this study.

The subjects were randomly divided into 4 groups, and DEX alone or DEX and MDZ were administered according to the treatment protocols (Table 1). In group 1, MDZ (0.02 mg/kg) was administered intravenously, and an additional dose of 0.01 mg/kg was given every 45 minutes thereafter. After the first dose of MDZ, preloading with DEX (2 µg/kg/h for 10 minutes) was started and maintained with a dosage of 0.5 µg/kg/h. In group 2, after an initial infusion of MDZ (0.02 mg/kg), an additional dose of 0.01 mg/kg was administered every 45 minutes. Immediately after the first dose of MDZ, preloading with DEX (1 µg/kg/h for 10 minutes) was performed and maintained at 0.3 µg/kg/h. In group 3, the initial MDZ dose was 0.03 mg/kg, and a dose of 0.01 mg/kg was administered every 30 minutes. DEX was preloaded at a dosage of 1 µg/kg/h for 10 minutes and was maintained at a dosage of 0.3 µg/kg/h. In group 4, preloading with DEX (2 µg/kg/h for 10 minutes) was performed and then

maintained at a dosage of 0.5 µg/kg/h without the administration of MDZ. In all groups, the administration of MDZ and DEX was terminated when suturing was started.

Age, sex, body height, and body weight were recorded as background factors, and systolic blood pressure (BPs), diastolic blood pressure (BPd), heart rate (HR), and arterial oxygen saturation (SpO₂) values were measured every 5 minutes. The values selected for analysis were those just before the sedation (start), the lowest values during the operation (during), and those after the sedation concluded (end). The anesthesiologist-in-charge assessed the sedation by determining the Ramsay sedation scores (RSS) during infiltration anesthesia, incision, cutting, and suturing. Before discharge from the clinic, the patients were questioned as to whether they remembered the infiltration anesthesia, incision, cutting, or suturing. Also, the patients were asked to evaluate their sedative state using the Wong-Baker FACES Pain Rating Scale (Figure 1).⁶

Differences in age, sex, body height, body weight, BPs, BPd, HR, and SpO₂ were tested for statistical significance among the groups using a 2-way analysis of variance (ANOVA) and the Tukey range test. The evaluations of the sedation level and the degree of satisfaction were analyzed using the Kruskal-Wallis test and the Steel-Dwass multivariate analysis, and evaluations of whether the patients had any memories were analyzed using the chi-square test. A *P* value less than .05 was considered statistically significant for all tests.

RESULTS

Age, sex, body height, and body weight are shown as background factors for each of the groups in Table 2. No significant differences were seen among the groups. The BPs, BPd, HR, and SpO₂ before and after the sedation and the lowest values during the operation are shown in Figures 2 and 3. Comparisons

Figure 1. Wong-Baker FACES Pain Rating Scale.

Table 2. The Subjects' Background Factors*

	<i>M</i>	<i>F</i>	<i>Age, y</i>	<i>Height, cm</i>	<i>Weight, kg</i>
Group 1	3	8	57.18 ± 7.55	159.09 ± 7.02	54.50 ± 8.69
Group 2	2	8	48.82 ± 13.63	163.18 ± 5.60	53.64 ± 8.51
Group 3	6	6	48.36 ± 14.36	162.91 ± 7.19	62.50 ± 8.45
Group 4	6	4	55.64 ± 9.68	163.64 ± 9.81	57.18 ± 9.14

* Data are shown as number of patients and mean ± SD. There were no significant differences among the groups.

among the groups showed clearly higher intraoperative and postoperative BPs values in group 2 than in group 4. No other differences in BPd, HR, or SpO₂ were recognized. In each group, the BP values were obviously lower during and after sedation than before sedation. In all groups except group 1, a decrease in HR was seen during sedation, compared with before sedation. The results of SpO₂ showed a decrease in group 4 during and after sedation compared with before sedation, whereas in groups 1, 2, and 3, a decrease was only seen during sedation. The intraoperative sedation level (RSS) during infiltration anesthesia was significantly lower in group 2 (low DEX/low MDZ) than in group 1 (high DEX/low MDZ) or group 3 (low DEX/high MDZ), and the anesthesiologist evaluated the sedation levels in group 2 as a lighter state. The RSS during cutting was also significantly lower in group 2 than in group 1 or group 3. However, no significant differences among the groups were observed during the incision or suturing, and the sedation levels were comparable (Figure 4). No significant differences

Figure 2. Effect of dexmedetomidine and midazolam on systemic hemodynamics. Values are measured at the start of sedation (start), lowest during sedation (during), and end of sedation (end). Values represent median (interquartile range [range]). * $P < .05$. BPs indicates systolic blood pressure; BPd, diastolic blood pressure; HR, heart rate; and SpO₂, oxygen saturation.

Figure 3. Effect of dexmedetomidine and midazolam on systemic hemodynamics. Values are measured at the start of sedation (start), lowest during sedation (during), and end of sedation (end). Values represent median (interquartile range [range]). † $P < .05$ vs start. BPs indicates systolic blood pressure; BPd, diastolic blood pressure; HR, heart rate; and SpO₂, oxygen saturation.

Figure 4. The sedation levels in the groups. * $P < .05$. RSS indicates Ramsay sedation score; G1, group 1; G2, group 2; G3, group 3; and G4, group 4.

were observed among any of the other groups. On the other hand, the results for intraoperative memories showed that the amnesic effect in group 4 during the infiltration of local anesthesia and the incision were lower than in Group 1. Furthermore, the same tendency regarding memories was observed. However, no significant differences in the amnesic effect during cutting or suturing were observed among the groups (Figure 5). An evaluation of the degree of patient satisfaction did not show any differences among the groups (Figure 6).

DISCUSSION

No differences in the heart rate or arterial hemoglobin oxygen saturation level were seen among the 4 groups in the present study. The intraoperative systolic blood pressure and postoperative systolic blood pressure were higher in group 2 than in group 4, but no excessive bradycardia or

decrease in blood pressure were observed. These results indicate that the combination of DEX and MDZ can be used for sedation in dentistry in terms of hemodynamics.

In this study, the Ramsay sedation scores during infiltration anesthesia and during cutting were lower in group 2 (low DEX/low MDZ) than in group 1 (high DEX/low MDZ). Although the difference was not significant, the score during the incision tended to be similar during the incision as well, and thus a tendency was seen for objective sedation to be lighter in group 2. However, no difference was observed during cutting and suturing. In addition, when compared with group 3 (low DEX/high MDZ), the scores of group 2 were lower during infiltration anesthesia and cutting, but no differences were observed during incision or suturing. When we used a 3-compartment model and parameters described by Dyck et al¹⁰ with STUMPUMP software to estimate the predicted blood concentrations of the initial loading and maintenance doses of DEX, they were approximately 0.5 ng/mL in the intermediate-dose group and 0.3 ng/mL in

Figure 5. The amnesic effect in the groups. * $P < .05$. G1 indicates group 1; G2, group 2; G3, group 3; and G4, group 4.

Figure 6. Degree of satisfaction using Wong-Baker FACES Pain Rating Scale. There were no significant differences among the groups. G1 indicates group 1; G2, group 2; G3, group 3; and G4, group 4.

the low-dose group; these doses were estimated to be lighter sedation doses or lower than sedation doses.^{1,7–10} Because of the distinctive characteristic of DEX allowing arousal even during sedation, some patients undergoing dental and oral surgery may be aroused by the sound of voices or vibrations when only DEX is administered. The sedation may have become lighter during the lower-dose sedation with the combination of MDZ and DEX (group 2) used in this study because the painful procedure or the relatively highly invasive nature of bone cutting acted as a severe surgical intervention. On the other hand, maintaining a high level of sedation was possible in group 1 and group 3, in which the dose of one of the 2 drugs used was higher. This revealed that the initial dose of MDZ provided rapid sedation until later sedation was achieved by the preloading dose of DEX and that both DEX and MDZ complemented each other intraoperatively, enabling an optimal level of sedation to be achieved and maintained. Moreover, there have even been reports of the synergistic enhancement of their sedative effects when MDZ and DEX are used in combination.^{3,11,12} However, no clear synergistic effect was observed by the combined administration used in this study, and a certain dose of either drug was needed to acquire a state of sedation in which the RSS was stable. In addition, although DEX has a simultaneous antinociceptive action and has the potential to be of benefit for analgesia in head and neck surgery,^{3,13,14} this feature was not observed clearly in this study. However, whether the dosages of either DEX or MDZ or both in the present study were comparable pharmacodynamically remains unclear.^{3,15} Further investigations, including investigations of the dosages, will be required.

To evaluate differences in the amnesic effects among the groups, we assessed whether the combination of medium-dose MDZ with low-dose DEX or the combination of low-dose MDZ with medium-dose DEX was superior. When the patients were asked postoperatively whether they had memories at the time of each of the maneuvers, no difference in the responses was observed between group 1 (high DEX/low MDZ) and group 3 (low DEX/high MDZ).

However, the levels of amnesia between group 1 and group 3 tended to differ when either group was compared with group 4 (high DEX). The group 1 (high DEX/low MDZ) patients hardly remembered the infiltration anesthesia or incision, compared with the group 4 (high DEX) patients. This finding suggests that an earlier amnesic effect after the start of DEX was acquired as a result of the administration of low-dose MDZ; however, whether the effect was additive or synergistic remains undetermined. During cutting or suturing intraoperatively, no difference in memory was seen between group 1 and group 4, revealing that sufficient sedation was achieved with DEX alone as a result of the high blood concentration. Arain and Ebert⁹ also reported that more time was required to achieve optimal sedation with DEX and other reports show that the amnesic effect increased with higher doses of DEX without any particular adverse events.^{9,16,17} In addition, if high doses are administered or a certain amount of time is taken for induction, optimal sedation can be performed with DEX alone.^{9,18} However, when higher doses of DEX are administered, adverse effects such as hypotension or bradycardia can be predicted.^{16,19} In our preliminary study, we administered DEX at a dosage of 0.7 µg/kg/h continuously after preloading with 3 µg/kg/h for 10 minutes, which caused severe hypotension and excessive bradycardia, resulting in suspension of the pilot study.

On the other hand, no difference in the amnesic effect was observed in group 3 (low DEX/high MDZ), compared with group 4 (high DEX), at the time of each of the maneuvers, suggesting that the amnesic effect of group 3 was weak. The dose used in the medium-dose MDZ group in this study was regarded as light sedation. When used alone, an anxiolytic effect is obtained, but it is difficult to achieve an adequate amnesic effect.^{5,20} Even the addition of low-dose DEX to MDZ might be insufficient to obtain an effective amnesic effect. It is also possible that continuous low-dose DEX was incapable of compensating for the loss of the amnesic effect, since MDZ was administered at 30-minute intervals.²¹

The anesthesiologists evaluated sedation and the patients' amnesic effect differently. More specifically, the evaluations performed by the anesthesiologist-in-charge stated that the sedation level was lighter in the group that received a low dose of both MDZ and DEX (group 2) than in the groups in which the dose of just one of the drugs was low (group 1, group 3). However, no differences in the amnesic effect were seen among the 3 groups, group 1 to group 3. Hall et al³ compared the sedation level, memory, and analgesic effect during administration at DEX dosages of 0.6 µg/kg/h and 0.2 µg/kg/h and reported no difference in the

effect at dosages comparable to the dosages of DEX used in our study.

The RSS, which we used to evaluate sedation, is generally used in intensive care and similar units, and a score of 3 or 4 is considered an appropriate level.²² The Sedation-Agitation Scale (SAS) and the Richmond Agitation-Sedation Scale (RASS), which allow the evaluation of agitated states, are also available.^{23,24} We selected the RSS because the SAS states were too imprecise in some degree and an eye movement check is needed to assess the RASS. However, some problems may also exist with the RSS. As a result of being rapidly awakened in response to these external stimuli during sedation with DEX, it appears that the sedation level became similar regardless of the dose of DEX and that a divergence from the amnesic effect developed as a result.³ Thus, it might be difficult to evaluate precisely the state of sedation induced by DEX using any of the existing methods, and a specific evaluation method without stimulation may be needed.

Although it is not clear why differences in the degree of satisfaction with sedation were not found among the groups in the interview survey, the fact that the amnesic effects during cutting, which is in the middle part of the operation, were equal among the groups may be one explanation. However, since the few patients who responded with an unsatisfactory evaluation (Wong-Baker scale of 4) were in group 1 (high DEX/low MDZ) and group 4 (high DEX), the high DEX groups may require more attention for improvement. One hour for cognitive function recovery and approximately 2 hours for the half-life of DEX in the blood are needed after ordinary doses of DEX.^{3,25} The interview regarding the degree of satisfaction was conducted when the patients were about to return home, almost 2 hours after treatment with DEX, at which time persisting effects resulting in unpleasant feelings such as drowsiness or lassitude may have affected their evaluations.^{9,19,25,26} It is considered that the amnesic effect by sedation using Dex is poorly associated with the degree of intraoperative comfort. Further studies are required to clarify the relationship between the degree of satisfaction and the sedation level.²⁷

No serious circulatory complications were recorded with the combination of 0.3–0.5 µg/kg/h DEX and 0.02–0.03 mg/kg MDZ in this study. The highest quality of sedation with the combined use of MDZ and DEX was likely achieved in this study when an initial MDZ dose of 0.02 mg/kg and the intermittent administration of 0.01 mg/kg every 45 minutes was accompanied by the continuous infusion of DEX at 0.5 µg/kg/h. However, more studies are needed to ensure a higher per-

centage of satisfactory patient responses regarding the combined use of MDZ and DEX for sedation.

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