Original Article

Analysis of intravenous sedation for dental treatment in elderly patients with severe dementia-a retrospective cohort study of a Japanese population

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Abstract *Background/purpose:* Patients with severe dementia require intravenous sedation during dental treatment. However, few reports have compared the outcomes of intravenous sedation management among sedatives. Intravenous sedation in the elderly with severe dementia undergoing dental treatment was evaluated retrospectively.

Materials and methods: Patients' characteristics and type of dementia were obtained from medical records. Midazolam (MID), dexmedetomidine (DEX), and propofol (PRO) were administered as sedatives. The systolic blood pressure (SBP), heart rate (HR), SpO_2, bispectral index (BIS) values and complications were evaluated.

Results: Nineteen patients with severe dementia who underwent 62 instances of sedation were included. There was no difference in patient background between sedatives. The sedation time and permission time to return home were significantly longer in DEX than in MID or PRO group. Half the usual dose in MID and lower limits of the routine dose was effective in DEX and PRO. HR was significantly lower in DEX group. There were 3 cases with airway obstruction requiring nasopharyngeal airway and 4 cases of apnea when MID was administered. Two cases of Cheyne-Stokes-like respiration when MID or DEX was administered. $SpO_2 <94\%$ was found in 22 cases (35%) irrespective of the sedative. A patient with dementia with Lewy bodies had experienced hallucinations during the recovery period after sedation when MID or DEX was administered. The BIS value of ≤ 80 was noted during complications.

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Conclusion: Intravenous sedation for dental treatment in the elderly with severe dementia, needs a dose titration. All sedatives had respiratory-related complications which mandate close monitoring.

Introduction

Intravenous sedation is used as for behavior modification during dental treatment of patients with severe dementia who offer resistance or refuse to undergo dental treatment. Previous studies showed that intravenous sedation using midazolam (MID), diazepam, or propofol (PRO) was performed in patients with dementia, with few complications.[1,2] However, as the severity of dementia was unknown (91 cases) or given the smaller sample size (11 cases) in these reports, it is unclear how elderly patients with dementia respond to each sedative.[1,2] In intravenous sedation with MID and PRO in patients with dementia, cardiovascular complications occurred in 46.2% (bradycardia 13.8%, hypotension 12.3%) patients, respiratory complications in 52.3%, and snoring in 16.9%.[3] Currently, MID, dexmedetomidine (DEX), and PRO are frequently used for intravenous sedation during dental treatment.[4] However, to our knowledge, few reports compared the outcome of intravenous sedation management using MID, PRO and DEX for patients with dementia.

Like other benzodiazepines, MID is a gamma-aminobutyric acid (GABA) receptor agonist that is thought to induce cognitive impairment, such as postoperative delirium (POD) and postoperative cognitive dysfunction (POCD). Propofol, another GABA receptor agonist, may exert similar effects.[5–7] Unlike GABA receptor agonists, DEX acts on central α2-adrenergic receptors. Sedation with DEX has a minimal effect on respiratory rate and percutaneous arterial oxygen saturation (SpO_2) and is associated with fast recovery from sedation with physical stimulation if needed.[8–10] It might be an appropriate sedative for elderly patients with dementia since animal studies have shown that it has cerebral protective effects, such as maintenance of cerebral blood flow during hypoxia and focal cerebral ischemia.[8–10] A factor that may trigger POD and POCD is inflammation from surgery that spreads to the central nervous system.[5–7] The anti-inflammatory effect of DEX is responsible for a low incidence rate of POD and POCD after cardiac and non-cardiac surgeries.[11,12]

Hence, this study retrospectively analyzed intravenous sedation in this vulnerable population and compared efficacy and complications of MID, DEX, and PRO.

Materials and methods

Subjects

This study was conducted adhering to the tenets of Declaration of Helsinki, and it was approved by the Institutional Research Board and the Ethics Committee of our institute (Approval No. 472).

The patients who visited the Geriatric Dental Clinic, Kanagawa Dental University Hospital from August 2015 to March 2020 and who underwent dental treatment with intravenous sedation because they could not tolerate the procedure at all or refused it due to severe dementia were included. Medical specialists made the diagnosis of dementia and severity using functional assessment staging test (FAST) for patients with Alzheimer's type dementia and clinical dementia rating (CDR) for all patients.

Sedation management

Intravenous sedation was managed by a dental anesthesiologist (YM) without preanesthetic medication, and the patient was positioned supine on the dental treatment table. Besides non-invasive blood pressure monitoring, an electrocardiograph, and a percutaneous arterial oxygen saturation monitor (SpO_2) placement, a bispectral index (BIS) sensor probe was attached to the forehead. A peripheral venous route was secured and administration of Ringer's acetate solution (Fisio 140®: Otsuka Co. Tokyo, Japan) was slowly started.

Sedative was administered to reach Modified Observer's Assessment of Alertness/Sedation score (OAA/S) 2 (responds only after mild prodding or shaking). Initially, 1 mg of MID was administered followed by 0.5–1 mg as needed. DEX was maintained at 0.2 μg/kg/h following an initial load at 3.0 μg/kg/h for 10 min, and titrated by 0.1–0.2 μg/kg/h as needed. With an initial loading dose of 2 mg/kg/min, PRO was titrated by 0.5–1 mg/kg/h or a bolus of 10 mg was administered as needed. The OAA/S was evaluated after 3–10 min of initial administration and sedatives were continued until OAA/S- 2, and then the procedure was started. Once the refusals decreased, a nasal cannula was attached and oxygen at 1–3 L/min was started. Sedatives were adjusted appropriately while assessing the patient's response to the invasive/painful procedural steps.

Survey items

We evaluated age, sex, height, weight, type and severity of dementia, other complications and medications as patient background from the medical records. Sedation time, treatment time, the time from the end of sedation to permission to return home (permission time to return home), dose of each sedative at the time when OAA/S-2 was reached and during maintenance were investigated. The blood pressure and heart rate (HR) were measured every 5 min, and SpO_2 was continuously measured, and the highest and lowest value of systolic blood pressure (SBP), and the lowest value of HR and SpO_2

when OAA/S-2 was obtained (before the start of treatment) and during treatment were documented. The BIS values captured ranged from 1: immediately before administration of sedatives, 2: when scored as OAA/S 2, 3: immediately before the start of treatment, 4: the lowest value during treatment, and 5: the highest value during treatment.

For each sedative, initial dose (dose at the time when scored as OAA/S 2) and average dose (mg/kg/h for MID and PRO, μg/kg/h for DEX) were analyzed. The average dose of each sedative was defined as the average per hour of total dose for MID and PRO. Whereas in DEX, the average of the total amount of maintenance dose per hour after the initial infusion of 3.0 mg/kg/h for 10 min was calculated as the average dose. Adverse effects and the countermeasures were also documented.

Statistical analysis

For statistical analysis, SPSS version 16.0 software (SPSS Japan, Tokyo, Japan) was used. Data are presented as median (interquartile range [IQR]). For comparison between sedatives, χ^2 test was used for male-female ratio, and the Kruskal—Wallis test was used for other items among MID, DEX and PRO groups. The Mann—Whitney U test was used as a post-hoc analysis with Bonferroni correction. For comparison within each group, SBP, HR and SpO_2 values were analyzed by Wilcoxon signed-rank test. BIS values were analyzed by the Friedman test, and Wilcoxon signed-rank test was used as post-hoc analysis with Bonferroni correction. $P < 0.05$ was set as a significant difference in all comparison. BIS 5 does not reflect the effect of sedatives because it can increase by the stimulation of dental treatment; it is considered that the same comparison with other measurement points is not possible. Therefore, BIS 1 to 4 were compared within each group.

Results

Patient background

Among the 19 patients, sedation was performed 62 times (Table 1). The median age was 73 (72—84) years, height was 156 (150—157.5) cm, and body weight was 48.5 (42—60) kg. Nine patients underwent multiple sedation management (Table 2). Unless there are contraindications, MID was principal sedative. However, if complications occur in sedation with MID, DEX was used. When sedation with MID or DEX does not provide enough sedative effect, PRO was substituted (Table 2).

As anti-dementia drugs, ten patients were administered memantine hydrochloride, five patients donepezil hydrochloride, two patients galantamine hydrobromide and one patient a transdermal rivastigmine preparation. Due to severe dementia none of the patients communicated or responded purposefully (FAST ≥6e, CDR = 3; Table 1). The medications were statins (n = 6), antipsychotics (n = 4), antithrombotic drugs (n = 3), drugs for Parkinson's disease (n = 1) (the number of patients overlapped).

The median sedation time was 80 (65—97) minutes, treatment time was 52 (43—70) minutes, permission time to return home was 75 (50—110) minutes. The case distribution based on the sedatives used were MID 26, DEX 16 and PRO 20 cases.

Comparison of patient backgrounds

Comparison of each sedative group showed no difference in sex, age, height, weight, and treatment time. The sedation time and permission time to return home were significantly longer in DEX group than in MID or PRO group (Table 3).

Dose of sedatives used

With MID, the initial dose was 0.025 mg/kg (median) and the average dose was 0.041 mg/kg/h. In DEX, the initial load was 3.0 μg/kg/h and the average dose for maintenance was 0.24 μg/kg/h. In PRO, the initial dose was 3.3 mg/kg/h and the average dose was 2.84 mg/kg/h (Table 3).

Comparison of SpO_2, SBP and HR

SpO_2 was maintained well compared to the baseline value as oxygen was supplemented during treatment (Table 4). In each drug group, the highest or lowest SBP during

Table 1 Characteristics of patients at the first sedation.

Type of dementia	Sex (M/F)	Age at the first sedation (years)	Severity of dementia	Complications besides dementia
Alzheimer	M 1/F 14	72 (69—83)	FAST 6e 1	Hypertension 3, Dyslipidemia 3, Chronic heart failure 1, Stroke 2
			7a 7	Arrhythmia 2, Chronic obstructive pulmonary disease 1
			7b 5	Osteoporosis 5, Others 9
			7c 2	
Lewy body	M 0/F 1	87		Hypertension 1, Stroke 1
Cerebrovascular	M 1/F 1	83/84		Hypertension 1, Chronic heart failure 1, Stroke 1 Thoracic aortic aneurysm 1, Osteoporosis 1
Frontotemporal	M 0/F 1	66		Epilepsy 1

M: male, F: female, FAST: functional assessment staging test.
All patients indicated clinical dementia rating as score 3 (severe).
The number of complications overlapped.

Table 2   Multiple sedation cases and selection of sedatives.

Case	Sex	Age (years)	Times of sedation	Sedatives (times)	Reason for drug selection
1	F	66	2	PRO 2	no enough sedative effect when MID was used
2	F	84	6	MID 5/DEX 1	decease of oxygenation when DEX was used
3	M	74	4	MID 4	
4	F	72	11	PRO 10/DEX 1	no enough sedative effect when MID or DEX was used
5	F	72	12	MID 7/DEX 5	three times of deoxygenation when MID was used
6	F	72	4	MID 2/DEX 2	two times of deoxygenation when MID was used
7	F	69	6	MID 6	
8	F	87	5	MID 1/DEX 4	decrease of oxygenation when MID was used
9	M	84	2	DEX 2	contraindication of MID (narrow-angle glaucoma)

M: male, F: female, MID: midazolam, DEX: dexmedetomidine, PRO: propofol.

treatment suggested no clinical difference among seda-tives. Significantly lower HR in DEX group than in MID or PRO group was observed; however, inotropes were not used (Table 4).

Comparison of BIS value

In the comparison of BIS values among sedatives, no dif-ference was observed at any measurement points. In each group comparison, BIS 2, 3 and 4 showed a similar decrease compared to BIS 1 in both MID and DEX groups. PRO showed a similar trend, but post-hoc analysis showed no statistical difference (Table 4).

Complications during treatment

Table 5 shows the complications of each sedative and the BIS value at the time of occurrence. There were 4 cases of apnea: 3 cases (1 patient) when MID 1 mg was administered

and 1 case (another patient) when 2 mg was administered, and positive pressure ventilation were performed with a bag valve mask (BVM). There were two cases of Cheyne-Stokes-like breathing (MID 2.5 mg and DEX 3.0 μg/kg/h administration).

One case with airway insertion due to airway obstruction was observed in DEX use (SpO_2 decreased to 85% during treatment at 0.7 μg/kg/h) and 2 cases in PRO use (another patient). Patients with snoring who were treated by elevating the mandible were one in MID, seven in DEX (during initial loading), and 2 in PRO. A measured value of SpO_2 <94% was noted in 22 cases (35%), 9 cases in MID (4 patients), 8 cases in DEX (5 patients), and 5 cases in PRO (3 patients). One case each in MID or DEX occurred during treatment, and in others, it occurred in the pretreatment period. The BIS value at the time of each complication occurred was 80 or less.

In 6 cases (2 patients with hypertension), nicardipine hydrochloride was administered when SBP >180 mmHg. One patient (SBP>200 mmHg), 4 times during sedation with

Table 3   Comparison of background data.

	Midazolam	Dexmedetomidine	Propofol	P value	χ^2 value	post-hoc analysis among groups
Sex (Male/Female)	4/26	2/16	0/20	0.201	3.205	
Age (yo)	72.5 (71.5—84)	78 (72—86.3)	72.5 (71.3—75)	0.179	3.438	
Height (cm)	156 (151.0—157.5)	154.7 (151.0—157.5)	152.5 (142.5—158.5)	0.772	0.519	
Weight (cm)	47.5 (41.5—60)	57.9 (44—60)	48.5 (40.5—57.9)	0.593	1.046	
Sedation time (min)	72.5 (61—90)	99 (85—117.3)	75 (60.5—95.3)	<0.001	15.617	MID vs DEX:<0.001 (62.0) DEX vs PRO: 0.001 (61.0)
Treatment time (min)	49.5 (40.8—65)	54 (46.5—79.8)	60 (43.5—70)	0.202	3.202	
Permission time to return home (min)	57.5 (50—75)	152.5 (131.3—189.5)	70 (45—90)	<0.001	29.312	MID vs DEX: <0.001 (19.0) DEX vs PRO: <0.001 (13.5)
Initial dose of drug (average)	0.025 (0.017—0.051) mg/kg	3.0μg/kg/h	3.3 (2.47—4.17) mg/kg/h			
Dose of drug (average)	0.041 (0.032—0.059) mg/kg/h	0.24 (0.19—0.36) μg/kg/h	2.84 (2.00—3.65) mg/kg/h			

MID: midazolam, DEX: dexmedetomidine, PRO: propofol.

Table 4 Comparison of measured data.

	Midazolam	Dexmedetomidine	Propofol	P value	χ^2 value	post-hoc analysis among groups
SpO$_2$ (before treatment)	95.5 (90.5—98)	94.5 (92—96)	96 (93—97)	0.527	1.282	
SpO$_2$ (during treatment)	97 (96.8—98)	96 (93.5—97)	98 (96.3—99)	<0.001	15.541	MID vs DEX: 0.001 (81.0) DEX vs PRO:<0.001 (51.0)
P value	0.001 (−3.253)	0.459 (−7.40)	0.002 (−3.087)			
The lowest of SBP	112 (105.5—143.5)	105 (81.3—122.3)	97 (96.3—99)	0.009	9.461	MID vs DEX: 0.016 (105.0) MID vs PRO: 0.006 (101.0)
The highest of SBP	153.5 (143.3—197.8)	149 (130.5—160.5)	151 (135—164.5)	0.27	2.617	
P value	<0.001 (−4.286)	<0.001 (−3.517)	<0.001 (−3.623)			
The lowest of HR	58 (51.3—62.5)	48 (42.3—53)	58 (53—63)	<0.001	16.102	MID vs DEX: <0.001 (64.5) DEX vs PRO: <0.001 (38.5)
BIS values BIS 1	93.5 (83.3—98)	93 (90.5—96.5)	86 (66.5—98)	0.629	0.929	
BIS 2	84 (69.5—91)	79 (60—92)	58.5 (30.8—80)	0.064	5.499	
BIS 3	81 (60.8—90)	57.5 (45.5—90)	54.5 (29—73.8)	0.162	3.646	
BIS 4	73 (48.3—81.5)	51 (44—65.5)	55 (33.8—83.3)	0.194	3.283	
BIS 5	97 (96—97.3)	95.5 (82.8—98)	92 (90—92.3)	0.285	2.510	
P value (Friedman test)	<0.001 (χ^2 = 27.684)	<0.001 (χ^2 = 32.482)	0.003 (χ^2 = 16.104)			
post-hoc analysis in each group	BIS 1—4: 0.003 (−2.934)	BIS 1—2: 0.004 (−2.901) BIS 1—3: 0.005 (−2.831) BIS 1—4: 0.001 (−3.180)	NS			

SBP: systolic blood pressure, HR: heart rate, MID: midazolam, DEX: dexmedetomidine, PRO: propofol, NS: no significance.

MID, but the SBP was stable when DEX was used once. A patient with dementia with Lewy bodies had hallucinations during the recovery period. The breakdown was once when using MID and twice when using DEX.

Discussion

This retrospective study on intravenous sedation during dental treatment in elderly patients with severe dementia were evaluated using MID, PRO and DEX. The sedation time and permission time to return home were longer in DEX. The BIS values showed a similar decrease (baseline comparison) after administration of each sedative. Serious complications were airway obstruction in 3 cases (5%) and apnea and Cheyne-Stokes-like breathing due to MID or DEX administration in 6 cases (10%).

The sedation time and permission time to return home were significantly longer in DEX group due to slower onset of action and prolonged sedation after the termination of the infusion.[13] The sedative dose is generally 0.05—0.07 mg/kg in MID, whereas DEX is maintained at 0.2—0.7 μg/kg/h after an initial load of 6.0 or 3.0 μg/kg/h for 10 min, and PRO is infused at 2.0—6.0 mg/g/h.[13] From this study, MID showed effective at approximately 1/2 dose

in the elderly with severe dementia, but a lower limit of the usual dose was required in DEX or PRO sedation.

As for reports on intravenous sedation for patients with dementia, Galli et al. showed a large dose range of 0.5—10 mg of MID, and Fujisawa et al. reported at 0.5—3.5 mg of MID in a case report without any complications.[1,14] So et al. maintained PRO at a target controlled infusion concentration of 2.4 μg/mL initially and maintained at 1.8 μg/mL, and BIS level at 60—80.[2] Morita et al. reported sedation with 4 mg MID and a total of 49 mg PRO with no complications.[15] In this study, MID was used at about half the usual dose (1—1.5 mg), which is equivalent to that reported by Fujisawa et al.[14] The report by Galli et al. was submitted when the sedation with PRO was not widely prevailing and the MID was used primarily, which led to a higher dose of MID. The OAA/S 2 was obtained at the lower limit of the usual dose of PRO, which was equivalent to the previous report.[15]

SpO$_2$<94% was found in 22 patients (35%), MID 41%, DEX 36% and PRO 23%, mostly modulated by the lifting of the mandible. Four instances (2 patients) of apnea by MID 1—2 mg administration were observed, and positive pressure ventilation by BVM was performed. These findings suggest occurrence of severe respiratory adverse events even with a small dose of MID in these patients. In addition,

Table 5 Comparison of complications.

	Midazolam	Dexmedetomidine	Propofol
Hypoventilation			
Apnea (BVM used)	4 (2 patients)	0	0
drug dose	1 mg or 2 mg		
the lowest values of SpO_2/BIS	78—87%/UM[a] or 58		
Cheyne-Stokes-like breathing	1	1	0
drug dose	2.5 mg	3.0 µg/kg/h	
fluctuation of SpO_2/BIS	90—98%/29-36	90—98%/58-73	
Airway obstruction (insertion of NPA)	0	1	2 (one patient)
drug dose		0.7µg/kg/h	3.5 or 6.0 mg/kg/h
the lowest values of SpO_2/BIS		85%/45	97 or 96%/UM[c]
Airway obstruction (snoring/mandibular lifting)	1	7 (5 patients)	2 (2 patients)
drug dose	2 mg	3.0 µg/kg/h	3 or 6 mg/kg/h
the lowest values of SpO_2/BIS	96%/UM[b]	85—96%/32-73	90 or 92%/44 or 30
SpO_2<94%	9 (4 patients; before treatment 8/during treatment 1)	8 (5 patients; before treatment 7/during treatment 1)	5 (3 patients; before treatment 5)
drug dose/the lowest values of BIS	1—2.5 mg/29- 81	3.0 or 0.7µg/kg/h/33- 45	2—5 mg/kg/h/11- 53
Hypertension (use of nicardipine)	5 (one patient)	0	1
Hallucination (during recovery time)	1	2 (the same patient in MID)	0

BVM: bag valve mask, NPA: nasopharyngeal airway, UM: unmeasured.

[a] BIS was not calculated based on the brain wave in a patient (3 times).

[b] BIS was not calculated based on the brain wave in a patient.

[c] BIS was not calculated based on the brain wave in a patient.

Cheyne-Stokes-like breathing was observed in 2 instances when 3 mg of MID or 3.0 µg/kg/h of DEX (during initial loading) was administered, and NPA insertion was required in 3 instances (2 patients). One of them was administered DEX leading to deep sedation when 0.7 µg/kg/h of DEX was used to suppress body movement during treatment, and SpO_2 had fallen to 84% due to severe airway obstruction.

About 1/3 cases (8/22 cases) of SpO_2 <94% was observed when DEX was used, and most of them occurred during 5 min in the latter half of the initial load of 3.0 µg/kg/h and BIS value was 33—45. Respiratory depression is rarely seen with DEX and BIS value of 70—80 can be maintained by 0.7 µg/kg/h infusion.[13] However, the risk of airway obstruction due to deep sedation can occur in the elderly with severe dementia even when DEX is used. In the report of Sugimura et al., 89.5% of all complications occurred in combination with MID and PRO at BIS <70. In this study, the BIS value when available, during serious respiratory complications occurred was mostly <80, this concurs with findings of Sugimura et al.[3]

Regarding SBP, there were cases where nicardipine hydrochloride was used in hypertensive patients, but no extreme hypotension due to DEX (α2 receptor agonist) was observed. Significantly lower HR without any inotrope support was observed in the DEX group.[13]

The BIS value similarly decreased (BIS 4, 50—70) with each sedative. Even though BIS decreased briefly to 20 to 30, it did not affect the awakening after sedation. These observations concurs with the BIS range noted in the previous study, indicating that BIS value is likely to show a significant decrease in patients with dementia.[3]

In the recovery period from sedation, there were 3 cases (1 person with dementia with Lewy bodies) in whom continuous visual hallucinations appeared more frequently than usual. It was not only when using MID but also when using DEX. Benzodiazepine induced POD and POCD have been reported, but caution is required in Lewy body dementia, who are prone to have hallucinations induced by DEX.

The limitation of the present study is its retrospective design. In the future, a large-scale prospective study is needed to evaluate the outcomes of sedation in elderly patients with severe dementia.

In conclusion, intravenous sedation for dental treatment in the elderly with severe dementia, needs a dose titration to about half the usual dose in MID, whereas DEX and PRO require the lower limit of the usual dose. All sedatives had respiratory-related complications which mandate close monitoring.

Declaration of Competing Interest

The authors declare no conflicts of interest with respect to the research and publication of this article.

Acknowledgements

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