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Intranasal midazolam for the sedation of geriatric patients with care-resistant behaviour during essential dental treatment: An observational study

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Abstract

Objectives: To describe the efficacy and safety of intranasal midazolam for sedation during essential dental treatment of geriatric patients with major neurocognitive disorder (MND) and care-resistant behaviour (CRB).

Background: Dental treatment is often impossible in geriatric MND patients with CRB. Intranasal midazolam may provide a non-invasive sedation method, but there is currently no information on its use in geriatric patients.

Methods: In this observational study, we included geriatric patients with severe MND and CRB needing urgent dental treatment. Each patient received 5 mg midazolam intranasally. Agitation/sedation levels, heart rate, respiration rate and oxygen saturation were recorded at 5-minute intervals.

Results: Thirty two patients were included. Mean age was 84 (±7) years. Mean (SD) time to treatment start was 13 (±5) minutes, and mean time to maximum sedation 17 (±11) minutes. Sedation was sufficient to enable dental treatment to be completed in 31 (97%) patients. Anxiolysis/light sedation occurred in 16 (50%) patients, and moderate to deep sedation occurred in 16 (50%) patients. No patients suffered from apnoea, although 3 patients required a chin-lift manoeuvre. Hypoxaemia occurred in 1 of these patients and in 2 other patients without airway obstruction. All patients recovered uneventfully. In a regression model, age, weight and other sedative medication use were found not to be associated with maximum sedation depth.

Conclusions: Of 5 mg intranasal midazolam facilitates treatment of geriatric patients with MND in the comfort of their own environment. More information is needed to guide titration to balance the desired sedation level and patient safety.

KEYWORDS

anaesthesia, gerodontology, sedation

1 | INTRODUCTION

The global population is ageing, and the incidence of major neurocognitive disorders (MND) such as Alzheimer's disease is consequently increasing. Worldwide, approximately 50 million people have been diagnosed with MND, and nearly 10 million new patients are identified each year.[1,2] Cognitive decline is often accompanied by worsening of self-care, absent or reduced care-seeking behaviour and impaired motor skills, all of which are factors that increase the risks of general and more specifically oral health problems.[3,4] A recent study performed in the Netherlands found that over 70% of elderly people who were admitted to a nursing home because of severe MND had poor oral health.[5] In people with MND, poor oral health causes painful oral conditions which often go undetected.[6,7] It is known that when these problems are detected and treated this has a positive impact on the quality of life.[8,9] In summary, poor dental health is a large, modifiable burden in the geriatric population causing many elderly patients to suffer from undetected chronic pain in the last days of their lives.[6,10-12]

Dental treatment of patients with MND are often complicated as they not only exhibit a high incidence of painful dental pathology, their cognitive decline is also often accompanied by fear and agitation, leading to uncooperative and aggressive, care-resistant behaviour (CRB) in as many as 40% to 60% of patients.[5,13] When non-pharmacological strategies fail to achieve satisfactory treatment conditions, procedural sedation, for instance with a benzodiazepine, can be used to achieve anxiolysis or sedation in order to allow essential dental treatment to be performed.

Midazolam (MDZ) is a benzodiazepine which is often used for procedural sedation of anxious patients, and oral administration in geriatric patients has been studied before.[14] The time to maximum effect of midazolam after oral administration may range from 30 to 90 minutes (Dutch National Formulary (Farmacotherapeutisch Kompas, FTK)).[15] This makes it very difficult to gauge when the maximum sedative effect has been reached and whether or not additional sedation is needed. Furthermore, the published figures for bioavailability of oral midazolam range from 30% to 70% which compounds the previous problem because this causes not only the timing of the maximum effect to be unclear but also the extent of the effect, that is the sedation depth.[15] Hence, it is impractical and potentially unsafe to administer repeat doses of oral midazolam if the initial effect appears to be suboptimal, until 90 minutes after administration.

Intranasal drug administration is an alternative to oral or intravenous administration. Intranasal midazolam administration has been shown to result in a fast and reliable sedation onset time and a predictable plasma concentration profile in young, healthy adults and children.[16,17] It has been used to facilitate dental care for patients with special needs[18] and may have advantages in the treatment of geriatric patients with CRB because it may allow caregivers to titrate midazolam more easily than the oral route. This would enhance the efficacy and safety of sedation for this vulnerable patient group.

Currently, there are no published data on the use of intranasal midazolam in geriatric patients who are unable to cooperate with their dental care. Most available literature reports the results of studies in younger adults.[16] This knowledge hiatus needs addressing as geriatric patients respond differently to midazolam and often take other medications with sedative properties, and these factors may compromise the safety of its use.[19,20] The aim of this study was to thus evaluate the efficacy and safety of intranasal administration in geriatric MND patients with CRB who require dental treatment. The results will indicate whether intranasal midazolam can be safely used for this purpose and whether there are potential benefits and risks.

2 | METHODS

This was an observational study of the use of intranasal midazolam for the sedation of geriatric patients who are living in nursing homes, suffering from MND and who display care-resistant behaviour during dental treatment in two northern regions in the Netherlands. The study was approved by the Institutional Review Board (METc 2018/343).

2.1 | Patients

The study period lasted from February 2019 to January 2020. All included patients were aged 65 and over, suffered from late-stage MND (nearly or completely dependent on care) and were living permanently in a nursing home. Each patient had an indication for essential dental treatment and an indication for procedural sedation because of CRB. Exclusion criteria were as follows: failure to obtain informed consent and contraindications for the use of midazolam or flumazenil (hypersensitivity to benzodiazepines, respiratory insufficiency, myasthenia gravis and sleep–apnoea syndrome).[15] Informed consent was obtained from each patient's legal guardian as all patients lacked mental capacity to provide consent for treatment. The indication for essential dental treatment was determined by an experienced gerodontologist.

2.2 | Treatment procedure

The gerodontologist visited all patients to confirm the indication for examination and treatment and the need for sedation due to CRB. All indications were confirmed, and all procedures were performed by the same gerodontologist. For each patient, the nursing home's geriatrician was informed about the planned treatment and was consulted to confirm the absence of any contraindications and to give permission for the dental extractions under midazolam sedation. All treatments were carried out in the patient's own living room or bed room. The gerodontologist was assisted by an experienced dental assistant. Patients were treated in their own

bed or reclining wheelchair. Each patient received 5 mg of midazolam administered intranasally by a unit dose spray (2.5 mg/unit dose of 50 μL, two unit doses, one per nostril), administered by the gerodontologist or by a trusted caregiver, with the gerodontologist and an anaesthesiologist present in the room. The gerodontologist commenced the dental procedure when she deemed the sedation depth to be adequate or when it had been stable for at least ten minutes. Monitoring consisted of clinical monitoring, and continuous measurement and monitoring of the heart rate and peripheral oxygen saturation (SpO_2) using a NONIN 8500 M pulse oximeter (NONIN Medical Inc.). For the purpose of this study, all observations were performed by the same anaesthesiologist. Clinical monitoring consisted of confirmation of airway patency, respiration rate and sedation depth. All monitored values were recorded at 5 minute intervals. The anaesthesiologist was equipped with basic airway equipment (Guedel airways (various adult sizes), nasopharyngeal airways (various adult sizes), a bag-mask ventilation system, intravenous cannulae for emergency intravenous access, flumazenil, a MAD-atomiser (LMA® MAD Nasal™ Intranasal Mucosal Atomization Device, Teleflex Medical, Westmeath, Ireland) and a syringe for emergency administration of flumazenil in case intravenous access failed). Sedation depth was assessed using a modified version of the Richmond Agitation and Sedation Scale[21,22] (mRASS, Table 1). All patients were monitored for at least 60 minutes after the administration of midazolam or longer if necessary until the patient had recovered. For the purpose of this study, all monitoring activities were performed by an anaesthesiologist. All extractions were performed under local anaesthesia with 0.5 to 7.2 mL articaine 4% with 1:100.000 adrenaline. After patients had recovered from the sedation, their care was handed over to the institution's caregivers along with post-procedural instructions for wound care and analgesia. Patients' caregivers were contacted the next day to enquire about complications of dental treatment or the sedation (increased agitation, signs of delirium and prolonged drowsiness).

2.3 | Outcome parameters

The study outcome parameters were divided into demographic parameters, sedation parameters and safety parameters. Demographic parameters included age, sex, bodyweight, use of other sedative medication and use of any other medication with significant effect on the metabolism of midazolam (ie CYP3A4 inducing or inhibiting medication). Sedation parameters included the following: time to maximum sedation depth, time to start of treatment, time to recovery and maximum attained sedation depth. Safety parameters included the following: incidence of apnoea necessitating assisted ventilation, incidence of airway obstruction necessitating airway manoeuvres, incidence of bradypnea (respiration rate (RR) <8 per minute), incidence of hypoxaemia (SpO_2 < 90%) and incidence of bradycardia (heart rate (HR) <40 bpm). Furthermore, we investigated the association of three patient-related factors (age, weight and use of other sedative medication) with the patient's deepest level of sedation (mRASS).

2.4 | Statistical analysis

All analyses were performed with IBM SPSS Statistics, Version 23.0.0.3 (IBM). Descriptive data are presented as mean (±SD). Frequency distributions are presented as n (%). A linear regression model was constructed to investigate the association of three patient-related factors with the deepest attained sedation depth. Patient age, weight and the use of other sedative medication were

TABLE 1 Modified RASScale (mRASS)

Score	Term	Description	Modified description
4	Combative	Overtly combative or violent; immediate danger to staff	Overtly combative or violent; immediate danger to staff
3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour towards staff	Pulls on or removes **bib, instruments** or has aggressive behaviour towards staff
2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony	**Frequent nonpurposeful movement**
1	Restless	Anxious or apprehensive but movements not aggressive or vigorous	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, to voice	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 s) awakens with eye contact to voice	Briefly (less than 10 s) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation	No response to voice or physical stimulation

included as covariates in this model. Variables were tested for normality, homoscedasticity and collinearity. *P*-values < .05 were considered statistically significant.

3 | RESULTS

3.1 | Patients

A total of 32 consecutive patients were included. Mean age of the patients was 84 (±7) years. Twenty-eight (87,5%) patients were female.(Table 2) The weight of two patients was unknown and could not be measured because they were bedridden, and the nursing home had no equipment to measure their weight in bed. Mean (SD; range) weight-related dose of midazolam administered was 0.08 (0.01; 0.06 to 0.11) mg/kg. Out of the 32 included patients, a total of 27 (84.3%) underwent extraction of one or more dental elements, and five (15.6%) had to undergo inspection and intensive dental cleaning due to suspected pain complaints or infections. Figure 1 illustrates clinical examples of the dental pathology encountered during the course of this study. Medications with sedative effects, such as opioids, other benzodiazepines or haloperidol, were being used by nine (28%) patients. No patients used CYP3A4-enhancing or CYP3A4-inhibiting medication.

TABLE 2 Patient characteristics

	Age	Weight	MDZ dose (mg/kg)	Sex	mRASS before MDZ administration	Lowest mRASS	Use of other sedative medication
Patient number							
1	84	48.0	0.10	F	2	-1	No
2	88	51.0	0.10	F	1	-3	No
3	85	73.0	0.07	F	2	-1	No
4	77	63.0	0.08	M	3	-1	No
5	85	45.0	0.11	F	0	-3	No
6	86	80.0	0.06	F	2	-1	No
7	84	68.0	0.07	M	0	-2	No
8	72	55.0	0.09	F	2	-3	No
9	74	68.2	0.07	F	0	-1	No
10	89	54.0	0.09	F	1	-3	No
11	65	64.0	0.08	F	3	-1	No
12	72	Unknown		F	1	-4	Yes
13	85	72.0	0.07	F	3	-2	Yes
14	77	57.0	0.09	F	1	-4	No
15	87	51.0	0.10	F	1	-3	No
16	92	52.6	0.10	F	4	0	Yes
17	87	49.0	0.10	M	0	-2	Yes
18	91	76.0	0.07	F	0	-3	No
19	89	60.0	0.08	F	0	-4	Yes
20	88	Unknown		F	0	-1	No
21	86	55.0	0.09	F	-3	-4	No
22	91	67.0	0.07	F	0	-1	Yes
23	90	62.0	0.08	F	4	-3	No
24	83	68.0	0.07	F	0	-3	No
25	87	59.0	0.08	F	0	-1	Yes
26	77	58.0	0.09	M	1	-2	No
27	94	73.0	0.07	F	3	-4	Yes
28	86	46.0	0.11	F	3	-4	No
29	93	63.0	0.08	F	3	0	No
30	88	60.0	0.08	F	3	-4	No
31	72	73.5	0.07	F	0	-2	Yes
32	77	56.5	0.09	F	1	-3	No

Note: mRASS, modified Richmond Agitation and Sedation Scale (Table 1); MDZ, midazolam.

FIGURE 1 Clinical examples of the dental pathology encountered during the study

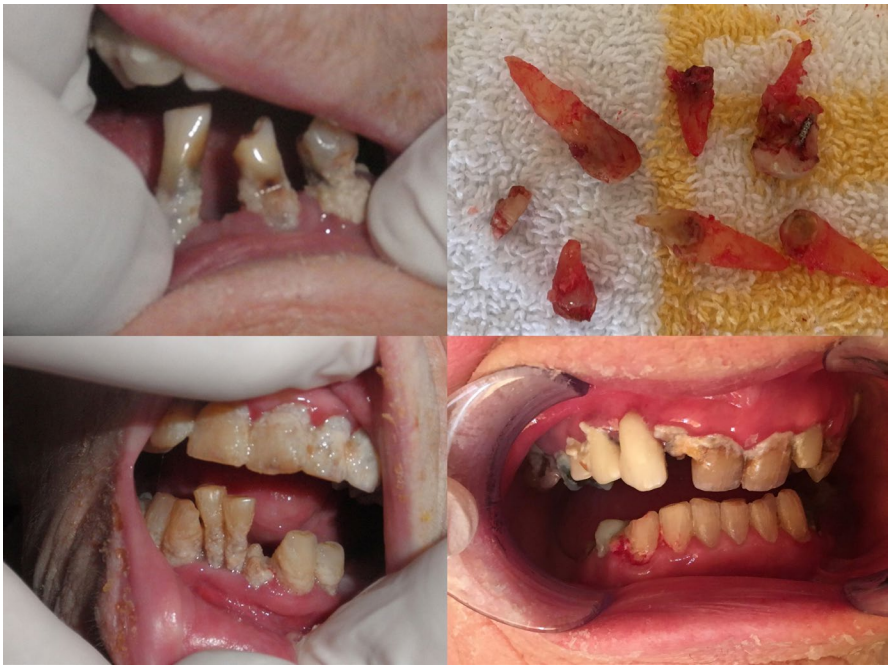
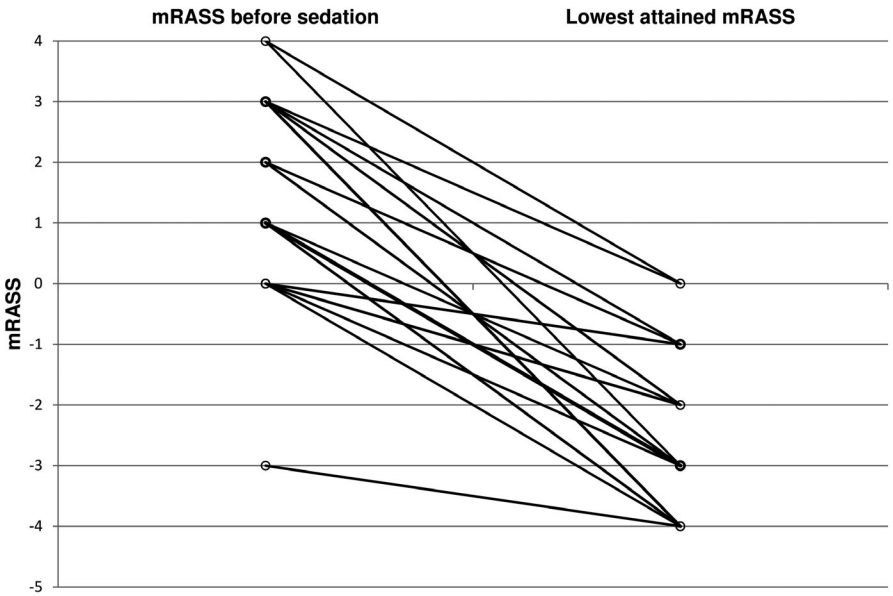


TABLE 3 Frequency distribution of mRASS sedation depth before treatment and lowest attained sedation depth

mRASS before MDZ administration	**4**	**3**	**2**	**1**	**0**	**-1**	**-2**	**-3**	**-4**	**-5**
n (%) patients	2 (6.3)	7 (21.9)	4 (12.5)	7 (21.9)	11 (34.4)	0 (0)	0 (0)	1 (3.1)	0 (0)	0 (0)
Lowest attained mRASS	**4**	**3**	**2**	**1**	**0**	**-1**	**-2**	**-3**	**-4**	**-5**
n (%) patients	0 (0)	0 (0)	0 (0)	0 (0)	2 (6.3)	9 (28.1)	5 (15.6)	8 (25)	8 (25)	0 (0)

Note: mRASS, modified Richmond Agitation and Sedation Scale (Table 1); MDZ, midazolam. (%-total >100% due to rounding).

FIGURE 2 Change in mRASS for individual patients (patients with similar results are represented by overlapping lines and bold circles)



3.2 | Sedative effects

In 31 of the 32 included patients (97%), sedation was sufficient to enable the completion of the planned dental procedures. The dental procedure had to be aborted in one (3.0%) patient (Table 2, patient 29) because of inadequate sedation depth during the treatment. One patient (Table 2, patient 21) was in a deep natural sleep (mRASS −3) before the midazolam was administered. Despite this, she was treated under sedation because she was known to become combative when touched or woken.

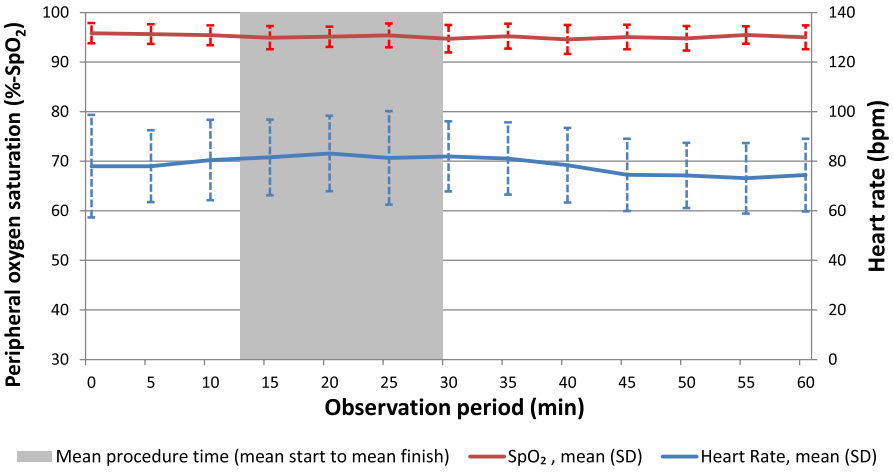


FIGURE 3 Mean (±SD) SpO_2 and heart rate over time

Dental procedures could commence on average 13 (±5) minutes after midazolam administration. Time to maximum sedation depth was 17 (±11), range: 5-55 minutes. A total of 25 patients (76%) recovered before the end of the 60-minute observation; four patients needed an additional 15 minutes to recover and four patients remained sedated for a longer period (maximum 110 minutes). All patients recovered uneventfully.

Maximum sedation depth differed between patients; minimal to deep sedation (mRASS −1 to −4) was reached in 30 (90%) patients during the period between MDZ administration and recovery (Table 3, Figure 2). Three (9%) patients were restless (mRASS 1), and two patients (6%) were agitated (mRASS 2) at the start of the dental procedure. The former three patients remained restless throughout the dental procedures and reached sedation levels of mRASS-1 to mRASS-3 only after the dental procedure had been completed. The latter two reached moderate to deep sedation (mRASS −3 and −4) a few minutes after the start of the procedures. No patients were more agitated at the start of the dental procedure than before the administration of midazolam. Table 3 lists the frequency distribution (n (%)) of the mRASS scores before midazolam administration and the maximum attained sedation depth.

3.3 | Safety parameters

No patients suffered from central apnoea or bradypnea. Three (9%) patients developed obstructed breathing during dental treatment that required manual airway manoeuvres, but all three had a maintained respiratory drive. In all of these cases, a chin-lift manoeuvre restored airway patency. Only one of these patients suffered transient hypoxaemia which recovered after the chin-lift manoeuvre. Two further patients had transient hypoxaemia lasting less than 5 minutes which resolved before the end of the treatment. In one of these patients, the SpO_2 reached a nadir of 85% before improving to normal within the recovery period. It was later established that she suffered from an inter-current lower respiratory tract infection.

No patients suffered from bradycardia or cardiac arrest. In total, 13 (40%) patients had a heart rate increase of more than 20 per cent during the dental treatment. Figure 3 shows the mean (SD) measurements for peripheral oxygen saturation and heart rate over time.

3.4 | Factors associated with maximum sedation depth

In the linear regression model, neither patient age (B: −0.01, 95%CI: −0.08 to 0.06, $P = .73$), patient weight (B: 0.03, 95%CI −0.02 to 0.09, $P = .22$) nor use of other sedative medication (B: 0.04, 95%CI: −1.09 to 1.17, $P = .95$) was found to be significantly associated with the maximum sedation depth.

4 | DISCUSSION

In this observational study, we investigated the efficacy and safety of intranasal midazolam for sedation during dental procedures in 32 geriatric patients with MND and care-resistant behaviour. The onset of sedation was found to be fast, treatment was possible in 97% of the patients and almost all patients recovered within 60-75 minutes. Although airway obstruction was present in three patients (9%), ventilatory drive was preserved during all procedures and airway patency could be restored by chin-lift manoeuvres alone. These results indicate that intranasal midazolam is a viable option for the treatment of elderly patients who are uncooperative or show aggressive care-resistant behaviour due to major neurocognitive disorders. It is, however, important to be aware that the procedure is not without risk as 9% of our patients developed airway obstruction and 50% reached moderate to deep levels of sedation.

While most patients' sedation level allowed their planned dental procedures to be completed, we found a wide range in the maximum attained sedation depths, with a sedation depth deeper than desired in several cases. Depth of procedural sedation is generally seen as a continuum from light or minimal sedation to deep sedation and general anaesthesia. Deeper levels of sedation are known to pose higher risks of complications, most importantly cardiovascular and respiratory compromise.[23] Because of these risks, current Dutch

and European guidelines dictate that moderate and deep sedation should be carried out in a controlled environment with backup facilities and advanced monitoring equipment such as ECG, non-invasive blood pressure measurement and capnography, and only by a dedicated caregiver trained in the administration of moderate to deep sedation (an anaesthesiologist or trained anaesthetic nurse) who focuses solely on the patient's comfort and safety. Such equipment and staffing are almost never available in nursing homes. Dutch guidelines permit lighter depths of sedation under less controlled circumstances, provided that a caregiver trained in light sedation trained is present and continuous clinical monitoring is performed.[24] The maximum sedation level of 50% of patients was mRASS-0 to mRASS-2, indicating a safe level of anxiolysis to minimal sedation, but on the other hand, 50% of the patients reached moderate to deep sedation levels. Three patients (9%) required manual airway manoeuvres to maintain airway patency, and two other patients suffered from transient hypoxaemia. This indicates that this method of sedation, though effective, needs to be improved to avoid health risks accompanying deeper levels of sedation. Delivery of sedation treatment in the nursing home environment by an anaesthesia team would most probably improve the patient's safety and comfort, and the operator's success rate. Intranasal midazolam could, for instance, also be used to facilitate placement of an intravenous cannula by an anaesthesiologist to titrate sedatives intravenously. This is currently, however, considered not to be cost-effective in the Netherlands.

We administered a single dose of intranasal midazolam – 5 mg – to all patients. The incidence of excessively deep levels of sedation could theoretically be reduced by adapting the dose of MDZ according to the patient characteristics. The results of our regression analysis indicate, however, that the maximum attained sedation level could not be predicted from the available patient information. It would be desirable if readily known parameters such as weight, age and use of other sedative medication could be used to predict the level of sedation attained after a given dose of intranasal midazolam.

We analysed the above-mentioned three patient-related factors based on existing literature. Age has been shown to be an important factor in the patient's response to MDZ.[20,25] These studies, however, report the effect of ageing on the response to MDZ across the entire range of adult life years. To the best of our knowledge, no studies have examined age-related differences in MDZ pharmacokinetics and pharmacodynamics within the geriatric population. The second included covariate, bodyweight, also did not influence the maximum attained sedation depth in our patients. This is surprising as midazolam dosing is often done relative to the patient's bodyweight.[15] The dose range in the current study (0.06 to 0.11 mg/kg) is wide and thus could be expected to have been a significant determinant of sedation depth. Interestingly, a similar disparity in the relationship between weight and response was found by Rignell et al who concluded that "poor and no acceptance were found among women with low weight and men with high weight.[14]" Lastly, the use of other sedative medication was included as a covariate in the regression model but was also not found to have a significant influence on sedation depth. Many patients in nursing homes use drugs that have interactions with benzodiazepines. Opioid use was common among the patients in our study, as was the use of other benzodiazepines or sedative drugs such as haloperidol. Each of these concomitant medications can enhance the effect of benzodiazepines, but we found no significant relationship between the use of these drugs and the maximum attained sedation depth.[26,27] We are as yet unable to explain these results, but they demonstrate a paucity in the knowledge of the pharmacokinetics and pharmacodynamics of midazolam in the geriatric population and further studies are needed to inform the safe and efficient use of midazolam in this vulnerable patient group. While the administration of a lower dose (eg 2.5 mg or 1 unit dose spray) could have resulted in a better safety profile, it would probably also have resulted in a higher proportion of insufficiently sedated patients. Inadequate sedation can of course be remedied by administering an additional dose, but at present there are insufficient data upon which to recommend the timing and size of the second dose.

The current study has several noteworthy strengths and limitations. We were able to increase the spectrum of observations of patient reactions by using a modified version of the Richmond Agitation and Sedation Scale.[21,22] Most sedation scales do not include assessment of agitation levels, and measuring agitation as part of the patient's comfort level was an important part of this study. Therefore, we did not choose to use the OAA/S or mOAA/S score proposed and validated for MDZ sedation as it does not include an assessment of agitation levels.[28] Instead, we modified the Richmond Agitation and Sedation Scale. Although this scale was developed for observations of mechanically ventilated ICU patients, it was chosen specifically because it includes an assessment of agitation and thus allowed us to observe a wider spectrum of patient reactions during the observations. To avoid inter-observer bias, all observations were performed by the same anaesthesiologist, who is chair of the quality and safety committee for procedural sedation in the University Medical Center Groningen. Our use of a modified version has not been validated but to our knowledge no validated scales exist for sedation measurements in elderly patients with late-stage MND. The modified RASS scale we used provides an objective measurement tool that allows measurement of both sedation and agitation. Further to this, we realise that sedation depth does not necessarily reflect patient acceptance or operator satisfaction. When sedation depth can be reliably predicted, further studies may also use acceptance scales to investigate the optimal sedation depth for this group of patients.[29]

We used a midazolam preparation developed especially for intranasal administration because it had been shown to have fast and predictable pharmacokinetics.[16] The low pH and the high volume of standard intravenous formulations make intranasal administration an uncomfortable, even painful option, requiring co-administration of lignocaine. The preparation we used has been specifically designed to minimise discomfort after intranasal administration. It has a higher pH and is more concentrated than standard intravenous preparations which are administered intranasally. Alternative routes of administration such as the buccal and rectal routes are available and effective, but both have been shown to result in a longer time to

maximum plasma concentration and lower bioavailability compared to intranasal administration.[30,31]

The following limitations must also be taken into account when interpreting the results of this study. Firstly, this was an observational study. No randomisation was performed, and no placebo group was included. We considered it unethical to perform a placebo controlled study pertaining to fear and agitation in vulnerable elderly people lacking the capacity to consent. Secondly, the group size is relatively small which limits the generalisability to some extent and it prevents us from making any definitive statement about the safety of this use of midazolam. In light of this small group size, we have limited ourselves to mainly descriptive statistics and have performed the necessary assumption tests for the regression analysis. Furthermore, the number of covariates in our analysis was limited to 3, which is compliant with the recommendation of a maximum of n/10, where n is the number of study subjects.

The aim of the study was to investigate whether intranasal midazolam would enable dentists to safely treat geriatric patients in their own environment and to spare them disturbing hospital visits and the accompanying agitating medical interruptions of their lives. There is no doubt that in the foreseeable future greater numbers of patients will require a solution for their inability to tolerate necessary dental or medical treatments, and procedural sedation may allow them to be treated in the comfort of their own environment. In the current study, only extractions and cleaning treatments were performed. Procedural sedation may, however, also become a useful tool to facilitate restorative treatments or small medical interventions. It is important for elderly people to retain their own dentition and to keep this dentition in good shape because maintaining a natural dentition has important consequences for physical and psychosocial wellbeing.[9,10]

The results of this study suggest that intranasal midazolam can be a viable option for this purpose in fearful and agitated MND patients. The wide variety in sedation depths without readily available predictors is, however, a safety concern. We have not identified a significant relationship between sedation depth and age, weight or co-medication and as yet no studies exist to guide the titration of intranasal midazolam in this patient group. Intranasal midazolam should thus be used with caution in geriatric patients living in nursing homes. The possibility to titrate intranasal midazolam to a safe and adequate sedation depth is an area in which further research is needed because currently there is insufficient pharmacological information to guide more adaptable dosing regimens for this particular age group.

In conclusion, 5 mg intranasal midazolam allows uncooperative geriatric patients suffering from major neurocognitive disorders such as Alzheimer's disease to be treated in the comfort of their own environment. Caregivers need to be aware, however, that they are striking a balance between the desired level of sedation and the required safety standards.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

AUTHORS CONTRIBUTIONS

We declare that all listed authors have made substantial contributions to: the research design, or the acquisition, analysis or interpretation of data, and to drafting the paper or revising it critically, and that all authors have approved the submitted version. We also declare that nobody who qualifies for authorship has been excluded from the list of authors. The study was conceptualised by CB and AV. The data collection was done by CB and AV. The analysis of the data was done by CB, AV and AA, who also interpreted the results and wrote the manuscript. All authors reviewed the final draft of the manuscript.

DATA AVAILABILITY STATEMENT

The data are available through the corresponding author.

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REFERENCES

1. Alzheimer Nederland. Factsheet alzheimer. https://www.alzheimer-nederland.nl/sites/default/files/directupload/factsheet-dementie-algemeen.pdf. Updated 2017. Accessed 08/07:2018.
2. WHO. Dementia. Dementia Web site. https://www.who.int/news-room/fact-sheets/detail/dementia. Published 9/19/2019. Updated. 2019. Accessed 4/12:2020.
3. Noble JM, Scarmeas N, Papapanou PN. Poor oral health as a chronic, potentially modifiable dementia risk factor: review of the literature. *Curr Neurol Neurosci Rep*. 2013;13(10):384.
4. Delwel S, Binnekade TT, Perez RS, Hertogh CM, Scherder EJ, Lobbezoo F. Oral health and orofacial pain in older people with dementia: a systematic review with focus on dental hard tissues. *Clin Oral Investig*. 2017;21(1):17-32.
5. Hoeksema AR, Vissink A, Raghoebar GM, et al. Oral health in care-dependent elderly: an inventory in a nursing home in the north of the netherlands. *Ned Tijdschr Tandheelkd*. 2014;121(12):627-633.
6. Cohen-Mansfield J, Lipson S. The underdetection of pain of dental etiology in persons with dementia. *Am J Alzheimers Dis Other Demen*. 2002;17(4):249-253.
7. Chen X, Clark JJ, Naorungroj S. Oral health in nursing home residents with different cognitive statuses. *Gerodontology*. 2013;30(1):49-60.
8. Rolim Tde S, Fabri GM, Nitrini R, et al. Evaluation of patients with Alzheimer's disease before and after dental treatment. *Arq Neuropsiquiatr*. 2014;72(12):919-924.
9. Müller F, Shimazaki Y, Kahabuka F, Schimmel M. Oral health for an ageing population: the importance of a natural dentition in older adults. *Int Dent J*. 2017;67:7-13.
10. Kossioni AE, Hajto-Bryk J, Maggi S, et al. An expert opinion from the European college of gerodontology and the European geriatric medicine society: European policy recommendations on oral health in older adults. *J Am Geriatr Soc*. 2018;66(3):609-613.
11. Delwel S, Scherder EJA, de Baat C, et al. Orofacial pain and its potential oral causes in older people with mild cognitive impairment or dementia. *J Oral Rehabil*. 2019;46(1):23-32.
12. Tonsekar PP, Jiang SS, Yue G. Periodontal disease, tooth loss and dementia: is there a link? A systematic review. *Gerodontology*. 2017;34(2):151-163.

13. Chalmers JM, Levy SM, Buckwalter KC, Ettinger RL, Kambhu PP. Factors influencing nurses' aides' provision of oral care for nursing facility residents. *Spec Care Dentist*. 1996;16(2):71-79.
14. Rignell L, Mikati M, Wertsen M, Hagglin C. Sedation with orally administered midazolam in elderly dental patients with major neurocognitive disorder. *Gerodontology*. 2017;34(3):299-305.
15. Zorginstituut Nederland. Farmacotherapeutisch kompas:Midazolam. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/m/midazolam#eigenschappen. Accessed 04/06, 2020.
16. Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. *Br J Clin Pharmacol*. 2002;53(5):501-507.
17. Musani I, Chandan N. A comparison of the sedative effect of oral versus nasal midazolam combined with nitrous oxide in uncooperative children. *Eur Arch Paediatric Dent*. 2015;16(5):417-424.
18. Ransford N, Manley M, Lewis D, et al. Intranasal/intravenous sedation for the dental care of adults with severe disabilities: a multicentre prospective audit. *Br Dent J*. 2010;208(12):565-569.
19. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. 2009;41(2):67-76.
20. Bell GD, Spickett GP, Reeve PA, Morden A, Logan RF. Intravenous midazolam for upper gastrointestinal endoscopy: a study of 800 consecutive cases relating dose to age and sex of patient. *Br J Clin Pharmacol*. 1987;23(2):241-243.
21. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond agitation-sedation scale (RASS). *JAMA*. 2003;289(22):2983-2991.
22. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344.
23. ASA Committee on Quality Management and Departmental Administration. Continuum of depth of sedation: Definition of general anesthesia and levels of Sedation/Analgesia. www.asahq.org Web site. https://www.asahq.org/standards-and-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedationanalgesia. Published 10/23/2019. Updated 2019. Accessed 06/29, 2020.
24. Knape JT. Richtlijn sedatie en/of analgesie (psa) op locaties buiten de operatiekamer. *IGJ*. 2012;45-78.
25. Albrecht S, Ihmsen H, Hering W, et al. The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clin Pharmacol Ther*. 1999;65(6):630-639.
26. Nordt SP, Clark RF. Midazolam: a review of therapeutic uses and toxicity. *J Emerg Med*. 1997;15(3):357-365.
27. Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69(2):213-217.
28. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of Alertness/Sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10(4):244-251.
29. Collado V, Hennequin M, Faulks D, et al. Modification of behavior with 50% nitrous oxide/oxygen conscious sedation over repeated visits for dental treatment a 3-year prospective study. *J Clin Psychopharmacol*. 2006;26(5):474-481.
30. Clausen T, Wolff J, Hansen P, et al. Pharmacokinetics of midazolam and alpha-hydroxy-midazolam following rectal and intravenous administration. *Br J Clin Pharmacol*. 1988;25(4):457-463.
31. Schwagmeier R, Alincic S, Striebel H. Midazolam pharmacokinetics following intravenous and buccal administration. *Br J Clin Pharmacol*. 1998;46(3):203-206.

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