FULL-LENGTH ORIGINAL RESEARCH

Intranasal midazolam during presurgical epilepsy monitoring is well tolerated, delays seizure recurrence, and protects from generalized tonic–clonic seizures

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Summary

Objective: To evaluate the tolerability and efficacy of the ictal and immediate postictal application of intranasal midazolam (in-MDZ) in adolescents and adults during video–electroencephalography (EEG) monitoring.

Methods: Medical records of all patients treated with in-MDZ between 2008 and 2014 were reviewed retrospectively. For each single patient, the time span until recurrence of seizures was analyzed after an index seizure with and without in-MDZ application. To prevent potential bias, we defined the first seizure with application of in-MDZ as the in-MDZ index seizure. The control index seizure was the preceding, alternatively the next successive seizure without application of in-MDZ.

Results: In total, 75 epilepsy patients (mean age 34 ± 14.7 years; 42 male, 33 female) were treated with in-MDZ (mean dose 5.1 mg). Adverse events were observed in four patients (5.3%), and no serious adverse events occurred. The median time after EEG seizure onset before administration of in-MDZ was 2.17 min (interquartile range [IQR] 03.82; range 0.13–15.0 min). Over the next 12 h after in-MDZ, the number of seizures was significantly lower ($p = 0.031$). The median seizure-free interval was significantly longer following treatment with in-MDZ (5.83 h; IQR 6.83, range 0.4–23.87) than it was for those with no in-MDZ treatment (2.37 h; IQR 4.87, range 0.03–21.87; $p = 0.015$). Conversely, the likelihood of the patient developing a subsequent seizure was four times higher (odds ratio [OR] 4.33, 95% confidence interval [CI] 1.30–14.47) in the first hour and decreased gradually after 12 h (OR 1.5, 95% CI 1.06–2.12). The occurrence of generalized tonic–clonic seizures was lower in the in-MDZ group in the 24-h observation period (OR 4.67, 95% CI 1.41–15.45; $p = 0.009$).

Significance: Ictal and immediate postictal administration of in-MDZ was well tolerated and not associated with serious adverse events. We demonstrated a significant reduction of subsequent seizures (all seizure types) for a 12 h period and of generalized tonic–clonic seizures for 24 h following in-MDZ.

KEY WORDS: Intranasal, Midazolam, Seizure control, Emergency, Epilepsy, Benzodiazepine.

Lara Kay is doing her doctoral thesis at Epilepsy Center Hessen, Philipps-University Marburg.

The management of repetitive and prolonged seizures requires a rapid, safe, and easy administration of anticonvulsive agents such as diazepam, lorazepam, or midazolam. Intravenous lorazepam is considered the drug of choice, and its efficacy and safety have been proven in different settings.[1–3] However, obtaining peripheral venous access may be difficult in a patient having a seizure. Furthermore, the intravenous application of lorazepam is not feasible for a layperson in an out-of-hospital setting and may even be difficult for health care professionals during seizures.

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Key Points

- Periictal administration of intranasal midazolam is readily carried out, well tolerated, and not associated with serious adverse events.
- Intranasal midazolam reduces recurrence of all seizure types within 12 h of administration.
- There is a significant reduction of generalized tonic–clonic seizures for 24 h following intranasal midazolam.
- Regular on-demand use during presurgical monitoring might prevent generalization of seizures and associated morbidity and mortality.

Rectal administration of diazepam is an alternative route and has been established for home use for decades.[4] However, rectal emergency treatment is not universally accepted and is associated with negative psychosocial effects, such as embarrassment, social fear, shame, and increased stigmatization.[5,6]

Alternatives include intranasal application and buccal application of midazolam, the latter of which has been approved for children and adolescents in parts of Europe. The intranasal application of midazolam is an emerging technique for periprocedural sedation and for acute seizure control in children, as it allows a rapid and easy administration without need for additional medical training.[7–11]

At present, some studies have compared intranasal midazolam (in-MDZ) with intravenous diazepam[12–14] for acute seizures in children and with rectal diazepam[15,16] examining home treatment of seizures. In the latter studies, no differences in efficacy or complications have been observed between treatment groups, but caregivers have conveyed more satisfaction with in-MDZ and have reported that it was easier to administer.[15,16]

We have used concentrated midazolam nasal spray since 2008 in the video–electroencephalography (EEG) monitoring unit of our tertiary epilepsy center for seizure termination and the prevention of seizure clusters and generalized tonic–clonic seizures (GTCS) during video-EEG monitoring. To gain a better understanding of the effects of in-MDZ on seizures and of any adverse effects, we retrospectively analyzed the data of all patients who were ictally or immediately postictally treated with in-MDZ.

Table 1. Formulation for preparation of 5 ml of intranasal midazolam

Midazolam hydrochloride[a]	99.25 mg
Sodium chloride	32 mg
Benzalkonium chloride	0.5 mg
Sodium EDTA	5 mg
Aqua purificata	to 5 ml

[a]Midazolam hydrochloride 99.25 mg ≙ midazolam 89.3 mg.

Methods

The medical records of all patients treated with in-MDZ between August 2008 and 2014 at the Epilepsy Center Hessen in Marburg were reviewed, and a standardized questionnaire was used to collect data on epilepsy syndrome, including information regarding the following: etiology, anticonvulsant treatment, seizure frequency, treatment suc-

Figure 1.
Ready-to-use nasal spray for midazolam application. The atomization device delivers a reproducible and standardized dosing of 2.5 mg midazolam in 140 μl solution per puff. The low puff volume ensures rapid absorption via the nasal mucosa.
Epilepsia © ILAE

cess, and side effects upon treatment with in-MDZ. We used the definition of seizures and epilepsies following the revised terminology and classification of 2010.[17] Seizures were also classified according to the semiologic seizure classification.[18] The study was granted approval by the local ethics committee. This study was not sponsored or funded by any company.

The concentrated midazolam nasal spray was manufactured and supplied by the central pharmacy of the university hospitals of Giessen and of Marburg. The formulation was composed as described previously,[19–23] and adapted for in-house use. (For the formulation details, refer to Table 1). The nasal spray contained midazolam hydrochloride in a mixture of water at a pH 3.3 (adjusted with 1 N hydrochloride acid). Benzalkonium chloride with sodium ethylenediaminetetraacetic acid (EDTA) was added as an antimicrobial preservative. The nasal spray can be stored at room temperature with light protection for up to 3 months. The solution remained clear and colorless. A ready-to-use nasal spray applicator (Zscheile & Klinger, Hamburg, Germany) delivered an equivalent dose of 2.5 mg midazolam per puff (140 µl) (Fig. 1). For acute seizure treatment, one puff of in-MDZ was administered in each nostril, amounting to a total of 5 mg midazolam. In selected patients, up to four puffs were applied. In-MDZ was prescribed by the attending physician p.r.n. (as needed) in case of recurrent or prolonged seizures to be administered by trained technicians.

Because the total midazolam content in one nasal spray exceeded 15 mg, the spray had to be considered as a marketable and prescribable drug under Appendix III of German narcotic law. Therefore, the midazolam nasal spray must be prescribed personally for each patient, and each prescription must be documented. Therefore, all patients treated with in-MDZ were easily and completely identified from the hospital's mandatory narcotic drug documentation.

EEG, electrocardiography (ECG), and video data were reviewed in patients who underwent video-EEG monitoring while in-MDZ was administered. Patients were monitored with scalp electrodes according to the 10–20 international system.[24] Sphenoidal electrodes or intracranial electrodes were placed in selected patients when clinically indicated. Heart rate analysis was based on the co-registered ECG tracing.

We used a study design with an intraindividual comparison to evaluate potential prevention of further seizures and clusters. We analyzed for each single patient the time span until recurrence of seizures after an index seizure with and without in-MDZ application. We also evaluated the number of patients who had seizures within 24 h after an index seizure with and without in-MDZ application. To prevent potential bias, we defined the first seizure with a periictal application of in-MDZ as the in-MDZ index seizure. The control index seizure was the preceding seizure without an application of in-MDZ to minimize bias due to different anticonvulsant medication. If there was no preceding seizure without an application of in-MDZ, the next successive seizure was defined as the control index seizure.

Data were analyzed using PASW Statistics 22 (SPSS Inc., Chicago, IL, U.S.A.). Comparisons between groups

Table 2. Demographic and clinical characteristics

	% (n)
Patients treated with in-MDZ (n = 75)	
Age in years[a]	35.1 ± 14.7
Age at epilepsy onset[a]	18.9 ± 14.6
Epilepsy duration in years[a]	16.1 ± 13.4
Epilepsy syndrome	
Focal epilepsy	93.3 (70)
Right hemisphere	38.6 (27)
Left hemisphere	44.3 (31)
Bilateral	17.1 (12)
Idiopathic generalized epilepsy	6.7 (5)
History of status epilepticus	
No	92.0 (69)
Yes	8.0 (6)
Etiology or risk factors	
Not known	25.3 (19)
Epilepsy in family	14.6 (11)
Febrile convulsions	12.0 (9)
Pre- or perinatal complications	12.0 (9)
Tumor	9.3 (7)
CNS infections	8.0 (6)
Traumatic brain injury	6.7 (5)
Vascular lesion	4.0 (3)
Other	8.0 (6)
Imaging findings	
No appreciable disease	33.3 (26)
Hippocampal sclerosis	17.9 (14)
Parenchymal lesion	1.5 (9)
Vascular lesion	9.0 (7)
Focal dysplasia	7.7 (6)
Tumor	6.4 (5)
Previous neurosurgery	6.4 (5)
Other	7.7 (6)
Comorbidities (n = 73)	
Abuse of nicotine	21.9 (16)
Arterial hypertension	15.1 (11)
Adipositas	13.6 (10)
Depression	12.3 (9)
Endocrine disease	11.0 (8)
Intellectual disability	9.6 (7)
Psychiatric conditions	5.4 (4)
Other	11.0 (8)
Anticonvulsants	
Levetiracetam	25.7 (43)
Lamotrigine	19.1 (32)
Valproate	13.8 (23)
Lacosamide	10.8 (18)
Oxcarbazepine	7.2 (12)
Topiramate	4.8 (8)
Carbamazepine	4.8 (8)
Other	13.8 (23)

[a]Mean ± standard deviation.

Table 3. Seizure recurrence in patients with and without periictal application of intranasal midazolam as per protocol analysis

	Index seizure with in-MDZ treatment				Index seizure without midazolam				
Time (h)	Seizure remission number of patients	Seizure recurrence number of patients	Patients with GTCS	Total number seizures (GTCS)	Seizure remission number of patients	Seizure recurrence number of patients	Patients with GTCS	Total number seizures (GTCS)	p-Value
1	60	3	1	4 (1)	50	13	5	15 (5)	0.016
2	56	7	1	12 (1)	42	21	7	27 (8)	0.005
3	55	8	1	15 (1)	33	30	10	41 (11)	<0.001
4	50	13	1	22 (1)	32	31	11	53 (12)	0.001
5	47	15	2	32 (2)	28	35	11	60 (13)	0.001
6	46	16	3	36 (4)	26	37	11	64 (13)	<0.001
9	37	24	3	53 (4)	24	37	10	76 (13)	0.030
12	35	26	3	70 (4)	22	39	10	91 (13)	0.029
24	21	32	3	124 (4)	13	47	13	147 (16)	0.061

were performed using the Wilcoxon-Mann-Whitney test for nonparametric (time to next seizure) or Student's *t*-test test for parametric values (heart rate). Chi-square tests were performed to assess the distribution of patients with seizures between the two groups. To increase statistical accuracy, we analyzed the measurements by applying a continuity correction factor, which was needed because we evaluated around 60 patients. The time between seizures was depicted with the Kaplan-Meier methodology in an intention-to-treat analysis, and the log-rank test was performed for comparison between the in-MDZ and the control group. All p-values were two sided and were regarded as statistically significant <0.05.

Patients and Results

Patient characteristics

Seventy-five patients were treated with in-MDZ during video-EEG monitoring. Their mean age was 35.1 years (standard deviation [SD] 14.7, range 12–70); 56% (n = 42) of them were male, and 44% (n = 33) were female. On average, epilepsy onset was at the age of 18.9 years (SD 14.7, range 0–69 years). At the time of their admission, they had had epilepsy for a mean of 16.1 years (SD 13.4, range 0.7–58 years). Prior to the video-EEG monitoring, the patients had failed a mean number of 2.3 antiepileptic drugs (AEDs; SD 2.5, range 0–12 failed AEDs) and were taking a mean number of 2.2 AEDs (SD 0.9, range 2–5 AEDs) at admission to video-EEG monitoring. Only 11 patients (14.7%) were on AED monotherapy, whereas 62 (82.7%) received a polytherapy. Two patients had discontinued their medication prior to admission. (For details of their anticonvulsant usage, see Table 2). In total, 86.7% (n = 65) of these patients had drug-resistant epilepsy, as defined by the International League Against Epilepsy (ILAE).[25] A history of status epilepticus was present in six patients (8%). All patients were admitted with a presumed diagnosis of focal epilepsy, and this diagnosis was confirmed in 93.3% (n = 70), whereas 6.7% (n = 5) were finally diagnosed with idiopathic generalized epilepsy. The neurologic examination was unremarkable in 76% (n = 57) of the patients; 21.3% (n = 16) had minor and 2.6% (n = 2) had major neurologic impairments requiring constant nursing. In total, 43 (57.3%) of the 75 patients had been diagnosed with other medical conditions in addition to epilepsy. (For details of epileptic syndrome—etiology, risk factors, imaging, and comorbidities—see Table 2).

Characteristics and safety of in-MDZ applications during video and EEG monitoring

The average duration of video and EEG recordings was 102 h (SD 36.6, range 38–189 h), during which in 96% (n = 72) of the patients, anticonvulsants were tapered off. One patient was monitored for 2 h due to an ongoing status epilepticus.

Overall, in-MDZ was administered 110 times: 87 times (79.1%) in-MDZ was given during a seizure with 19 administrations within the generalized tonic–clonic phase or within the 15 s prior the onset of the generalized tonic–clonic phase. In-MDZ was given 22 times (20%) after EEG seizure cessation. One patient received in-MDZ during status epilepticus. Twenty-two patients (29.3%) received in-MDZ two or more times during their monitoring. The median dose of administered in-MDZ was 5 mg (range 2.5–10 mg, mean 5.1 mg, SD 1.2), corresponding to one puff of the nasal spray per nostril. In selected patients, lower doses (2.5 mg [n = 4]) or higher doses (7.5 mg [n = 2] or 10 mg [n = 3]) were applied due to body weight or age.

Administration of in-MDZ occurred a median of 2.17 min (interquartile range [IQR] 03.82, range 0.13–15.0 min) after EEG seizure onset and 2.03 min (IQR 03.62, range 0.13–14.80 min) after clinical seizure onset. In-MDZ was given in less than a minute after EEG seizure onset 20 times.

In total, adverse reactions were recorded in four patients (5.3%; 4/75) during the 110 applications of in-MDZ. In

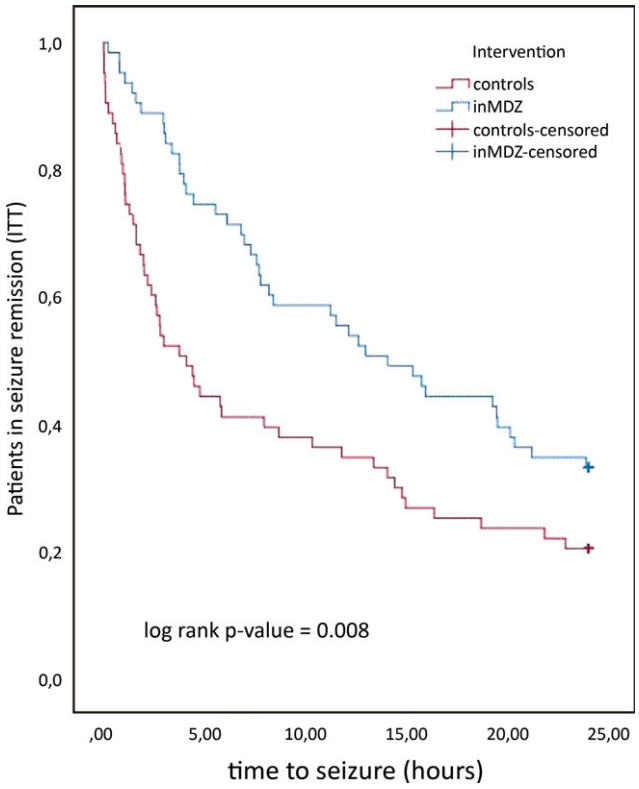

Figure 2.
Time to seizure recurrence after index seizure with or without application of intranasal midazolam (in-MDZ) for an observation period of 24 h as per intention-to-treat analysis.
Epilepsia © ILAE

three patients, nasal irritations occurred. In one patient, the administration was delayed by the patient's ictal automatisms and head turning. We did not observe any respiratory or circulation difficulties due to administration of in-MDZ. Analysis of preictal, immediate, and 10-min-postictal heart rates showed no significant changes between seizures with administration of in-MDZ and without (see Table S1).

Prevention of further seizures and clusters by in-MDZ

To evaluate the prevention of further seizures and clusters for a postictal period of 24 h, we compared pairs of seizures in each single patient, with and without administration of in-MDZ. A comparison was feasible in 63 patients. Eight patients were excluded because they received in-MDZ during every seizure and four because they had seizure clusters without the possibility of delineating single seizures (n = 2), continuous spiking patterns (n = 1), or status epilepticus (n = 1). The index seizures with and without administration of in-MDZ did not differ regarding generalization (in-MDZ-group: 19/63; control-group: 13/63; p = 0.26). In 42 patients, the control index seizure preceded the in-MDZ index seizure by a median time distance of 3.3 h (IQR 13.9, range 0.03–181.5 h), whereas in 21 patients, the control index seizure occurred in a median of 7.7 h (IQR 12.4; range 0.82–54.9 h) after the in-MDZ index seizure (p = 0.083).

Table 3 shows the number of patients with and without recurrence following the application of in-MDZ and without the application of in-MDZ for different points in time, analyzed as per protocol. The recurrence of seizures was significantly less frequent in patients treated with in-MDZ for the first 12 h, but there was no difference at 24 h. The likelihood of seizure recurrence without in-MDZ treatment was four times higher (odds ratio [OR] 4.33, 95% confidence interval [CI] 1.30–14.47) in the first hour and decreased gradually after 12 h (OR 1.5, 95% CI 1.06–2.12). Overall, the number of patients with GTCS was lower in the in-MDZ group in the 24-h observation period (OR 4.67, 95% CI 1.41–15.45; p = 0.009).

The median time between seizures increased significantly in patients who were treated with in-MDZ at 5.83 h (IQR 6.83, range 0.4–23.87 h), whereas the next seizure occurred within a median time of 2.37 h (IQR 4.87, range 0.03–21.87 h) without administration of in-MDZ (p = 0.015).

Using the Kaplan-Meier method, we depicted the time to seizure reoccurrence for both groups as per intention-to-treat analysis. Figure 2 shows the significant proportion of seizure-free patients in the in-MDZ group (log-rank p-value: <0.008).

Discussion

This study provides evidence that ictal and immediate postictal administration of in-MDZ is a well-tolerated procedure and prevents subsequent seizures for a 12-h period and especially GTCS for a 24-h period following the application of in-MDZ.

Previous studies[15,16] comparing in-MDZ with the rectal application of diazepam did not show a difference in the time until seizure cessation. de Haan et al.[16] analyzed the treatment of prolonged seizures in a residential epilepsy center. Among 21 adult patients with medically refractory epilepsy, their caregivers treated 124 seizure exacerbations, alternatively with 10 mg of rectal diazepam and 10 mg of in-MDZ. Two or three treatments with each medication were evaluated for each patient, and no difference was identified in efficacy or time to effect between the two drugs. Both caregivers and patients preferred the nasal spray over the rectal solution.[16]

Holsti et al.[12] investigated the administration of midazolam with a mucosal atomization device in seizures lasting more than 5 min. Their primary outcome measure was total seizure time after medication administration. Overall, the study medication was administered during a child's seizure in 92 cases, 50 times using in-MDZ (mean dose 0.2 mg/kg) and 42 times using a rectal diazepam (mean dose 0.41 mg/kg). The median time from medication administration to seizure cessation was 3.0 min for in-MDZ and 4.3 min for rectal diazepam. The difference of 1.3 min did not reach statistical

significance (95% CI 0.0–3.5 min; p = 0.09). Repeated seizures within 12 h occurred only in one patient (2%) per treatment group. In our evaluation, repeated seizures occurred 28 times (45%) within 12 h of administration of in-MDZ and significantly less than the 39 times (63%) without in-MDZ. The vast difference in the number of patients who had repeated seizures in our study was due to the reduction of anticonvulsants in 96% of the patients. The recording of a representative number of habitual seizures is an essential part of a presurgical evaluation; however, seizure clusters, status epilepticus, and GTCS can be associated with increased morbidity and mortality.[26,27] In-MDZ prevents the occurrence of GTCS within 24 h of administration, whereas seizures without generalization persist in a substantial number of patients. Accordingly, the administration of in-MDZ may prevent GTCS and associated discomfort and injuries for the next 24 h while still allowing minor seizure to be recorded during that time.

Previous investigations have demonstrated a favorable pharmacokinetic profile of in-MDZ in healthy volunteers without serious complications.[19] In one study, local irritations with in-MDZ, such as sneezing, coughing, dry mouth, and tear flow were reported in 17 (29%) of 59 events,[13] whereas nasal irritation was documented in only four patients (5.3%). Reports of local irritation were due to the acidic midazolam solutions and represent an expected adverse reaction. The low incidence of nasal irritations may be due to underreporting within a postictal state of reduced vigilance. In addition, the retrospective design of this study may result in an underreporting and underrecording of adverse experiences. Overall, the application of in-MDZ was well tolerated, and none of our patients experienced respiratory depression due to in-MDZ. We did not quantify sedation, as this might be caused by the seizures themselves, so attributing such to in-MDZ versus a seizure remains debatable. Other studies examining the use of in-MDZ in patients also reported a good level of tolerability.[12–16,28]

Furthermore, nasal midazolam spray is easy to employ, and it can be delivered from any position. Even during a seizure, it takes little time to administer the dose, and patients do not need to be restrained. These findings are in line with caregivers' and patients' opinions from other studies,[15,16] indicating that in-MDZ was easier to use than is rectal diazepam. In our study, only in one patient was administration delayed by the patient's ictal automatisms and head turning. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART)[29] demonstrated the importance of a reliable and rapid administration of midazolam in status epilepticus. The chosen, early administration of intramuscular midazolam was the best option for the prehospital treatment of status epilepticus by paramedics.[29] The authors concluded that the RAMPART results should be taken to be generally supportive of nonintravenous midazolam administration.[30]

The strength of this study is its aim to compare the time between seizures in a single patient after receiving in-MDZ to the time in a control seizure without in-MDZ. The investigation of in-MDZ under controlled conditions of video-EEG monitoring is novel and ensures excellent data quality. Also all technicians (n = 5) were well-trained in the administration of the nasal spray, ensuring a high quality of delivery. We were able to exactly define EEG, clinical seizure onset, and cessation in relation to the administration of in-MDZ. For the evaluation of the effects of in-MDZ, an EEG follow-up of up to 24 h was available in most cases. In contrast to studies performed in a home setting and relying on the observations of lay persons, we could detect all seizures occurring during the follow-up, which might also explain the high number of seizure recurrences in the in-MDZ group. Studies in a home setting have reported difficulties in exact determination of seizure onset and cessation, and such reports also have a recall bias.[15,16]

Due to the retrospective design, this study has inherent weaknesses as we were not able to randomize or blind the administration of in-MDZ. Although we protocolled in detail the delivery of in-MDZ, and the administration and temporary discontinuation of AEDs, we did not systematically obtain serum levels. We, therefore, cannot exclude the possibility that an anticonvulsant effect was not identical for the follow-up periods after the index seizures. However, the rather short median time distance–of 3.3 to 7.7 h–between the index seizures suggests that the background effect of the AEDs was similar for both index seizures in a single patient.

Early treatment of prolonged seizures reduces morbidity and mortality associated with seizure activity and may prevent the development of cost-intensive status epilepticus.[31] Prehospital use of in-MDZ may be a less expensive and a nonstigmatizing alternative for the acute treatment of seizures. A cost-effectiveness study on oromucosal midazolam (Buccolam) for the treatment of prolonged acute convulsive seizures in children and adolescents (<18 years) evaluated the use in the context of treatment pathways in seven European countries.[32,33] An efficacy and effectiveness advantage over rectal diazepam and other medications, such as buccal lorazepam and unlicensed buccal midazolam, was achieved.[32] This evaluation of cost-effectiveness demonstrated potential cost savings due to a prehospital treatment of prolonged seizures, which might be comparable for in-MDZ and needs further attention.

Conclusions

In-MDZ might be an effective, safe, and easily applicable treatment for acute seizures. To date, no commercial preparation is available, so individual prescriptions have to be used. Our study confirms the efficacy of in-MDZ for the reduction of seizure recurrences within 12 h of administration. Larger and randomized studies are warranted to confirm our results. Regular on-demand use of in-MDZ should be considered in patients undergoing video-EEG monitoring to prevent the generalization of seizures and associated

morbidity and mortality while anticonvulsants are temporally discontinued.

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Disclosure of Conflict of Interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Periictal heart rate measurements in beats per minute.