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# Intranasal Midazolam versus Rectal Diazepam for the Management of Canine Status Epilepticus: A Multicenter Randomized Parallel-Group Clinical Trial

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**Background:** Intranasal administration of benzodiazepines has shown superiority over rectal administration for terminating emergency epileptic seizures in human trials. No such clinical trials have been performed in dogs.

**Objective:** To evaluate the clinical efficacy of intranasal midazolam (IN-MDZ), via a mucosal atomization device, as a first-line management option for canine status epilepticus and compare it to rectal administration of diazepam (R-DZP) for controlling status epilepticus before intravenous access is available.

**Animals:** Client-owned dogs with idiopathic or structural epilepsy manifesting status epilepticus within a hospital environment were used. Dogs were randomly allocated to treatment with IN-MDZ (n = 20) or R-DZP (n = 15).

**Methods:** Randomized parallel-group clinical trial. Seizure cessation time and adverse effects were recorded. For each dog, treatment was considered successful if the seizure ceased within 5 minutes and did not recur within 10 minutes after administration. The 95% confidence interval was used to detect the true population of dogs that were successfully treated. The Fisher's 2-tailed exact test was used to compare the 2 groups, and the results were considered statistically significant if $P < .05$.

**Results:** IN-MDZ and R-DZP terminated status epilepticus in 70% (14/20) and 20% (3/15) of cases, respectively ($P = .0059$). All dogs showed sedation and ataxia.

**Conclusions and Clinical Importance:** IN-MDZ is a quick, safe and effective first-line medication for controlling status epilepticus in dogs and appears superior to R-DZP. IN-MDZ might be a valuable treatment option when intravenous access is not available and for treatment of status epilepticus in dogs at home.

**Key words:** Benzodiazepine; Dog; Emergency; Epileptic seizures.

**Abbreviations:**

| | |
|---|---|
| AED(s) | antiepileptic drugs |
| CI | confidence interval |
| CRI | continuous rate infusion |
| CSF | cerebrospinal fluid |
| DZP | diazepam |
| EEG | electroencephalogram |
| ICU | intensive care unit |
| IN | intranasal |
| IVETF | International Veterinary Epilepsy Task Force |
| MAD | mucosal atomization device |
| MDZ | midazolam |
| MRI | magnetic resonance imaging |
| R | rectal |
| VAS | visual analogue scale |

Emergency epileptic seizures, including status epilepticus and severe cluster seizures, commonly occur in dogs either at home or during hospitalization.[1,2] Status epilepticus can be caused by toxic and metabolic causes or structural brain disease. It can also occur as a manifestation of idiopathic epilepsy,[3] with an estimated 20–60% of affected dogs experiencing at least 1 episode of status epilepticus during their lifetime.[2,4]

Status epilepticus is a life-threatening condition in dogs with an estimated case fatality rate of 25.3–38.5%[5,6] and requires immediate management in order to avoid primary and secondary permanent damage to the brain[7–11] or other severe systemic complications such as hyperthermia, acidosis, disseminated intravascular coagulation, and renal and cardiopulmonary failure.[12] Status epilepticus can shorten a dog's lifespan

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by 2 years due to the increased likelihood for euthanasia.[2] Therefore, effective first-line management of emergency seizures both at home and in the hospital environment is vital and potentially life-saving.

Benzodiazepines, such as diazepam (DZP) and midazolam (MDZ), are commonly used as a first-line management option for status epilepticus in both humans and dogs[10,13–16] and can be effective at low doses.[17] Rectal (R), intranasal (IN), intramuscular (IM), buccal or sublingual administration may be useful, especially when intravenous access (IV) is not available.[18]

DZP is commonly used for the management of emergency seizures.[19–21] IV administration of DZP provides good pharmacokinetic properties[20] and is commonly used by veterinarians as a first- or second-line medication. R-DZP is a relatively easy and quick method by which owners or veterinarians can attempt to terminate acute seizures when IV access is not available. Based on pharmacokinetic studies, injectable DZP solution administered per rectum has been recommended for the management of emergency seizures in dogs.[15,21,22] However, in another study, R-DZP did not result in presumed therapeutic plasma concentrations quickly enough to be effective for the management of emergency seizures.[23] On the other hand, in 1 clinical trial, R-DZP was considered effective for treating canine generalized cluster seizures.[24] Pharmacokinetic studies indicate that MDZ, administered via IV and IM routes, might be useful to treat seizures, but that rectal application was unlikely to be effective.[25]

Several human clinical trials have been performed to evaluate IN-MDZ in children and adults with emergency seizures, with or without comparison to R-DZP. These have shown that IN-MDZ is an effective and safe medication within the hospital and home settings.[18,26–38] In dogs, only pharmacokinetic studies have been performed and showed that DZP,[20,39] MDZ,[40,41] triazolam, and flurazepam[41] were efficiently absorbed and rapidly reached maximum serum concentrations after IN administration. To our knowledge, this study is the first clinical trial to evaluate the efficacy of IN administration of a benzodiazepine in dogs with status epilepticus. The primary objective of this study was to evaluate the clinical efficacy of IN-MDZ as a first-line management option for status epilepticus and compare IN-MDZ to the widely used R-DZP for controlling emergency seizures when there is no IV access. Toward that goal, a nasal mucosal atomization device (MAD) (Fig 1), which converted the liquid drug into a fine mist, was used to effectively deliver the MDZ into the nasal cavity. The study was performed within a hospital environment with the results anticipated to form the basis for using IN-MDZ for the treatment of emergency seizures at home.

## Materials and Methods

### *Evaluation of Clinical Efficacy and Safety Under Field Conditions*

The study was conducted as an open-labeled randomized parallel-group clinical trial with client-owned animals in combination with good clinical practice. It aimed to compare the clinical effectiveness of IN-MDZ, delivered by the MAD, to R-DZP, as a first-line treatment option for canine status epilepticus. The study was approved by the universities' ethical committees (reference number, CR87). An animal test certificate from the Veterinary Medicines Directorate was obtained for the use of IN-MDZ. Owner consent and information forms were provided and signed by the owners. The dogs were under constant observation and monitoring throughout the study.


**Fig 1.** Mucosal administration device (MAD). The device consists of a syringe (1 mL or 3 mL) and the, attached to the syringe, atomizer. The latter turns the medication into a fine mist (30–100 μm).

### *Study Population*

Dogs with status epilepticus without age, breed, or sex limitations were considered for enrollment in the study. Dogs with idiopathic and structural epilepsy and epilepsy of unknown origin were included, but those with known reactive seizures (i.e, metabolic or toxic causes) were excluded. Dogs with generalized or focal epileptic seizures characterized clinically by any type of motor activity (e.g, tonic, clonic, tonic-clonic, myoclonic) were included. As status epilepticus is considered a medical emergency, diagnostic investigation (if diagnosis was not already known) followed the initial treatment and stabilization of each case. Therefore, dogs were first included in the trial and treated but, if the subsequent diagnostic tests indicated reactive seizures, dogs were excluded from the study. Dogs were excluded from the study if any medications had been administered before 5 minutes of continuous epileptic seizure activity had passed.

The classification of epilepsy types defined by etiology and the classification by seizure semiology, as well as the approach for the diagnosis of idiopathic and structural epilepsy, epilepsy of unknown origin, and reactive seizures, was based on the recommendations of the International Veterinary Epilepsy Task Force (IVETF) consensus reports[42,43]. For the diagnosis of idiopathic epilepsy cases, the Tier classification was used to provide a confidence level scale.[43] Tier I and Tier III provided the weakest and strongest level of confidence for the diagnosis of idiopathic epilepsy, respectively. Status epilepticus was defined as a continuous epileptic seizure with a duration of more than 5 minutes, or 2 or more discrete epileptic seizures between which there was incomplete recovery of consciousness.[12,42]

## Procedure

The procedure is summarized as a flowchart (Fig 2). Animals arriving at the participating hospital and hospitalized patients with status epilepticus were recruited to the trial. In the first scenario, it was assumed that dogs had been already seizuring for a period longer than 5 minutes, unless indicated otherwise by the owner or referring veterinarian, and therefore, the protocol process was immediately initiated for those patients. For hospitalized patients, a different procedure was applied to ensure that only dogs for which seizure activity had been occurring for greater than 5 minutes were enrolled.[44] Specifically, the veterinary student, nurse, or technician in the ward that was observing and monitoring the patients called the on-call or onsite veterinarian after 3 minutes of observed continuous epileptic seizure activity. After 5 minutes of recorded seizure activity, or if the dog was still seizing upon the veterinarian's arrival and therefore it was assumed that 5 minutes had passed (unless indicated otherwise), the protocol process was initiated. Standardized sheets were used to record the relevant information needed to assess the outcomes. The veterinarian was responsible for preparing and administering the medication, and the nurse, technician, or student was responsible for handling the stopwatch and recording the relevant times. Recording of the appropriate information on the sheets was performed by the veterinarian or the assistant under veterinary supervision.

Dogs were assigned into the 2 groups (IN-MDZ and R-DZP) using randomized sealed envelopes. The envelopes were randomly numbered and opened following a numeric sequence starting from the envelope number one. A box containing all the materials required for the trial (i.e, atomization devices, medications, record and information sheets, randomization envelopes, stopwatch) was kept in a safe place within the intensive care unit (ICU) or similar area in each center in order to achieve easy and rapid access to the materials. MDZ injectable solution (5 mg/mL) at the dose of 0.2 mg/kg was administered intranasally by the use of the MAD. If there were excessive nasal secretions, these were quickly removed before administration using gauze. If the MDZ's administered dose was greater than 1 milliliter, then the drug was administered into the nasal cavities via both nostrils rather than only one to prevent underdosing through drug outflow. A chart reporting the total amount of the drug in milliliters (including the MAD device's dead space) per kilogram was provided to each center by the primary author with the aim of increasing the practicality and feasibility of the drug administration process. Similarly, DZP injectable solution (5 mg/mL) at the dose of 1 mg/kg was given per rectum with the aid of a standard needleless syringe that was applied as deep as possible into the rectum. A chart reporting the total dose in milliliters for dogs between 0.5 and 70 kg was also provided. After administration of the allocated drug, a catheter was placed, if not done previously, to provide IV access. All dogs were treated within a hospital environment, and the dogs were hospitalized in an ICU, or similar area, for continuous observation and monitoring for at least 1 hour after benzodiazepine administration. In all, observation was performed for at least 24 hours.

## Outcomes Assessment

***Primary Outcome.*** The aim of the study was the evaluation of the clinical efficacy of the IN-MDZ or R-DZP. This was assessed by the "seizure cessation" time (i.e, time between drug administration and seizure cessation) and "seizure relapse" time (i.e, time between seizure cessation and the next seizure). Successfulness of treatment was determined as follows:

*Successful Cases*. Treatment was considered successful if the seizure cessation time was less than 5 minutes and the seizures did not relapse or the seizure relapse time was at least 10 minutes.[30] Seizure cessation was defined as the termination and absence of visible seizure-related motor activity. No other drug was administered during that period.

*Unsuccessful Cases*. Treatment was considered unsuccessful if the seizure cessation time was greater than 5 minutes or the seizure relapse time was less than 10 minutes after the benzodiazepine administration. In this case, the protocol was no longer applicable for the patient, and IV DZP 0.5–1 mg/kg was immediately administered. Time needed for IV DZP to cease the epileptic seizures was recorded, if applicable. Further additional antiepileptic drug therapy (e.g, levetiracetam, phenobarbital, potassium bromide, propofol) was chosen at the discretion of the clinician in charge and the cascade used in each individual hospital.

***Secondary Outcomes.***

(a) "Call to doctor" time, that is, time period between the call and arrival of the veterinary surgeon. This was expressed in seconds and presented as median and range values for each group.
(b) "Doctor to drug" time, that is, time needed by the veterinary surgeon for the preparation and administration of the drug. This was expressed in seconds and presented as median and range values for each group.
(c) Complications and adverse effects. Heart rate and rhythm, respiratory rate and pattern, blood pressure (by use of Doppler), and oxygen saturation (by use of pulse oximetry) were measured 10 (T10) and 60 (T60) minutes after drug administration. Any other unusual events or adverse effects, such as dyspnoea, sneezing, vomiting, as well as sedation or ataxia that occurred within 60 minutes, were recorded. A visual analogue scale was provided to determine levels of sedation and ataxia at 0 (T0), 10 (T10), and 60 (T60) minutes after initial administration. Specifically, a 9.0 centimeter horizontal line was drawn on the record sheets by the primary author. This was used by the attending clinician to intersect a second perpendicular line to indicate the subjective severity of sedation and ataxia on 2 separate sheets. The point at "0" centimeters was considered as "bright, alert, and responsive dog" and "dog with normal gait and stance". The point at "9.0" centimeters was considered as "unconscious and nonresponsive dog" and "dog unable to stand or walk". The primary author assessed this visual analogue scale as marked by the observers based on the following assessment: "0.1–2.9", "3.0–5.9", "6.0–8.9" centimeters corresponded to mild, moderate, and severe degree of sedation or ataxia.
(d) Ease of administration. Any concerns were recorded by the attending clinician, with examples including but not limited to the administrator's fear of being bitten or injured by the seizing animal and difficulties in applying the MAD device into the nostrils or the syringe into the anus.
(e) Further information (if known or applicable), including the cause of seizures, duration of seizures before drug

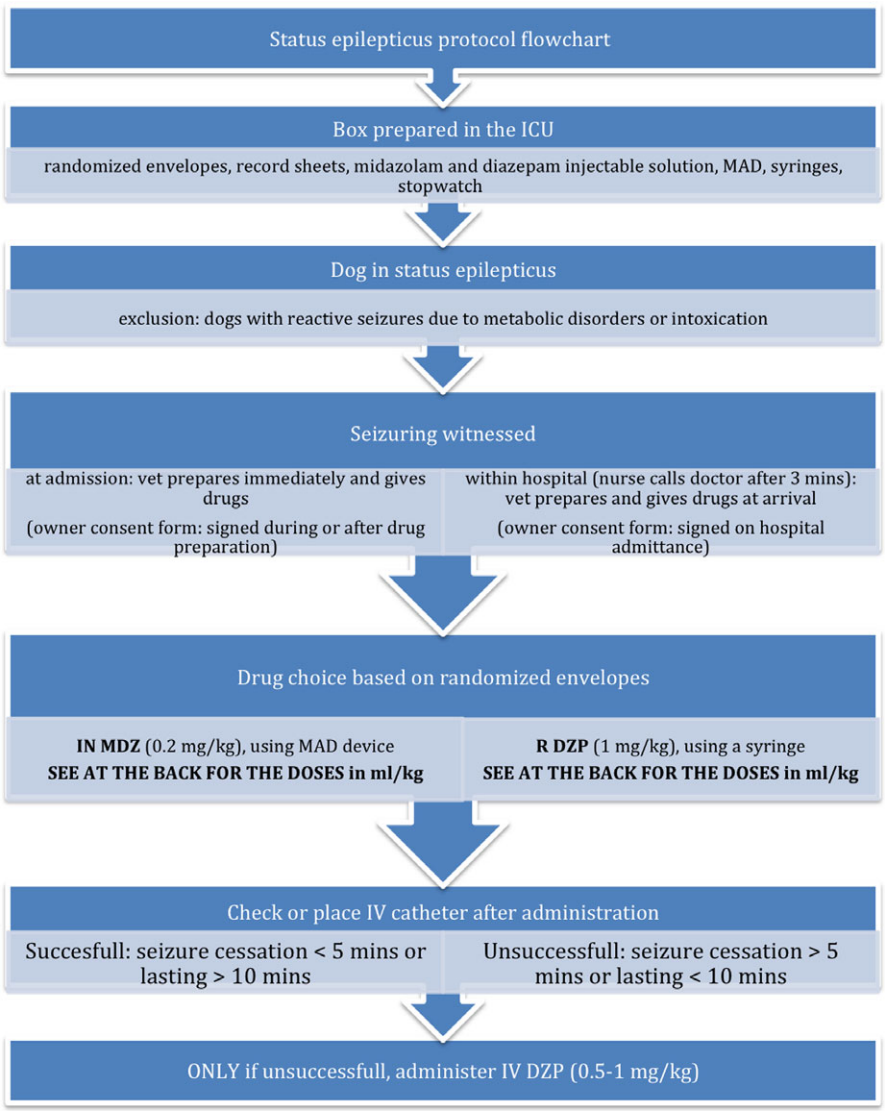


**Fig 2.** Flowchart presenting a summary of the protocol.

administration, number of previous seizures over the last 24 hours, AEDs administered before status epilepticus as well as during between 10 and 60 minutes after the IN-MDZ or R-DZP administration, was recorded.

### *Statistical Analysis*

The primary outcome was assessed by the number of dogs in each group for which treatment was recorded as successful. The true population of dogs in each group that were successfully treated was calculated based on the 95% confidence interval (95% CI) by standard methods.[45] The Fisher's 2-tailed exact test was used to detect statistical differences between the 2 groups. Results were considered statistically significant at a significance level of $P < .05$. Sample size calculation for an alpha cutoff of 0.05 and a power of 80% was based on the data from a relevant human-based trial[28] and resulted in 36 dogs per group. An interim analysis was also performed to assess whether or not a significant difference could be detected between the groups.

## Results

### *Signalment and Baseline Characteristics of Study Subjects*

The recruited dogs represented multiple breeds, both sexes and a wide range of ages at study entry (Table 1).

### *Disease Characterization*

Thirty-eight dogs were initially included in the trial and treated. Three of these dogs were subsequently excluded because they manifested reactive seizures due to hypoglycemia (1 dog) and presumed intoxication (2 dogs). For 2 dogs (7.4 and 8.2 years old at seizure onset), there was no confirmed diagnosis of the cause of seizures (focal structural brain lesion was suspected, but MRI and/or CSF analysis was not performed for confirmation). These dogs were included in the study because the history, hematology and serum biochemistry evaluation,

**Table 1.** Details of the dogs' basic characteristics in each group.

| Groups | IN-MDZ | R-DZP |
|---|---|---|
| Breed | Crossbreeds (48%), Labrador Retriever (2%), Golden Retrievers (11%), German Shepherd dogs (15%), Beagles (7%), Boxers (3%), English Setters (2%), Alaskan Malamute (2%), Border Collies (4%), Pugs (1%), and Pekingese dogs (5%) | Crossbreeds (41%), Labrador Retriever (12%), Golden Retrievers (10%), German Shepherd dogs (13%), Beagles (5%), Boxers (2%), Dogo Argentino (1%), English Setters (3%), Shetland Sheepdog (4%), Border Collies (9%) |
| Age | Median, 5.1 (range 0.5–7 years) | Median, 4.8 (range 0.9–6.8 years) |
| Sex | 12 males (60%) and 8 females (40%) | 8 males (53%) and 7 females (47%) |
| Epilepsy classification | 13 dogs (65%) with idiopathic epilepsy, 6 dogs (30%) with structural epilepsy (neoplasia, 4 dogs; MUO, 2 dogs) and 1 dog (5%) with epilepsy of unknown origin | 8 dogs (53%) with idiopathic epilepsy, 6 dogs (40%) with structural epilepsy (neoplasia, 3 dogs; MUO, 3 dogs), and 1 dog (7%) with epilepsy of unknown origin |
| Chronic/ Maintenance AEDs | 9 dogs (45%) were not receiving chronic antiepileptic medication. The remaining dogs were receiving phenobarbital monotherapy (3 dogs; 15%), phenobarbital/ potassium bromide combination therapy (2 dogs; 10%), phenobarbital/potassium bromide/levetiracetam combination (4 dogs; 20%), levetiracetam monotherapy (1 dog; 5%), imepitoin monotherapy (1 dog; 5%) | 5 dogs (33%) were not receiving chronic antiepileptic medication. The remaining dogs were receiving phenobarbital monotherapy (4 dogs; 27%), phenobarbital/potassium bromide combination therapy (5 dogs; 33%), phenobarbital/potassium bromide/ levetiracetam combination therapy (1 dog; 7%) |
| Cluster epilepsy (before occurrence of status epilepticus) | Twelve dogs (60%) | Seven dogs (47%) |

AEDs, antiepileptic drugs; DZP, diazepam; IN, intranasal; MDZ, midazolam; R, rectal.

and urinalysis showed no evidence of intoxication or metabolic disorder. Thirty-five cases were finally included in the trial (20 in IN-MDZ group and 15 in R-DZP group) and analyzed.

These cases represented dogs with idiopathic epilepsy (21/35, 60%), structural epilepsy (12/35, 34%), or epilepsy of unknown origin (2/35, 6%). The final diagnoses in cases with structural epilepsy were neoplasia (7/12, 58%) or meningoencephalitis of unknown origin (MUO) (5/12, 42%), after brain MRI and/or CSF analysis. The majority of the dogs diagnosed with idiopathic epilepsy were classified as Tier II confidence level (11/21, 52%), followed by Tier I (10/21, 48%). Thirty-three dogs presented with generalized tonic and/or clonic seizures and 2 dogs with focal (facial motor activity) status epilepticus seizure activity. The latter were allocated in the IN-MDZ group. Further details for each group are provided in Table 1.

### *Primary Outcome*

The primary outcome for each dog and treatment group is summarized in the text and provided in detail in Table 2 and Tables S1 and S2.

### *IN-MDZ Group*

For the successful cases, the median "seizure cessation" time was 47 seconds (range, 6–280). In 3/14 (21%) of the successful cases, there was no relapse of the seizures. For the remaining 11/14 (79%) of the cases, the median "seizure relapse" time was 904 seconds (range, 612–1146).

### *R-DZP Group*

For the successful cases, the median "seizure cessation" time was 214 seconds (range, 204–290). All of the successful cases relapsed. The median "seizure relapse" time was 645 seconds (range, 638–672).

### *IN-MDZ versus R-DZP*

Based on the fisher's 2-tailed exact test, there was a statistically significant difference ($P = .0059$) between the 2 groups. For the idiopathic epilepsy cases in particular, IN-MDZ was significantly more effective compared to R-DZP ($P = .018$). Therefore, dogs treated with IN-MDZ were more likely to show seizure cessation compared to dogs treated with R-DZP.

### *Secondary Outcomes*

The secondary outcomes for each dog and treatment group are summarized in the text and provided in detail in Table 2 and Tables S1, S2, and S3.

### *IN-MDZ Group*

The median "call to doctor" and "doctor to drug" time was 56 seconds (range, 12–182) and 29 seconds (range, 14–185), respectively. For the unsuccessful cases, IV DZP was administered in 3/6 (50%) of those and the median "seizure cessation" time was 45 seconds (range, 40–240). For all the cases, the most common AEDs used between 10 and 60 minutes after IN-MDZ administration were IV levetiracetam and/or IV or IM phenobarbital, followed by IV DZP

**Table 2.** Summary of the primary and secondary outcomes.

| | IN-MDZ | | | | R-DZP | | | |
|---|---|---|---|---|---|---|---|---|
| Successful cases | Total 14/20 (70%) | IE 11/13 (85%) | SE 2/6 (33%) (MUO, 0%; Neoplasia, 50%; of total number of SE cases) | EUO 1/1 (100%) | Total 3/15 (20%) | IE 2/8 (25%) | SE 1/6 (17%) (Neoplasia, 33%; of total number of SE cases) | EUO 0 (0%) |
| | 95% CI: 48–85% | | | | 95% CI: 6.6–43% | | | |
| "Seizure cessation" time (mins) (median, range) | 0.8 minutes (0.1–5) | | | | 3.5 minutes (3.4–5) | | | |
| "Seizure cessation" time (mins) after IV DZP (unsuccessful cases) (median, range) | 0.75 minutes (0.6–4) | | | | 0.5 minutes (0.3–0.9) | | | |
| "Seizure relapse" time (mins) (median, range) | 15 minutes (10–19) | | | | 10.8 minutes (10.6–11.2) | | | |
| "Call to doctor" (mins) (median, range) | 1 minute (0.2–3) | | | | 1.1 minutes (0.4–3) | | | |
| "Doctor to drug" (mins) (median, range) | 0.5 minutes (0.2–3) | | | | 0.3 minutes (0.1–0.6) | | | |
| Adverse effects (within 60 minutes of drug administration) | Severe sedation and ataxia in all dogs and a brief episode of sneezing in 7/20 (35%) dogs | | | | Severe sedation and ataxia in all dogs | | | |
| Difficulties in administration | Mild difficulties in applying the MAD in 2/20 (10%) dogs | | | | Difficulties in applying the syringe in 2/15 (13%) dogs | | | |

CI, confidence interval; DZP, diazepam; EUO, epilepsy of unknown origin; IE, idiopathic epilepsy; IN, intranasal; MDZ, midazolam; SE, structural epilepsy; R, rectal.

and constant rate infusion (CRI) MDZ. Severe sedation and ataxia were recorded for all the dogs that were worse at T10 and T60, in particular, compared to T0. No signs of respiratory (e.g, dyspnea, bradypnea, cough, cyanosis) or cardiovascular (e.g, arrhythmias, hypotension/hypertension, cardiac arrest) dysfunction were reported in any of the dogs. A brief episode of sneezing during or after administration of IN-MDZ and mild difficulties in regard to the application of the MAD were reported in a few dogs. No nasal discharge was reported before and/or during administration.

### *R-DZP Group*

The median "call to doctor" and "doctor to drug" time was 68 seconds (range, 25–180) and 16 seconds (range, 8–38). For the unsuccessful cases, IV DZP was administered in 10/12 (83%) of those and was unsuccessful in 2/10 (20%) cases. The median "seizure cessation" time after IV DZP was 32 seconds (range, 17–52). The most common AEDs used between 10 and 60 minutes after R-DZP administration were similar to the IN-MDZ group. Severe sedation and ataxia were detected for all the dogs and, as for IN-MDZ, the degree of sedation and ataxia was worse at T10 and T60 compared to at T0. No signs of respiratory (e.g, dyspnea, bradypnea, cough, cyanosis) or cardiovascular (e.g, arrhythmias, hypotension/hypertension, cardiac arrest) dysfunction were reported in any of the dogs. Difficulties during administration were reported in a few dogs in regard to insertion of the syringe into the rectum during severe tonic/clonic seizure activity.

## Discussion

The results of the present study indicate that IN administration of MDZ is likely to be an effective and safe method for short-term management of emergency seizures in dogs. In this study, IN-MDZ was significantly more effective than R-DZP for terminating status epilepticus in a hospital environment. It is likely that this finding could be extrapolated to at-home treatment of emergency seizures before hospital admittance and, as such, IN-MDZ might be a more appropriate and effective prehospital seizure management method than R-DZP.

Studies compared IN-MDZ to R-DZP in humans and showed statistically significant superiority of IN-MDZ for cessation of seizures.[18,26,28] In one study, IN-MDZ was compared to R-DZP in 23 and 22 patients, respectively, within the emergency department setting, and it was found that IN-MDZ was significantly more likely to successfully control seizure activity within the first 10 minutes compared to R-DZP.[28] In another study, IN-MDZ was compared to R-DZP in a total number of 46 children and found seizure control to be faster with IN-MDZ.[26] In a third study, IN-MDZ was compared to R-DZP in 39 and 18 children, respectively, and showed superiority of IN-MDZ over R-DZP for seizure control.[18] However, a larger study did not

demonstrate a significant difference in cessation of seizures between IN-MDZ and R-DZP.[30] Ease of administration was considered higher in IN-MDZ group in this study, although this factor is likely to be significantly different for human trials compared to canine patients. Interestingly, IN-MDZ has also been compared to IV DZP, and it was shown that both medications were effective and safe, although IV DZP was rather quicker in controlling seizures.[33,35] In a recent human systematic review/meta-analysis, non-IV administration of MDZ, including IN-MDZ, was as effective and safe as IV DZP in terminating early status epilepticus.[46] In the present study, the "seizure cessation" time of IN-MDZ (median, 47 seconds) was relatively similar to IV DZP (median, 32–45 seconds). However, this result should be interpreted with caution because IV DZP was administered only after the initial administration of IN-MDZ or R-DZP and in a small number of the unsuccessfully treated dogs.

IN administration of 0.2 mg/kg MDZ[40] and 0.5 mg/kg DZP[20] has shown favorable pharmacokinetic properties and bioavailability in studies on healthy dogs, and it has been suggested that both could be useful for treatment of seizures in dogs by owners or when IV access is not available. Although IN-DZP could potentially be as effective as IN-MDZ for dogs with status epilepticus, this was not evaluated in the current clinical trial. Instead, based on the canine pharmacokinetic studies and human trials mentioned, IN-MDZ was chosen in this study. Also, MDZ is a water-soluble medication (in contrast to DZP) and small enough (i.e, molecular weight of 325.8 Daltons) to permeate nasal mucosa.[47,48] The results indicated that it might be effective as a first-line medication for ceasing emergency seizures and appeared superior to R-DZP for this role. It was also demonstrated that the majority of the dogs with structural epilepsy were unsuccessful cases. However, the small number of dogs with structural epilepsy and the difference in proportion of dogs with structural epilepsy between the groups preclude definite conclusions. In comparison, the majority of the dogs with idiopathic epilepsy were successful (9/12, 75%). In addition, the 2 dogs that manifested focal seizures and treated with IN-MDZ were also unsuccessful cases. These findings are supported by another study in dogs with status epilepticus, which reported a significantly worse outcome associated with MUO and focal status epilepticus.[5] Therefore, IN-MDZ appears a more effective first-line management option for idiopathic epilepsy cases rather than those dogs with underlying neoplasia or MUO. IN-MDZ was not evaluated for reactive seizures because immediate etiological treatment is usually needed for these cases (e.g, glucose for hypoglycemic cases) to abolish seizure activity; a fact that could have influenced the apparent drug efficacy and the results of this study.

The safety of IN-MDZ has been evaluated in humans with emergency seizures, and it was reported to be a safe drug without significant adverse effects. In one study, mild adverse effects including vomiting, hypoxia, and excessive drowsiness were reported for both IN-MDZ and R-DZP.[26] However, R-DZP resulted in more adverse effects compared to the IN-MDZ group. In another study,[33] IN-MDZ was compared to IV DZP and although mild hypertension, bradycardia and hypoxia occurred in some adults and children in both groups, no significant complications were reported. In the current clinical trial, severe progressive sedation and ataxia was reported in all the dogs, regardless of the drug administered. However, these signs could equally be attributed to the postictal phase and severe seizure activity (for the period within the first 10 minutes after drug administration), or a postictal phase and other AEDs used (for the period after the first 10 minutes), and were all self-limiting. No cardiovascular or respiratory dysfunction (e.g, no increased risk of aspiration pneumonia or similar) or hypoxia was reported in these cases.

In terms of ease of administration, a previous study reported no difficulties in 90% (27 of 30) of patients relating to IN administration of MDZ.[33] In the current study, difficulties were reported in 45% of the cases but were mild and included brief sneezing during administration or difficulty in applying the device to the small nostrils of some dogs. These could potentially lead to leakage of a small amount of the drug out of the nasal cavity, although this was not specifically reported as an issue in these cases. The atomized form of the drug is also less likely to overflow out of the nostrils compared to liquid forms.

The anatomic structures of the nasal cavity as well as the physiological and pharmacokinetic mechanisms of the IN administration of drugs might provide an explanation for the effectiveness of IN-MDZ. The nasal (sub)mucosa provides a large, highly vascular absorptive surface adjacent to the brain and offers a direct pathway for drug absorption into the bloodstream, avoiding the first-pass hepatic metabolism.[49–51] This is advantageous for benzodiazepines that need to rapidly accumulate in the brain during emergency management of seizures, but have a relatively short latency of action and undergo extensive hepatic metabolism. MDZ is absorbed by the (sub)mucosal nasal vessels and enters the central nervous system by crossing the blood-brain barrier, with a rapid clinical effect.[47] In addition, based on laboratory animal and human studies, some drugs, including benzodiazepines, might be able to reach the brain directly via the olfactory and trigeminal neural pathways.[50–56] The latter might be quite advantageous for refractory cases, where there is inadequate penetration of AEDs across the BBB due to overexpression of drug vascular transporters such as P-glycoprotein.[57] These pharmacological advantages of IN administration of MDZ allow the drug to reach the systemic circulation more rapidly and may make it more effective in controlling emergency seizures with a lower "seizure cessation" time compared to the rectally administered drugs.

A mucosal atomization device was chosen in this study over a plain syringe for the IN drug administration because atomization of a liquid medication has been suggested to provide the benefit of increased and

more rapid absorption.[58–60] The absorption rate and plasma concentration of drugs delivered by atomization has been suggested to be comparable to IV administration in some studies.[53,61,62] In humans, this delivery method also results into a broader distribution of the medication across the nasal mucosa, an increased bioavailability, and improved time to onset and efficacy of the drug with regard to seizure cessation.[18] Finally, because the medication is atomized as a mist, it is less likely to overflow out of the nasal cavity compared to administration as a liquid form.[53,61,62] Indeed, in the current study, the MAD provided a simple and quick method for administering the medication. The soft edge of the device, which is in direct contact with the nostrils and the entrance of the nasal cavity, prevents expulsion of the drug and injuries to the soft tissues that could occur with the hard tip of a plain syringe in seizuring animals experiencing severe motor activity. The use of the MAD may have contributed toward the increased effectiveness of IN-MDZ in this study, although this cannot be confirmed, as administration with the MAD was not compared to a plain syringe for IN administration of the medication. Lastly, slightly more time was needed to prepare the IN-MDZ (29 seconds) compared to R-DZP (16 seconds), which was attributed to the use of the MAD in the IN-MDZ group. However, doctor and owner's familiarization with the device would be expected to reduce the time of preparation and minimize any delays in administration.

This is the first randomized parallel-group clinical trial evaluating the effectiveness of IN-MDZ for ceasing status epilepticus in dogs; however, there are a few study limitations that should be considered. Firstly, it was an open-label trial, which could introduce a risk of bias toward either medication. However, a randomization procedure and objective assessment methods (e.g, recording times by the use of a stop-watch) were used to reduce this possibility as far as possible. Secondly, the number of included dogs per group was not particularly large, and although a statistically significant result could be obtained, these results should be also confirmed by a larger trial. Despite this initial sample size calculation, due to the difficulty to gather status epilepticus cases and the fact that the calculation was based on human data rather than canine data, an interim analysis was performed. The interim analysis showed that there was already a significant result, and therefore, it was thought that it was unethical to continue the trial. Similar approach was followed in another study.[63] There was also a difference in the size of the 2 groups, but this was attributed to the fact that this study was multi-institutional and a few centers could not complete the envelope numeric series at the time of trial's termination. Thirdly, dogs that have been seizuring for periods longer than 5 minutes might have developed some degree of pharmacoresistance toward either medication. However, there was a relatively equal distribution of such cases in each group that could affect the effectiveness of both drugs in a similar manner. Lastly, only specific doses of each drug were tested and therefore higher or lower MDZ and DZP doses could result in different outcomes. In terms of the DZP dose, in particular, this can also depend on the concurrent administration of phenobarbital. However, the majority of these dogs were not receiving phenobarbital, and therefore, these results are less likely to have been impacted by this factor.

## Conclusion

IN-MDZ might be an effective, quick, and safe first-line medication for controlling canine status epilepticus and appears superior to R-DZP. The results support the use of IN-MDZ for treating emergency seizures, in particular idiopathic epilepsy cases, before IV access. These findings could be extrapolated to treatment of emergency seizures at home before hospital admission.

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*Off-label Antimicrobial Declaration:* Authors declare no off-label use of antimicrobials.

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Table S1.** Details of the successfully treated dogs in each group.

**Table S2.** Details of the unsuccessfully treated dogs in each group.

**Table S3.** Details of the assessment for the adverse effects and clinical parameters. For each parameter the median, mean and range values are reported.