

Lorazepam Therapy for Canine Status Epilepticus

R.S. Parin, M. Ranjithkumar*, A. Elamurugan, M. Chandrasekar, S. Kavitha

Resident Veterinary Services Section, Madras Veterinary College, Chennai - 600007.

Tamil Nadu Veterinary and Animal Sciences University, Chennai

Abstract

Canine status epilepticus is naturally occurring epilepsy in dogs, a life-threatening emergency needs to be treated immediately. Prolonged episodes are known to cause damage in multiple areas of brain. For instantly stopping the seizure activity benzodiazepines are chosen as first-line therapy in dogs. The effectiveness of intravenous lorazepam has not yet been well established in veterinary patients. The purpose of the study was to find the seizure free interval in status epilepticus dogs when compared to diazepam. Twelve actively seizing dogs were randomly divided into two groups and administered with intravenous lorazepam @ 0.2mg/kg and diazepam @ 0.5 mg/kg. The parameters like physical parameters, seizure free period, level of consciousness and motor activity were analysed in both the groups. On evaluating the physical parameters there was a significant post ictal temperature when compare to control animals. There was a significant increase in seizure free period when compare to diazepam group. Lorazepam didn't alter the level of consciousness and motor activity in treated dogs. To conclude, lorazepam significantly increased the seizure free period when compared to diazepam in status epilepticus dogs.

Keywords: Status Epilepticus, Lorazepam, Diazepam, Seizure free Period

A seizure is one of the common neurological emergencies noted in dogs (Kobata *et al.*, 2020). Cluster seizures (CS) and status epilepticus (SE) have the terrible distinction of being the most lethal and are difficult to treat in dogs, cats as well as people (Dewey, 2006). They are a life-threatening emergency, it must be recognised right at once and treated as soon as possible (Golubovic and Rossmeisl Jr, 2017a; Kobata, *et al.*, 2020). Prolonged episodes are known to cause damage in multiple areas of brain (Golubovic and Rossmeisl Jr, 2017a). Poorly controlled epilepsy is known to cause a huge emotional as well as a financial burden for pet parent witnessing the pet undergo an epileptic episode. The persistence of a seizure has a high potential to increase mortality and morbidity as well as the financial burden (Coles *et al.*, 2013). For the purpose of instantly stopping the seizure activity benzodiazepines are chosen as first-line therapy in both veterinary and human medicine (Kobata *et al.*, 2020; Almohaish *et al.*, 2021; Charalambous *et al.*, 2021). Delay in administering a benzodiazepine medication reduces the ability to manage a seizure and can result in increased chances of mortality (Almohaish *et al.* 2021). The effectiveness of intravenous lorazepam has not yet been well established in children as well as in veterinary patients (Sreenath *et al.*, 2010). Insufficient clinical trials in veterinary medicine have limited the clinical use and understanding of lorazepam (Heller, 2015). There is a huge paucity of veterinary data in lorazepam usage to

canine status epilepticus and cluster seizures not only in India but also in other countries. With this the study was aimed to rule out inter-ictal period, level of consciousness and motor activity in lorazepam administered SE cases.

Materials and Methods

The clinical study was conducted at Critical Care Unit of Madras Veterinary College for a period of one year. The actively seizing and/or dogs who had repetitive seizures in a short period of day were rushed to the Critical Care Unit and were taken for this study. These cases were identified to have status epilepticus. A total of 12 actively seizing dogs were randomly taken for this study. Animals with a known metabolic, toxic, traumatic and neoplastic cause of seizure were excluded from this study. These 12 animals were randomly grouped as follows: group I administered with Lorazepam at 0.2mg/kg body weight as a bolus dose (n=6). Group II administered with diazepam (n=6) at the dose rate of 0.5 mg /kg body weight after the establishment of intravenous line. Great care while administering the bolus dose of lorazepam to avoid the arterial spasms. Animals were kept under observation for up to 12 hours post administration of intravenous lorazepam and diazepam for stabilization and observation. The owners were encouraged to report the epileptic episode within this 12-hour post drug administration period as per Naeser *et al.*, (2004). Further they were encouraged to report the timing of seizure onset and its duration. The

*Corresponding author Email: clmranjith@gmail.com

inter ictal period for these drugs were assessed for up to 12 hours post administration or upto occurrence of seizure in case seizure occurred prior to the said time. Apparently healthy animals which were brought for general check-up or for routine vaccinations were taken as control group(n=6).

The level of consciousness was determined as per Silverstein and Hopper, (2014).

Motor Activity Assessment Score (MAAS)

The motor activity was extrapolated from a human study (Umunna *et al.*, 2015) and modified to veterinary needs. The scoring of animals was done on basis of observations noted during post drug administration period directly by clinician. Animals which do not move even with noxious stimuli were considered as unresponsive, scored 0. Those animals with open eyes and had limb movement to noxious stimuli considered as responsive only to noxious stimuli, scored 1. Animals with open eyes, turns head toward loud auditory stimulus or moves limb when touched are scored 2. Calm and cooperative animals (score 3) don't require external stimulus to elicit movement and the animal responding to its name. Score 4 animals are restless and cooperative and stimulus is required to elicit movement and patient is trying to lick catheter or tubes. Agitated animals are scored 5 and dangerously agitated, uncooperative animals are scored 6.

The collected data were subjected to descriptive analysis by using SPSS software (version 21) to derive

Mean $\pm$ S.E., t-test (two paired) for comparison of interictal period. Single factor one way ANOVA was used for physical, hematological and biochemical parameters and Mann Whitney- U test for qualitative parameters analysis in this study.

Results

The clinical cases with status epilepticus were subjected to two different drugs of benzodiazepines viz., Lorazepam and Diazepam and their effect was analyzed in this study. Both the drugs were administered through intravenous route. The changes in physical parameters were given in table 1. There was a significant increase in immediate post ictal temperature of SE affected animals when compared to control animals. The difference in temperature was significant within the affected groups also. The difference between the rectal temperature 5 minutes after stabilization, pulse rate, heart rate were non-significant with control and between them. The respiratory rate in the lorazepam treated group i.e., Group I (n= 6) ranged from 20 breaths per minute to 66 breaths per minute with a mean $\pm$ S.E. of 44.5 ± 6.66 breaths per minute. The respiratory rate for diazepam treated i.e., Group II (n=6) ranged from 14 breaths per minute to 58 breaths per minute with a mean $\pm$ S.E. of 40 ± 6.41 breaths per minute. A highly significant difference was noted between the control (Group III) and the status epilepticus animals even after therapy. This indicates that cases presented with seizures had tachypnoea. Other parameters vary without any significance.

Table 1. Mean $\pm$ S.E. values of Physical Parameters (ANOVA: Single factor)

Parameters	Mean $\pm$ S.E.			F	P-value	F crit
	Group I	Group II	Group III			
Immediate Post Ictal Temperature ($^{\circ}$ F)	103.43 $\pm$ 0.48 ^a	101.97 $\pm$ 0.3 ^b	100.75 $\pm$ 0.22 ^c	14.48	0.0**	3.68
Temperature Post Stabilization ($^{\circ}$ F)	101.75 $\pm$ 0.51	101.13 $\pm$ 0.35	100.75 $\pm$ 0.22	1.77	0.20	3.68
Pulse Rate (/min)	134.33 $\pm$ 21.37	102.33 $\pm$ 14.52	120.17 $\pm$ 11.5	0.96	0.4	3.68
Heart Rate (/minute)	135.17 $\pm$ 19.72	102.67 $\pm$ 13.89	111.67 $\pm$ 6.71	1.35	0.29	3.68
Respiration Rate (/minute)	44.5 $\pm$ 6.66 ^a	40 $\pm$ 6.41 ^a	17 $\pm$ 1.75 ^b	7.37	0.01**	3.68
SpO2 (%)	96 $\pm$ 1.10	93.83 $\pm$ 2.15	98.5 $\pm$ 0.43	2.72	0.1	3.68
Blood Pressure (mmHg)	118 $\pm$ 11.60	122.50 $\pm$ 5.59	120 $\pm$ 7.07	0.07	0.93	3.68

* $P < 0.05$ (Significant at 5% level); ** $P < 0.01$ (Significant at 1% level).

NS: Non-significant, Mean bearing same superscript (a, b, c) did not differ significantly.

The level of consciousness score (LOC) for Group I and II ranged from 1 to 4 and 2 to 4 respectively. The motor activity assessment score (MAAS) for Group I and II ranged from 1 to 4 and 1 to 3 respectively. The

study did not show a significant difference in level of consciousness and MAAS using either of the drugs. On Mann-Whitney U test analysis (Table 2) there was no significant difference between LOC and MAAS of SE animals with control.

Table 2. Mann-Whitney U test analysis for comparison of LOC score and MAAS Between lorazepam and diazepam group

S.No	Null Hypothesis	test	Sig.	Decision
1.	The distribution of score LOC is the same across categories of drug	Independent samples Mann-Whitney U test	0.589 ¹	Retain the null hypothesis
2.	The distribution of motor activity assessment (MAAS) is the same across categories of drug	Independent samples Mann-Whitney U test	0.180 ¹	Retain the null hypothesis
Asymptomatic significant differences are displayed. The significance level is 0.05 ¹ Exact significance is displayed for this test.				

The inter ictal period for lorazepam treated Group I ranged from 80 minutes to 300 minutes. For Group II, diazepam treated group, the period ranged from 34 minutes to 290 minutes. The test of significance revealed a significant difference in seizure free Period between Group I and Group II at 5% level ($P < 0.05$).

Lorazepam appears to have a significant difference ($p = 0.044$) with diazepam in regard to duration of seizure control post injection for dogs with cluster seizures and status epilepticus. Lorazepam appears to have a significant difference ($p = 0.044$) with diazepam in regard to duration of seizure control post injection for dogs with status epilepticus.

Table 3. The significance level of inter-ictal period between the groups.

Parameter	Group I	Group II
Seizure free interval (Minutes)	218.5± 35.18	94± 41.13
t- value (Equal variances assumed)	2.300	
Sig. (2-tailed)	0.044*	
*Significant at 5% level (P<0.05)		

Discussion

Benzodiazepines represent the first-line and widely-used treatment choice and still remain crucial for management of canine SE (Golubovic and Rossmeisl Jr, 2017b). In a human study, lorazepam was as effective as phenobarbital or diazepam plus phenytoin in patients with generalized convulsive status epilepticus (Treiman et al., 1998). In a study on dogs with emergency seizure disorders 3% of pet owners were used lorazepam as primary medicine to control seizure episodes in dogs (Kahn, 2023). Lorazepam may be useful as antiepileptic therapy with IV administration in the dog (Podell et al., 1998). The mean ± S.E. of seizure free period for

diazepam treated animals (Group II) was 94 ± 41.13 minutes i.e., 1.57 hours whereas it was 218.5 ± 35.18 minutes (3.6 hrs) for lorazepam. The result from our study correlate with Naeser *et al.*, (2004) where they compared the median seizure-free interval between lorazepam and diazepam administration in canines. They indicated the median seizure free interval was 2.8 hr (i.e. 168 min) and 3.4 hr (i.e., 204 min) for diazepam and lorazepam respectively. Further it also correlates with a study using SAS detection algorithm for seizure reoccurrence detection. This study stated that the dog administered diazepam had a reoccurrence of another seizure 1.5 hour after administration (Coles *et al.*, 2013).

Lorazepam has more potent activity at benzodiazepine receptor and has longer half-life after IV administration to dogs with SE (Thomas and Dewey, 2016). The distribution half-life of lorazepam is also high than that of diazepam due to its low lipid solubility i.e 2-3 hours for lorazepam and 15 minutes for diazepam (Sirven and Waterhouse, 2003). Lorazepam may have enhanced antiepileptic potency due to increased binding to the high affinity benzodiazepine receptors and elevated concentrations of parent drug in the brain after serum concentrations has declined and help in controlling status epilepticus (Podell *et al.*, 1998). Status epilepticus animals significantly had higher post ictal temperature than control group. These findings correlates with Wachtel *et al.*, (1987) who stated that generalized tonic-clonic seizures are similar to a vigorous workout and hence can cause a rise in body temperature. Hence it was proved in our study that the increase in body temperature was due to increased muscular activity, loss of electrolyte and hypovolemic shock. Devinsky, (2004) stated that in some cases ictal parasympathetic activity or sympathetic inhibition and may result in tachypnoea. Our findings correlates with it. The intravenous administration of lorazepam increased the interictal period to 3.6 hours and lorazepam administration doesn't alter the level of consciousness and motor activity at therapeutic doses. Lorazepam causes some rare adverse reactions, including a manic-like reaction on withdrawal, delirium, and paradoxical precipitation of tonic seizures or myoclonus in children. It can both relieve and worsen behavioral disturbances in demented elderly patients (Lee *et al.*, 1994; Tueth, 1995). However, there was no significant difference in level of consciousness and motor activity in dogs treated with lorazepam and control. To conclude lorazepam significantly increased the seizure free period when compared to diazepam in status epilepticus dogs.

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