Running head: Post-attenuation seizures in dogs with single cEHPSS

Title: The effect of prophylactic treatment with levetiracetam on the incidence of post-attenuation seizures in dogs undergoing surgical management of single congenital extrahepatic portosystemic shunts.

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Objectives: To report (1) the incidence of post-attenuation seizures (PAS) in dogs that underwent single congenital extrahepatic portosystemic shunt (cEHPSS) attenuation and (2) to compare incidence of PAS in dogs that either did or did not receive prophylactic treatment with levetiracetam (LEV).

Study Design: Multi-institutional retrospective study.

Sample Population: Nine-hundred-and-forty dogs.

Methods: Medical records were reviewed to identify dogs that underwent surgical attenuation of a single cEHPSS from January 2005 through July 2017 and developed PAS within seven days postoperatively. Dogs were divided into three groups: no LEV (LEV-); LEV at ≥15mg/kg TID for ≥24 hours or a 60mg/kg intravenous loading dose preoperatively, followed by ≥15mg/kg TID postoperatively (LEV1); and LEV at <15mg/kg TID, for <24 hours preoperatively, or continued at <15mg/kg TID postoperatively (LEV2).

Results: Nine-hundred-and-forty dogs were included. Seventy-five (8.0%) developed PAS. Incidence of PAS was 35/523 (6.7%), 21/188 (11.2%) and 19/228 (8.3%) in groups LEV-, LEV1 and LEV2, respectively. This difference was not statistically significant (p=0.14). No significant differences between groups of dogs that seized with respect to variables investigated were identified.

Conclusions: The overall incidence of PAS was low (8%). Prophylactic treatment with LEV according to the protocols investigated in our study was not associated with a reduced incidence of PAS.

Clinical Significance:

Prophylactic treatment with LEV does not afford protection against development of PAS. Surgically treated dogs should continue to be monitored closely during the first seven days postoperatively for seizures.

Introduction

Development of post-attenuation seizures (PAS) is a devastating and frequently fatal postoperative complication in dogs undergoing surgical attenuation of congenital portosystemic shunts, with survival rates ranging from 0-53.8% in previous studies that included more than three affected dogs.[1-7] Incidence of PAS has been reported as high as 18.2%,[1,2,4-8] and up to 4.7-8.1% in more recent literature.[7,8] Seizures typically occur within 96 hours postoperatively and have been reported following congenital extrahepatic- (cEHPSS)[1-18] and less commonly intrahepatic portosystemic shunt (cIHPSS) attenuation.[13,14,19-25] Such seizures appear different to those observed preoperatively in that they are often very challenging to control, being refractory to typical first line anti-seizure medications.[1-8,10-12,14-16,21,22]

The etiopathogenesis of PAS remains unknown. The most commonly cited cause is a decrease in systemic concentrations of endogenous benzodiazepines/benzodiazepine-like substances from the portal circulation following shunt attenuation.[26] Other suggested causes include hypoglycemia, hepatic encephalopathy, hypoxemia/hypoxic brain injury, systemic hypertension, electrolyte disturbances, and concurrent brain disease.[2,3,17,18,21] None of these; however, has been consistently identified in affected dogs.[1-3,6-11,15,17,18,21,22] Anecdotally, prolonged surgical and anesthetic times, and intraoperative hypotension, have been suggested to be implicated in PAS; however, these are not supported by results of a recent study.[6]

Risk factors for development of PAS are not well established.[7] Development of seizures has not been prevented by partial ligation,[1-3,9,12,20,21] use of delayed attenuation devices,[3-5,10,12,14,15,17,22,23] or coil embolization.[24,25] In a recent study, increasing age and the presence of hepatic encephalopathy (HE) immediately preoperatively were identified as risk factors for

development of post-attenuation neurologic signs (PANS) and PAS.[7] Matushek et al reported that 40% of dogs that developed PAS had a history of preoperative HE.[1] In a study by Tisdall et al,[3] dogs with cEHPSSs were significantly more likely to develop PANS than dogs with cIHPSSs; however, this is not supported by two more recent studies.[7,14] In the study by Tisdall et al,[3] there was also a trend towards dogs with portoazygous shunts being at greater risk of PANS than those with other shunt morphologies. Certain breeds have been suggested to be at increased risk of PANS/PAS including Pugs,[3,10,17] Jack Russell terriers,[14] and Maltese terriers.[9]

Efforts to reduce the incidence of PAS in dogs undergoing cEHPSS attenuation have included pre-treatment with phenobarbital,[3,10,15] potassium bromide,[4,23] and levetiracetam (LEV).[5-7] In one study,[3] no dog that received prophylactic phenobarbital experienced postoperative generalized seizures; however, the overall incidence of PANS was not significantly decreased. Development of seizures has also been described following pre-treatment with potassium bromide.[4,23] There are conflicting reports in the literature regarding the possible protective effects of LEV against development of PAS.[5-7] Results of a retrospective study in 2011 led to a paradigm shift in the preoperative management of dogs undergoing shunt attenuation in many institutions.[5] In that study,[5] no dog that received LEV at 20mg/kg every eight hours (TID) for a minimum of 24 hours preoperatively experienced PAS. Conversely, 5% of dogs that did not receive LEV pre-treatment experienced PAS leading to a decision for humane euthanasia.[5] These results; however, are not supported by two more recent studies,[6,7] wherein pre-treatment with LEV was not associated with reduced incidence of PAS. Therefore, the objectives of this study were to report the (1) incidence of PAS in a large cohort of dogs that underwent cEHPSS attenuation and (2) compare incidence of PAS in dogs that either did or did not receive prophylactic LEV. Our hypothesis was that there would be no significant difference in incidence of PAS among dogs that either did or did not receive prophylactic LEV.

Materials and Methods

Inclusion and exclusion criteria

Medical records at ten veterinary institutions were retrospectively reviewed to identify dogs that underwent surgical attenuation (suture ligation [SL], thin film banding [TFB], or ameroid ring constrictor [ARC] placement) of a single cEHPSS from January 2005 through July 2017. Additionally, two of the authors (RNW, KMP) performed surgery at more than one institution during the study period. All cEHPSSs operated by these two surgeons during this timeframe were reviewed and incidence of PAS was calculated on an individual rather than institutional basis. Exclusion criteria included cIHPSSs; multiple cEHPSSs; cEHPSSs with apparent portal vein aplasia that precluded shunt attenuation; pre-treatment with anti-seizure medication(s) other than LEV within one month prior to surgery; dogs that died or were euthanized within 24 hours postoperatively for reasons unrelated to seizure activity; dogs that received LEV preoperatively but did not have it continued postoperatively, dogs that received LEV postoperatively only; and dogs with incomplete medical records to permit stratification into the appropriate group. Institutions that biased administration of LEV towards dogs perceived to be at greater risk of PAS were not included in this study. Post-attenuation seizures were defined as those that occurred within seven days postoperatively. Dogs that experienced onset of seizure activity after seven days were recorded as not having developed PAS.

Data collection

All dogs

Each contributing institution/surgeon assigned all dogs that satisfied the inclusion criteria to one of three groups:

Group LEV-: Dogs that received no anti-seizure prophylaxis.

Group LEV1: Dogs that received LEV at ≥15mg/kg TID for ≥24 hours preoperatively or a 60mg/kg intravenous loading dose of LEV perioperatively, with continuation of LEV postoperatively at ≥15mg/kg TID.

Group LEV2: Dogs that received LEV at <15mg/kg TID, for <24 hours preoperatively, or continued at <15mg/kg TID postoperatively.

Dogs that received less than TID administration of LEV (regardless of accompanying dose) were assigned to group LEV2. Postoperative duration of LEV was also recorded for all dogs in groups LEV1 and LEV2.

Dogs that developed post-attenuation seizures

Additional data retrieved only from the medical record of dogs that developed PAS within seven days postoperatively and compared between groups of affected dogs included breed, age, sex/neuter status, and body-weight at time of surgery; shunt morphology (portocaval, portoazygous or portophrenic); concurrent/historical conditions at presentation; presence of preoperative neurologic signs; presence of preoperative seizures; method of shunt identification (abdominal ultrasound, computed tomography angiography [CTA], scintigraphy, intraoperative portovenography [IOPV], magnetic resonance imaging [MRI]); details of preoperative medical management (diet, antimicrobial, lactulose); method of shunt attenuation (SL, TFB, ARC) and degree of acute intraoperative attenuation (none, partial, or complete); type and timing of PAS; and electrolyte (sodium, potassium and chloride), glucose and ammonia concentrations around the time of PAS occurrence (where available). Dogs that received preoperative antimicrobial and lactulose medication were recorded as either having received these medications for a minimum of one week prior to surgery, or not. In cases where prophylactic LEV was administered, timing of last preoperative dose in relation to

commencement of surgery, and most recently administered dose relative to seizure onset (in hours) was recorded. Timing of occurrence of seizures was recorded in hours where available or converted to hours if recorded in days. Dogs were stratified as having experienced partial/focal seizures only, or generalized seizures with or without partial/focal seizures. For dogs that developed PAS, short-term survival, defined as survival to 30 days, was also recorded.

Statistical analyses

Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed continuous data were presented as mean and standard deviation. Non-normally distributed continuous data were presented as median and range. Categorical variables were presented as frequency and percentages (with 95% confidence intervals [CI]). Normally distributed continuous data were compared between groups of dogs that experienced PAS using One-Way ANOVA. Non-normally distributed continuous data were compared using the Kruskal-Wallis and Mann-Whitney U tests, while categorical variables were compared between PAS groups using Pearson's Chi-Squared test. A power analysis was performed based on a modification of previously published data.[5] In that study,[5] dogs that did or did not receive pre-treatment with LEV had a 0% and 5% incidence of PAS, respectively. Using an incidence of 1% and 5%, respectively, a total of 284 dogs per group would be required to show a true difference between two groups if it were to exist, with a power of 80% and an alpha of 0.05. P values < 0.05 were considered significant. Statistical analyses were performed using commercially available software[a].

Results

A total of 940 dogs satisfied the inclusion criteria and were included in the study. Of these, 75 (8.0%;CI:6.4-9.9%) dogs developed PAS. Details of three dogs were partially reported previously.[15,16] Incidence of PAS within individual institutions is listed in **Table 1**.

Group LEV- (no anti-seizure prophylaxis)

Five-hundred-and-twenty-three dogs were included in group LEV-; 35 (6.7%;CI:4.9-9.2%) developed PAS.

Group LEV1 (≥15mg/kg TID for ≥24 hours preoperatively or a 60mg/kg intravenous loading dose of LEV perioperatively, with continuation of LEV postoperatively at ≥15mg/kg TID)

One-hundred-and-eighty-eight dogs were included in group LEV1; 21 (11.2%;CI:7.4-16.5%) developed PAS. All 21 dogs were still receiving LEV at the time of PAS occurrence. Median (range) postoperative duration of LEV of 167 dogs in group LEV1 that did not develop PAS was ten (1-760) days; recorded as indefinitely (n=1), not recorded (n=2). Of those that developed PAS (n=21), median (range) duration of pre-treatment (excluding two dogs that received a 60mg/kg intravenous loading dose perioperatively) was six (1-237) days; median (range) preoperative dose was 20mg/kg (15-60mg/kg [76.2% dogs received ≥20mg/kg]); all received TID administration of LEV pre- and postoperatively (excluding two dogs that received a 60mg/kg intravenous loading dose perioperatively); and median (range) postoperative dose was 20mg/kg TID (15-23mg/kg [85.7% dogs received ≥20mg/kg]).

Group LEV2 (<15mg/kg TID, for <24 hours preoperatively, or continued at <15mg/kg TID postoperatively)

Two-hundred-and-twenty-nine dogs were included in group LEV2; 19 (8.3%;CI:5.4-12.6%) developed PAS. All 19 dogs were still receiving LEV at the time of PAS occurrence. Median (range) postoperative duration of LEV administration of 209 dogs in group LEV2 that did not develop PAS was seven (2-66) days; not recorded (n=3). Of those that developed PAS (n=19), median (range) duration of pre-treatment was 72 hours (12.7 hours-97 days), with two additional dogs recorded as having commenced LEV treatment perioperatively (n=1; 20mg/kg, and continued at 20mg/kg TID postoperatively) or intraoperatively (n=1; 60mg/kg loading dose but continued at 19.23mg/kg BID postoperatively); median (range) preoperative dose was 20mg/kg (10-20mg/kg); ten received TID administration preoperatively, six dogs received BID administration, while three received a single dose preoperatively (two perioperatively/intraoperatively and one 12.6 hours preoperatively); median (range) postoperative dose was 20mg/kg (10-20mg/kg); 13 dogs received TID administration postoperatively, while the remaining 6 dogs received BID administration.

No significant difference in incidence of PAS between groups was identified (p=0.14). No significant differences between groups of dogs that seized with respect to variables investigated were identified (**Table 2)**.

Demographics of dogs that developed post-attenuation seizures (n=75)

The most common breeds were mixed breed (n=16), Bichon Frise (n=10), Yorkshire terrier (n=9), Shih Tzu (n=8), and Pug (n=8). Median (range) age was 34 (4-115) months. There were 25 neutered males, 22 spayed females, 13 sexually-intact males, 13 sexually-intact females, and two unspecified females. Median (range) weight was 6.2 kg (2.0-21.0 kg).

Method of shunt identification and shunt morphology of dogs that developed post-attenuation seizures (n=75)

Method of shunt identification included abdominal ultrasound (n=61;81.3%), CTA (n=21;28.0%), IOPV (n=17;22.7%), scintigraphy (n=1;1.3%), and MRI (n=1;1.3%). Information regarding shunt morphology was available for 73/75 (97.3%) dogs. Overall, shunt types included portocaval (n=53), portoazygous (n=13) and portophrenic (n=7).

Concurrent/historical conditions at presentation in dogs that developed post-attenuation seizures (n=75)

Concurrent/historical conditions were recorded in 25/75 (33.3%) dogs and most commonly included urolithiasis (n=17), urinary tract infection (n=6), and cardiac murmur (n=3). Two dogs had previously undergone cEHPSS attenuation but did not develop PAS following initial surgery.

Incidence of preoperative neurologic signs and seizures in dogs that developed post-attenuation seizures (n=75)

Preoperative neurologic signs were recorded in 61/75 (81.3%) dogs and most commonly included lethargy (n=28), pacing/compulsive walking (n=12), dullness (n=10), head pressing (n=10), ataxia (n=10), abnormal/change in behavior (n=10), hypersalivation/drooling (n=9), circling (n=5), (possible) blindness (n=4), disorientation (n=4), sleepy/inappropriate sleeping/sleeps a lot (n=4), depression (n=4), and two each of twitching, weakness, and restlessness. Preoperative seizures were recorded in 11/75 (14.7%) dogs.

Details of preoperative medical management of dogs that developed post-attenuation seizures (n=75)

Information regarding preoperative medical management was available for 74/75 (98.7%) dogs. One dog (group LEV2) was prescribed hepatic diet, an antimicrobial and lactulose but it could not be confirmed if this occurred. Overall, 48/75 (64.0%) dogs received a prescription hepatic diet; eight (10.7%) received an unspecified protein restricted diet; three (4.0%) received a prescription hypoallergenic diet; two (2.7%) received an unspecified vegetarian diet; and four dogs received one each of protein restricted renal diet, prescription gastrointestinal diet, homemade protein restricted diet, and chicken and vegetables. Sixty-six (88.0%) dogs received a minimum of seven days of preoperative antimicrobial, while 68 (90.7%) received a minimum of 7 days of preoperative lactulose.

Method and degree of acute intraoperative shunt attenuation in dogs that developed post-attenuation seizures (n=75)

Shunts were attenuated using TFB (n=30; 40.0%), SL (n=23; 30.7%), ARC (n=21; 28.0%), or a combination of SL and TFB (n=1; 1.3%).

Type and timing of post-attenuation seizures

Sixty-two (82.7%) dogs experienced generalized PAS, while the remaining 13 (17.3%) dogs experienced focal PAS only. Onset of seizure activity (focal or generalized; whichever occurred first) occurred after a median (range) of 48 (8-128) hours.

Clinicopathologic variables at time of seizures (Table 2)

Sodium, potassium and chloride

Sodium and potassium concentrations at the time of seizures were available for review in 31/75 (41.3%) dogs and recorded as normal in a further three dogs. Sodium and potassium concentrations were available for 14/35 (40%), 5/21 (23.8%), and 12/19 (63.2%) dogs in groups LEV-. LEV1 and LEV2, respectively. Chloride concentration was available for review in 22/75 (29.3%) PAS dogs, recorded as normal in two dogs and high in a further one dog. Chloride concentration was available for 10/35 (28.6%), 4/21 (19.0%) and 8/19 (42.1%) dogs in groups LEV-, LEV1 and LEV2, respectively.

Ammonia and glucose

Ammonia concentration was available for review in 30/75 (40.0%) dogs, recorded as within normal limits for four (5.3%) and high for a further dog (1.3%). Overall, 76.7% of values were <70.0 μmol/l. Ammonia concentration was available for 9/35 (25.7%), 10/21 (47.6%) and 11/19 (57.9%) dogs in groups LEV-, LEV1 and LEV2, respectively. Glucose concentration was available for 36/75 (48.0%) dogs and recorded as normal for a further two dogs. Overall, 34/37 (91.9%) values were ≥3.3 mmol/l. Glucose concentration was available for 14/35 (40%), 7/21 (33.3%) and 15/19 (78.9%) dogs in groups LEV-, LEV1 and LEV2, respectively.

Timing of last preoperative dose of LEV in relation to surgery

Timing of last preoperative dose of LEV in relation to surgery was available for 9/21 (42.9%) dogs in group LEV1 and 7/19 (36.8%) dogs in group LEV2. In addition, timing of last preoperative dose was recorded as perioperative in 7/21 (33.3%) dogs in group LEV1 and 6/19 (31.6%) dogs in group LEV2. One additional dog in group LEV2 received the last preoperative dose of LEV the previous day.

Timing of last (most recent) dose of LEV relative to seizure onset

Timing of last dose of LEV in relation to seizure onset was available for 16/40 (40.0%) dogs; 5 (23.8%) dogs in group LEV1 and 11 (57.9%) dogs in group LEV2 (**Table 2**).

Short-term survival of dogs that developed PAS

Overall, 23/75 (30.7%) dogs survived to 30 days postoperatively.

Discussion

The main findings of this study are: (1) the overall incidence of PAS was low (8%) and similar to that reported in recent literature,[6,7] and (2) prophylactic treatment with LEV, at either ≥15mg/kg TID for ≥24 hours preoperatively or a 60mg/kg intravenous loading dose perioperatively, with continuation postoperatively at ≥15mg/kg TID (group LEV1), or other less standardized LEV protocols (LEV2), did not result in a reduced incidence of PAS compared to dogs that did not receive any prophylactic LEV (group LEV-). No significant differences between groups of dogs that seized with respect to signalment; shunt morphology; concurrent conditions; incidence of preoperative neurologic signs and seizures; preoperative medical management; method and degree of shunt attenuation; timing of and type of PAS; electrolyte, ammonia and glucose concentrations at the time of seizures, and short-term survival were identified. The results of this study corroborate findings of two recent studies[6,7] that prophylactic treatment with LEV does not afford protection against development of PAS in contrast to what has been suggested by Fryer et al.[5]

In a pharmacokinetic study by Moore et al,[27] administration of LEV at ~20mg/kg TID consistently produced plasma LEV concentrations within the 5-45 μg/ml therapeutic range in healthy dogs. This therapeutic range is based on extrapolations from humans and the plasma LEV concentrations required to prevent seizures in dogs undergoing cEHPSS attenuation is unknown. In our study, we included dogs that received LEV at ≥15mg/kg TID in group LEV1 to accommodate for expected small deviations from the recommended 20mg/kg dose due to tablet size limitations. The median preoperative dose of LEV in dogs that developed PAS in group LEV1 was 20mg/kg, with over 75% of dogs receiving ≥20mg/kg TID pre- and postoperatively. In the study by Moore et al,[27] mean terminal half-life of LEV was 3.6 hours, which resulted in steady-state after 18 hours (Moore et al, personal communication). These

pharmacokinetic data support that steady-state should have been achieved at the time of surgery in dogs in group LEV1 in our study. Furthermore, these data would suggest that there is no benefit in pre-treating dogs for >24 hours prior to surgery. We also included in group LEV1 dogs that received a 60mg/kg intravenous loading dose of LEV perioperatively. Based on a pharmacokinetic study,[28] administration of a single intravenous 60mg/kg loading dose resulted in plasma LEV concentrations within or above the recommended therapeutic range for at least 8 hours. This was followed with postoperative administration of LEV at ≥15mg/kg TID in such dogs in our study. We did not include in our study dogs that received other anti-seizure medication concurrently with LEV due to expected alterations in the pharmacokinetics of LEV.[29,30]

The median age (34 months) of dogs that developed PAS in our study was greater than the expected age of dogs undergoing cEHPSS attenuation.[31] This observation that older dogs may be at increased risk of experiencing PANS/PAS has been made by several other investigators.[1-4,7,17] In a recent study by Strickland et al, increasing age was found to be a significant risk factor for development of PANS and PAS.[7]

Postoperative administration of LEV in our study was very variable, reflecting its multicenter nature, with similar variation reported in the literature.[5-7] In a recent study by Strickland et al, all dogs that were administered LEV received the drug for a minimum of five days postoperatively.[7] In the study by Fryer et al,[5] median postoperative duration of LEV was 33 days; however, some dogs appear not to have received any postoperative LEV, with the authors placing emphasis on pre-treatment of dogs. Similarly, in the study by Brunson et al,[6] the authors do not specifically report postoperative duration of LEV. Based on pharmacokinetic data by Moore et al, dogs that do not have administration of LEV continued postoperatively would be

400 expected to have drug plasma concentrations fall below the recommended therapeutic range
401 after approximately 12 hours.[27] In our study, all dogs that developed PAS in groups LEV1 and
402 LEV2 were still receiving LEV at the time of seizure occurrence. We acknowledge that there
403 is an important reliance on owners to administer anti-seizure medication(s) at home. We
404 defined PAS as seizures that occurred within seven days postoperatively in accordance with
405 what has been reported in the literature.[1-25] Occurrence of seizures was recorded up to 128
406 hours postoperatively in our study. It would therefore seem intuitive, if considering
407 prophylactically treating dogs with LEV, to continue postoperative administration for a
408 minimum of six days.
409
410 In the current study, we did not exclude dogs that developed PAS that had a history of
411 preoperative seizures. In a recent study by Brunson et al,[6] dogs with a history of preoperative
412 seizure activity that subsequently developed PAS had a significantly increased probability of
413 survival compared to those that had not. It is possible that both subsets did not experience
414 seizures of the same etiopathogenesis, although this is purely speculative. It is also possible
415 that some dogs that had a history of preoperative seizures had continuation of these seizures
416 postoperatively. Dogs that had a history of preoperative neurologic signs were also not
417 excluded in our study. Strickland et al reported the presence of HE immediately preoperatively
418 a risk factor for development of PANS and PAS.[7] In a study by Matushek et al, 40% of dogs
419 that experienced PAS had a history of preoperative HE.[1] We also did not exclude dogs in whom
420 hypoglycemia, hyperammonemia, or electrolyte derangements were identified at the time of
421 PAS occurrence. While it is possible that some dogs may have experienced seizures directly
422 attributable to these disturbances, we suspected that there would be an even distribution of such
423 cases across all three groups, which was subsequently confirmed by statistical comparisons.
424 None of these derangements have consistently been identified within or among previous

studies,[1-6,8-11,15,17,21,22] nor has correction of such abnormalities been found to abolish seizure activity in all cases.[1-4] Seizures have also been demonstrated to occur in the face of ammonia concentrations lower than those obtained preoperatively,[1,2,11] and at glucose concentrations, albeit decreased, not typically associated with seizure activity.[2,4] Unfortunately, these clinicopathologic variables were not available for review for all dogs in our study, which may have led to underestimation of the incidence of these derangements overall and within individual PAS groups.

We acknowledge a number of important limitations in this study. This was a retrospective study, wherein accuracy of recorded data depends on accuracy and completeness of the medical records. Details concerning variables other than administration of LEV were not available for all 940 dogs in this study and it is possible that a confounding factor may have biased one or more groups towards a higher rate of PAS. This study did not include institutions that biased administration of LEV towards dogs perceived to be at greater risk of PAS (eg, older dogs or those that had a history of preoperative neurologic signs or seizures). Therefore, the authors speculate that a homogenous population of dogs exists overall within the three groups. Moreover, if it were the case that the LEV groups are in fact biased towards a higher proportion of at risk dogs, these are the dogs clinicians would be expected to select for prophylactic treatment with LEV; however, 8.3-11.2% of these treated dogs continued to develop PAS in our study. Owing to the non-prospective nature of this study, administration of LEV within individual institutions was not randomized, with the decision to pre-treat with LEV based on the attending clinician's belief regarding its possible protective effects against development of PAS. All dogs that developed PAS in groups LEV1 and LEV2 were still receiving LEV at the time of seizure occurrence; however, exact timing of last dose relative to seizure onset could not be verified in all cases. If this were greater than the recommended 8-hour dosing interval,

PAS may have developed due to inadequate plasma LEV concentrations rather than a lack of efficacy of the drug. Based on a modification of results of Fryer et al,[5] a power analysis indicated that 284 dogs would be required in groups LEV- and LEV1 to show a true difference in incidence of PAS if it were to exist. Due to administration of less standardized LEV protocols (group LEV2) within institutions in our study, a total of only 188 dogs met the inclusion criteria for group LEV1. It is possible that this shortfall may have resulted in a type II error in our study and that a small difference does exist between groups but could not be detected. Further prospective randomized studies are required to confirm our results. The incidence of PAS in group LEV1 was almost twice that in group LEV- and it is possible that this is reflective of the relatively smaller number of dogs in group LEV1. Measurement of plasma LEV concentrations was not performed in our study and is not routinely performed in clinical practice. We excluded dogs that died or were euthanized within 24 hours postoperatively for reasons unrelated to seizure activity. Ideally, this would have been extended to at least five days; however, several dogs were discharged prior to five days postoperatively following an uncomplicated recovery and we could not guarantee that they did not die of other causes within this timeframe and thus were not given the opportunity to develop PAS. Due to its retrospective nature, the categorization of seizure type as focal or generalized in this study reflects what was recorded in the medical record. Serum electrolyte, ammonia and glucose concentrations were not available for review for all dogs in this study, which will affect the results of our study. Furthermore, due to its multicenter nature, where clinicopathologic variables were available, they were obtained from several different analyzers. Finally, we acknowledge the subjectivity in assessing the degree shunt attenuation intraoperatively, particularly concerning partial attenuation.

Disclosure Statement

The authors report no conflict of interest.

References

1. Matushek KJ, Bjorling D, Mathews K, et al. Generalized motor seizures after portosystemic shunt ligation in dogs: five cases (1981-1988). *J Am Vet Med Assoc.* 1990;196:2014-2017.
2. Hardie EM, Kornegay JN, Cullen JM, et al. Status epilepticus after ligation of portosystemic shunts. *Vet Surg.* 1990;19:412-417.
3. Tisdall PL, Hunt GB, Youmans KR, et al. Neurological dysfunction in dogs following attenuation of congenital extrahepatic portosystemic shunts. *J Small Anim Pract.* 2000;41(12):539-546.
4. Mehl M, Kyles AE, Hardie EM, et al. Evaluation of ameroid ring constrictors for treatment for single extrahepatic portosystemic shunts in dogs: 168 cases (1995-2001). *J Am Vet Med Assoc.* 2005;226:2020-2030.
5. Fryer KJ, Levine JM Peycke LE, et al. Incidence of postoperative seizures with and without levetiracetam pretreatment in dogs undergoing portosystemic shunt attenuation. *J Vet Intern Med.* 2011;25:1379-1384.
6. Brunson BW, Case JB, Ellison GW, et al. Evaluation of surgical outcome, complications, and mortality in dogs undergoing preoperative computed tomography angiography for diagnosis of an extrahepatic portosystemic shunt: 124 cases (2005-2014). *Can Vet J.* 2016;57:59-64.
7. Strickland R, Tivers MS, Adamantos SE, et al. Incidence and risk factors for neurological signs after attenuation of single congenital portosystemic shunts in 253 dogs. *Vet Surg*. 2018;00:1-11. https://doi.org/10.1111/vsu.12925
8. Hunt GB, Hughes J. Outcomes after extrahepatic portosystemic shunt ligation in 49 dogs. *Aust Vet J.* 1999;77:303-307.

9. Mathews K, Gofton N. Congenital extrahepatic portosystemic shunt occlusion in the dog: gross observations during surgical correction. *J Am Anim Hosp Assoc.* 1988;24:387-394.
10. Youmans KR, Hunt GB. Cellophane banding for the gradual attenuation of single extrahepatic portosystemic shunts in eleven dogs. *Aust Vet J.* 1998;76(8):531-537.
11. Heldmann ED, Holt E, Brockman DJ, et al. Use of propofol to manage seizure activity after surgical treatment of portosystemic shunts. *J Small Anim Pract.* 1999;40:590-594.
12. Hurn SD, Edwards GA. Perioperative outcomes after three different single extrahepatic portosystemic shunt attenuation techniques in dogs: partial ligation, complete ligation and ameroid constrictor placement. *Aust Vet J.* 2003;81(11):666-670.
13. Kummeling A, Van Sluijs FJ, Rothuizen J, et al. Prognostic implications of the degree of shunt narrowing and of the portal vein diameter in dogs with congenital portosystemic shunts. *Vet Surg.* 2004;33:17-24.
14. Hunt GB, Kummeling A, Tisdall PL, et al. Outcomes of cellophane banding for congenital portosystemic shunts in 106 dogs and 5 cats. *Vet Surg.*2004;33:25-31.
15. Gommeren K, Claeys S, de Rooster H, et al. Outcome from status epilepticus after portosystemic shunt attenuation in 3 dogs treated with propofol and phenobarbital. *J Vet Emerg Crit Care* (San Antonio). 2010;20(3):346-351.
16. Heidenreich DC, Giordano P, Kirby BM. Successful treatment of refractory seizures with phenobarbital, propofol, and medetomidine following congenital portosystemic shunt ligation in a dog. *J Vet Emerg Crit Care* (San Antonio). 2016;26(6):831-836.
17. Wallace ML, MacPhail CM, Monnet E. Incidence of Postoperative Neurologic Complications in Pugs Following Portosystemic Shunt Attenuation Surgery. *J Am Anim Hosp Assoc.* 2017 Nov 13. doi: 10.5326/JAAHA-MS-6534.

18. Torisu S, Washizu M, Hasegawa D, et al. Sustained severe hypoglycemia during surgery as a genesis of global brain damage in post ligation seizure of congenital portosystemic shunts dogs. *J Vet Intern Med.*2006;20(3)753.
19. Komtebedde J, Forsyth SF, Breznock EM, et al. Intrahepatic portosystemic venous anomaly in the dog: perioperative management and complications. *Vet Surg.* 1991;20:37-42.
20. White RN, Burton CA, McEvoy FJ. Surgical treatment of intrahepatic portosystemic shunts in 45 dogs. *Vet Rec.* 1998;142(14):358-365.
21. Yool DA, Kirby BM. Neurological dysfunction in three dogs and one cat following attenuation of intrahepatic portosystemic shunts. *J Small Anim Pract.* 2002;43:171-176.
22. Connery NA, McAllister H, Skelly C, et al. Cellophane banding of congenital intrahepatic portosystemic shunts in two Irish wolfhounds. *J Small Anim Pract.* 2002;4: 345-349.
23. Mehl ML, Hardie AE, Case JB, et al. Surgical Management of Left-Divisional Intrahepatic Portosystemic Shunts: Outcome After Partial Ligation of, or Ameroid Ring Constrictor Placement on, the Left Hepatic Vein in Twenty-Eight Dogs (1995-2005). *Vet Surg.* 2007;36:21-30.
24. Weisse C, Berent AC, Todd K, et al. Endovascular evaluation and treatment of intrahepatic portosystemic shunts in dogs: 100 cases (2001-2011). *J Am Vet Med Assoc*. 2014;244(1):78-94.
25. Case JB, Marvel SJ, Stiles MC, et al. Outcomes of cellophane banding or percutaneous transvenous coil embolization of canine intrahepatic portosystemic shunts. *Vet Surg*. 2017 Nov 27. doi:10.1111/vsu.12750.

26. Aronson LR, Gacad RC, Kaminskyruss K, et al. Endogenous benzodiazepine activity in the peripheral and portal blood of dogs with congenital portosystemic shunts. *Vet Surg.* 1997;26:189-194.
27. Moore S, Munana KR, Papich MG, et al. Levetiracetam pharmacokinetics in healthy dogs following oral administration of single and multiple doses. *Am J Vet Res.* 2010;71:337–341.
28. Dewey CW, Bailey KS, Boothe, DM, et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. *J Vet Emerg Crit Care* (San Antonio). 2008;18:153-157.
29. Moore SA, Muñana KR, Papich MG, et al. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. *J Vet Pharmacol Ther.* 2011;34(1):31-34.
30. Muñana KR, Nettifee-Osborne JA, Papich MG. Effect of chronic administration of phenobarbital, or bromide, on pharmacokinetics of levetiracetam in dogs with epilepsy. *J Vet Intern Med.* 2015;29(2):614-619.
31. Berent AC, Tobias KM. Hepatic Vascular Anomalies. In: Tobias KM, Johnston SA, eds. Veterinary Surgery: Small Animal. St. Louis: Elsevier Saunders;2012:16241658.

Footnotes

aSPSS Statistics, Version 24, IBM,USA

Institution/Group	LEV-	LEV1	LEV2
1	2/114 (1.8%)	-	3/41 (7.3%)
2*	5/59 (8.5%)	3/18 (16.7%)	0/24 (0.0%)
3	1/17 (5.9%)	1/18 (5.6%)	1/12 (8.3%)
4	6/161 (3.7%)	-	-
5	1/19 (5.3%)	2/31 (6.5%)	1/17 (5.9%)
6	4/40 (10.0%)	2/14 (14.3%)	2/7 (28.6%)
7	1/6 (16.7%)	1/10 (10.0%)	-
8	-	4/24 (16.7%)	5/20 (25.0%)
9	0/12 (0.0%)	5/59 (8.5%)	0/25 (0.0%)
10	4/34 (11.8%)	3/7 (42.9%)	5/43 (11.6%)
11	5/32 (15.6%)	0/7 (0.0%)	1/11 (9.1%)
12*	6/30 (20.0%)	-	1/28 (3.6%)
Total number of dogs	524	188	228
Number of dogs that developed PAS	35	21	19
Incidence of PAS (%, 95% CI)	**6.7%** (CI: 4.9-9.2%)	**11.2%** (CI: 7.4-16.5%)	**8.3%** (CI:5.4-12.6%)

Table 1: Incidence of post-attenuation seizures among 940 dogs that underwent single cEHPSS attenuation.

*EHPSSs operated by an individual surgeon rather than institution.

Group/Variable	LEV-	LEV1	LEV2	P-value
Breed	▪ Mixed breed (n=7) ▪ Bichon Frise (n=7) ▪ Yorkshire terrier (n=6) ▪ Shih Tzu (n=5) ▪ Maltese terrier (n=4) ▪ Pug (n=4) ▪ Miniature Schnauzer (n=1) ▪ Jack Russell terrier (n=1)	▪ Mixed breed (n=4) ▪ Yorkshire terrier (n=3) ▪ Shih Tzu (n=3) ▪ Chihuahua (n=3) ▪ Pug (n=2) ▪ Maltese terrier (n=1) ▪ Miniature Schnauzer (n=1) ▪ Jack Russell terrier (n=1) ▪ Dachshund (n=1) ▪ Norfolk terrier (n=1) ▪ Border terrier (n=1)	▪ Mixed breed (n=5) ▪ Bichon Frise (n=3) ▪ Jack Russell terrier (n=3) ▪ Pug (n=2) ▪ Dachshund (n=2) ▪ Maltese terrier (n=1) ▪ West Highland White terrier (n=1) ▪ Brussels Griffon (n=1) ▪ Setter (n=1)	0.06
Age **Median (range)**	35 (4-115) months	34 (6-59) months	35 (8-105) months	0.68
Sex/neuter status	▪ Male intact (n=7) ▪ Male neutered (n=13) ▪ Female intact (n=6) ▪ Female spayed (n=7) ▪ Unspecified female (n=2)	▪ Male intact (n=5) ▪ Male neutered (n=4) ▪ Female intact (n=3) ▪ Female spayed (n=9)	▪ Male intact (n=1) ▪ Male neutered (n=8) ▪ Female intact (n=4) ▪ Female spayed (n=6)	0.34
Weight **Median (range)**	6.8 (2.2-11.9) kg	6.0 (2.0-13.6) kg	6.5 (4.2-21.0) kg	0.46
Shunt morphology	▪ Portocaval (n=26) ▪ Portoazygous (n=5) ▪ Portophrenic (n=3)	▪ Portocaval (n=14) ▪ Portoazygous (n=4) ▪ Portophrenic (n=2)	▪ Portocaval (n=13) ▪ Portoazygous (n=4) ▪ Portophrenic (n=2)	0.97
Presence of concurrent/historica	9/35 (25.7%)	10/21 (47.6%)	6/19 (31.6%)	0.24

l conditions at presentation				
Presence of preoperative neurologic signs	29/35 (82.9%)	16/21 (76.2%)	16/19 (84.2%)	0.77
Presence of preoperative seizures	4/35 (11.4%)	5/21 (23.8%)	2/19 (10.5%)	0.38
Preoperative diet	▪ Hepatic diet (n=23) ▪ Unspecified protein-restricted diet (n=3) ▪ Protein-restricted renal diet (n=1) ▪ Other diet (n=2)	▪ Hepatic diet (n=14) ▪ Unspecified protein-restricted diet (n=4) ▪ Hypoallergenic diet (n=1) ▪ Vegetarian diet (n=1)	▪ Hepatic diet (n=11) ▪ Unspecified protein-restricted diet (n=1) ▪ Hypoallergenic diet (n=2) ▪ Gastrointestinal diet (n=1) ▪ Vegetarian diet (n=1)	0.47
Minimum of 7 days of preoperative antimicrobial(s)	33/35 (94.3%)	19/21 (90.5%)	14/18 (77.8%)	0.18
Minimum of 7 days of preoperative lactulose	34/35 (97.1%)	19/21 (90.5%)	15/18 (83.3%)	0.21
(i) Method and (ii) degree of acute intraoperative shunt attenuation	SL (n=13) ▪ Complete ligation (n=11) ▪ Partial ligation (n=2) TFB (n=11) ▪ No attenuation (n=1) ▪ Partial attenuation (n=10) ARC (n=10) ▪ No attenuation (n=10) Combination of SL and TFB (n=1) ▪ Partial attenuation (n=1)	TFB (n=9) ▪ No attenuation (n=5) ▪ Partial attenuation (n=4) ARC (n=8) ▪ No attenuation (n=8) SL (n=4) ▪ Complete ligation (n=4)	TFB (n=10) ▪ No attenuation (n=6) ▪ Partial attenuation (n=4) SL (n=6) ▪ Complete ligation (n=5) ▪ Partial ligation (n=1) ARC (n=3) ▪ No attenuation (n=3)	(i) 0.45 (ii) 0.27

Type of post-attenuation seizures	▪ 28/35 (80.0%) generalized PAS ▪ 7/35 (20.0%) focal PAS only	▪ 17/21 (81.0%) generalized PAS ▪ 4/21 (19.0%) focal PAS only	▪ 17/19 (89.5%) generalized PAS ▪ 2/19 (10.5%) focal PAS only	0.66
Onset of seizure activity Median (range) hours	60 (8-120)	60 (17-128)	47 (20-120)	0.06
Sodium (n=31) Median (range) mmol/l	143.0 (135.1-171.0)	148.0 (142.5-155.0)	144.0 (138.3-150.3)	0.24
Potassium (n=31) Mean (± SD) mmol/l	4.1 (±0.6)	3.7 (±0.6)	4.1 (±0.3)	0.37
Chloride (n=22) Mean (± SD) mmol/l	114.6 (±6.7)	112.5 (± 5.8)	117.4 (±7.5)	0.49
Ammonia (n=30) Median (range) µmol/l	39 (8.0-72.6)	37.1 (0.0-104.0)	25 (2.0-261.6)	0.84
Glucose (n=36) Median (range) mmol/l	4.9 (2.4-7.2)	5.3 (3.6-6.4)	5.5 (1.1-6.3)	0.56
Timing of last preoperative dose of LEV in relation to surgery (n=16) Median (range) minutes	-	240 (80-480)	180 (95-750) ▪ >480 minutes (750 minutes) (n=1)	0.54
Timing of last (most recent) dose of LEV relative to seizure onset (n=16) Mean (+ SD) minutes	-	383.8 (±52.7)	278.2 (±162.5) ▪ >480 minutes (530 minutes) (n=1)	0.07
Short-term survival	14/35 (40%)	6/19 (31.6%)	3/19 (15.8%)	0.19

615
616 **Table 2:** Comparison of variables between groups of dogs that developed PAS.

617 Abbreviations: PAS; post-attenuation seizures, SL; suture ligation, ARC; ameroid ring
618 constrictor, TFB; thin-film banding, LEV; levetiracetam, SD; standard deviation.