EXPERIENCE THE FREEDOM OF GOING MOBILE.

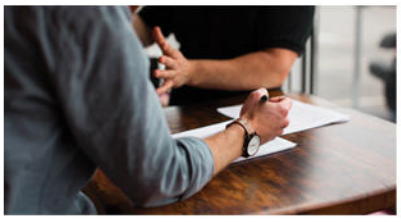
A career in mobile surgery offers you...

JOB FREEDOM

MOVES is a national mobile surgery company that emphasizes **quality of life** as our number one value. Our surgeons manage their own schedules with **no emergency or on-call** requirement. MOVES is hiring surgeons in markets across the country.

REWARDING COMPENSATION

All MOVES™ surgeons receive a competitive base salary and **industry-leading production rates.** Our benefits package includes a new company vehicle, healthcare, flexible time off, and retirement. Tenured employees are eligible to participate in our **profit-sharing** program and employee liquidity pool.



WORLD-CLASS SUPPORT

MOVES™ makes starting a mobile surgery practice easy. Our dedicated support tream walks you through everything from choosing and ordering equipment to marketing and invoicing. We make start-up simple so you can **focus on your patients.**

MOVES™

Now hiring small animal surgeons nationwide!

Click to apply now or visit us at www.VetMoves.com for more info.

APPLY NOW

Learn More and Apply at VetMoves.com

Received: 26 May 2018 | Revised: 12 October 2018 | Accepted: 6 November 2018

DOI: 10.1111/vsu.13141

WILEY

ORIGINAL ARTICLE – CLINICAL

Effect of prophylactic treatment with levetiracetam on the incidence of postattenuation seizures in dogs undergoing surgical management of single congenital extrahepatic portosystemic shunts

Ronan A. Mullins MVB[1] | Carlos Sanchez Villamil DVM[1] | Hilde de Rooster DVM, MVM, PhD, DECVS[2] | Anne Kummeling DVM, PhD, DECVS[3] | Robert N. White BSc(Hons), BVetMed, DSAS(ST), DECVS, SFHEA[4,5,6] | Kelley M. Thieman Mankin DVM, MS, DACVS-SA[7] | Michael S. Tivers BVSc(Hons), PhD, DECVS[8] | Donald A. Yool BVMS, PhD, DECVS, SFHEA[9] | Davina M. Anderson MA VetMB, PhD, DSAS(ST), DECVS[10] | Kathryn M. Pratschke MVB, MVM, DECVS[11,12] | Ines Gordo DVM, MS[13] | Herve Brissot DEDV, DECVS[13] | Ameet Singh BSc, DVM, DVSc, DACVS[14] | Melanie Olive DVM[15] | Jean Phillipe Billet Dr.vét, Cert SAS, DECVS[15] | Laura E. Selmic BVetMed (Hons), MPH, DACVS-SA, DECVS[16] | Barbara M. Kirby DVM, MS, DACVS, DECVS[1]

[1]Section of Veterinary Clinical Sciences, University College Dublin, Belfield, Dublin, Ireland

[2]Small Animal Department, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

[3]Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

[4]Willows Veterinary Centre and Referral Service, Shirley, Solihull, West Midlands, United Kingdom

[5]Abbey House Veterinary Hospital, Morley, Leeds, United Kingdom

[6]School of Veterinary Medicine & Science, University of Nottingham, Sutton Bonington Campus, Loughborough, United Kingdom

[7]Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas

Abstract

Objective: To report the incidence of postattenuation seizures (PAS) in dogs that underwent single congenital extrahepatic portosystemic shunt (cEHPSS) attenuation and 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.

Population: Nine hundred 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 7 days postoperatively. Dogs were divided into 3 groups: no LEV (LEV−); LEV at ≥15 mg/kg every 8 hours for ≥24 hours preoperatively or a 60 mg/kg intravenous loading dose perioperatively, followed by ≥15 mg/kg every 8 hours postoperatively (LEV1); and LEV at <15 mg/kg every 8 hours, for <24 hours preoperatively, or continued at <15 mg/kg every 8 hours postoperatively (LEV2).

Preliminary results of this study were presented at the Association of Veterinary Soft Tissue Surgeons' Annual Spring Meeting; April 4, 2018; Birmingham, United Kingdom; and the ACVS Surgery Summit, October 25–27, 2018; Phoenix, Arizona. This study represents part of a thesis submitted by Dr. Mullins to the University College Dublin in partial fulfillment of a Doctorate of Veterinary Medical Specialization.

[8]Bristol Veterinary School, University of Bristol, Langford House, Langford, Bristol, United Kingdom

[9]The Royal (Dick) School of Veterinary Studies, Easter Bush Campus, Midlothian, Edinburgh, United Kingdom

[10]Anderson Moores Veterinary Specialists, Hursley, Winchester, United Kingdom

[11]North East Veterinary Referrals, Northumberland Business Park West, Cramlington, Northumberland, United Kingdom

[12]University of Glasgow School of Veterinary Medicine, Bearsden, Glasgow, United Kingdom

[13]Pride Veterinary Centre, Derby, Derbyshire, United Kingdom

[14]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada

[15]Centre Hospitalier Vétérinaire Atlantia, Nantes, France

[16]Department of Veterinary Clinical Sciences, The Ohio State University, 601 Vernon L Tharp St, Columbus, OH 43210

Correspondence
Ronan A. Mullins, Section of Veterinary Clinical Sciences, University College Dublin, Belfield, Dublin 4, Ireland.
Email: ronan.mullins@ucd.ie

Current address
Dr. Yool, University of Glasgow Small Animal Hospital, School of Veterinary Medicine, College of Medical, Veterinary & Life Sciences, 464 Bearsden Road, Glasgow G61 1QH.
Dr. Sanchez Villamil, Department of Clinical Science and Services, Royal Veterinary College, University of London, London, United Kingdom.
Dr. Tivers, Paragon Veterinary Referrals, Paragon Business Village, Red Hall Crescent, Wakefield, WF1 2DF.

Results: Seventy-five (8.0%) dogs developed PAS. Incidence of PAS was 35 of 523 (6.7%), 21 of 188 (11.2%), and 19 of 228 (8.3%) in groups LEV-, LEV1, and LEV2, respectively. This difference was not statistically significant ($P = .14$). No differences between groups of dogs that seized with respect to investigated variables were identified.

Conclusion: The overall incidence of PAS was low (8%). Prophylactic treatment with LEV according to the protocols that were 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 7 days postoperatively for seizures.

1 | INTRODUCTION

Development of postattenuation 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 3 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.[6,7] Seizures typically occur within 96 hours postoperatively and have been reported after congenital extrahepatic portosystemic shunt (cEHPSS)[1–18] and, less commonly, intrahepatic portosystemic shunt (cIHPSS) attenuation.[13,14,19–25] Such seizures appear different from those observed preoperatively in that they are often very challenging to control, often being refractory to typical first-line antiseizure 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 after 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, have been consistently identified in affected dogs.[1–3,6–11,15,17,18,21,22] Prolonged surgical and anesthetic times and intraoperative hypotension have anecdotally been suggested to be implicated in PAS; however, these are not supported by results from 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 postattenuation neurologic signs (PANS) and PAS.[7] Matushek et al[1] reported that 40% of dogs that developed PAS had a history of preoperative HE. In a study by Tisdall et al,[3] dogs with cEHPSS were significantly more likely to develop PANS compared with dogs with cIHPSS; however, this is not supported by 2 more recent studies.[7,14] In the study by Tisdall et al,[3] there was also a trend toward dogs with portoazygous shunts being

at greater risk of PANS compared with 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 pretreatment 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 after pretreatment 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] Findings of a retrospective study by Fryer et al in 2011 led to a paradigm shift in the preoperative management of dogs undergoing shunt attenuation in many institutions. In that study, no dog that received LEV at a dose of 20 mg/kg every 8 hours for a minimum of 24 hours preoperatively experienced PAS. Conversely, 5% of dogs that did not receive LEV pretreatment experienced PAS, leading to a decision for humane euthanasia.[5] These results, however, are not supported by 2 more recent studies[6,7] in which pretreatment with LEV was not associated with reduced incidence of PAS. Therefore, the objectives of our study were (1) to report the incidence of PAS in a large cohort of dogs that underwent cEHPSS attenuation and (2) to 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.

2 | MATERIALS AND METHODS

2.1 | Inclusion and exclusion criteria

Medical records at 10 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. In addition, 2 of the authors (RNW, KMP) performed surgery at more than 1 institution during the study period. All cEHPSS operated by these 2 surgeons during this time frame were reviewed, and incidence of PAS was calculated on an individual rather than institutional basis. Exclusion criteria included cIHPSS; multiple cEHPSS; cEHPSS with apparent portal vein aplasia that precluded shunt attenuation; pretreatment with antiseizure medication(s) other than LEV within 1 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 toward dogs perceived to be at greater risk of PAS were not included in this study. Postattenuation seizures were defined as those that occurred within 7 days postoperatively. Dogs that experienced onset of seizure activity after 7 days were recorded as not having developed PAS.

2.2 | Data collection

2.2.1 | All dogs

Each contributing institution/surgeon assigned all dogs that satisfied the inclusion criteria to 1 of 3 groups:

1. Group LEV−: Dogs that received no antiseizure prophylaxis
2. Group LEV1: Dogs that received LEV at a dose of ≥15 mg/kg every 8 hours for ≥24 hours preoperatively or a 60 mg/kg intravenous loading dose of LEV perioperatively, with continuation of LEV postoperatively at a dose of ≥15 mg/kg every 8 hours
3. Group LEV2: Dogs that received LEV at a dose of <15 mg/kg every 8 hours, for <24 hours preoperatively, or continued at <15 mg/kg every 8 hours postoperatively

Dogs that received less than every 8 hours 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.

2.2.2 | Dogs that developed PAS

Additional data retrieved only from the medical record of dogs that developed PAS within 7 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], 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 about the time of PAS occurrence (when available). Dogs that received preoperative antimicrobial and lactulose medication were recorded as either having received these medications for a minimum of 1 week prior to surgery or not. For dogs that received prophylactic LEV, timing of the last preoperative dose in relation to commencement of surgery and the most recently administered dose relative to seizure onset (in hours) were recorded. Timing of occurrence of seizures was recorded in hours when available or converted to hours if recorded in days. Dogs were stratified as having experienced partial/focal seizures only or as having

TABLE 1 Incidence of postattenuation seizures among 940 dogs that underwent single cEHPSS attenuation

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

…, no data; LEV, levetiracetam; PAS, postattenuation seizures.
[a] cEHPSS by an individual surgeon rather than an institution.

experienced 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.

2.3 | Statistical analysis

Continuous variables were tested for normality by using the Shapiro-Wilk test. Normally distributed continuous data are presented as mean and standard deviation. Nonnormally distributed continuous data are presented as median and range. Categorical variables are presented as frequency and percentages (with 95% CI). Normally distributed continuous data were compared among groups of dogs that experienced PAS by using 1-way ANOVA. Nonnormally distributed continuous data were compared by using the Kruskal-Wallis and Mann-Whitney U tests, whereas categorical variables were compared among PAS groups by using Pearson's χ^2 test. A power analysis based on a modification of previously published data[5] was performed. In that study,[5] dogs that did and did not receive pretreatment with LEV had a 0% and 5% incidence of PAS, respectively. With an incidence of 1% and 5%, respectively, a total of 284 dogs per group would be required to show a true difference between 2 groups if a difference were to exist, with a power of 80% and an α of .05. $P < .05$ was considered significant. Statistical analyses were performed in SPSS Statistics version 24 (IBM, Armonk, New York).

3 | RESULTS

In total, 940 dogs satisfied the inclusion criteria and were included in the study. Among these, 75 (8.0%; CI: 6.4%-9.9%) dogs developed PAS. Details of 3 dogs were partially reported previously.[15,16] Incidence of PAS within individual institutions is listed in Table 1.

3.1 | Group LEV−

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

3.2 | Group LEV1

One hundred eighty-eight dogs were included in group LEV1; 21 (11.2%; CI: 7.4%-16.5%) dogs developed PAS. All 21 dogs were still receiving LEV at the time of PAS occurrence. Median postoperative duration of LEV of 167 dogs in group LEV1 that did not develop PAS was 10 days (range, 1-760), recorded as indefinitely (n = 1), not recorded (n = 2). Among those that developed PAS (n = 21), duration of pretreatment (excluding 2 dogs that received a 60 mg/kg intravenous loading dose perioperatively) was 6 days (range, 1-237); preoperative dose was 20 mg/kg (range, 15-60 mg/kg [76.2% of dogs received ≥20 mg/kg]); all received every 8 hours administration of LEV preoperatively and postoperatively (excluding 2 dogs that received a 60 mg/kg intravenous loading dose perioperatively); and median postoperative dose was 20 mg/kg every 8 hours (range, 15-23 mg/kg [85.7% of dogs received ≥20 mg/kg]).

3.3 | Group LEV2

Two hundred twenty-nine dogs were included in group LEV2; 19 (8.3%; CI: 5.4%-12.6%) dogs developed PAS. All 19 dogs were still receiving LEV at the time of PAS occurrence. Median postoperative duration of LEV administration of 209 dogs in group LEV2 that did not develop PAS was 7 days (range, 2-66); not recorded (n = 3). Among those that developed PAS (n = 19), median duration of pretreatment was 72 hours (range, 12.7 hours to 97 days), with 2 additional dogs recorded as having commenced LEV pretreatment perioperatively (n = 1; 20 mg/kg and continued at 20 mg/kg every 8 hours postoperatively) or intraoperatively (n = 1; 60 mg/kg loading dose but continued at 19.23 mg/kg every 12 hours postoperatively); median preoperative dose was 20 mg/kg (range, 10-20 mg/kg); 10 dogs received every 8 hours administration preoperatively, and 6 dogs received every 12 hours administration, whereas 3 dogs received a single dose preoperatively (2 dogs perioperatively/intraoperatively and 1 dog 12.6 hours preoperatively); median postoperative dose was 20 mg/kg (range, 10-20 mg/kg); 13 dogs received every 8 hours administration postoperatively, whereas the remaining 6 dogs received every 12 hours administration.

The incidence of PAS did not differ between groups ($P = .14$). No significant differences between groups of

TABLE 2 Comparison of variables among groups of dogs that developed PAS

Variable	Group			*P*-value
	LEV−	LEV1	LEV2	
Breed (n)	Mixed breed (7)	Mixed breed (4)	Mixed breed (5)	.06
	Bichon frise (7)	Yorkshire terrier (3)	Bichon frise (3)	
	Yorkshire terrier (6)	Shih tzu (3)	Jack Russell terrier (3)	
	Shih tzu (5)	Chihuahua (3)	Pug (2)	
	Maltese terrier (4)	Pug (2)	Dachshund (2)	
	Pug (4)	Maltese terrier (1)	Maltese terrier (1)	
	Miniature schnauzer (1)	Miniature schnauzer (1)	West Highland white terrier (1)	
	Jack Russell terrier (1)	Jack Russell terrier (1)	Brussels griffon (1)	
		Dachshund (1)	Setter (1)	
		Norfolk terrier (1)		
		Border terrier (1)		
Age, median (range), mo	35 (4-115)	34 (6-59)	35 (8-105)	.68
Sex/neuter status (n)	Male intact (7)	Male intact (5)	Male intact (1)	.34
	Male neutered (13)	Male neutered (4)	Male neutered (8)	
	Female intact (6)	Female intact (3)	Female intact (4)	
	Female spayed (7)	Female spayed (9)	Female spayed (6)	
	Unspecified female (2)			
Weight, median (range), kg	6.8 (2.2-11.9)	6.0 (2.0-13.6)	6.5 (4.2-21.0)	.46
Shunt morphology (n)	Portocaval (26)	Portocaval (14)	Portocaval (13)	.97
	Portoazygous (5)	Portoazygous (4)	Portoazygous (4)	
	Portophrenic (3)	Portophrenic (2)	Portophrenic (2)	
Presence of concurrent/historical conditions at presentation, n (%)	9/35 (25.7)	10/21 (47.6)	6/19 (31.6)	.24
Presence of preoperative neurologic signs, n (%)	29/35 (82.9)	16/21 (76.2)	16/19 (84.2)	.77
Presence of preoperative seizures, n (%)	4/35 (11.4)	5/21 (23.8)	2/19 (10.5)	.38
Preoperative diet (n)	Hepatic diet (23)	Hepatic diet (14)	Hepatic diet (11)	.47
	Unspecified protein-restricted diet (3)	Unspecified protein-restricted diet (4)	Hypoallergenic diet (2)	
	Protein-restricted renal diet (1)	Hypoallergenic diet (1)	Unspecified protein-restricted diet (1)	
	Other diet (2)	Vegetarian diet (1)	Gastrointestinal diet (1)	
			Vegetarian diet (1)	
Minimum of 7 days of preoperative antimicrobial(s), n (%)	33/35 (94.3)	19/21 (90.5)	14/18 (77.8)	.18
Minimum of 7 days of preoperative lactulose, n (%)	34/35 (97.1)	19/21 (90.5)	15/18 (83.3)	.21
(i) Method and (ii) degree of	SL (13)	TFB (9)	TFB (10)	(i) .45
acute intraoperative shunt	Complete ligation (11)	No attenuation (5)	No attenuation (6)	(ii) .27
attenuation (n)	Partial ligation (2)	Partial attenuation (4)	Partial attenuation (4)	
	TFB (11)	ARC (8)	SL (6)	
	No attenuation (1)	No attenuation (8)	Complete ligation (5)	
	Partial attenuation (10)		Partial ligation (1)	
	ARC (10)	SL (4)	ARC (3)	
	No attenuation (10)	Complete ligation (4)	No attenuation (3)	
	Combination of SL and TFB (1)			
	Partial attenuation (1)			
Type of postattenuation	28/35 (80) generalized PAS	17/21 (81) generalized PAS	17/19 (89.5) generalized PAS	.66
seizures, n (%)	7/35 (20) focal PAS only	4/21 (19) focal PAS only	2/19 (10.5) focal PAS only	
Onset of seizure activity median (range), h	60 (8-120)	60 (17-128)	47 (20-120)	.06
Sodium, n = 31, median (range), mmol/L	143.0 (135.1-171)	148.0 (142.5-155)	144.0 (138.3-150.3)	.24
Potassium, n = 31, mean (SD), mmol/L	4.1 (±0.6)	3.7 (±0.6)	4.1 (±0.3)	0.37

(*Continues*)

TABLE 2 (Continued)

Variable	Group			*P*-value
	LEV−	LEV1	LEV2	
Chloride, n = 22, mean (SD), mmol/L	114.6 (±6.7)	112.5 (±5.8)	117.4 (±7.5)	.49
Ammonia, n = 30, median (range), μmol/L	39 (8.0-72.6)	37.1 (0.0-104)	25 (2.0-261.6)	.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)	.56
Timing of last preoperative dose of LEV in relation to surgery (n = 16), median (range), min	…	240 (80-480)	180 (95-750); > 480 min (750 min; n = 1)	.54
Timing of last (most recent) dose of LEV relative to seizure onset, n = 16, mean (SD) min	…	383.8 (±52.7)	278.2 (±162.5); > 480 min (530 min; n = 1)	.07
Short-term survival, n (%)	14/35 (40)	6/19 (31.6)	3/19 (15.8)	.19

…, no data; ARC; ameroid ring constrictor, LEV, levetiracetam; PAS; postattenuation seizures, SL; suture ligation, TFB; thin film banding.

dogs that seized with respect to variables investigated were identified (Table 2).

3.4 | Demographics of dogs that developed PAS

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 age was 34 months (range, 4-115). There were 25 neutered males, 22 spayed females, 13 intact males, 13 intact females, and 2 unspecified females. Median weight was 6.2 kg (range, 2.0-21.0).

3.5 | Method of shunt identification and shunt morphology of dogs that developed PAS

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 of 75 (97.3%) dogs. Overall, shunt types included portocaval (n = 53), portoazygous (n = 13), and portophrenic (n = 7).

3.6 | Concurrent/historical conditions at presentation in dogs that developed PAS

Concurrent/historical conditions were recorded in 25 of 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 after initial surgery.

3.7 | Incidence of preoperative neurologic signs and seizures in dogs that developed PAS

Preoperative neurologic signs were recorded in 61 of 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 2 each of twitching, weakness, and restlessness. Preoperative seizures were recorded in 11 of 75 (14.7%) dogs.

3.8 | Details of preoperative medical management of dogs that developed PAS

Information regarding preoperative medical management was available for 74 of 75 (98.7%) dogs. One dog (group LEV2) was prescribed a hepatic diet, an antimicrobial, and lactulose, but it could not be confirmed if this occurred. Overall, 48 of 75 (64.0%) dogs received a prescription hepatic diet; 8 (10.7%) dogs received an unspecified protein-restricted diet; 3 (4.0%) dogs received a prescription hypoallergenic diet; 2 (2.7%) dogs received an unspecified vegetarian diet; and 4 dogs received 1 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 7 days of preoperative antimicrobial, whereas 68 (90.7%) dogs received a minimum of 7 days of preoperative lactulose.

3.9 | Method and degree of acute intraoperative shunt attenuation in dogs that developed PAS

Shunts were attenuated by 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%).

3.10 | Type and timing of PAS

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

3.11 | Clinicopathologic variables at time of seizures (Table 2)

3.11.1 | Sodium, potassium, and chloride

Sodium and potassium concentrations at the time of seizures were available for review in 31 of 75 (41.3%) dogs and

recorded as normal in a further 3 dogs. Sodium and potassium concentrations were available for 14 of 35 (40%), 5 of 21 (23.8%), and 12 of 19 (63.2%) dogs in groups LEV−, LEV1, and LEV2, respectively. Chloride concentration was available for review in 22 of 75 (29.3%) PAS dogs, recorded as normal in 2 dogs and high in a further 1 dog. Chloride concentration was available for 10 of 35 (28.6%), 4 of 21 (19.0%), and 8 of 19 (42.1%) dogs in groups LEV−, LEV1, and LEV2, respectively.

3.11.2 | Ammonia and glucose

Ammonia concentration was available for review in 30 of 75 (40.0%) dogs, recorded as within normal limits for 4 (5.3%) and high for 1 further dog (1.3%). Overall, 76.7% of values were <70.0 μmol/L. Ammonia concentration was available for 9 of 35 (25.7%), 10 of 21 (47.6%), and 11 of 19 (57.9%) dogs in groups LEV−, LEV1, and LEV2, respectively. Glucose concentration was available for 36 of 75 (48.0%) dogs and recorded as normal for a further 2 dogs. Overall, 34 of 37 (91.9%) values were ≥3.3 mmol/L. Glucose concentration was available for 14 of 35 (40%), 7 of 21 (33.3%), and 15 of 19 (78.9%) dogs in groups LEV−, LEV1, and LEV2, respectively.

3.12 | Timing of last preoperative dose of LEV in relation to surgery

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

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

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

3.14 | Short-term survival of dogs that developed PAS

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

4 | DISCUSSION

The main findings of this study are (1) that the overall incidence of PAS was low (8%) and similar to that reported in recent literature[6,7] and (2) that prophylactic treatment with LEV, at either ≥15 mg/kg every 8 hours for ≥24 hours preoperatively or a 60 mg/kg intravenous loading dose perioperatively with continuation postoperatively at ≥15 mg/kg every 8 hours (group LEV1) or other less standardized LEV protocols (LEV2), did not result in a reduced incidence of PAS compared with dogs that did not receive any prophylactic LEV (group LEV−). No significant differences were identified 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; type and timing of PAS; electrolyte, ammonia and glucose concentrations at the time of seizures; and short-term survival. The results of this study provide evidence to corroborate findings of 2 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 ∼20 mg/kg every 8 hours 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; 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 ≥15 mg/kg every 8 hours in group LEV1 to accommodate for expected small deviations from the recommended 20 mg/kg dose because of tablet size limitations. The median preoperative dose of LEV in dogs that developed PAS in group LEV1 was 20 mg/kg, with over 75% of dogs receiving ≥20 mg/kg every 8 hours preoperatively 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 (K. Muñana, personal communication, March 2018). These pharmacokinetic data provide evidence to support that steady-state should have been achieved at the time of surgery in dogs in group LEV1 in our study. Furthermore, these data provide evidence to suggest that there is no benefit in pretreating dogs for >24 hours prior to surgery. We also included in group LEV1 dogs that received a 60 mg/kg intravenous loading dose of LEV perioperatively. According to a pharmacokinetic study,[28] administration of a single intravenous 60 mg/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 a dose of ≥15 mg/kg every 8 hours in such dogs in group LEV1 in our study. We did not include in our study dogs that received other antiseizure medication concurrently with LEV because of 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,[7] increasing age was found to be a significant risk factor for development of PANS and PAS.

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,[7] all dogs that were administered LEV received the drug for a minimum of 5 days postoperatively. 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 pretreatment of dogs. In the study by Brunson et al,[6] the authors similarly do not specifically report postoperative duration of LEV. According to pharmacokinetic data by Moore et al,[27] dogs that do not have continued administration of LEV postoperatively would be expected to have drug plasma concentrations fall below the recommended therapeutic range after approximately 12 hours. In our study, all dogs that developed PAS in groups LEV1 and LEV2 were still receiving LEV at the time of seizure occurrence. We acknowledge that there is an important reliance on owners to administer antiseizure medication at home. We defined PAS as seizures that occurred within 7 days postoperatively, in accordance with what has been reported in the literature.[1–25] Occurrence of seizures was recorded up to 128 hours postoperatively in our study. It would therefore seem intuitive, when considering prophylactically treating dogs with LEV, to continue postoperative administration for a minimum of 6 days.

In the current study, we did not exclude dogs that developed PAS that had a history of preoperative seizures. In a recent study by Brunson et al,[6] dogs with a history of preoperative seizure activity that subsequently developed PAS had a significantly increased probability of survival compared to those that had not. It is possible that both subsets did not experience seizures of the same etiopathogenesis, although this is purely speculative. It is also possible that some dogs that had a history of preoperative seizures had continuation of these seizures postoperatively. Dogs that had a history of preoperative neurologic signs were also not excluded in our study. Strickland et al[7] reported that the presence of HE immediately preoperatively was a risk factor for development of PANS and PAS. In a study by Matushek et al,[1] 40% of dogs that experienced PAS had a history of preoperative HE. We also did not exclude dogs in which hypoglycemia, hyperammonemia, or electrolyte derangements were identified at the time of PAS occurrence. Although it is possible that some dogs may have experienced seizures directly attributable to these disturbances, we suspected that there would be an even distribution of such cases across all 3 groups, which was subsequently confirmed by statistical comparisons. 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] These clinicopathologic variables unfortunately 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, in which 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 1 or more groups toward a higher rate of PAS. This study did not include institutions that biased administration of LEV toward 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 3 groups. Moreover, were it the case that the LEV groups are in fact biased toward 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. Because of the nonprospective nature of this study, administration of LEV within individual institutions was not randomized, with the decision to pretreat 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 the last (most recent) 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. A power analysis based on a modification of results from Fryer et al[5] 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. Because of 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. Additional 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. This ideally would have been extended to at least 5 days; however, several dogs were discharged prior to 5 days

postoperatively after an uncomplicated recovery, so we could not guarantee that they did not die of other causes within this time frame and, thus, were not given the opportunity to develop PAS. Because of this study's retrospective nature, the categorization of seizure type as focal or generalized 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, and this will have affected the results of our study. Furthermore, because of this study's multicenter nature, in cases where clinicopathologic variables were available, these variables were obtained from several different analyzers. Finally, we acknowledge the subjectivity in assessing the degree of shunt attenuation intraoperatively, particularly concerning partial attenuation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

ORCID

Ronan A. Mullins https://orcid.org/0000-0003-1159-2382
Michael S. Tivers https://orcid.org/0000-0001-7047-9334

REFERENCES

1. Matushek KJ, Bjorling D, Mathews K. 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. Status epilepticus after ligation of portosystemic shunts. *Vet Surg*. 1990;19:412-417.
3. Tisdall PL, Hunt GB, Youmans KR, Malik R. 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, Thompson JA, Cohen ND. 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, Harcourt-Brown TR, Fowkes RC, Lipscomb VJ. Incidence and risk factors for neurological signs after attenuation of single congenital portosystemic shunts in 253 dogs. *Vet Surg*. 2018;47(6):745-755.
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 E, Holt DE, Brockman DJ, Brown DC, Perkowski SZ. 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. 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, Hamaide A, Daminet S. Outcome from status epilepticus after portosystemic shunt attenuation in 3 dogs treated with propofol and phenobarbital. *J Vet Emerg Crit Care*. 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*. 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*. 2018;54(1):46-49.
18. Torisu S, Washizu M, Hasegawa D, Orima H. 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, Koblik PD. 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, Kyles AE, Case JB, Kass PH, Zwingenberger A, Gregory CR. 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, Solomon JA, Cope C. 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*. 2018;47(S1):O59-O66.
26. Aronson LR, Gacad RC, Kaminsky-Russ K, Gregory CR, Mullen KD. Endogenous benzodiazepine activity in the peripheral and portal blood of dogs with congenital portosystemic shunts. *Vet Surg*. 1997;26:189-194.
27. Moore SA, Muñana KR, Papich MG, Nettifee-Osborne J. 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, Badgley BL, Cruz-Espindola C. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. *J Vet Emerg Crit Care*. 2008;18:153-157.
29. Moore SA, Muñana KR, Papich MG, Nettifee-Osborne JA. 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: Johnston SA, Tobias KM, eds. *Veterinary Surgery: Small Animal* 2nd edition. St Louis, MO: Elsevier Saunders; 2018:1852-1886.

How to cite this article: Mullins RA, Sanchez Villamil C, de Rooster H, et al. Effect of prophylactic treatment with levetiracetam on the incidence of post-attenuation seizures in dogs undergoing surgical management of single congenital extrahepatic portosystemic shunts. *Veterinary Surgery*. 2019;48:164–172. https://doi.org/10.1111/vsu.13141