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

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

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

78 **Study Design:** Multi-institutional retrospective study.

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

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

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

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

94 **Clinical Significance:**

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

98 **Introduction**

99 Development of post-attenuation seizures (PAS) is a devastating and frequently fatal
100 postoperative complication in dogs undergoing surgical attenuation of congenital
101 portosystemic shunts, with survival rates ranging from 0-53.8% in previous studies that
102 included more than three affected dogs.¹⁻⁷ Incidence of PAS has been reported as high as
103 18.2%,^{1,2,4-8} and up to 4.7-8.1% in more recent literature.^{7,8} Seizures typically occur within 96
104 hours postoperatively and have been reported following congenital extrahepatic- (cEHPSS)¹⁻¹⁸
105 and less commonly intrahepatic portosystemic shunt (cIHPSS) attenuation.^{13,14,19-25} Such
106 seizures appear different to those observed preoperatively in that they are often very
107 challenging to control, being refractory to typical first line anti-seizure medications.<sup>1-8,10-12,14-
108 16,21,22</sup>

109
110 The etiopathogenesis of PAS remains unknown. The most commonly cited cause is a decrease
111 in systemic concentrations of endogenous benzodiazepines/benzodiazepine-like substances
112 from the portal circulation following shunt attenuation.²⁶ Other suggested causes include
113 hypoglycemia, hepatic encephalopathy, hypoxemia/hypoxic brain injury, systemic
114 hypertension, electrolyte disturbances, and concurrent brain disease.^{2,3,17,18,21} None of these;
115 however, has been consistently identified in affected dogs.^{1-3,6-11,15,17,18,21,22} Anecdotally,
116 prolonged surgical and anesthetic times, and intraoperative hypotension, have been suggested
117 to be implicated in PAS; however, these are not supported by results of a recent study.⁶

118
119 Risk factors for development of PAS are not well established.⁷ Development of seizures has
120 not been prevented by partial ligation,^{1-3,9,12,20,21} use of delayed attenuation devices,<sup>3-
121 5,10,12,14,15,17,22,23</sup> or coil embolization.^{24,25} In a recent study, increasing age and the presence of
122 hepatic encephalopathy (HE) immediately preoperatively were identified as risk factors for

123 development of post-attenuation neurologic signs (PANS) and PAS.⁷ Matushek et al reported
124 that 40% of dogs that developed PAS had a history of preoperative HE.¹ In a study by Tisdall
125 et al,³ dogs with cEHPSSs were significantly more likely to develop PANS than dogs with
126 cIHPSSs; however, this is not supported by two more recent studies.^{7,14} In the study by Tisdall
127 et al,³ there was also a trend towards dogs with portoazygous shunts being at greater risk of
128 PANS than those with other shunt morphologies. Certain breeds have been suggested to be at
129 increased risk of PANS/PAS including Pugs,^{3,10,17} Jack Russell terriers,¹⁴ and Maltese terriers.⁹
130
131 Efforts to reduce the incidence of PAS in dogs undergoing cEHPSS attenuation have included
132 pre-treatment with phenobarbital,^{3,10,15} potassium bromide,^{4,23} and levetiracetam (LEV).⁵⁻⁷ In
133 one study,³ no dog that received prophylactic phenobarbital experienced postoperative
134 generalized seizures; however, the overall incidence of PANS was not significantly decreased.
135 Development of seizures has also been described following pre-treatment with potassium
136 bromide.^{4,23} There are conflicting reports in the literature regarding the possible protective
137 effects of LEV against development of PAS.⁵⁻⁷ Results of a retrospective study in 2011 led to
138 a paradigm shift in the preoperative management of dogs undergoing shunt attenuation in many
139 institutions.⁵ In that study,⁵ no dog that received LEV at 20mg/kg every eight hours (TID) for
140 a minimum of 24 hours preoperatively experienced PAS. Conversely, 5% of dogs that did not
141 receive LEV pre-treatment experienced PAS leading to a decision for humane euthanasia.⁵
142 These results; however, are not supported by two more recent studies,^{6,7} wherein pre-treatment
143 with LEV was not associated with reduced incidence of PAS. Therefore, the objectives of this
144 study were to report the (1) incidence of PAS in a large cohort of dogs that underwent cEHPSS
145 attenuation and (2) compare incidence of PAS in dogs that either did or did not receive
146 prophylactic LEV. Our hypothesis was that there would be no significant difference in
147 incidence of PAS among dogs that either did or did not receive prophylactic LEV.

148 **Materials and Methods**

149 **Inclusion and exclusion criteria**

150 Medical records at ten veterinary institutions were retrospectively reviewed to identify dogs
151 that underwent surgical attenuation (suture ligation [SL], thin film banding [TFB], or ameroid
152 ring constrictor [ARC] placement) of a single cEHPSS from January 2005 through July 2017.
153 Additionally, two of the authors (RNW, KMP) performed surgery at more than one institution
154 during the study period. All cEHPSSs operated by these two surgeons during this timeframe
155 were reviewed and incidence of PAS was calculated on an individual rather than institutional
156 basis. Exclusion criteria included cIHPSSs; multiple cEHPSSs; cEHPSSs with apparent portal
157 vein aplasia that precluded shunt attenuation; pre-treatment with anti-seizure medication(s)
158 other than LEV within one month prior to surgery; dogs that died or were euthanized within
159 24 hours postoperatively for reasons unrelated to seizure activity; dogs that received LEV
160 preoperatively but did not have it continued postoperatively, dogs that received LEV
161 postoperatively only; and dogs with incomplete medical records to permit stratification into the
162 appropriate group. Institutions that biased administration of LEV towards dogs perceived to be
163 at greater risk of PAS were not included in this study. Post-attenuation seizures were defined
164 as those that occurred within seven days postoperatively. Dogs that experienced onset of
165 seizure activity after seven days were recorded as not having developed PAS.

166

167 **Data collection**

168 **All dogs**

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

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

172 **Group LEV1:** Dogs that received LEV at ≥ 15 mg/kg TID for ≥ 24 hours preoperatively or a
173 60mg/kg intravenous loading dose of LEV perioperatively, with continuation of LEV
174 postoperatively at ≥ 15 mg/kg TID.

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

177

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

181

182 **Dogs that developed post-attenuation seizures**

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

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

203

204 **Statistical analyses**

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

219

220 **Results**

221 A total of 940 dogs satisfied the inclusion criteria and were included in the study. Of these, 75
222 (8.0%;CI:6.4-9.9%) dogs developed PAS. Details of three dogs were partially reported
223 previously.^{15,16} Incidence of PAS within individual institutions is listed in **Table 1**.

224 **Group LEV- (no anti-seizure prophylaxis)**

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

227 **Group LEV1 (≥ 15 mg/kg TID for ≥ 24 hours preoperatively or a 60mg/kg intravenous
228 loading dose of LEV perioperatively, with continuation of LEV postoperatively at
229 ≥ 15 mg/kg TID)**

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

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

242 Two-hundred-and-twenty-nine dogs were included in group LEV2; 19 (8.3%;CI:5.4-12.6%)
243 developed PAS. All 19 dogs were still receiving LEV at the time of PAS occurrence. Median
244 (range) postoperative duration of LEV administration of 209 dogs in group LEV2 that did not
245 develop PAS was seven (2-66) days; not recorded (n=3). Of those that developed PAS (n=19),
246 median (range) duration of pre-treatment was 72 hours (12.7 hours-97 days), with two
247 additional dogs recorded as having commenced LEV treatment perioperatively (n=1; 20mg/kg,
248 and continued at 20mg/kg TID postoperatively) or intraoperatively (n=1; 60mg/kg loading
249 dose but continued at 19.23mg/kg BID postoperatively); median (range) preoperative dose was
250 20mg/kg (10-20mg/kg); ten received TID administration preoperatively, six dogs received BID
251 administration, while three received a single dose preoperatively (two
252 perioperatively/intraoperatively and one 12.6 hours preoperatively); median (range)
253 postoperative dose was 20mg/kg (10-20mg/kg); 13 dogs received TID administration
254 postoperatively, while the remaining 6 dogs received BID administration.

255

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

259

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

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

265

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

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

272

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

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

279

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

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

288

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

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

300

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

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

305

306 **Type and timing of post-attenuation seizures**

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

310

311 **Clinicopathologic variables at time of seizures (Table 2)**

312 **Sodium, potassium and chloride**

313 Sodium and potassium concentrations at the time of seizures were available for review in 31/75
314 (41.3%) dogs and recorded as normal in a further three dogs. Sodium and potassium
315 concentrations were available for 14/35 (40%), 5/21 (23.8%), and 12/19 (63.2%) dogs in
316 groups LEV-, LEV1 and LEV2, respectively. Chloride concentration was available for review
317 in 22/75 (29.3%) PAS dogs, recorded as normal in two dogs and high in a further one dog.
318 Chloride concentration was available for 10/35 (28.6%), 4/21 (19.0%) and 8/19 (42.1%) dogs
319 in groups LEV-, LEV1 and LEV2, respectively.

320 **Ammonia and glucose**

321 Ammonia concentration was available for review in 30/75 (40.0%) dogs, recorded as within
322 normal limits for four (5.3%) and high for a further dog (1.3%). Overall, 76.7% of values were
323 $<70.0 \mu\text{mol/l}$. Ammonia concentration was available for 9/35 (25.7%), 10/21 (47.6%) and
324 11/19 (57.9%) dogs in groups LEV-, LEV1 and LEV2, respectively. Glucose concentration
325 was available for 36/75 (48.0%) dogs and recorded as normal for a further two dogs. Overall,
326 34/37 (91.9%) values were $\geq 3.3 \text{ mmol/l}$. Glucose concentration was available for 14/35 (40%),
327 7/21 (33.3%) and 15/19 (78.9%) dogs in groups LEV-, LEV1 and LEV2, respectively.

328

329 **Timing of last preoperative dose of LEV in relation to surgery**

330 Timing of last preoperative dose of LEV in relation to surgery was available for 9/21 (42.9%)
331 dogs in group LEV1 and 7/19 (36.8%) dogs in group LEV2. In addition, timing of last
332 preoperative dose was recorded as perioperative in 7/21 (33.3%) dogs in group LEV1 and 6/19
333 (31.6%) dogs in group LEV2. One additional dog in group LEV2 received the last preoperative
334 dose of LEV the previous day.

335

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

337 Timing of last dose of LEV in relation to seizure onset was available for 16/40 (40.0%) dogs;
338 5 (23.8%) dogs in group LEV1 and 11 (57.9%) dogs in group LEV2 (**Table 2**).

339

340 **Short-term survival of dogs that developed PAS**

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

342

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350 **Discussion**

351 The main findings of this study are: (1) the overall incidence of PAS was low (8%) and similar
352 to that reported in recent literature,^{6,7} and (2) prophylactic treatment with LEV, at either
353 $\geq 15\text{mg/kg}$ TID for ≥ 24 hours preoperatively or a 60mg/kg intravenous loading dose
354 perioperatively, with continuation postoperatively at $\geq 15\text{mg/kg}$ TID (group LEV1), or other
355 less standardized LEV protocols (LEV2), did not result in a reduced incidence of PAS
356 compared to dogs that did not receive any prophylactic LEV (group LEV-). No significant
357 differences between groups of dogs that seized with respect to signalment; shunt morphology;
358 concurrent conditions; incidence of preoperative neurologic signs and seizures; preoperative
359 medical management; method and degree of shunt attenuation; timing of and type of PAS;
360 electrolyte, ammonia and glucose concentrations at the time of seizures, and short-term
361 survival were identified. The results of this study corroborate findings of two recent studies^{6,7}
362 that prophylactic treatment with LEV does not afford protection against development of PAS
363 in contrast to what has been suggested by Fryer et al.⁵

364

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

375 pharmacokinetic data support that steady-state should have been achieved at the time of surgery
376 in dogs in group LEV1 in our study. Furthermore, these data would suggest that there is no
377 benefit in pre-treating dogs for >24 hours prior to surgery. We also included in group LEV1
378 dogs that received a 60mg/kg intravenous loading dose of LEV perioperatively. Based on a
379 pharmacokinetic study,²⁸ administration of a single intravenous 60mg/kg loading dose resulted
380 in plasma LEV concentrations within or above the recommended therapeutic range for at least
381 8 hours. This was followed with postoperative administration of LEV at ≥ 15 mg/kg TID in such
382 dogs in our study. We did not include in our study dogs that received other anti-seizure
383 medication concurrently with LEV due to expected alterations in the pharmacokinetics of
384 LEV.^{29,30}

385

386 The median age (34 months) of dogs that developed PAS in our study was greater than the
387 expected age of dogs undergoing cEHPSS attenuation.³¹ This observation that older dogs may
388 be at increased risk of experiencing PANS/PAS has been made by several other investigators.¹⁻
389 ^{4,7,17} In a recent study by Strickland et al, increasing age was found to be a significant risk factor
390 for development of PANS and PAS.⁷

391

392 Postoperative administration of LEV in our study was very variable, reflecting its multicenter
393 nature, with similar variation reported in the literature.⁵⁻⁷ In a recent study by Strickland et al,
394 all dogs that were administered LEV received the drug for a minimum of five days
395 postoperatively.⁷ In the study by Fryer et al,⁵ median postoperative duration of LEV was 33
396 days; however, some dogs appear not to have received any postoperative LEV, with the authors
397 placing emphasis on pre-treatment of dogs. Similarly, in the study by Brunson et al,⁶ the authors
398 do not specifically report postoperative duration of LEV. Based on pharmacokinetic data by
399 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

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

432

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

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

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475 **Disclosure Statement**

476 The authors report no conflict of interest.

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594 **Footnotes**

595 aSPSS Statistics, Version 24, IBM,USA

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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%)

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

613 *EHPSSs operated by an individual surgeon rather than institution.

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Group/Variable	LEV-	LEV1	LEV2	P-value
Breed	<ul style="list-style-type: none"> ▪ 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) 	<ul style="list-style-type: none"> ▪ 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) 	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Male intact (n=7) ▪ Male neutered (n=13) ▪ Female intact (n=6) ▪ Female spayed (n=7) ▪ Unspecified female (n=2) 	<ul style="list-style-type: none"> ▪ Male intact (n=5) ▪ Male neutered (n=4) ▪ Female intact (n=3) ▪ Female spayed (n=9) 	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Portocaval (n=26) ▪ Portoazygous (n=5) ▪ Portophrenic (n=3) 	<ul style="list-style-type: none"> ▪ Portocaval (n=14) ▪ Portoazygous (n=4) ▪ Portophrenic (n=2) 	<ul style="list-style-type: none"> ▪ 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

I 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	<ul style="list-style-type: none"> ▪ Hepatic diet (n=23) ▪ Unspecified protein-restricted diet (n=3) ▪ Protein-restricted renal diet (n=1) ▪ Other diet (n=2) 	<ul style="list-style-type: none"> ▪ Hepatic diet (n=14) ▪ Unspecified protein-restricted diet (n=4) ▪ Hypoallergenic diet (n=1) ▪ Vegetarian diet (n=1) 	<ul style="list-style-type: none"> ▪ 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	<p>SL (n=13)</p> <ul style="list-style-type: none"> ▪ Complete ligation (n=11) ▪ Partial ligation (n=2) <p>TFB (n=11)</p> <ul style="list-style-type: none"> ▪ No attenuation (n=1) ▪ Partial attenuation (n=10) <p>ARC (n=10)</p> <ul style="list-style-type: none"> ▪ No attenuation (n=10) <p>Combination of SL and TFB (n=1)</p> <ul style="list-style-type: none"> ▪ Partial attenuation (n=1) 	<p>TFB (n=9)</p> <ul style="list-style-type: none"> ▪ No attenuation (n=5) ▪ Partial attenuation (n=4) <p>ARC (n=8)</p> <ul style="list-style-type: none"> ▪ No attenuation (n=8) <p>SL (n=4)</p> <ul style="list-style-type: none"> ▪ Complete ligation (n=4) 	<p>TFB (n=10)</p> <ul style="list-style-type: none"> ▪ No attenuation (n=6) ▪ Partial attenuation (n=4) <p>SL (n=6)</p> <ul style="list-style-type: none"> ▪ Complete ligation (n=5) ▪ Partial ligation (n=1) <p>ARC (n=3)</p> <ul style="list-style-type: none"> ▪ No attenuation (n=3) 	<p>(i) 0.45</p> <p>(ii) 0.27</p>

Type of post-attenuation seizures	<ul style="list-style-type: none"> ▪ 28/35 (80.0%) generalized PAS ▪ 7/35 (20.0%) focal PAS only 	<ul style="list-style-type: none"> ▪ 17/21 (81.0%) generalized PAS ▪ 4/21 (19.0%) focal PAS only 	<ul style="list-style-type: none"> ▪ 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 (\pm 0.6)	3.7 (\pm 0.6)	4.1 (\pm 0.3)	0.37
Chloride (n=22) Mean (\pm SD) mmol/l	114.6 (\pm 6.7)	112.5 (\pm 5.8)	117.4 (\pm 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) <ul style="list-style-type: none"> ▪ >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 (\pm 52.7)	278.2 (\pm 162.5) <ul style="list-style-type: none"> ▪ >480 minutes (530 minutes) (n=1) 	0.07
Short-term survival	14/35 (40%)	6/19 (31.6%)	3/19 (15.8%)	0.19

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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.