

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Epidural anesthesia in dogs undergoing hindlimb orthopedic surgery: effects of two injection sites

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1857539> since 2022-05-04T19:16:01Z

Published version:

DOI:10.1292/jvms.21-0289

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Advance Publication

The Journal of Veterinary Medical Science

Accepted Date: 4 January 2022

J-STAGE Advance Published Date: 24 January 2022

©2022 The Japanese Society of Veterinary Science

Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

1 **Surgery**

2 **Full paper**

3 **Epidural anesthesia in dogs undergoing hindlimb orthopedic surgery: effects of two injection**
4 **sites.**

5 Diego SAROTTI¹; Ugo ALA²; Paolo FRANCI²

6 ¹Centro Veterinario Fossanese, Fossano, Italy

7 ²Department of Veterinary Science – University of Turin, Grugliasco, Italy

8 Corresponding author: Diego Sarotti c/o CVF, Via Cuneo 29/E, 12045 – Fossano (CN), Italy. E-
9 mail: diegosarotti@gmail.com; Tel. +39 339 7799 642

10 **Running title:** EFFECT OF 2 SITES OF EPIDURAL INJECTION

11 **Abstract**

12 This prospective clinical trial evaluated the effects of epidural anesthesia (EA) placed at the
13 lumbosacral compared to the L5-L6 junction in dogs undergoing hindlimb orthopedic surgery. In all,
14 98 dogs were randomly assigned to receive injection at either L7-S1 (LS group) or L5-L6 (LL group)
15 at the same local anesthetic regimen (1 mg/kg bupivacaine 0.5% and 0.1 mg/kg morphine 1%).
16 Fentanyl (1 µg/kg) was the intraoperative rescue analgesia (iRA) administered if mean arterial
17 pressure increased by 30% above pre-stimulation value. Procedural failure, iRA, hypotension, motor
18 block resolution, and postoperative side effects were recorded. There were 7/47 (15%) epidural
19 procedural failures in the LS group and 8/51 (16%) ($P=1.00$) in the LL group; iRA was administered
20 in 21/40 (52%) LS group dogs and in 13/43 (30%) LL group dogs, respectively ($P=0.047$). The
21 incidence of hypotension was 10/40 (25%) and 16/43 (37%) in the LS group and the LL group,
22 respectively ($P=0.25$). Proprioceptive residual deficit at 8 hr after EA was recorded in 3/26 (12%) in
23 group LS dogs and in 13/26 (50%) group LL dogs, respectively ($P=0.01$). The proprioceptive residual
24 deficit at 24 hr in one dog (LL group) resolved within 36 hr. No episodes of postoperative urinary

25 retention, pruritus or neurological damage were recorded. The L5-L6 EA decreased significantly iRA
26 but delays the proprioceptive recovery time. Further studies are needed to determine whether a lower
27 bupivacaine dose reduces the duration of the residual block retaining the same incidence of iRA.

28

29 **KEYWORDS:** dog, epidural anesthesia, injection site, intraoperative rescue analgesia, orthopedic
30 surgery.

31

32 **Introduction**

33 Epidural anesthesia (EA) has become less attractive in veterinary clinical research, whereas
34 peripheral nerve block, which uses electrical impulses or echography to locate nerves, has gained
35 wider acceptance with higher success rates and fewer side effects [9]. Despite the loss of research
36 interest, EA retains unique clinical features: simplicity of execution, bilateral block, and long-lasting
37 and effective postoperative analgesia, which can be extended with an epidural catheter. While EA
38 placed in a midline approach at the lumbosacral junction has been extensively investigated in small
39 animals, more cranial administration in a paramedian approach with cephalad angulation has been
40 anecdotally reported [7]. In humans, the injection site is one of the factors affecting the spread of the
41 solution through the epidural space [27], its concentration in the cerebrospinal fluid, and its
42 accumulation in the epidural fat [4, 12]. In dogs undergoing combined general and EA with
43 bupivacaine 0.5% (0.2 ml/kg) and morphine 1% (0.01 ml/kg) at the lumbosacral space for hindlimb
44 surgery, 36% needed intraoperative rescue analgesia (iRA) within 60 min and 48% within 80 min,
45 respectively, after epidural injection [24].

46 The lumbosacral plexus serves the entire pelvic limb; it is formed by the ventral branches of L3 to
47 S3 intervertebral nerves. The main nerves of this plexus which need to be blocked to provide
48 analgesia to the hind limb are (from cranial to caudal): lateral cutaneous femoral, femoral,
49 obturator, sciatic, caudal cutaneous femoral [6]. The nerves that form the cranial part of the
50 lumbosacral plexus can be blocked only with an optimal epidural cranial spread of local anesthetic

51 (LA), exiting the vertebral canal far cranial from the lumbosacral space, while the nerves caudal to
52 the obturator nerve run in the lumbo-sacral epidural space before leaving the vertebral canal and for
53 this reason they are more exposed to LA [6]. More cranial LA injection compared to lumbosacral
54 junction may increase the probability to block the cranial part of the lumbosacral plexus.
55 In this view, injecting the LA at the L5-L6 interspinous space seems the best compromise, given its
56 middle position along the lumbosacral plexus and vicinity to the lumbar intumescence that reducing
57 the epidural space from L3 to L6 metamers, may facilitate LA cranial spread. Furthermore, the
58 spinal process of L6 is higher than that of L7, so it can be easily palpated while positioning the
59 Tuohy needle.

60 Our hypothesis was that an epidural injection placed at L5-L6 rather than at the lumbosacral joint
61 would reduce the need for iRA in dogs undergoing hindlimb orthopedic surgery. The primary
62 endpoint was to compare the incidence of iRA after epidural injection of bupivacaine and morphine
63 at either the lumbosacral junction (LS group) or between the fifth and the sixth lumbar vertebra (LL
64 group). The secondary endpoint was the occurrence of postoperative complications (prolonged
65 neurological deficit, urinary retention, pruritus, neurological damage).

66

67 **Materials and Methods**

68 The study protocol was approved by University of Padua (Prot. no. 206437); informed written consent
69 was obtained from all dog owners. Client-owned dogs presenting to the Centro veterinario fossanese
70 between September 2018 and September 2019 for scheduled surgery of the hindlimb were evaluated.
71 All dogs deemed healthy on physical examination, with complete blood count and serum
72 biochemistry were enrolled. Exclusion criteria were: American Society of Anesthesiologists
73 classification (ASA) >2, age <6 months, skin infection involving the lumbosacral area, history of
74 bleeding disorders, uncorrected hypovolemia, central or peripheral nervous diseases, spinal
75 anatomical abnormality, and history of intervertebral disc disease.

76 *Study Design*

77 For this prospective randomized clinical trial, the dogs were assigned to one of two treatment groups
78 (LS or LL group) by simple randomization based on a computer-generated randomization sequence
79 (www.randomizer.org). All anesthetic procedures were performed by the same experienced operator,
80 and all surgical procedures were performed by the same surgeon who was unaware of the assigned
81 anesthesia technique. All procedures were conducted preferably in a day-surgery regimen, and the
82 dogs were discharged home as soon as they were able to walk. The manuscript conforms to the
83 Consolidated Standards of Reporting Trials (CONSORT) Statement 2010 for reporting randomized
84 clinical trials [16].

85 *Anesthesia Protocol*

86 All dogs were fasted for at least 6 hr before undergoing surgery; water was freely available. A
87 cephalic vein was catheterized, and general anesthesia was induced with 2 µg/kg of fentanyl (50
88 µg/ml; Fentadon; Dechra Eurovet Animal Health BV, Bladel, Holland) and propofol (10 mg/kg;
89 Propofur; Merial Corden Pharma, Milan, Italy) administered intravenously (IV) to effect. General
90 anesthesia was maintained using a variable rate of propofol (Syringe-driver Graseby 3500; Smiths
91 Medical, Saint Paul, MN, USA) titrated to keep a sluggish palpebral reflex. Patients received
92 intermittent positive pressure ventilation (Cato; Draeger, Lübeck, Germany) to maintain normocapnia
93 with an oxygen and medical air mixture to provide a fraction of inspired oxygen (FIO₂) of 0.4. A
94 dorsal-pedal artery was catheterized to monitor arterial blood pressure invasively. Lactated Ringer's
95 solution (Fresenius Kabi, Isola della Scala, Italy) was administered IV at a rate of 5 ml/kg/hr during
96 anesthesia. A multiparametric monitor (AS/3; Datex Ohmeda, Salo, Finland) was used to assess
97 cardiovascular (systolic [SAP], mean [MAP], and diastolic [DAP] arterial blood pressure, heart rate
98 [HR]), and respiratory parameters (PECO₂, peak inspiratory pressure, respiratory rate, tidal volume,
99 FIO₂), and esophageal temperature (T, °C). Data were manually recorded every 5 min until the end
100 of anesthesia. During the perioperative period, body temperature was maintained above 36 °C with
101 an active heating system (Bair Hugger Warmer Model 505; Augustine Biomedical Design, Eden
102 Prairie, MN, USA). The propofol dose for anesthesia induction and maintenance after epidural

103 injection, the time from induction to epidural injection, from epidural injection to skin incision, from
104 skin incision to end of the surgery, and the median anesthesia time were recorded.

105 *Epidural Anesthesia*

106 Epidural anesthesia was administered after clipping the hair from the spinous process of L4 to S2;
107 the skin was aseptically prepared with chlorhexidine (4%) and alcohol (70%). Epidural anesthesia
108 was administered using a Tuohy needle (Perican 22, 20 or 18 gauge; B. Braun, Melsungen, Germany)
109 with the dog in lateral recumbency and the pelvic limbs held forward. A radiograph of the body area
110 was taken to check for correct needle positioning before epidural injection [15]. If the radiograph
111 showed incorrect positioning, two further attempts to reach the epidural space could be undertaken.
112 After the third attempt, the procedure was aborted, and the case was recorded as a procedural failure.
113 An isobaric solution of bupivacaine (5 mg/ml; Bupisen, Galenica Senese, Monteroni d'Arbia (SI),
114 Italy) at 1 mg/kg and morphine (10 mg/ml; morphine hydrochloride, Monico, Mestre (VE), Italy) at
115 0.1 mg/kg was slowly administered. The administered bupivacaine 0.5% dose was limited to 30 mg
116 (6 ml) in dogs weighing over 30 kg [10].

117 *LS Group*

118 In a midline approach at the lumbosacral intervertebral space (L7-S1), the needle was advanced
119 perpendicularly into the skin until an increase in resistance was felt, indicating that the ligamentum
120 flavum had been reached. The stylet was removed, and an air-filled loss of resistance (LOR) syringe
121 (Perifix; B. Braun) was connected to the needle. While the needle was advanced, the operator pressed
122 the syringe plunger until a LOR to air injection and a sudden LOR to needle advancement were felt.

123 *LL Group*

124 In a paramedian approach, the needle was inserted on the dependent side, lateral to the caudal margin
125 of the spinous process of the 6th lumbar vertebra. The needle was advanced in a slightly ventral,
126 cranial, and medial direction while aiming for the vertebral lamina. When the needle reached the
127 lamina, it was withdrawn and then advanced again in a more cephalad angulation until the hard-
128 elastic consistency of the ligamentum flavum, positioned between the 5th and the 6th lumbar

129 intervertebral space (L5-L6), could be felt with the tip of the needle. The operator used the LOR
130 technique to identify the epidural space as described above.

131 *Intraoperative Evaluation and Treatment*

132 A bolus of fentanyl (1 µg/kg IV) was used as iRA if the mean arterial pressure (MAP) rose by more
133 than 30% of the pre-incisional value, defined as the mean value of the MAP measured during the 5
134 min before skin incision. The fentanyl bolus was repeated every 3 min until the MAP reached the
135 pre-incisional value. The iRA incidence and the number of fentanyl boluses were recorded for each
136 group.

137 In the event of intraoperative movement, a brisk palpebral reflex or spontaneous breathing against
138 mechanical ventilation, propofol 1 mg/kg was administered IV. Such cases were recorded as arousal
139 events. The occurrence of iRA in relation to body weight and age was recorded.

140 Events of bradycardia (HR <60 beats/min and hypotension [MAP <60 mmHg for at least 5 min or
141 MAP <55 mmHg] were recorded. Hypotension was treated by reducing the propofol infusion rate by
142 20% and giving a 3 ml/kg bolus of Lactated Ringer's solution IV over 60 sec. An additional 2 ml/kg
143 of fluid over 60 sec was administered if the MAP was increased after the first bolus. If hypotension
144 persisted, a bolus of ephedrine (50–100 µg/kg) and/or a continuous rate infusion of norepinephrine
145 (0.1–0.3 µg/kg/min) was given. At 30 min before the end of the operation, 0.2 mg/kg of meloxicam
146 (5 mg/ml; Meloxidolor; Dechra, Raamsdonksveer, Holland) were administered subcutaneously (SC).
147 At the end of the operation, the urinary bladder was voided manually. Intraoperative evaluation was
148 performed by the same operator who administered the epidural anesthesia.

149 *Postoperative Evaluation and Treatment*

150 An experienced operator blinded to treatment evaluated postoperative pain at 4, 6, and 8 hr after
151 epidural injection according to the Glasgow composite pain scale short form [21]. Methadone (10
152 mg/ml; Semfortan; Dechra Eurovet Animal Health BV) 0.1 mg/kg was administered IM if the pain
153 score was $\geq 6/24$. The dogs were re-evaluated 30 min later to check whether it was sufficient, or a
154 further methadone IM dose (0.1 mg/kg) was needed.

155 The ability to walk was tested at 3, 4, 5, 8, and 12 hr after the neuraxial technique. The dogs were
156 assisted to stand up, if necessary, but they had to walk on their own. The ability to walk was not
157 evaluated in the dogs unable to walk before surgery or had postoperative leg bandaging. In the dogs
158 without postoperative bandaging of the operated leg, the proprioceptive residual deficit was assessed
159 by supporting the dog's weight and placing the dorsum of the paw on the ground. A delayed response
160 was defined as a greater than 2-sec lag between paw placement and correction.

161 Urinary retention was defined as the inability to spontaneously void in the presence of bladder
162 overdistension. Bladder overdistention was evaluated by abdominal palpation and ultrasonography
163 in the dogs that did not spontaneously urinate within 12 hr after discharge from the veterinary clinic.
164 The owners were instructed to monitor their dog's micturition and to report episodes of prolonged
165 sedation and marked lameness. If the owner noted that the dog had not urinated for at least 12 hr, the
166 dog was to be returned to the veterinarian hospital.

167 *Statistical Analysis*

168 The estimated sample size to detect a difference in the primary endpoint (power of 80% and alpha
169 error of 5%) assuming an iRA incidence (derived from a pilot study) of 50% in the LS group and
170 25% in the LL group, respectively, [28] was 55 dogs per group. Accounting for possible dropouts,
171 we enrolled 60 dogs per group, with interim statistics planned after at least 80 or 100 dogs met the
172 inclusion criteria to interrupt the study if the data indicated superiority of one of the two groups.
173 Categorical variables are reported as frequency and percentage; Fisher's exact test was used to
174 determine frequency distribution independence between the two groups. The Lilliefors test was
175 performed on continuous variables to check for normal distribution. Not normally distributed data
176 are reported as the median and the range (minimum-maximum) and were analyzed by using the
177 Mann–Whitney *U* test. The intraoperative time-to-event probability of iRA was analyzed using
178 Kaplan–Meier survival analysis. The curves were analyzed using the log-rank test, and the hazard
179 ratio statistic was computed. Potential confounding factors between groups were investigated with a
180 univariate logistic regression model.

181 Statistical analysis was performed using MedCalc Software for Windows version 12.5
182 (MedCalcSoftware, Ltd., Belgium). Significance was set at 5% for all statistical methods. The odds
183 ratio (OR) and confidence intervals (CI) were calculated using the odds ratio function of the
184 epitools library in R version 4.1.2.

185

186 **Results**

187 Demographics (breed, age, weight, ASA class, type of surgery) are presented in Appendix A1. There
188 was no difference between the two groups for median weight, age, or area of surgery (Appendix A1).
189 Procedural data for median interval time in the LS and the LL group from induction to epidural
190 injection (min), from epidural injection to skin incision (min), from skin incision to end of surgery
191 (min), and the median anesthesia time (min) are presented in Table 1. The CONSORT diagram shows
192 the number of dogs entered in intraoperative and postoperative analysis (Fig 1).

193 The study sample was 98 dogs: 47 in the LS group and 51 in the LL group. Epidural injection failed
194 in 7/47 (15%) group LS dogs and 8/51 (16%) group LL dogs ($P = 1.00$), respectively. No cases of
195 accidental dural puncture with outflow of cerebrospinal fluid were recorded.

196 The overall iRA percentage in the LL group (13/43; 30%) was lower than that in the LS group
197 (21/40; 52%) (OR 0.40 with $P = 0.047$, 95% CI 0.16 to 0.97).

198 The probability of iRA over time described by a Kaplan-Meier survival curve is shown in Fig. 2. The
199 median fentanyl ($\mu\text{g}/\text{kg}$) consumption during surgery was 1 (0-3) $\mu\text{g}/\text{kg}$ in the LS group and 0 (0-2)
200 $\mu\text{g}/\text{kg}$ in the LL group, respectively ($P = 0.15$). The median time to the first fentanyl bolus was 45
201 min (range, 35-110) in the LS group and 48 min (range, 35-80) in the LL group, respectively ($P =$
202 0.76).

203 Body weight was checked as a confounding factor and a logistic regression was made with body
204 weight as predictor of iRA as dependent variable. In neither group (LL and LS) body weight was
205 shown to be a significant predictor of iRA (OR in LS group: 1.03 with $P = 0.25$; 95% CI 0.97 to

206 1.09; OR in LL group: 1.05 with $P = 0.24$; 95% CI 0.97 to 1.13). The median body weight was 14 kg
207 (range, 2-46) in the dogs that needed iRA and 8 kg (range, 3-34) in those that didn't ($P = 0.12$).

208 Also, the age was not a predictor of iRA in both groups (OR in LS group: 0.93 with $P = 0.48$; 95%
209 CI 0.79 to 1.12; OR in LL group: 1.046 with $P = 0.08$; 95% CI 0.64 to 1.03). The median age was
210 4.5 years (range, 0.58-12) in the dogs that received iRA and 5 years (range, 0.5-12.5) in those that
211 didn't. ($P = 0.11$)

212 Hypotension developed in 10/40 (25%) LS group dogs and in 16/43 (37%) LL group dogs,
213 respectively ($P = 0.25$) and bradycardia in 3/40 (7%) LS group dogs and in 5/43 (11%) LL group
214 dogs, respectively ($P = 0.71$). No arousal events during surgery were recorded.

215 Postoperative ability to walk was evaluated in 52 dogs; no differences between the two groups were
216 noted (Table 2).

217 The odds ratio to have a proprioceptive residual deficit at 8 hr in Group LL compared to group LS
218 was 7.14 ($P = 0.01$; 95% CI 33.33 to 1.85). Proprioceptive residual deficit at 8 hr was recorded in
219 3/26 (12%) group LS dogs and in 13/26 (50%) group LL dogs ($P = 0.01$).

220 Median body weight is 8 (2-33) kg and 20 (3-34) kg in group LS and LL respectively and differs for
221 body weight ($P = 0.01$). Body weight was checked as a confounding factor and a logistic regression
222 was made with body weight as predictor of proprioceptive residual block as dependent variable. In
223 neither group (LL and LS) body weight was shown to be a significant predictor of residual blockage
224 (OR in LL group: 1.07 with $P = 0.23$; 95% CI 0.98 to 1.17; OR in LL group: 1.05 with $P = 0.55$; 95%
225 CI 0.94 to 1.17).

226 A proprioceptive residual deficit at 24 hr after epidural injection was recorded in 1 LL group dog,
227 which resolved completely within 36 hr.

228 All dogs were evaluated according to the Glasgow pain scale at 4 hr after epidural injection, 35/43
229 (81%) and 30/40 (75%) at 6 hr, and 17/43 (39%), and 15/40 (37%) at 8 hr in the LS group and the
230 LL group, respectively. None required postoperative rescue analgesia during the observation period.

231 No episodes of postoperative urinary retention, pruritus, or neurological damage were recorded.

232

233 **Discussion**

234 To our best knowledge, this is the first clinical experimental study in dogs to show that the space of
235 epidural injection affects EA efficacy and to report a consistent number of epidural punctures
236 performed via the paramedian approach. Less need for iRA was recorded for the dogs that received
237 a more cranial injection of LA in the epidural space (LL group) than those that received lumbosacral
238 administration (LG group). A possible explanation for the difference is the better matching between
239 the spinal metamers innervating the body area operated and the local anesthetic block in the LL group
240 [5, 19]. The more cranial LA injection into the epidural space may have allowed for a more cranial
241 spread of the LA throughout the epidural canal, thus providing a more profound nerve block of the
242 L4-L6 spinal metamers from which the femoral nerve derives [18, 22]. In addition, the abundant fat
243 surrounding the cauda equina, which works as a reservoir of LA, may limit the cranial spread of LA
244 when an epidural injection is given at the lumbosacral intervertebral space. Furthermore, the lumbar
245 intumescence reduces the epidural space from the L3 to the L6 intervertebral space and this may have
246 facilitated the spread of the LA in the LL group [14, 26].

247 The need for iRA was significantly lower in the LL group, though its incidence remained relatively
248 high (30%). The success rate of epidural analgesia is a frequent clinical problem in human
249 medicine, where epidural block fails to provide adequate surgical analgesia in up to 50% of cases
250 [4, 11]. At any rate, we may speculate that epidural anesthesia is subjected to a certain degree of
251 failure no matter a failure in the technical execution of the block and the dosing regimen, which
252 could stem from the difficulty to achieve an even distribution of the LA within the epidural space
253 [8]. There is some evidence that the use of air for identifying the epidural space with the LOR
254 technique [13] can affect epidural spread and reduce block quality [23]. We cannot rule out that the
255 use of air in the LOR technique may have contributed to increasing the incidence of iRA.

256 We noted, however, that immediate postoperative analgesia was sufficient in all dogs in which
257 postoperative pain was evaluated. Nevertheless, the brevity of postoperative pain monitoring
258 precludes a comparison of the overall duration of postoperative analgesia between the two techniques.
259 Nearly 90% of the dogs in both groups were able to walk at 8 hr postoperative; however, a
260 proprioceptive residual deficit at 8 hr was recorded in 50% of the LL group dogs and in 13% of the
261 LS group dogs. It is reasonable to assume that a longer residual block ensued after the more profound
262 block in the LL group (lower iRA incidence).

263 Body weight didn't reach a statistical significance as predictor of proprioceptive residual deficit.
264 For this study we limited the LA dosage to 6 ml in dogs weighing >30 kg [10]. Though this cut-off
265 lacks scientific evidence, it has been suggested [2] to shorten motor recovery in big sized dog. The
266 dose regimen used in our study did not seem to increase the incidence of prolonged motor block and
267 the need for iRA in the large dogs. Previous studies have suggested dose regimens according to length
268 of the spine [2, 17] based on the hypothesis that there is no linear relationship between body weight
269 and LA dose requirement. This notion is largely supported by anatomical studies performed with
270 methylene blue in dogs [25]. However, correlating the level of an effective nerve block with the
271 spread of a marker solution can be misleading. Studies using contrast medium in humans failed to
272 find a strong correlation between the epidural spread of a solution and the level of the sensitive block
273 [26].

274 Ours is the first clinical study to report a consistent number of epidural punctures performed via the
275 paramedian technique and to show that it is not burdened by a higher incidence of procedural failure
276 than the median approach to L7-S1 although the intervertebral spaces cranial to L7-S1 are much
277 smaller. The paramedian approach offers bony landmarks (e.g., the spinal process and the vertebral
278 lamina) that help direct the needle toward the interspinous space. Differently, in the median
279 technique, if the bone instead of the ligamentous flavum is reached at the first attempt, the operator
280 does not know where to redirect the needle. One concern with using a more cranial epidural approach
281 is the potentially higher risk of damaging the spinal cord than at the L7-S1 level. In humans, however,

282 when thoracic epidural catheterization is performed by a trained operator, the incidence of permanent
283 neurological complications can be as low as $<0.02\%$ [1]. Monitoring needle insertion into the epidural
284 space remains a criticality that impacts on the success of the block and reduces the risk of iatrogenic
285 nerve damage. In our study, we used the LOR technique coupled with radiography to increase the
286 accuracy of the epidural technique, which can be achieved only with LOR. Nonetheless, the risk of
287 intrathecal puncture or nerve damage cannot be completely ruled out. Future studies are required to
288 prove the safety profile of the paramedian epidural anesthesia technique in dogs.

289 A proprioceptive residual block at 24 hr was recorded in one LL group dog. The transient neurological
290 syndrome following epidural anesthesia is a well-known complication in humans [3, 20]. The
291 syndrome is unlikely related to mechanical problems. A more plausible explanation is the profound
292 effect of the nerve response spectrum to the LA, since neuronal reaction to LA is variable in nature
293 [20].

294 Our study has several limitations. The lack of standardization of the type of surgery may have
295 introduced a bias in the evaluation of iRA, though the type of surgery did not differ between the two
296 groups. The anesthesiologists involved in the study were not blinded to group treatment, and they
297 were free to manage anesthetic depth without a pre-set protocol. This limitation may have been an
298 additional source of bias. Finally, the postoperative observation period was too short to evaluate
299 postoperative rescue analgesia needs thoroughly. Further studies are needed to define this aspect
300 better.

301 In this sample of dogs undergoing hindlimb orthopedic surgery, the occurrence of iRA was lower in
302 the group that received an epidural injection of LA at the L5-L6 level than in the group that received
303 an epidural injection at the lumbosacral level, but the recovery of nerve function was slower. Further
304 studies are needed to determine whether injection at L5-L6 with a lower LA dosage can reduce the
305 duration of postoperative residual block without increasing the need for iRA.

306
307 Conflict of Interest Statement: The authors declare no conflict of interest

308 Acknowledgments: none

309

310 REFERENCES

- 311 1. Absalom, A. R., Marinelli, G. and Scott, N. B. 2001. Spinal cord injury caused by direct
312 damage by local anaesthetic infiltration needle. *Br. J. Anaesth.* **87**: 512-515.
- 313 2. Caniglia, A. M., Driessen, B., Puerto, D. A., Bretz, B., Boston, R. C. and Larenza, B. P. 2012.
314 Intraoperative antinociception and postoperative analgesia following epidural anaesthesia
315 versus femoral and sciatic nerve blockade in dogs undergoing stifle joint surgery. *J. Am.*
316 *Vet. Med. Assoc.* **241**: 1605-1612.
- 317 3. Cuerden, C., Buley, R. and Downing, J. W. 1977. Delayed recovery after epidural block in
318 labour. A report of four cases. *Anaesthesia* **32**: 773-776.
- 319 4. Curatolo, M., Orlando, A., Zbiden, A. M., Scaramozzino, P. and Venuti, F.S. 1995. A
320 multifactorial analysis to explain inadequate surgical analgesia after extradural block. *Br. J.*
321 *Anaesth.* **75**: 274–281.
- 322 5. Dogliotti, A. M. 1931. Ein neu methode der regionaren anaesthesia. Die peridurale
323 segmentare anesthesie. *Zentralblatt fur chirurgia* **58**: 3141-3145.
- 324 6. Evans, E.H. and de Lahunta, A. 2013. Spinal nerves Miller’s anatomy of the dog. 4th
325 edition. St Louis (MO): Elsevier; pp. 611–657.
- 326 7. Franci, P., Leece, EA. and Corletto, F., 2012. Thoracic epidural catheter placement using a
327 paramedian approach with cephalad angulation in three dogs. *Vet. Surg.* **41**: 884-889.
- 328 8. Freire, C. D., Torres, M. L., Fantoni, D. T., Cavalcanti, R. L. and Noel-Morgan, J. 2010.
329 Bupivacaine 0.25% and Methylene Blue Spread with Epidural Anesthesia in Dog. *Vet.*
330 *Anaesth. Analg.* **37**: 63-69.
- 331 9. Gerrard, A. D., Brooks, B., Asaad, P., Hajibandeh, S. and Hajibandeh, S. 2017. Meta-analysis
332 of Epidural Analgesia Versus Peripheral Nerve Blockade After Total Knee Joint
333 Replacement. *Eur. J. Orthop. Surg. Traumatol.* **27**: 61-72.

- 334 10. Hendrix, P. K., Raffe. M. R., Robinson, E. P., Felice, L. J. and Randall, D. A. 1996. Epidural
335 administration of bupivacaine, morphine, or their combination for postoperative analgesia in
336 dogs. *J. Am. Vet. Med. Assoc.* **209**: 598–607.
- 337 11. Hermanides, J., Hollmann, M. W., Stevens, M. F. and Lirk, P. 2012. Failed epidural: causes
338 and management. *Br. J. Anaesth.* **109**: 144-154.
- 339 12. Higuchi, H., Adachi, Y. and Kazama, T. 2004. Factors Affecting the Spread and Duration of
340 Epidural Anesthesia with Ropivacaine. *Anesthesiology* **101**: 451-460.
- 341 13. Iseri, T., Nishimura R., Nagahama S., Mochizuki M., Nakagawa T., Fujimoto Y., Zhang D.,
342 Sasaki N. 2010. Epidural spread of iohexol following the use of air or saline in the 'loss of
343 resistance' test. *Vet. Anaesth. Analg.* **37**: 526-530.
- 344 14. Macdonald, A., Chatrath, P., Spector, T. and Ellis, H. 1999. Level of termination of the spinal
345 cord and the dural sac: a magnetic resonance study. *Clin. Anat.* **12**: 149-152.
- 346 15. Manchikanti, L., Cash, K. A., Pampati, V., McManus, C. D. and Damron, K. S. 2004.
347 Evaluation of fluoroscopically guided caudal epidural injections. *Pain Physician* **7**: 81-92.
- 348 16. Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J.,
349 Elbourne, D., Egger, M. and Altman, D. G. 2010. CONSORT 2010 explanation and
350 elaboration: updated guidelines for reporting parallel group randomised trials. *J. Clin.*
351 *Epidemiol.* **63**: e1ee37.
- 352 17. Otero, P. and Campoy, L. 2013. Epidural and Spinal Anesthesia pp. 232-233. In: Small animal
353 regional anesthesia and analgesia, 1st ed. (Campoy. L. and Read. M. R. eds) Wiley-Blackwell,
354 Ames.
- 355 18. Otero, P. and Portela, D. 2019. Manual of small animal regional anaesthesia pp. 138-139, 2th
356 ed., Intermedica Editorial, Republica Argentina, Buenos Aires.
- 357 19. Pagés, F. 1991. Metameric anesthesia. *Rev. Esp. Anesthesiol. Reanim.* **38**: 318-326.
- 358 20. Pathy, G. V. and Rosen, M. 1975. Prolonged Block with Recovery After Extradural Analgesia
359 for Labour. *Br. J. Anaesth.* **47**: 520-522.

- 360 21. Reid, J., Nolan, A. M., Hughes, J. M. L., Lascelles, D. and Scott, E. M. 2007. Development
361 of the short-form Glasgow Composite Measure Pain Scale (CMPS- SF) and derivation of an
362 analgesic intervention score. *Animal. welfare suppl.* **1**: 97-104.
- 363 22. Schaller, O. 1992. Nomenclatura anatomica veterinaria illustrata (1st edn), Antonio Delfino
364 Editore, Italia, pp. 488-492.
- 365 23. Saberski L. R., Kondamuri S., Osinubi O.Y. 1997. Identification of the epidural space: is loss
366 of resistance to air a safe technique? A review of the complications related to the use of air.
367 *Reg. Anesth.* **22**: 3-15.
- 368 24. Sarotti, D., Rabozzi, R. and Franci, P. 2015. Comparison of epidural versus intrathecal
369 anaesthesia in dogs undergoing pelvic limb orthopaedic surgery. *Vet. Anaesth. Analg.* **42**: 405-
370 413.
- 371 25. Son, W. G., Kim, J., Seo, J. P., Yoon, J., Choi, M., Lee, L. Y. and Lee, I. 2011. Cranial
372 epidural spread of contrast medium and new methylene blue dye in sternally recumbent
373 anaesthetised dogs. *Vet. Anaesth. analg.* **38**: 510-515.
- 374 26. Usubiaga, J., Wikinski, J., Wikinski, R., Usubiaga, L. E. and Pontremoli, M. 1964. Transfer
375 of Local Anesthetics to the Subarachnoid Space and Mechanisms of Epidural Block.
376 *Anesthesiology* **25**: 752-759.
- 377 27. Visser, W. A., Lee, R. A. and Gielen, M. J. 2008. Factors affecting the distribution of neural
378 blockade by local anesthetics in epidural anesthesia and a comparison of lumbar versus
379 thoracic epidural anesthesia. *Anest. Analg.* **107**: 708-721.
- 380 28. Wang, H. and Chow, S. C. 2007. Sample Size Calculation for Comparing Proportions.
381 Wiley Encyclopedia of Clinical Trials. doi.org/10.1002/9780471462422.eoct005.

382

383

384

385

386 **Appendix A:** Demographic data of dogs [median (range)] that met the inclusion criteria for
 387 allocation to the LS group or the LL group in which EA was successful performed. ASA class (American
 388 Society of Anaesthesiologists); TPLO (tibial plate levelling osteotomy); FHNO (femoral head and neck
 389 ostectomy).

	Group LS (n=40)	Group LL (n=43)	<i>P</i>
Breed (no.)	13 Mixed breed 3 Labrador 3 Yorkshire 2 Pincher 2 Dachshund 2 Beagle 2 Jack Russel 13 Other breeds	17 Mixed breed 4 Labrador 4 AMSTAF 3 Beagle 2 Pincher 2 Setter 2 Yorkshire 9 Other breeds	
Age (years)	5.5 (range, 0.5-12)	4 (range, 0.6-13)	0.24
Weight (kg)	8 (range, 2-46)	15 (range, 3-34)	0.15
Type of surgery	1 Achilles tendon repair 1 Osteosynthesis of a tibial fracture 11 FHNO 3 Medial patellar luxation repair 5 Extracapsular repair of anterior cruciate ligament 18 TPLO 1 Osteosynthesis of femoral fracture	1 Achilles tendon repair 3 Osteosynthesis of a tibial fracture 4 FHNO 3 Medial patellar luxation repair 4 Extracapsular repair of anterior cruciate ligament 24 TPLO 4 Osteosynthesis of femoral fracture	

ASA Class	ASA I 37/40	ASA I 35/43	0.20
(no.)	ASA II 3/40	ASA II 8/43	0.20

390

391

392

Table 1 Procedural data for the Group LS (epidural anesthesia placed at the lumbosacral junction) and the Group LL (epidural anesthesia placed to the L5-L6 junction).

393

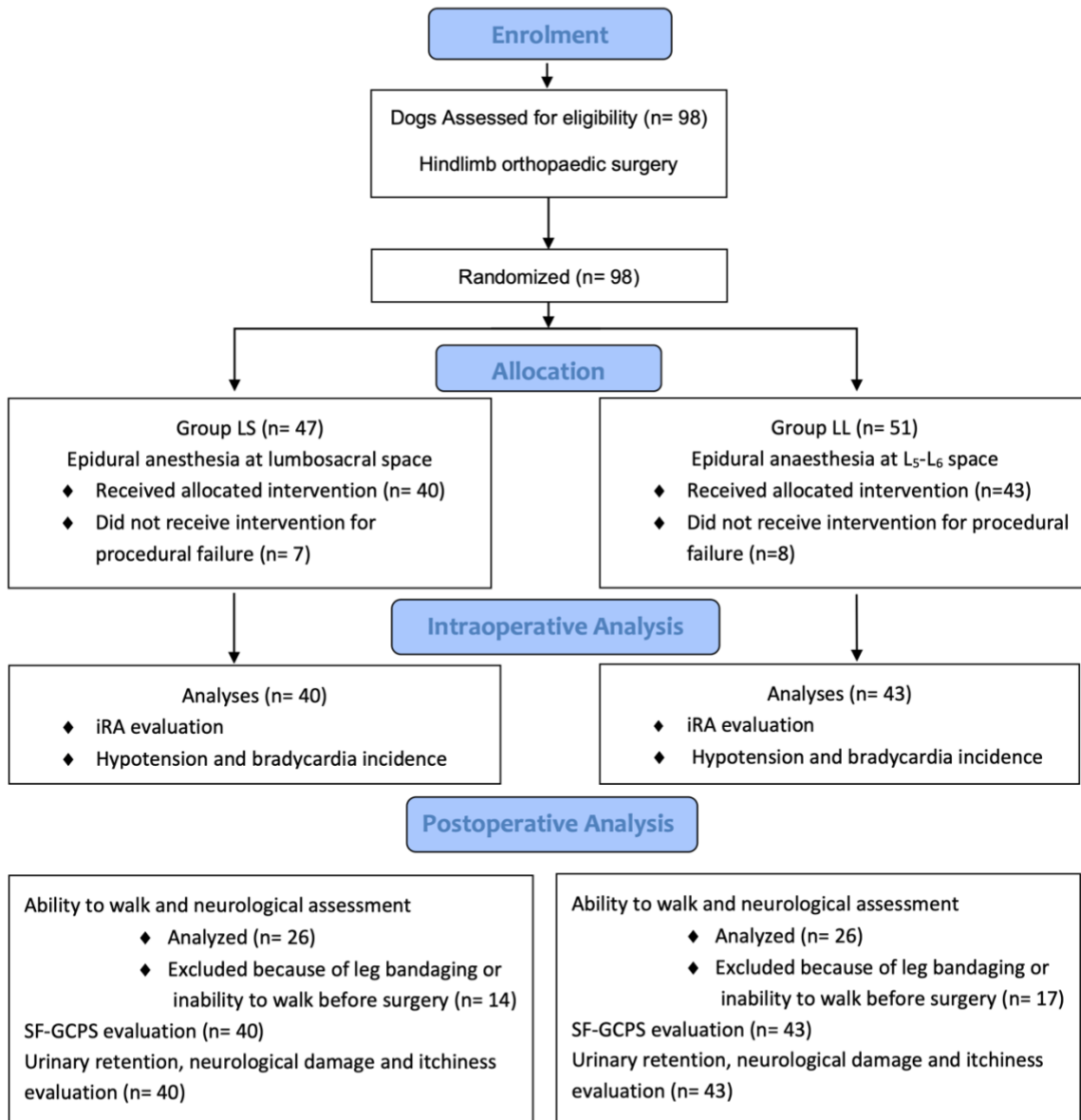
	Group LS (n=40)	Group LL (n=43)	<i>P</i>
Median propofol induction bolus (mg/kg)	5.5 (range, 4.0-8.0)	5.0 (range, 4.0-7.0)	0.43
Median propofol rate infusion (mg/kg/hr) after epidural injection	24 (range, 15-30)	23 (range, 15-35)	1.00
Median time between induction and epidural injection (min)	16 (range, 15-35)	17 (range, 15-28)	0.70
Median time between epidural injection and skin incision (min)	25 (range, 21-28)	28 (range, 22-35)	0.42
Median time between epidural injection and end of surgery (min)	90 (range, 60-120)	95 (range, 60-110)	0.65
Median time of entire anaesthesia duration (min)	115 (range, 90-160)	110 (range, 85-140)	0.51

394
395
396
397
398
399
400
401

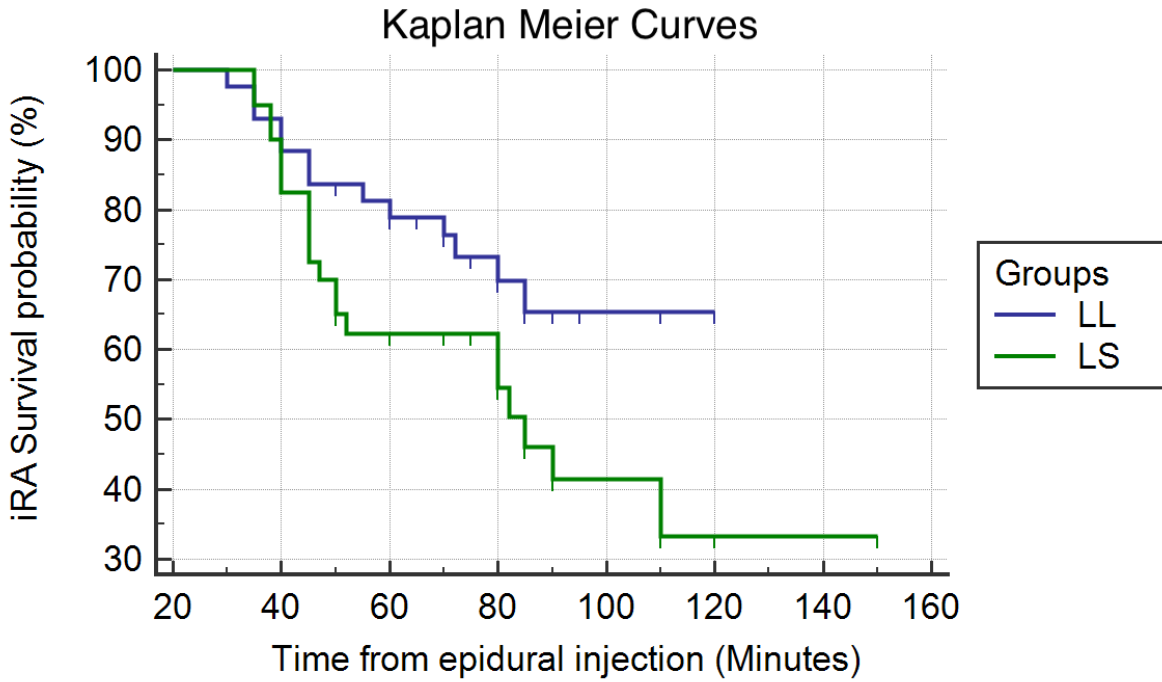
Table 2. Percentage of dogs able to walk (%) at 3, 4, 5, 8, and 12 hr after local anaesthetic injection and proprioceptive residual deficit at 8 hr in 52 dogs. No differences between the two groups concerning the ability to walk were recorded. Proprioceptive residual deficit at 8 hr results higher in Group LL (epidural anesthesia placed at the lumbosacral junction), ($P = 0.01$). Group LL (epidural anesthesia placed to the L5-L6 junction).

	Group LS n=26 (%)	Group LL n=26 (%)	<i>P</i>
Ability to walk			
At 3 hr	1/26 (4)	3/26 (12)	0.35
At 4 hr	5/26 (19)	5/26 (19)	1.00
At 5 hr	18/26 (70)	11/26 (42)	0.09
At 8 hr	24/26 (92)	23/26 (88)	1.00
At 12 hr	26/26 (100)	25/26 (96)	1.00
Proprioceptive residual deficit			
At 8 hr	3/26 (12)	13/26 (50)	0.01

FIG. 1 CONSORT 2010 Fw Diagram



402 Figure 2 The time-to-event probability of intraoperative rescue analgesia (iRA) was analyzed using
 403 a Kaplan–Meier survival analysis for the two groups. The iRA percentage (100-iRa survival
 404 probability) at 80 min after epidural injection was 45% in the LS group and 30% in the LL group,
 405 respectively. The iRA survival curves differed significantly for the observation period (P = 0.046 log-
 406 rank test). Hazard ratios for the LL group with 95% CI were 0.50 (0.25 to 0.99). Censored' refers to
 407 subjects for which no events (iRA) were observed during surgery. A small vertical line denoted
 408 censored data in the graph.



Number at risk

Group: LL

43	38	32	16	6	0	0	0
----	----	----	----	---	---	---	---

Group: LS

40	33	19	13	5	1	1	0
----	----	----	----	---	---	---	---