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**Post-operative analgesia following TPLO surgery: A comparison between cimicoxib and tramadol**

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1 **Post-operative analgesia following TPLO surgery: a comparison**  
2 **between Cimicoxib and Tramadol**

3  
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15 INTRODUCTION

16

17 Tibial plateau levelling osteotomy (TPLO) is an orthopedic procedure commonly performed to  
18 stabilize a stifle joint affected by cranial cruciate ligament rupture (Kim et al., 2008; Slocum and  
19 Slocum, 1993). TPLO is an invasive technique that involves arthrotomy, moderate soft tissue  
20 elevation, osteotomy, and bone plate application. As with many major orthopedic procedures,  
21 dogs that have TPLO may be painful postoperatively.

22 Postoperative orthopaedic pain has an acute onset with an inflammatory and a somatic  
23 component (soft tissue and bone) in addition to the persistent pain condition secondary to the  
24 orthopaedic disease being treated. Accurate pain assessment and treatment with a multimodal  
25 protocol (Davila et al., 2013) represent the best approach to these patients in order to improve  
26 the quality of recovery and fasten the return to the normal function. Opioids and non-steroidal  
27 anti-inflammatory drugs (NSAIDs) are the systemic drugs most commonly used in the  
28 postoperative period to treat pain and inflammation (Horstman et al., 2004).

29 The NSAIDs are commonly included in the perioperative protocols for their duration of action,  
30 safety and efficacy as analgesics for both soft tissue and orthopaedic procedures. Moreover  
31 these drugs have clearly demonstrated a potential pre-emptive effect and the prolongation of  
32 analgesia during the recovery phase (Duncan et al., 2005). The NSAIDs exerts their anti-  
33 inflammatory effects inhibiting the isoforms of cyclo-oxygenases (COX-1 and COX-2) synthase  
34 which synthesize prostaglandins from the arachidonic acid, limiting inflammation and pain. In  
35 the last decade selective COX-2 inhibitors (COXIBs) has been developed in order to reduce  
36 the side effects related to the use of these drugs (Kukanich et al., 2012) although strong  
37 evidences in dogs are still lacking. Cimicoxib, is one of the latest COXIBs that has been licensed

38 in Europe for the long-term management of pain and inflammation associated with OA  
39 (Grandemange et al., 2013; Jeunesse et al., 2013; Kim et al., 2014; Kukanich et al., 2012;  
40 Murrell et al., 2014), and the management of perioperative pain due to orthopaedic or soft tissue  
41 surgery in dogs (Grandemange et al., 2013; Murrell et al., 2014).

42 Cimicoxib (2 mg/kg/24h) has been compared with carprofen (4 mg/kg/24h) for the control of the  
43 postoperative pain in dogs undergoing surgical procedures in which minor or moderate surgical  
44 pain was expected (Mich and Hellyer, 2009; Weil et al., 2016). The drugs proved to be non-  
45 inferior to the control treatment for the first 24 postoperative hours but also up to 6 days  
46 postoperatively. Another study published in 2018 (Bustamante et al., 2018) compared the  
47 postoperative analgesic effects of cimicoxib with that of buprenorphine in dogs undergoing  
48 ovariectomy and proved that the NSAID was non inferior to the opioid in providing pain relief.

49 Tramadol is a centrally acting analgesic with a low affinity for the mu- and delta-opioid receptors,  
50 and a weaker affinity for the kappa-subtype; it also interferes with the neuronal release and re-  
51 uptake of serotonin and norepinephrine in descending inhibitory pathways (Kukanich and  
52 Papich, 2004; Raffa et al., 1993, 1992). Its analgesic effects are mostly attributable to the  
53 production of active metabolites, in particular the M1 metabolite has 200 times the potency on  
54 mu receptors compared to the parent drug (Raffa et al., 1992). Tramadol is registered for use  
55 in dogs and cats in Italy and few other European countries. Its use has recently increased in  
56 popularity in veterinary practice and it is used for the treatment of both chronic and acute pain,  
57 because of the mild severity of side effects and large dosing intervals (Baraka et al., 1993;  
58 Benitez et al., 2015; Delgado et al., 2014; Dhanjal et al., 2009; Malek et al., 2012; Mastrocinque  
59 and Fantoni, 2003; Murphy et al., 2010; Pypendop et al., 2009; Sunshine et al., 1992; Vettorato  
60 et al., 2010). It has been reported to provide postoperative analgesia similar to morphine and  
61 buprenorphine, but also others investigators questioned its suitability for use in dogs because

62 of the rapid elimination of the active metabolites (Giorgi et al., 2009; Kögel et al., 2014; Perez  
63 Jimenez et al., 2018; Perez et al., 2016).

64 The aim of this study was to compare the clinical outcomes of a long term (30 days) oral  
65 administration of cimicoxib or tramadol in the postoperative period of dogs undergoing elective  
66 TPLO surgery. The primary end-points of the study were the assessment of pain and return of  
67 the limb to the normal function. Our hypothesis was that cimicoxib and tramadol would be  
68 similar in terms of pain control and return to normal function in the 30 postoperative days. To  
69 test our hypothesis dogs undergoing elective TPLO were subjected to periodical evaluation of  
70 computer assisted gait analysis and different scores for pain evaluation in the observational  
71 period.

## 72 MATERIALS AND METHODS

### 73 *Experimental design, animal population and sample size*

74 This was planned as a prospective, double blind, randomized clinical study and was approved  
75 by the Ethical Committee of the XXX, and written informed consent was obtained from the  
76 owners prior to the enrollment.

77 Client-owned dogs scheduled for TPLO between July 2014 and March 2016 were involved in  
78 the study. To be included in the study, all dogs were required to be affected by complete cranial  
79 cruciate ligament rupture with partial tear of the meniscus, to weigh between 15 kg and 55 kg,  
80 and to have normal findings on physical examination and results of pre-operative CBC and  
81 serum biochemical analyses. Only dogs with a partial meniscal tear in which a partial  
82 meniscectomy was required were considered, because this is the condition most commonly  
83 found in dogs and a meniscal integrity or a complete damage would have been a factor  
84 influencing the postoperative pain (Gatineau et al., 2011).

85 Dogs were excluded from the study if suffering of concurrent orthopedic or neurologic disease,  
86 appeared aggressive or highly anxious, had an unmanageable disposition, if at time of surgery  
87 menisci were intact or completely lacerated, or if laceration of the popliteal artery or fibular  
88 fracture had occurred during or after surgery.

89 The number of animals per treatment group was estimated on the basis of a sample size  
90 calculation considering the peak vertical force (PVF) variable as the primary outcome. The PVF  
91 means and SD values used for this purpose were identified in previous studies (Au et al., 2010;  
92 Bøddeker et al., 2012; Gordon-Evans et al., 2010) at a time in which a statistical difference  
93 between groups would be expected (3 - 5 weeks post surgery). To obtain a statistical  
94 significance, the expected mean PVF difference considered was 2.37% BW and the standard

95 deviation 1.9% BW. The calculation revealed that, in order to detect with one way analysis of  
96 variance a minimum difference between groups with power of 0.90, 95% level of confidence  
97 and  $\alpha$  value set at 0.05, each treatment group should have been composed of a minimum of  
98 15 subjects. Therefore, considering the difficulties of experimental analysis and potential  
99 missing values, 21 subjects were assigned to each group.

100

### 101 *Anesthetic protocol*

102 All dogs received 2 hours before surgery 2 mg/kg OS of cimicoxib and 30 minutes before the  
103 beginning of the procedure were premedicated with intramuscular (IM) methadone (0.2 mg/kg;  
104 Synthadon, Le Vet Beheer B.V., Netherlands). Thereafter, intravenous (IV) propofol  
105 (Proposure, Merial Italia Spa, Italy) was titrated to effect to induce general anaesthesia. After  
106 orotracheal intubation, isoflurane (Isoflo; Esteve Spa, Spain) was delivered in oxygen via a  
107 circle system and lactated Ringer's solution was perfused IV (3 ml/kg/h, Ringer's solution;  
108 Fresenius Kabi, Italy). The dogs were fully monitored and cardiovascular and respiratory  
109 parameters and esophageal temperature ( $T^{\circ}$ ) was manually recorded every 5 minutes until the  
110 end of anesthesia. Dogs received cefazolin (IV) (22 mg/kg, Cefafazolina Teva, Teva Italia Srl,  
111 Italy) at induction, every 90 minutes during surgery, and every 12 hours after surgery for 6 days.  
112 In the post-operative phase, dogs received regularly intravenous (IV) buprenorphine (0.01  
113 mg/kg, q 6 h, Buprenodale, Dechra Ltd, UK), for 24 hours, with the first dose given at the time  
114 of extubation. All patients were monitored for signs of pain after surgery at frequent intervals as  
115 a part of routine standard of care for surgery patients. If signs of pain were detected, analgesia  
116 with Methadone [0.25 to 0.5 mg/kg, IM, q 4 h or as needed] was administered, treatment failure

117 was recorded, and the patient was re-assessed to ensure any pain was below the minimum  
118 threshold. Any patient that required additional medication was excluded from the study.

119

### 120 *TPLO procedure*

121 All surgeries were performed by the same orthopedic surgeon (XX). Each stifle joint was  
122 inspected via a medial para-patellar arthrotomy. After debridement of the cranial cruciate  
123 ligament, menisci were evaluated. Partially damaged menisci were treated with a partial  
124 meniscectomy. Dogs with intact menisci or with complete meniscectomy were excluded from  
125 the study. A TPLO was performed as described by Slocum with jig application (Slocum and  
126 Slocum, 1993). Radial osteotomy and application of the bone plate was performed in a routine  
127 manner, using TPLO Synthes saw blade (DePuy Synthes Vet, West Chester, PA, USA) and  
128 TPLO-LCP Synthes plate (DePuy Synthes Vet, West Chester, PA, USA). Closure of the  
129 incisional wound was performed in a routine manner, using always the same type of suture  
130 materials. Radiographs were taken immediately after surgery. A modified Robert-Jones  
131 bandage was applied for 24 hours after surgery.

132

### 133 *Study Protocol*

134 At the follow-up at twenty-four hours after surgery animals were allocated to one of two post-  
135 operative treatment groups by block randomization method based on shuffle and drawing of  
136 treatment assignments inside an opaque, sealed envelope. Group 1 (CIM): dogs received 2  
137 mg/kg of cimicoxib orally SID for 30 days. Group 2 (TRM): dogs received 2 mg/kg of tramadol  
138 orally BID for 30 days. One operator not involved in the post-operative patient evaluation was



139 responsible for keeping the allocation list until the end of data collection. Owners were unaware  
140 of the drug administered to their dogs. To achieve appropriate blinding each dog also received  
141 placebo tablets to overcome the difference in dosing intervals between the two groups.

142 For the purposes of the study the following time points were considered: the day before surgery  
143 (T0), 24 hours after surgery (T1), 10 (T10), 20 (T20) and 30 (T30) days after surgery. At these  
144 time points, a single trained veterinary physician (XX), who was unaware of group-drug  
145 assignments, collected the following measurements: 1) computer-assisted force platform gait  
146 analysis; 2) subjective assessment of weight bearing while standing; 3) thigh circumference; 4)  
147 pain free stifle range of motion; 5) Visual Analogue Scale for pain; 6) assessment of the  
148 Glasgow composite measure pain scale short form; 7) assessment of the Helsinki Chronic Pain  
149 Index.

150

#### 151 *Computer-assisted force platform gait analysis*

152 Computer-assisted force platform gait analysis was performed using two force platforms  
153 mounted in series (BTS P-6000, BTS Bioengineering, Garbagnate Milanese, Italy) embedded  
154 in an 8 m walkway. Two cameras (BTS VIXTA, BTS Bioengineering, Garbagnate Milanese,  
155 Italy) connected to the acquisition software (3DGIVEC, BTS Bioengineering, Garbagnate  
156 Milanese, Italy) were used to record each trial. The dogs were weighed immediately before  
157 force plate data collection on a calibrated scale. Each dog was allowed to acclimate to the room  
158 before data collection began. The dogs were walked across the force platform until they  
159 appeared comfortable. The walking velocity and acceleration parameters were restricted to  
160 ranges of 1.1 to 1.3 m/s and  $\pm 0.5 \text{ m/s}^2$ , respectively. The velocity of each trial was measured  
161 by 3 photoelectric cells mounted 1 m apart on the force plate runway that were connected to a

162 millisecond timer in a start–interrupt fashion. The dogs were walked over the force plate by a  
163 trained assistant, data were collected independently from the left and right side of the body. A  
164 valid trial consisted of a forelimb strike, with the complete foot striking the center of the plate  
165 and without another foot being on the plate at the same time, followed by an ipsilateral hind foot  
166 strike in the same fashion. A single observer evaluated each foot strike and made the  
167 determination whether a trial was valid or not by means of camera recordings and curve  
168 morphology evaluation. The trial was discarded if the paw hit the edge of the force plate, if the  
169 contralateral paw hit the force plate or if the dog was distracted during the measurements. For  
170 each time point the data from at least 5 valid trials were selected and averaged. Stance time  
171 (ST), PVF and vertical impulse (VI) were evaluated. All of the forces were then normalized to  
172 the individual dog’s body weight.

173

#### 174 *Subjective assessment of weight bearing while standing (WB)*

175 Subjective assessment of weight bearing while standing was assessed (Monk et al.,  
176 2006) with a score from 1 to 5: typical weight bearing on limbs while standing; bears weight  
177 evenly on both pelvic limbs (1 point), stands on foot of affected limbs at all times but more  
178 weight on unaffected limb (2 points), stands on foot of affected limb most of the time but with  
179 minimal weight bearing (3 points), touches toes of affected limb to ground with rare or no weight  
180 bearing (4 points), no weight bearing on affected limb while standing (5 points).

181

#### 182 *Thigh circumference (TC)*

183 The thigh circumference was measured at the mid-point on the long axis of the femur. Length  
184 of the femur was measured by use of a standard 30-cm plastic ruler using the proximal most

185 aspect of greater trochanter and the distal most portion of the lateral femoral condyle as the  
186 proximal and distal points, and the point that was 50% along this length was used as the point  
187 for measuring the circumference of the thigh. The TC was measured by use of a specifically  
188 designed measuring tape (Gulick II Measuring Tape, Country Technology). The Gulick Tape  
189 design features a spring attached to an indicator designed to improve consistency in tape  
190 tension and thereby minimizes measurement variation resulting from differences in soft tissue  
191 compression. Measurements were obtained in triplicate with the stifle extended and the dogs  
192 positioned in lateral recumbency (Moeller et al., 2010). Each TC value was recorded and the  
193 mean of the three TC values were calculated and recorded. Due to the variation in TC that  
194 could be associated with breed and size of dogs the comparison of changes in TC rather than  
195 actual measurement were made.

196 The percentage change for the TC was calculated as:  $[(T_{30} - T_0)/T_0]*100$ .

197

#### 198 *Pain-free stifle range of motion (ROMs)*

199 ROMs of the stifle joint were measured (Jaegger et al., 2002) in triplicate by use of a single  
200 standard 18-cm full-circle plastic universal goniometer. Measurements were made for each limb  
201 with the dogs awake and positioned in lateral recumbency. The axis of the goniometer were  
202 placed over the lateral aspect of the stifle joint axis. The femoral arm was aligned with the  
203 greater trochanter and the tibial arm with the lateral malleolus. End of flexion or extension was  
204 determined when the dog flinched, vocalized, or pulled the limb away.

205

#### 206 *Visual Analogue Scale (VAS) assessment of post-operative pain*

207 Post procedural pain was also assessed on T1, T10, T20 and T30 by use of a visual analogue  
208 scale (VAS) that consisted of a 100-mm-long horizontal line with vertical bars at each end and  
209 was labelled “clinically sound” (0) at one end and “could not be more lame” (100) at the other  
210 end (Hielm-Björkman et al., 2011; Murrell et al., 2008).

211

212 *Glasgow Composite Measure Pain Scale – Short Form (CMPS-SF) assessment of*  
213 *post-operative pain*

214 Composite Measure Pain Scale – Short Form (Reid et al., 2007) was recorded by XX at times  
215 T1, T10, T20, T30 post-surgery. The scale ranges from 0 to 24 (0 = no pain and 24 = maximal  
216 pain measurable). The assessment was completed by the investigator after observation and  
217 manipulation of each dog (Monk et al., 2006; Murrell et al., 2008) as described in the instructions  
218 for use of the scale.

219

220 *Helsinki Chronic Pain Index*

221 We used the HCPI owner questionnaire that has been shown to have discriminatory and  
222 responsiveness validity (Hielm-Björkman et al., 2011) about the dog’s behavior and activity.  
223 The Helsinki chronic pain index total score was constructed as the sum of answers to 11  
224 questions. Each answer could be chosen from a 5-point descriptive scale. Answers were later  
225 tied to a value (0 to 4) and, when summed, gave a minimum total index score of 0 and a  
226 maximum of 44. Values and how to compute the total score were not available to owners while  
227 answering the questionnaire. Owners were asked to answer and to complete these questions  
228 on T10, T20 and T30.

229

230 *Drugs administration adverse effects*

231 Owners observed dogs for adverse effects and summarized observations in a questionnaire  
232 administered at the time of initiation of treatment. Types and frequency of adverse effects were  
233 recorded for each dog.

234

235 *Wound classification*

236 Wounds were inspected and scored (Murrell et al., 2008) from grade 0 to 4 as described in  
237 Appendix A 1 on T1, T10, T20 and T30. Grades II, III and IV with bacterial growth and varying  
238 degrees of inflammation or with obvious acute deep implants infection were managed according  
239 to the microbiological report of growth and sensitivity (Gaine et al., 2000).

240

241 *Statistical analyses*

242 Data were tested for normality with the Shapiro-Wilk test. Descriptive data (age, gender and  
243 weight) were compared between the two treatment groups by Student's T-test. For clinical and  
244 kinematic variables, statistical differences between the two groups at each time were assessed  
245 by Mann Whitney test (Table 1). Differences between the study times within each group were  
246 evaluated by Friedman test for all variables. A post-hoc analysis using Bonferroni correction  
247 was applied when necessary.

248 In addition, for the two groups the percentage change for the TC was calculated as:  $[(T_{30} -$   
249  $T_0)/T_0] * 100$ .

250 Data obtained from the owner questionnaire HCPI were compared with CMPS-SF and VAS  
251 score by means Spearman rank correlation.

252 Adverse effects were compared between groups by two-way ANOVA.

253 In all statistical analysis values of  $p < 0.05$  were considered for significance. In the graphs  
254 statistical differences are reported as follow: \*  $p < 0.05$ ; \*\*  $p < 0.001$ ; \*\*\*  $p < 0.0001$  (Appendix B).

255

## 256 RESULTS

257 Of 75 dogs treated by TPLO in the study period, forty-two dogs matched the inclusion criteria  
258 and were enrolled in the study. The characteristics of the dogs can be found in Table 2. No  
259 statistical differences (Table 3) were found between groups ( $p > 0.05$ ) in terms of age ( $p = 0.87$ ),  
260 gender ( $p = 0.06$ ) and weight ( $p = 0.54$ ). No patients required rescue analgesia, in the immediate  
261 post-operative period, to treat excessive post-operative pain.

### 262 *Computer-assisted force platform gait analysis*

263 Data related to the gait analysis are reported in table 4 while data related to the clinical  
264 evaluations are reported in table 5 and 6. Stance time was not statistically different between  
265 the two groups at each time point. Considering each group, no statistical differences were found  
266 over time: group 1 (CIM) ( $p = 0.50$ ) and group 2 (TRM) ( $p = 0.95$ ).

267 Peak vertical force was statistically different between the two groups at time T20 ( $p = 0.04$ ).  
268 Considering each group, statistical differences were found over time for group 1 (CIM) (0.002)  
269 and group 2 (TRM) ( $p = 0.0001$ ). Post-hoc for group 1 (CIM) showed a statistical difference  
270 between T0 and T10 ( $p = 0.004$ ) and T0 and T30 ( $p = 0.004$ ). Post-hoc showed for the group 2  
271 (TRM) a difference between T0 and T1 ( $p = 0.001$ ), T1 and T10 ( $p = 0.0001$ ), T1 and T20  
272 ( $p = 0.0001$ ), T1 and T30 ( $p = 0.0001$ ).

273 Vertical Impulse was statistically different between the two groups at time T1  
274 ( $p=0.04$ ), and T20 ( $p=0.05$ ). Considering each group, statistical differences were  
275 found over time for group 1 (CIM) ( $0.0001$ ) and group 2 (TRM) ( $p=0.0001$ ). Post-  
276 hoc showed for group 1 (CIM) a difference between T0 and T30 ( $p=0.003$ ), T1 and  
277 T20 ( $p=0.003$ ) and T1 and T30 ( $p=0.005$ ). For group 2 (TRM) a difference between  
278 T0 and T1 ( $p=0.001$ ), T1 and T10 ( $p=0.0001$ ), T1 and T20 ( $p=0.0001$ ), T1 and T30  
279 ( $p=0.0001$ ).

280

281 Subjective assessment of weight bearing while standing

282 No statistical differences were found between the two groups at each time ( $p_{T0}=0.052$ ;  
283  $p_{T1}=0.34$ ;  $p_{T10}=0.09$ ;  $p_{T20}=0.32$ ;  $p_{T30}=0.88$ ). Considering each group, statistical differences  
284 were found over time: group 1 (CIM) ( $p=0.0001$ ) and group 2 (TRM) ( $p=0.0001$ ). Post-hoc  
285 showed a difference for group 1 (CIM) between each time ( $p=0.0001$ ) and between T0 and T20  
286 ( $p=0.002$ ), T10 and T20 ( $p=0.002$ ); while no statistical differences were found between: T0 and  
287 T10, T20 and T30. For the group 2 (TRM) a statistical difference was showed between each  
288 time ( $p=0.0001$ ), except between T0 and T1, T0 and T10.

289

290 Thigh circumference (TC)

291 No statistical differences were found between the two groups at each time ( $p_{T0}=0.53$ ;  
292  $p_{T1}=0.51$ ;  $p_{T10}=0.49$ ;  $p_{T20}=0.39$ ;  $p_{T30}=0.42$ ). The percentage change for the group 1 (CIM)  
293 was  $-0.7\%$ , while for the group 2 (TRM) was  $-0.9\%$ . Considering each group, statistical  
294 differences were found over time: group 1 (CIM) ( $p=0.0001$ ) and group 2 (TRM) ( $p=0.0001$ ).  
295 Post-hoc showed a difference for group 1 (CIM) between: T0 and T10 ( $p=0.0001$ ), T1 and T10

296 (p=0.002), and T10 and T30 (p=0.002), and for group 2 (TRM) between: T0 and T10 (p=0.002),  
297 T10 and T30 (p=0.003). The percentage change for the group 1 (CIM) was -0.7%, while for the  
298 group 2 (TRM) was -0.9%.

299

300 Pain free stifle range of motions (ROMs)

301 Statistical differences were found between the two groups at time T20 (pT20=0.02) and T30  
302 (pT30=0.001). Considering each group, statistical differences were found over time: group 1  
303 (CIM) (p=0.0001) and group 2 (TRM) (p=0.0001). Post-hoc for group 1 (CIM) showed a  
304 difference (p=0.0001) between: T0 and T1, T1 and T10, T1 and T20, T1 and T30, while a  
305 difference (p=0.001) was found between T10 and T30. For group 2 (TRM) a statistical  
306 difference (p=0.0001) was found between T0 and T1, T1 and T10, T1 and T20, T1 and T30,  
307 T10 and T20, T10 and T30.

308

309 Wound classification

310 No statistical differences were found between the two groups at each time (pT1=0.2;  
311 pT10=0.11; pT20=0.95; pT30=0.32). Considering each group, statistical differences were found  
312 over time: group 1 (CIM) (p=0.002) and group 2 (TRM) (p=0.0001). Post-hoc showed a  
313 difference for group 1 (CIM) between T1 and T30 (p=0.008). For group 2 (TRM) statistical  
314 differences were found between T1 and T30 (p=0.001), T10 and T20 (p=0.004), T10 and T30  
315 (p=0.002), while no differences were found between: T1 and T10, T1 and T20, T20 and T30  
316 (p>0.05).

317



318 Visual Analogue Scale (VAS) assessment of post-operative pain

319 Significantly lower VAS score was seen in group 1 (CIM) compared to group 2  
320 (TRM) using the VAS on Day 10 ( $2.9 \pm 1.7$  vs.  $4.0 \pm 1.5$  in groups 1 (CIM) and 2  
321 (TRM) respectively;  $p=0.04$ ). No differences were found at the other times.  
322 Considering each group, statistical differences were found over time. Post-hoc  
323 showed a difference for group 1 (CIM) between each time except between: T0 and  
324 T10 ( $p=0.078$ ), T20 and T30 ( $p=0.14$ ). For the group 2 (TRM) a statistical difference  
325 was shown between each time, except between T0 and T10 ( $p=0.917$ ).

326

327 Glasgow Composite Measures Pain Scale – Short Form (CMPS-SF) assessment of  
328 post-operative pain

329 No statistical differences were found between the two groups at each time ( $p_{T1}=0.58$ ;  
330  $p_{T10}=0.39$ ;  $p_{T20}=0.33$ ;  $p_{T30}=0.60$ ). Considering each group, statistical differences were found  
331 over time: group 1 (CIM) ( $p=0.0001$ ) and group 2 (TRM) ( $p=0.0001$ ). Post-hoc for group 1 (CIM)  
332 showed no statistical difference between T20 and T30, while a statistical difference ( $p=0.001$ )  
333 was found between T10 and T20 and a difference ( $p=0.0001$ ) was found between each other  
334 couple of time. For the group 2 (TRM) no difference was found between T1 and T10, while a  
335 statistical difference ( $p=0.001$ ) was showed between T10 and T30 and a statistical difference  
336 ( $p=0.0001$ ) was found between all other time point comparisons.

337

338 Helsinki Chronic Pain Index (HCPI)

339 No statistical differences were found between the two groups at each time  
340 ( $p_{T10}=0.93$ ;  $p_{T20}=0.08$ ;  $p_{T30}=0.20$ ). Considering each group, statistical

341 differences were found over time for group 1 (CIM) ( $p=0.001$ ). Post-hoc showed a  
342 difference between T10 and T20 ( $p=0.003$ ) and between T10 and T30 ( $p=0.002$ ),  
343 while no statistical difference was found between T20 and T30 ( $p>0.05$ ).

344

#### 345 Adverse effects

346 Gastrointestinal adverse events were noted at a low level in each group. Group 1 (CIM) had  
347 five episodes of vomiting (one dog on T1, one dog on T20, and three dogs on T30) and one  
348 episode of diarrhea on T30. Group 2 (TRM) also had four episodes of vomiting (one dog on  
349 T10, two dogs on T20, and one dog on T30). Hock edema was reported in 9 dogs from group  
350 2 (TRM) on Day 2, but this was not seen in any dogs from group 1 (CIM). Statistical differences  
351 were found between groups concerning the presence/absence of hock edema ( $p=0.001$ ), while  
352 the gastrointestinal events did not underline any differences between groups ( $p=0.44$ ). All of  
353 the adverse events resolved without additional treatment, and drug administration continued as  
354 scheduled without further incident.

355

#### 356 DISCUSSION

357 The results of this study demonstrated that treatment with cimicoxib resulted in significantly  
358 improved limb function compared to tramadol, at the administered doses, in the postoperative  
359 period of dogs undergoing TPLO and partial meniscectomy, as proved by the improvement of VI  
360 on days 1 and 20, PVF on day 20, and ROM on days 20 and 30. In addition there was no  
361 difference in the weight bearing while standing, thigh circumference, wound classification, VAS,  
362 CMPS-SF and owner pain assessment questionnaire. Sporadic vomiting or diarrhea were the  
363 most common adverse events observed for both groups. One would expect a higher frequency

364 of gastrointestinal side effect from NSAIDs therapy compared to a synthetic opioid-like drug  
365 administration (Karrasch et al., 2015); however, gastrointestinal side effects reported in this  
366 study were comparable amongst groups. All wounds were evaluated in the post-operative  
367 period in order to detect signs of inflammation, infection and delays in the healing process.  
368 Higher (but not significant) scores were observed in group 2 (TRM) over time. It might be  
369 explained by the lack of anti-inflammatory effect of tramadol compared to cimicoxib, causing a  
370 delay in wound healing.

371 Orthopaedic surgery is always associated with post-operative pain. During TPLO procedure,  
372 soft tissue dissection, proximal tibia osteotomy, plate and screws application provide significant  
373 noxious stimuli. Surgical pain is considered adaptive, related to the physiological healing  
374 process of the tissues, with a prevalent inflammatory and nociceptive components (Pogatzki-  
375 Zahn et al., 2017). Its treatment is considered critical in order to limit postoperative discomfort,  
376 promote early return to function and therefore tissues healing (Capner et al., 1999; Hugonnard  
377 et al., 2004; Lascelles et al., 1995; Paul-Murphy et al., 2004).

378 Two different scales were used in this study to assess pain in the first 30 postoperative days.  
379 Only VAS was able to find a difference between the two treatments at 10 days after surgery,  
380 that was not confirmed by the CMPS-SF. VAS is a unidimensional scale that showed an  
381 unacceptable inter-observer variability (Holton et al., 1998) in the postoperative period (Hoelzler  
382 et al., 2005). In contrast CMPS-SF is a composite scale that assesses different components,  
383 making it more accurate and with a lower inter-observer variability compared to VAS (Reid et  
384 al., 2018). In this study we tried to limit the bias associated with pain evaluation by having the  
385 same blinded operator (XX) performing all pain evaluations. Therefore, considering the more  
386 subjective nature and lower accuracy of VAS we should give more relevance to the CMPS-SF  
387 results, concluding that there was not a clinically considerable difference on postoperative pain

388 between the two treatments. These results are not in line with previous studies in which NSAIDs  
389 proved to be superior compared to tramadol for postoperative pain treatment (Delgado et al.,  
390 2014). However, if we look at the data of the force plate gait analysis and ROM, there was a  
391 clear greater efficacy in improvement of joint function in dogs receiving cimicoxib as compared  
392 to tramadol in the first 20 days after surgery. Vertical forces (PVF, and VI) are the most objective  
393 evaluation of lameness available in clinical conditions (Budsberg, 1997; Conzemius et al., 2005;  
394 Gordon et al., 2003a, 2003b; Quinn et al., 2007; ROY et al., 1992; Waxman et al., 2008).  
395 Previous studies have already proved the absence of correlation between force plate gait  
396 analysis and behavioural composite scales to assess pain in dogs with osteoarthritis (Brown et  
397 al., 2013). Gait analysis is a pure physical evaluation of the gait and should not be considered  
398 as a pain assessment, which, on the contrary, implies the elaboration of the nociceptive input  
399 and its emotional expression, which is, on the other side, considered in the pain scales used in  
400 this study. The dog may have limb pain but not show limb disuse. The dog may redistribute gait  
401 forces to compensate for the lameness. Additionally, changes in limb use may not denote pain  
402 or intensity (Sharkey, 2013). Force plate gait analysis (FPGA) has been already used in  
403 previous studies to assess return to normal function after orthopaedic surgery in dogs  
404 (Van Klaveren et al., 2005).

405 Thus, it seems that cimicoxib was able to improve limbs function but not to give a clear  
406 difference in terms of pain, which was, however clinically acceptable i  
407 n both groups (no need of rescue analgesia). Inflammation is an important component of  
408 postoperative orthopaedic pain and should always be treated in order to reduce complication  
409 and to improve the return to the normal function of the treated area (Pogatzki-Zahn et al., 2017).  
410 We may suppose that, due to the type of surgery and the use of intra operative cimicoxib in

411 both groups, postoperative inflammation in these specific cases was not really determinant for  
412 the postoperative pain as assessed with VAS and CMPS-SF. Regarding inflammation we  
413 should considered also that in group 2 (TRM) almost 43% of the cases developed transitory  
414 hock oedema in the postoperative period which was not observed in dogs of group 1 (CIM),  
415 proving the clear efficacy of the antiinflammatory effects of cimicoxib over tramadol. These  
416 results confirm the findings of previous studies that underlined that administration of 2 mg/kg of  
417 cimicoxib once a day for up to 6 days after surgery is an effective and safe method of controlling  
418 peri-operative pain for dogs undergoing either orthopedic or soft tissue surgery (Carmichael,  
419 2011; Duncan et al., 2005; Kim et al., 2014).

420 Limitations of the study included the relatively small number of dogs. Indeed, even if the sample  
421 size was powered for the major parameters of FPGA we cannot exclude that a sample size  
422 calculation powered for pain (VAS or CMPS-SF) could have given different results also in terms  
423 of postoperative pain. Another important aspect that may limit the interpretation of the results  
424 of this study is the lack of a control group, without any analgesic treatment in the postoperative  
425 period. Ethical issues related to the clinical nature of the study prevented us to include a control  
426 group, however, previous literature (Hoelzler et al., 2005) clearly proved the need of adequate  
427 postoperative analgesia in dogs not receiving systematic postoperative treatment, starting  
428 since 2 hours after the end of surgery. Moreover we have not considered the variable  
429 pharmacokinetics of tradol in the dog. At the minimum dosing regimen of 2 mg/kg BID, without  
430 a precise titration of serum concentration, is not possible to affirm that the treatment is sufficient  
431 to reach the desired analgesic effect in all dogs. It is necessary to highlight that the results  
432 obtained in this study are related to this specific dosage regiment and different results could be  
433 obtained at higher dosages.

434

435 CONCLUSIONS

436 Cimicoxib and tramadol provide an adequate analgesic effect up to 30 days after surgery in  
437 dogs undergoing TPLO surgery. Nevertheless, the use of cimicoxib improved the limb function  
438 and ROM and reduced the occurrence of hock edema, in the first 20 days after surgery, without  
439 any additional side effects, compared to tramadol. Therefore, the use of cimicoxib should be  
440 preferred to tramadol alone in clinical cases similar to the ones included in this study. Future  
441 studies should clarify if the combination of the two drugs can provide a synergistic effect or if  
442 higher dosing regimen can provide a better analgesic effect.

443

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446

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