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INTRODUCTION

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

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

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

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

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

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

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

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

MATERIALS AND METHODS

Experimental design, animal population and sample size

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

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

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

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

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

Anesthetic protocol

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

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

TPLO procedure

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

Study Protocol

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

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

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

Computer-assisted force platform gait analysis

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

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

Subjective assessment of weight bearing while standing (WB)

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

Thigh circumference (TC)

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

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

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

Pain-free stifle range of motion (ROMs)

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

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

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

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

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

Helsinki Chronic Pain Index

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

Drugs administration adverse effects

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

Wound classification

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

Statistical analyses

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

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

Data obtained from the owner questionnaire HCPI were compared with CMPS-SF and VAS 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 ($p=0.0001$).

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

Subjective assessment of weight bearing while standing

No statistical differences were found between the two groups at each time (pT0=0.052; pT1=0.34; pT10=0.09; pT20=0.32; pT30=0.88). Considering each group, statistical differences were found over time: group 1 (CIM) (p=0.0001) and group 2 (TRM) (p=0.0001). Post-hoc showed a difference for group 1 (CIM) between each time (p=0.0001) and between T0 and T20 (p=0.002), T10 and T20 (p=0.002); while no statistical differences were found between: T0 and T10, T20 and T30. For the group 2 (TRM) a statistical difference was showed between each time (p=0.0001), except between T0 and T1, T0 and T10.

Thigh circumference (TC)

No statistical differences were found between the two groups at each time (pT0=0.53; pT1=0.51; pT10=0.49; pT20=0.39; pT30=0.42). The percentage change for the group 1 (CIM) was -0.7%, while for the group 2 (TRM) was -0.9%. Considering each group, statistical differences were found over time: group 1 (CIM) (p=0.0001) and group 2 (TRM) (p=0.0001). Post-hoc showed a difference for group 1 (CIM) between: T0 and T10 (p=0.0001), T1 and T10

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

Pain free stifle range of motions (ROMs)

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

Wound classification

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

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 ± 1.7 vs. 4.0 ± 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 (pT1=0.58;
330 pT10=0.39; pT20=0.33; pT30=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 (pT10=0.93; pT20=0.08; pT30=0.20). Considering each group, statistical

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

Adverse effects

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

DISCUSSION

The results of this study demonstrated that treatment with cimicoxib resulted in significantly improved limb function compared to tramadol, at the administered doses, in the postoperative period of dogs undergoing TPLO and partial meniscetomy, as proved by the improvement of VI on days 1 and 20, PVF on day 20, and ROM on days 20 and 30. In addition there was no difference in the weight bearing while standing, thigh circumference, wound classification, VAS, CMPS-SF and owner pain assessment questionnaire. Sporadic vomiting or diarrhea were the 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 significative) 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

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

(Van Klaveren et al., 2005).

Thus, it seems that cimicoxib was able to improve limbs function but not to give a clear difference in terms of pain, which was, however clinically acceptable i

n both groups (no need of rescue analgesia). Inflammation is an important component of postoperative orthopaedic pain and should always be treated in order to reduce complication and to improve the return to the normal function of the treated area (Pogatzki-Zahn et al., 2017). 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

CONCLUSIONS

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

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