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Preemptive carprofen for peri-operative analgesia in dogs undergoing Tibial Plateau Leveling Osteotomy (TPLO): A prospective, randomized, blinded, placebo controlled clinical trial

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Summary

Eighteen client-owned dogs undergoing Tibial Plateau Leveling Osteotomy (TPLO) were included in this blinded clinical study and randomly assigned to one of two treatment groups. Group C (carprofen) received intravenous (IV) carprofen, 4 mg/kg, prior to anesthesia, whereas group P (placebo) received IV saline. General anesthesia was maintained with isoflurane in oxygen and a constant rate infusion (CRI) of sufentanyl IV. Intra-operatively, assessment of nociception was based on changes in physiological parameters and on the analgesics requirement, whereas in the post-operative period evaluation of pain was performed by using a Hellyer and Gaynor pain score and by comparing the doses of rescue buprenorphine required by the two treatment groups. Although no statistically significant differences in intra-operative sufentanyl doses were found between treatment groups, group C had superior cardiovascular stability, and lower post-operative pain scores and rescue buprenorphine doses than group P. Our results indicate that administration of carprofen prior to surgery was effective in improving peri-operative analgesia in dogs undergoing TPLO.

Keywords: dog, preemptive analgesia, carprofen, NSAIDs, anesthesia

Präemptive Verabreichung von Carprofen zur perioperativen Schmerztherapie bei Hunden mit Tibial Plateau Leveling Osteotom (TPLO): Eine prospektive, randomisierte, plazebokontrollierte klinische Studie

Die vorgestellte Studie umfasst 18 Hunde aus privatem Besitz, die für eine Tibial Plateau Leveling Osteotomy (TPLO) vorgestellt wurden. Die Tiere wurden per Zufallsprinzip einer der beiden folgenden Gruppen zugeordnet: Gruppe C (Carprofen) erhielt vor der Narkose intravenös (IV) 4mg/kg Carprofen während Hunde der Gruppe P (Placebo) nur Natriumchlorid-Lösung intravenös verabreicht bekamen. Die Narkose wurde anschliessend mit Isofluran in Sauerstoff und einem Sufentanyl – Dauertropf aufrechterhalten. Zur Einschätzung der Nozizeption dienten intraoperativ Veränderungen der physiologischen Parameter sowie der Bedarf an Schmerzmittel. Die postoperative Schmerzevaluation erfolgte mit einer Schmerzskala nach Hellyer und Gaynor und dem Vergleich der benötigten Notfalldosierungen für Buprenorphin pro Gruppe. Obgleich es keine statistisch signifikanten Unterschiede zwischen den beiden Behandlungsgruppen gab, zeigte Gruppe C eine bessere kardiovaskuläre Stabilität und geringere Werte auf der Schmerzskala als Gruppe P. Ebenfalls wurde in Gruppe C perioperativ weniger Buprenorphin verabreicht als in Gruppe P. Unsere Ergebnisse deuten darauf hin, dass die präoperative Verabreichung von Carprofen die perioperative Analgesie der TPLO-Hunde verbessert hat.

Schlüsselwörter: Hund, preemptive Analgesie, Carprofen, NSAIDs, Anästhesie

Introduction

Tibial Plateau Leveling Osteotomy (TPLO) is an invasive surgical procedure, which is becoming increasingly popular in many veterinary clinics for treating cranial cruciate ligament rupture in dogs. In the anesthesia management of dogs undergoing invasive orthopedic procedures, adequate peri-operative analgesia is essential to reduce discomfort, improve recovery and facilitate an early return to limb function after surgery (Hoelzler et al., 2005). Because peripheral nociceptors stimulation during surgery can already lead to peripheral hypersensitivity and upregulation of central neuronal activity, it is desirable to prevent, rather than treat, surgical pain (Lascelles et al., 1998). Once neural pathways are sensitized, physiological and behavioral responses to nociceptive stimulation can persist even when the nociceptive stimuli terminate, and prolonged and intensified pain responses can be observed when further stimulation of the site occurs (Lamont, 2002).

Preemptive analgesics administration prevents central sensitization, thus limiting pain perception and improving the overall anesthetic outcome. Ideally, the analgesic drug to be administered prior to surgery for this purpose should have long duration of action, in order to optimize the patient comfort through the most painful period. Besides opioids and alpha-2 adrenoreceptor agonists, options for controlling peri-operative pain in dogs include non steroidal anti-inflammatory drugs (NSDs) (Hellyer and Gaynor, 1998; Lascelles et al., 1998; Shih et al., 2008).

Non steroidal anti-inflammatory drugs exert their peripheral anti-inflammatory action by inhibiting the cyclooxygenase mediated synthesis of prostaglandins. Besides the peripheral analgesic effect, there is increasing evidence that NSDs have a central mechanism of action which may be the result of both interference with the formation of prostaglandins within the central nervous system and blockade of serotonin release (Cashman, 1996). Carprofen is a relatively long lasting NSD that seems not to determine detectable adverse effects on renal function when administered pre-operatively in healthy dog (Ko et al., 2000; Boström et al., 2002; Frendin et al., 2006).The post-operative administration of carprofen in dogs undergoing ovariohysterectomy and orthopedic surgeries has been shown to consistently improve the quality of analgesia (Dee, 2001; Slingsby and Watermann-Pearson, 2002; Erol and Izci, 2011). However, to the authors' knowledge the efficacy of carprofen administered prior to surgery in dogs undergoing a standardized orthopedic procedure such as TPLO has never been investigated.

The purpose of this prospective, randomized, blinded, placebo controlled clinical trial was to evaluate the effectiveness of pre-operative administration of intravenous (IV) carprofen in dogs undergoing TPLO in improving peri-operative analgesia.

Animals, Material and Methods

Treatment groups

Eighteen client-owned dogs scheduled for TPLO at the University Teaching Hospital of Perugia (IT) in the years 2006–2008 were enrolled in the study. Pre-anesthetic physical examination and complete blood biochemistry and hematology were performed at arrival. Exclusion criteria were analgesics (NSDs and opioids) or steroids administration within the two weeks prior to surgery and corticosteroids intra-articular injections performed less than three months earlier. The dogs were randomly assigned to one of two treatment groups, each composed by 9 animals. Group C (Carprofen) received IV carprofen (Rimadyl®, Pfizer), 4 mg/kg, 30 minutes before the premedication, whereas group P (Placebo) received the correspondent volume of placebo saline. Each time a black tape-covered prefilled syringe containing either carprofen or placebo was given to the anesthetist, unaware of the treatment, immediately before the injection.

Anesthesia

In both groups, dogs were premedicated with IV sufentanyl (Fentatienil®, Angelini), 0.5 µg/kg, administered over 1 min. Fifteen min later, general anesthesia was induced with IV propofol (Rapinovet®, Schering), titrated to effect. The trachea was intubated and isoflurane (Isoflo®, Esteve) in 100 % oxygen delivered via circle breathing system. End tidal isoflurane concentration (EtISO) was targeted at 1,4 % (1.1 MAC; Steffey and Mama, 2007) throughout the procedure. Dogs were allowed to breath spontaneously unless the end tidal carbon dioxide concentration ($EtCO_2$) increased over 45 mmHg; if so, mechanical ventilation was performed with pressure controlled mode, set to deliver a peak inspiratory pressure of 10–12 cm H_2O at a respiratory rate of 8–10 breaths per minute. This resulted in a tidal volume of 10–12 ml/kg/h. Ringer lactated solution (Ringer Lattato, Galenica Senese) was administered IV at a rate of infusion of 10 ml/kg until the end of anesthesia. The dogs were fully instrumented with a multiparametric monitor (Mindray, PM 7000) and heart rate (HR), respiratory rate (RR), $EtCO_2$, EtISO and arterial oxygen hemoglobin saturation (SpO_2), were manually recorded every 5 min. Arterial blood pressure values (systolic, diastolic and mean; respectively SAP, DAP and MAP) were also measured non invasively via oscillometric technique and recorded at 5 min intervals. Intra-operative analgesia was provided by sufentanyl constant rate infusion (CRI) IV via infusion pump (bBraun Perfusor Compact®, Braun), starting with an infusion rate of 0.5 µg/kg/h after a loading dose of 0.5 µg/kg. If decreased level of unconsciousness (increased palpebral reflex or jaw tone) was observed, additional propofol, 1 mg/kg, was administered IV. At the end of the surgical procedure, sufentanyl CRI

was discontinued and a soft cast applied on the operated limb. When dysphoria (Defined as anxiety, restlessness and continuous vocalizations) was observed at recovery, 3 μg/kg medetomidine were administered IV.

Intra-operative nociception assessment

Sufentanyl rate of infusion was adjusted based on changes in HR, RR and MAP. Cut off values were defined as 20 % more of the baseline values, recorded before the beginning of the surgical stimulation. When increases of two of the above parameters (HR, RR and MAP) over the cut off value were observed, a loading dose of sufentanyl was administered IV (0.25 μg/kg); afterwards, the rate of infusion was incremented by 0.25 μg/kg/h every 10 minutes until cardiovascular and respiratory parameters normalized.

Post-operative pain assessment

Post-operative pain assessment was performed using numerical descriptive scale ranging from 0 to 24 as described by Hellyer and Gaynor at the following time points: 30, 60, 120, 180, 240, 300 and 360 minutes after extubation. The cut off value for the administration of rescue buprenorphine (Temgesic®, Schering Plough; 10 μg/kg IV) was a score exceeding 15. Intra-operative and post-operative nociceptive assessments were always performed by the same anesthetist, blind to the treatment.

Statistical analysis

Statistical analysis was performed with a software commercially available (NCSS 2007). Body weight and age of the animals and duration of the surgical procedure of each treatment group were analyzed with one way Anova. Intra-operative physiological variables were analyzed with Anova repeated measures, followed by Bonferroni multiple comparison test. The dosages of sufentanyl and propofol administered during anesthesia to each group were analyzed with one way Anova, followed by Bonferroni multiple comparison test. In both groups some dogs had a surgery time longer than 120 min; however, because in the majority of the animals (group C: n-4; group P: n-4) the surgical procedure ended 120 min after the incision (150 min after intubation), intra-operative variables were analyzed until this time point. The proportions of animals receiving medetomidine at recovery within each group were analyzed with Fisher exact test. Total rescue post-operative buprenorphine received by each group between 30 and 360 minutes after extubation was analyzed with one way Anova. P values less than 0.05 were considered statistically significant. Unless differently specified, data are indicated as means and standard deviations.

Results

Mean body weight and age of the dogs assigned to group C were 42.2 (± 12.3) kg and 4.3 (± 2.3) years respectively, whereas in group P mean body weight was 34.9 (± 9.6) kg and mean age 4.6 (± 2.2) years. No statistically significant differences in body weight and age were found among treatment groups. General anesthesia was uneventful and mean duration of surgery was 124 (± 12) min in group C and 118 (± 29) min in group P. As the procedure was standardized and the time required for preparation of the surgical field always the same, the surgical incision corresponded to time point 30 (30 min after intubation) in all animals. At this time point, group P showed a statistically significant increase in HR ($P = 0.0001$), SAP ($P = 0.0007$) and MAP ($P = 0.0001$), whereas in group C, although a slight increase in MAP was observed, this was not statistically significant (Fig. 1). Group P had significantly greater MAP and DAP than group C at time points 30, 60, 90, 120, 150 ($P < 0.05$), whereas no statistically significant differences in HR, SAP and RR were found among treatment groups at any time point. Intra-operatively, group P received a higher sufentanyl rate of infusion than group C (median and interquartile ranges 0.45 [0.68–0.18] μg/kg/h and 0.38 [0.65–0.38] μg/kg/h, respectively; Fig.2); however, this difference was not statistically significant. No statistically significant differences in intra-operative propofol doses were observed between treatment groups (Fig. 2).
Post-operatively, 2 dogs of group C and 7 dogs of group P showed dysphoria at recovery; for this reason, medetomidine was administered. In group P the proportion of animals receiving medetomidine at awakening was significantly higher than in group C ($P = 0.002$). All the dogs included in the study required the administration of buprenorphine within one hour from recovery; however, in the period of time between 30 and 360 minutes from extubation, group P received greater rescue buprenorphine doses than group C (medians and interquartile ranges 19.5 [19.5–20] μg/kg and 10.2 [10–15] μg/kg, respectively, $P = 0.02$; Fig. 2). Post-operative pain scores were significantly higher in group P than in group C at most of the time points (30, 60, 120, 180 and 300; $P < 0.05$; Fig. 3).

Discussion

The administration of carprofen prior to surgery resulted in superior intra-operative cardiovascular stability compared to placebo saline; this seems to indicate that group C had a more stable plane of anesthesia than group P, probably due to better intra-operative analgesia. As demonstrated by the higher doses of rescue buprenorphine and the greater pain scores achieved by group P compared to group C, and by the fact that the number of animals requiring post-operative medetomidine was higher in group P than in group C, pre-emptive carprofen contributed to improve quality of recovery and post-operative comfort and analgesia.

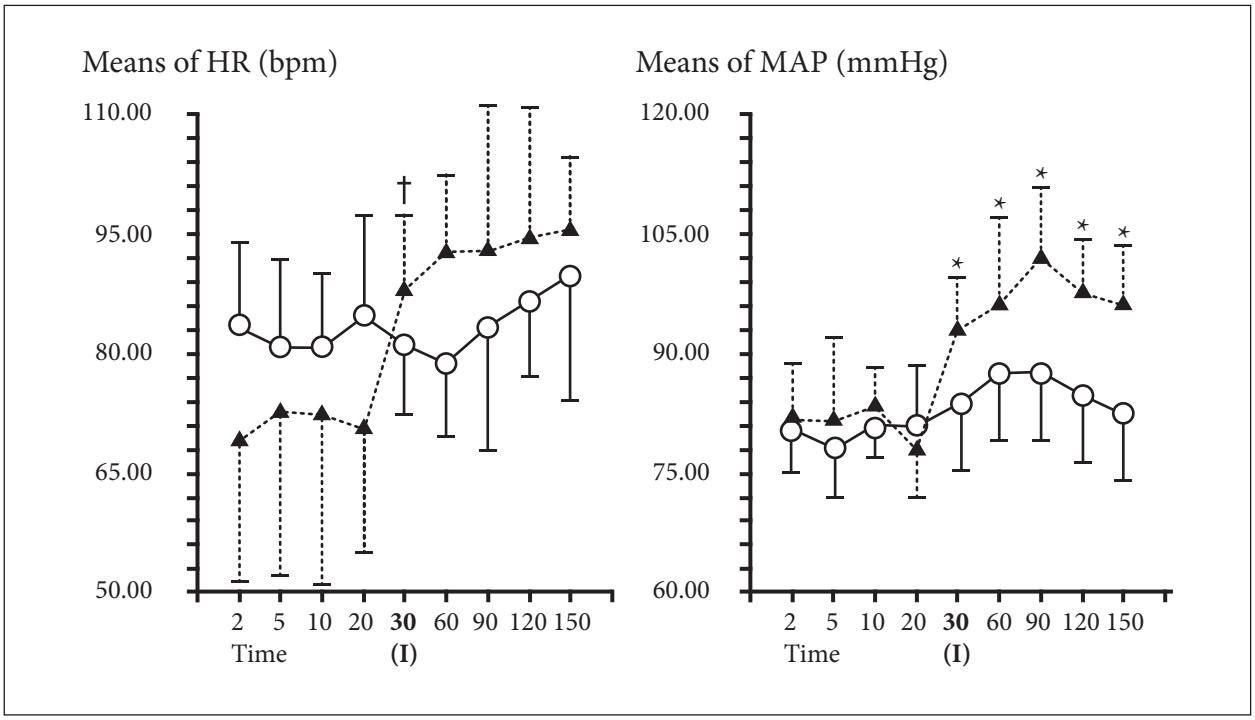

Figure 1: Means of intra-operative heart rate (HR) and mean arterial blood pressure (MAP) in Carprofen (C = ○) and Placebo (P = ▲) groups; 2, 5, 10, 30, 60, 90, 120 and 150 min after intubation; I: surgical incision. †P < 0.05 (for comparison among time points within the same treatment group); *P < 0.05 (for comparison among treatment groups).

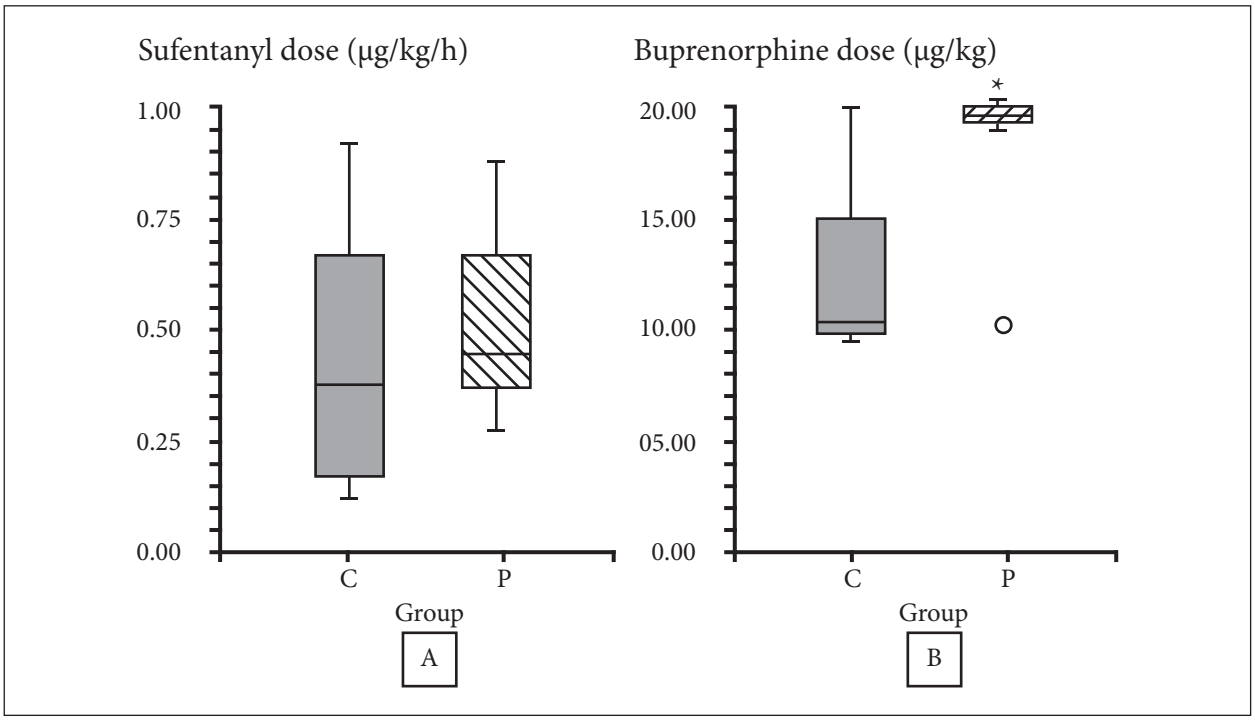

Figure 2: A. Intra-operative doses (rate of infusion) in groups Carprofen (C) and Placebo (P); B. Total post-operative doses of buprenorphine administered between 30 and 360 minutes after extubation in groups Carprofen (C) and Placebo (P). *P < 0.05 (for comparison among treatment groups). Whiskers indicate ranges.

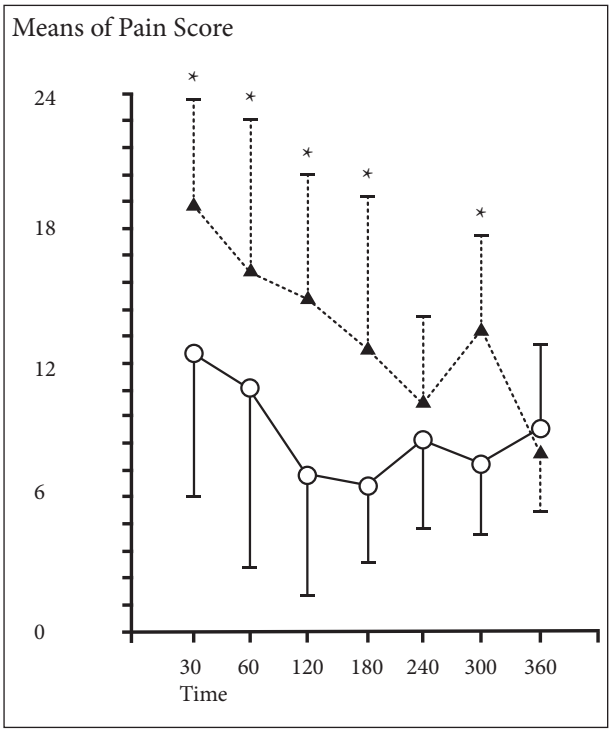

Figure 3: Means of pain scores (Hellyer and Gaynor, 1998) in Carprofen (C = ○) and Placebo (P = ▲) groups; 30, 60, 120, 180, 240, 300 and 360 min after extubation; *P < 0.05 (for comparison among treatment groups).

It is well recognized that multimodal analgesia can be achieved by additive or synergistic effects between analgesics with different mechanisms of action (Hoelzler et al., 2005; Tobias et al., 2006); therefore, it is reasonable to assume that the administration of carprofen prior to intra-operative sufentanyl improved the overall peri-operative analgesia through a pharmacodynamic mechanism. Additionally, carprofen may have enhanced the intra-operative analgesia provided by sufentanyl through a pharmacokinetic effect. As in humans the plasma protein binding is extremely high for both NSDs and sufentanyl (99 % and 92 %, respectively; Verbeeck et al., 1983; Scholz et al., 1996), we hypothesize that competition of the two drugs for the same binding sites could have displaced part of the sufentanyl from the plasma proteins, increasing the free sufentanyl concentration available in the system and actively exerting analgesic effects (Buur et al., 2009).

During surgery, the starting rate of infusion of sufentanyl was set at relatively low values (Bufalari et al., 2007; Lamont and Mathews, 2007). This decision was made with the purpose of using the least possible opioid dose, in order to increase the probability to detect differences in intra-operative analgesia between treatment groups. We expected group C to need lower intra-operative sufentanyl rates of infusion than group P, and it is difficult to explain why the two treatment groups required comparable opioid doses. One possible explanation is that the increase in free sufentanyl concentration in group C enhanced its analgesic effect, but also accelerated its clearance from the system, thus contributing to a concurrent decrease in total drug concentration (Buur et al., 2009). The continual input of sufentanyl from the CRI probably replaced the amount of opioid eliminated from the body, but it is possible that, due to the enhanced clearance, higher doses of the opioid were required to maintain the minimum drug concentration necessary to exert pharmacological effect.

Many dogs showed dysphoric recovery and required the administration of medetomidine. One limitation of this study is that the administration of a sedative drug in the early post-operative period could have influenced the results due to a more difficult pain assessment in sedated animals. Medetomidine also exerts some spinal analgesic effects (Lemke, 2007), which may have contributed to lower the pain scores in dogs which received it. The poor recovery observed in the majority of the dogs could have been the result of an inappropriate anesthetic protocol. The addition of a long-lasting sedative drug, such as acepromazine, in premedication, could have improved the recovery and decreased the probability of observing dysphoria at awakening.

In conclusion, preemptive carprofen was effective in improving the overall peri-operative analgesia in dogs undergoing TPLO and receiving intra-operative sufentanyl CRI; however, our results show that, when invasive orthopedic procedures are performed, the addition of a systemic analgesic, such as buprenorphine, in the post-operative period is necessary to maintain an adequate plane of analgesia.

Application préventive de Carprofen pour le traitement péri opératoire de la douleur chez des chiens avec TPLO (Tibial Plateau Leveling Osteotomy): Une étude clinique prospective randomisée et contrôlée par placebo

La présente étude comprend 18 chiens de propriétaires privés présentés pour une TPLO (Tibial Plateau

La somministrazione preventiva di carprofen per la terapia del dolore perioperatorio nei cani affetti da osteotomia di livellamento del piatto tibiale (TPLO): uno studio prevedibile, randomizzato, controllato con placebo in cieco clinico

Diciotto cani sottoposti ad osteotomia livellante del plateau tibiale (TPLO) sono stati inclusi in questo studio.

Leveling Osteotomy). Les animaux ont été attribués après randomization dans l'un des deux groupes suivants: Le groupe C (Carprofen) a reçu avant la narcose 4 mg/kg de Carprofen par voie intraveineuse alors que le groupe P (placebo) a reçu une solution de chlorure de sodium, également par voie intraveineuse. La narcose a ensuite été effectuée avec l'Isoflurane et l'oxygène ainsi que du Sufentanyl en perfusion. On a utilisé, pour estimer la nociception, les modifications intra opératoires des paramètres physiologiques ainsi que le besoin en antalgique. L'évaluation post opératoire a été realisée au moyen d'une échelle de la douleur selon Hellyer et Gaynor et par la comparaison de dosages totales de Buprenorphine dans chaque groupe. Bien qu'il n'y ait pas de différence statistiquement significative entre les deux groupes, le groupe C a montré une meilleure stabilité cardiovasculaire et des valeurs plus basses sur l'échelle de douleur que le groupe P. De même, le groupe C a nécessité une application plus faible de Buprenorphine que le group P. Ces constatations laissent à penser que l'application préopératoire de Carprofen a amélioré l'analgésie péri-opératoire des chiens.

Gli animali sono stati assegnati, previa randomizzazione, a uno dei due gruppi seguenti: al gruppo C (carprofen) è stato somministrato, prima dell'anestesia, carprofen, 4 mg/kg, per via endovenosa (IV), mentre al gruppo P (placebo) è stato somministrato un corrispondente volume di soluzione fisiologica, IV. L'anestesia è stata mantenuta con isofluorano in ossigeno e sufentanil in infusione endovenosa continua. La valutazione della nocicezione nella fase intra-operatoria è stata basata sui cambiamenti dei parametri fisiologici e sulla necessità di somministrare analgesici. La valutazione del dolore post-operatoria è stata effettuata utilizzando una scala del dolore secondo Hellyer e Gaynor e confrontando le dosi di buprenorfina somministrate nel periodo post-operatorio in ciascuno dei due gruppi. Benché non ci siano state differenze statisticamente significative tra i due gruppi, il gruppo C ha mostrato una migliore stabilità cardiovascolare e valori inferiori sulla scala del dolore rispetto al gruppo P. Inoltre si deve sottolineare che al gruppo C è stata somministrata nel periodo perioperatorio una dose inferiore di buprenorfina rispetto al gruppo P. I nostri risultati indicano che la somministrazione preoperatoria di carprofen migliora l'analgesia perioperatoria in cani sottoposti a TPLO.

References

Bufalari A., Di Meo A., Nannarone S., Padua, S., Adami C.: Fentanyl or sufentanyl in continuous rate infusion during isoflurane anaesthesia in dogs: clinical experiences. Vet. Res. Commun. 2007, 31: 277–280.

Boström I.M., Nyman G.C., Lord P.F., Häggström J., Jones B.E.V., Bohlin H.P.: Effects of carprofen on renal function and results of serum biochemical and hematologic analyses in anesthetized dogs that had low blood pressure during anesthesia. Am. J. Vet. Res. 2002, 63: 712–721.

Buur J., Baynes R., Smith G., Riviere J.: A Physiologically based pharmacokinetic model linking plasma protein binding interactions with drug disposition. Res. Vet. Sci. 2009, 86: 293–301.
Cashman J.: The mechanism of action of NSAIDs in analgesia. Drugs 1996, 52: 13–23.

Dee J.: Assessing the efficacy of perioperative carprofen administration in dogs undergoing surgical repair of a ruptured cranial cruciate ligament. J. Am. An. Hosp. Assoc. 2001, 37: 115–116.
Erol M. and Izci C.: Postoperative analgesic effects of carprofen following osteotomy and laparotomy in dogs. J. Anim. Vet. Adv. 2011, 10: 922–927.

Frendin J.H.M., Boström I.M., Kampa N., Eksell P., Häggström J.U., Nyman G.C.: Effects of carprofen on renal function during medetomidine-propofol-isoflurane anesthesia in dogs. Am. J. Vet. Res. 2006, 67: 1967–1973.

Hellyer P. and Gaynor J.S.: Post-surgical pain in dogs and cats. Comp. Cont. Ed. Pract. 1998, 20: 140–153.

Hoelzler M., Harvey R., Lidbetter D., Millis D.: Comparison of perioperative analgesic protocols for dogs undergoing tibial plateau levelling osteotomy. Vet. Surg. 2005, 34: 337–334.

Ko J.C.H., Miyabiyashi T., Mandsager R.E., Jones H.T.G., Mauragis D.F.: Renal effects of carprofen administered to healthy dogs anesthetized with propofol and isoflurane. J. Am. Vet. Med. Assoc. 2000, 217: 346–349.

Lamont L.: Feline perioperative pain management. Vet. Clin. N. Am. Small 2002, 32: 747–763.

Lamont L., Mathews K.: Opioids, Nonsteroidal anti-nflammatories, and analgesic adjuvants. In: Lumb & Jones' Veterinary Anesthesia and Analgesia. Eds. J.V. Tranquilli, J.C. Thurmon, K.A., Grimm, Iowa (USA), 2007, 241–271.

Lascelles B., Cripps P., Jones A., Watermann Pearson, A.E.: Efficacy and kinetics of carprofen, administered preoperatively and postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. Vet. Surg. 1998, 27: 568–582.

Lemke K.: Anticholinergics and sedatives, In: Lumb & Jones' Veterinary Anesthesia and Analgesia. Eds. J.V. Tranquilli, J.C. Thurmon, K.A. Grimm, Iowa (USA), 2007, 203–240.

Scholz J., Steinfath M., Schulz M.: Clinical pharmacokinetics of alfentanyl, fentanyl and sufentanyl. Clin. Pharmacokinet. 1996, 31: 275–292.

Shih A., Robertson S., Isaza N., Pablo L., Davies W.: Comparison between analgesic effects of buprenorphine, carprofen, and buprenorphine with carprofen for canine ovariohysterectomy. Vet. Anaesth. Analg. 2008, 35: 68–79.

Slingsby L.S., Watermann-Pearson A.E.: Comparison between meloxicam and carprofen for post-operative analgesia after feline ovariohysterectomy. J. Small Anim. Pract. 2002, 43: 286–289.

Steffey E., Mama K.: Inhalation Anesthetics In: Lumb & Jones' Veterinary Anesthesia and Analgesia. Eds. J.V. Tranquilli, J.C. Thurmon, K.A. Grimm, Iowa (USA), 2007, 355–393.

Tobias M., Harvey R., Byarlay J.: A comparison of four methods of analgesia in cats following ovariohysterectomy. Vet. Anaesth. Analg. 2006, 33: 309–398.

Verbeeck R., Blackburn J., Loewen G.: Clinical pharmacokinetics of non-steroidal anti-inflammatory drugs. Clin. Pharmacokinet. 1983, 8, 297–331.

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