Paracetamol add-on treatment for perioperative pain management in dogs undergoing single-site thoracolumbar hemilaminectomy: a prospective clinical study

Paracetamol als bijkomend analgeticum voor perioperatieve pijnbestrijding bij honden die een enkelvoudige thoracolumbale hemilaminectomie ondergaan: een prospectieve klinische studie

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ABSTRACT

In this prospective, double-blinded, randomized, clinical trial, it was evaluated whether paracetamol, as an adjunct to NSAID and opioid analgesia, might limit the requirements for intraoperative fentanyl and postoperative methadone administration in dogs undergoing a single-site thoracolumbar hemilaminectomy for surgical treatment of an intervertebral disc extrusion. Twelve client-owned dogs were randomly assigned to two multimodal analgesia groups: NSAID + paracetamol group (group NP) and NSAID + placebo group (group N). Intraoperative analgesic assessment was based on the clinical evaluation of a nociceptive response, whereas postoperative analgesic assessment was determined by using the short form of the Glasgow Composite Pain Scale. No statistically significant difference was found in both groups for the intraoperative need for fentanyl (P = 0.18). The probability of having to administer rescue analgesia postoperatively was significantly higher in group N than in group NP (P = 0.01). For both groups, there were no serious side effects reported, nor was any significant difference found between both groups regarding the occurrence of side effects (P = 0.55). Despite multimodal perioperative pain management consisting of a full μ-agonist opioid, a NSAID and paracetamol, intraoperative rescue analgesia was still required, although the need for postoperative opioid based analgesia was significantly lower in group NP.

SAMENVATTING

In deze prospectieve, dubbel-geblindeerde, gerandomiseerde klinische studie werd onderzocht of paracetamol gecombineerd met een NSAID en opioïde pijnstilling, de nood aan intraoperatieve fentanyl en postoperatieve methadontoediening kan beperken bij honden die een enkelvoudige thoracolumbale hemilaminectomie ondergaan omwille van een discus hernia-extrusie. Twaalf honden werden willekeurig toegewezen aan twee multimodale behandelgroepen: een NSAID + paracetamol-groep (groep NP) en een NSAID + placebo-groep (groep N). De aanwezigheid van pijn werd intraoperatief beoordeeld aan de hand van klinische parameters en postoperatief op basis van de short form of the Glasgow Composite Pain Scale. Er werd geen statistisch significant verschil vastgesteld met betrekking tot de noodzaak van intraoperatief gebruik van fentanyl (P = 0,18). De waarschijnlijkheid dat methadon postoperatief nodig was, was significant hoger voor groep N dan voor groep NP (P = 0,01).

Er werden geen ernstige bijwerkingen waargenomen, noch een significant verschil tussen de twee groepen wat betreft het voorkomen van deze bijwerkingen (P = 0,55). Ondanks multimodale perioperatieve pijnbestrijding bestaande uit een volledige opioïde μ-agonist, een NSAID en paracetamol, was intraoperatieve fentanyltoediening nog steeds nodig. De nood aan postoperatieve opioïde pijnstilling was echter significant lager in groep NP.

INTRODUCTION

Thoracolumbar intervertebral disc extrusion (IVDE) in dogs is a common painful neurological disease that often requires surgical decompression (hemilaminectomy) (Moore et al., 2020). Neurosurgery is associated with severe pain and perioperative analgesia is therefore crucial (Epstein et al., 2015). Opioids, such as fentanyl and methadone, provide sufficient intraoperative analgesia and are often included in analgesic protocols (Gutierrez-Blanco et al., 2013; Skelding et al., 2021). Postoperative pain management is necessary for maintaining optimal ani-mal welfare and surgical recovery. Methadone, a full μ-opioid which provides excellent analgesia, is also known to cause several mild to moderate clinically relevant side effects. Reported side effects include respiratory depression, sedation, dysphoria, ileus, opioid-induced hyperalgesia and potentially tolerance and addiction (Li et al., 2001; White et al., 2017; Ripplinger et al., 2018). Given that these side effects can interfere with the quality of the patients recovery and additionally prolong the hospitalization period, there is an ongoing search for alternative drugs that might reduce the need for postoperative methadone administration.

Paracetamol (acetaminophen) is a selective inhibitor of cyclooxygenase-1 (COX-1), COX-2 and COX-3, and has pharmacological effects similar to other COX inhibitors like non-steroidal anti-inflammatory drugs (NSAIDs) (Chandrasekharan et al., 2002; Hinz et al., 2008; Graham et al., 2013). The analgesic effect of paracetamol has a central origin as it interacts with the serotonergic descending pain pathways. It therefore has weak anti-inflammatory effects compared to NSAIDs, which have both central and peripheral effects. Short-term studies of paracetamol/NSAID combinations have not identified specific safety concerns (Ong et al., 2010; Thybo et al., 2020). Combining an NSAID with paracetamol might amplify the central analgesic effects and might generate a more effective multimodal analgesia approach (Anderson, 2008; Graham et al., 2013; White et al., 2017; Monteiro and Steagall, 2019). Adverse effects of paracetamol are rare, but toxicity has been reported when using high doses above 100 mg/kg. Possible side effects include anorexia, abdominal discomfort, vomiting, icterus, facial swelling, respiratory distress and lethargy (Omer and Mohammad, 1984; Salem et al., 2010; Fadel et al., 2021), whereas potential side effects of NSAIDs include gastrointestinal ulcerations, renal and hepatic toxicity and coagulation disorders (Lascelles et al., 2005). Several research groups have already studied the postoperative analgesic efficacy of paracetamol combined with NSAIDs in intervertebral disc disease and orthopedic surgeries in humans (Ong et al., 2010; Thybo et al., 2020). Similarly, the use of paracetamol in comparison to NSAIDs has also been studied in canine orthopedic surgeries (e.g. tibial plateau levelling osteotomy) and soft tissue surgeries (e.g. ovariohysterectomy) (Hernández-Avalos et al., 2019; Pacheco et al., 2020; Fadel et al., 2021). In the latter, the effectiveness of paracetamol in opioid-free anesthesia has also been investigated (White et al., 2017). In all these studies, positive outcomes have been reported. However, to the authors' knowledge, no studies have been performed using paracetamol as an add-on drug in dogs undergoing surgery for intervertebral disc disease. The aim of this study was to evaluate whether the effect of paracetamol, as an adjunct to NSAID and perioperative opioid analgesia, might limit the requirements for fentanyl intraoperatively and methadone postoperatively, in dogs undergoing single-site thoracolumbar hemilaminectomy for an intervertebral disc extrusion. The authors hypothesize that dogs receiving paracetamol will require less intraoperative fentanyl and less postoperative methadone and will therefore be less at risk for potential opioid-related side effects during the postoperative period.

MATERIAL AND METHODS

A prospective, double-blinded, randomized, clinical trial approved by the local Ethical Committee and the Flemish Laboratory Animal Council (EC 2020_035 and DWZ/KF/20/1.15/66) was performed at the Small Animal Department, Faculty of Veterinary Medicine, Ghent University. Dogs that were diagnosed with a single-site thoracolumbar intervertebral disc extrusion based on computed tomography (CT) of the thoracolumbar vertebral column were included. All owners signed a written informed consent. The dogs were randomly assigned in a 1-to-1 ratio to two treatment groups: NSAID + paracetamol group (group NP) or NSAID + placebo group (group N). Determination of whether a dog would be treated with paracetamol or not was made by using randomized sealed envelopes. The envelopes were randomly numbered and opened following a numeric sequence starting from envelope one. The appropriate envelope was opened by one of the supervisors and the paracetamol or placebo infusion (NaCl 0.9% Viaflo, Baxter S.A., Belgium) was prepared. The investigator performing the pain scoring and the anesthesiologists were blinded throughout the whole study period. Exclusion criteria included: 1) previous thoracolumbar spinal surgery,

2) multiple-site intervertebral disc extrusion, 3) preemptive administration of a non-injectable NSAID, 4) administration of prednisolone within 24 hours before a scheduled surgery, 5) biochemistry values that were contraindications for the administration of NSAIDs or paracetamol as reported by Ferrarin (2020) (e.g. a threefold increase in alanine transferase, increased alkaline phosphatase, gamma-glutamyltransferase or creatinine) or 6) the occurrence of complications during anesthesia, surgery or recovery that required additional analgesia apart from the analgesic medication used for this study (e.g. lidocaine, ketamine, maropitant, dexamethasone).

Dogs that were presented to the neurology service of Ghent University between 2020 and 2022 with an acute-onset T3-L3 myelopathy, were assessed for eligibility. A complete general physical and neurological examination was always performed by the same investigator. The neurological deficits were further classified as grade 1 – 5, using the Modified Frankel Score (MFS); grade 1: spinal hyperesthesia, no neurological dysfunction, grade 2: ambulatory paraparesis, grade 3: non-ambulatory paraparesis, grade 4: paraplegia with intact pain perception in both pelvic limbs and grade 5: paraplegia with loss of pain perception in both pelvic limbs (Frankel et al. 1969; Martin et al. 2020; Scott 1997; Van Wie et al., 2013). Additionally, a baseline pain scoring was performed by the blinded investigator using the short form of the Glasgow Composite Pain Scale. The 'gait' category in the short form of the Glasgow Composite Pain Scale was deleted if dogs were allocated to MFS grade 3-5 (non-ambulatory), reducing the total maximum score from 24 to 20. Following the pain scoring, all dogs received intravenous (IV) methadone (Insistor, Ecuphar NV/SA, Belgium) 0.2 mg/kg for analgesia, which was repeated at the same dose every four hours until further diagnostics or surgery was performed. A complete blood count and biochemistry profile, including electrolyte assessment, were conducted in every patient. Advanced diagnostic imaging consisting of a CT scan was subsequently performed under sedation or general anesthesia. Sedation was only preferred when the CT scan and the hemilaminectomy were not done on the same day, and consisted of IV dexmedetomidine (Dexdomitor, OrionPharma, Finland) 5 µg/kg, midazolam (Dormazolam, Dechra, Belgium) 0.2 mg/kg and methadone (Insistor, Ecuphar, Belgium) 0.2 mg/kg. Following exact localization of the intervertebral disc extrusion and the decision to go for a surgical hemilaminectomy procedure, the dogs were randomly assigned to group NP or group N. The dogs in group NP received both an NSAID registered for preoperative administration and paracetamol (Paracetamol Fresenius Kabi, Kabi nv, Belgium). When dogs had not been previously treated with an NSAID at the time of diagnosis, carprofen (Rycarfa, KRKA, Slovenia) 4 mg/kg IV was administered before induction. Whenever a NSAID treatment was ongoing, the selected NSAID was continued. Other NSAIDs that were used in this study were meloxicam (Acticam, Ecuphar NV, Belgium) 0.2 mg/kg IV and robenacoxib (Onsior, Elanco GmbH, Germany) 2 mg/kg subcutaneously. NSAIDs were preoperatively administered IV and subsequently every 24 hours for at least two consecutive days, followed by oral administration of the same dose, except for meloxicam that was reduced to 0.1 mg/kg/day. If the period between the last administration of the NSAID and the start of surgery was less than 24 hours, the NSAID administration was not repeated during premedication, but was instead repeated 24 hours after the last administration. In group NP, paracetamol at a dose of 10 mg/kg, was administered IV over twenty minutes at the start of anesthesia and was repeated every 12 hours for the next 24 hours. The study ended 24 hours postoperatively, after the third dose of paracetamol was given. In group N, paracetamol was replaced by a placebo infusion (NaCl 0.9% Viaflo, Baxter S.A., Belgium) administered over twenty minutes, containing a similar volume as the calculated paracetamol dose to ensure blinding of the anesthesiologist. Anesthesia and surgery (hemilaminectomy) were performed using a standardized protocol. A single dose of methadone (0.2 mg/kg) was repeated at the induction of anesthesia if the administration of the previous methadone dose was more than three hours ago. Induction was provided with propofol (Propovet Multidose, Zoetis, Belgium) to effect (1-6 mg/kg) and for maintenance anesthesia isoflurane (IsoFlo 100%, Zoetis, Belgium) vaporized in 100% oxygen was used, using a circle rebreathing system. All dogs were mechanically ventilated. Basic standard monitoring during general anesthesia consisted of pulse oximetry, airway pressure, end-tidal carbon dioxide, electrocardiogram and monitoring of non-invasive blood pressure. The evaluation of nociception was based on a sudden increase in heart frequency and/or blood pressure. If additional intraoperative analgesia was deemed necessary based on the clinical evaluation of nociception by the anesthesiologist for dogs in both groups, a fentanyl (Fentadon, Dechra, the Netherlands) IV bolus of 2-3 µg/kg was administered, and if necessary followed by an IV constant rate infusion (CRI) of 5-10 µg/kg/hour. All dogs received 5 ml/kg/h Ringer's lactate solution (Ringer Lactate, B. Braun Vet Care, Germany) IV during anesthesia that was continued during hospitalization for hydration. After surgery, all dogs were hospitalized in the recovery unit on soft bedding with absolute cage rest. The dogs were offered food and taken outside for urination and defecation four times daily. Pantoprazole (Pantomed, Takeda GmbH, Austria), a gastrointestinal protective agent, was administered to all dogs at a dose of 1 mg/kg IV at the time of extubation. Postoperative pain scoring was performed by the blinded investigator at the time of extubation and repeated every hour for the first eight hours, and once more twenty hours after extubation. Additional postoperative rescue analgesia was based on the short form of the Glasgow Composite Pain Scale. Rescue

analgesia, consisting of methadone 0.1 mg/kg IV, was administered by the blinded investigator when a total score of more than five out of 24 for ambulatory patients or four out of 20 for non-ambulatory patients was reached. No additional pain scoring was performed immediately after administration of rescue analgesia, but the next pain score was done at the same scheduled one-hour interval. In case rescue analgesia was required twice during the first eight hours period post extubation (T0-T8) or once at timepoint T8, methadone 0.1 mg/kg IV was repeated after six hours, at timepoint T14. This is halfway between the pain scoring at timepoint T8 and the last pain scoring at timepoint T20. The same investigator, who performed the pain scores, also reported the occurrence of side effects during the pre- and postoperative period. During the intraoperative period, the side effects were noted by the responsible anesthesiologist. The side effects were categorized in minor or major side effects. Minor side effects were side effects resulting in mild discomfort that did not require immediate intervention, e.g. sedation, anorexia, regurgitation, hypersalivation, diarrhea, vomiting and tachypnea. Major side effects were serious adverse events that were life-threatening or potentially fatal, e.g. anaphylaxis, dyspnea, shock, hypotension, gastrointestinal ulcerations, hematochezia or hematemesis. Dogs were discharged between 48 to 72 hours after surgery on oral medication containing an NSAID for another 14 days and tramadol (Tralieve, Dechra, the Netherlands) 4 mg/kg three times daily for seven days, followed by two times daily for another seven days. A four-week postoperative follow-up control was performed in every dog. The investigator performing the pain scoring was blinded for treatments until the entire study was completed. No changes to methods or trial outcomes were made after trial commencement.

For the clinical trial, the need for rescue analgesia with methadone in the postoperative period was considered the primary outcome measure and the need for intraoperative rescue analgesia with fentanyl and the occurrence of side effects were secondary variables. To calculate the sample size, a power analysis was conducted with the following settings: alpha = 0.05, power = 0.8, Cohen's d = 1.8 (i.e. a 30% dose-reduction of methadone postoperatively) with a two-sample t-test. This led to a total sample size of 12 (i.e. six dogs per group). All analyses were performed in R version 4.1.3 ('One Push-Up'), using the "pwr" and "lme4" packages (R Core Team, 2013; Bates et al., 2015; Champeley, 2020). Separate logistic mixed models with animal as random effect and timepoints or group (NSAID + paracetamol or NSAID + placebo) as fixed effect were used to evaluate whether rescue analgesia (= dependent variable) was needed postoperatively. A linear model with group as independent variable was used to compare the number of times (T0-T8) rescue analgesia needed to be administered postoperatively. Significance was evaluated with a likelihood ratio test. A Fisher exact test was used to compare the presence of side effects (yes/no) and the administration of fentanyl intraoperatively (yes/no) between the two groups (NSAID + paracetamol or NSAID + placebo). A Wilcoxon rank sum test was used to compare the duration of anesthesia and the duration of surgery between the two groups (NSAID + paracetamol or NSAID + placebo). The α-threshold was set at ≤ 0.05. Odds ratios (ORs), when appropriate, and 95% confidence intervals (95% CI) were provided.

RESULTS

A total of twelve dogs were included. The dogs were assigned to one of the two study groups: group NP (n=6) and group N (n=6). One dog of group N was excluded after the study was completed, because the anesthesia protocol was not followed correctly leading to a total sample size of 11 dogs. The demographic data of the dogs are provided in Table 1. None of the dogs had concomitant diseases or abnormalities of significant importance based on the general physical and blood examinations.

The Modified Frankel Score and short form of the

Table 1. Demographic data of included dogs in this study (n=11).

Groups	NSAID + paracetamol group (n=6)	NSAID + placebo group (n=5)
Breed	French bulldog (2), dachshund (1), basset hound (1), cavalier King Charles spaniel (1), Jack Russel terrier (1)	dachshund (2), pug (1), Chihuahua (1), French bulldog (1)
Sex	4 neutered females and 2 neutered males	3 neutered males and 1 neutered and 1 intact female
Age median (range) (years)	5 (4.3-6.8)	4.9 (4.2-6.6)
BW, median (range) (kg)	10.75 (5.05-32.60)	5.5 (3.40-11.30)

BW: body weight; kg: kilogram; NSAID: non-steroidal anti-inflammatory drug; y: year.

Table 2. The Modified Frankel score, the short form of the Glasgow Composite Pain Scale (SF-GCPS) score at presentation and the type of NSAID administered.

Case number	Group NP† or N‡	MFS§ at presentation (1-5)	SF-GCPS score at presentation (score/total score) †	NSAIDs
1	NP	3	8/20	Carprofen¶
2	NP	2	6/24	Meloxicam¶
3	NP	3	6/20	Meloxicam¶
4	NP	2	3/24	Carprofen¶¶
5	NP	3	5/20	Carprofen¶¶
6	NP	4	5/20	Meloxicam¶
7	N	2	6/20	Carprofen¶¶
8	N	3	4/20	Robenacoxib¶
9	N	2	4/24	Meloxicam¶
10	N	4	7/20	Meloxicam¶
11	N	2	13/24	Meloxicam¶

h: hours; IVDE: intervertebral disc extrusion; MFS: modified Frankel score; min: minutes; NSAID: non-steroidal anti-inflammatory drug; SF-GCPS: short form of the Glasgow Composite Pain Scale;
† Group NP: NSAID + paracetamol group.
‡ Group N: NSAID + placebo group.
§ Modified Frankel Score: a score of 1-5, depending on ambulation.
¶ NSAID administered preoperatively.
¶¶ NSAID administered for the first time at the start of surgery.

Glasgow Composite Pain Scale score for each dog at time of presentation and the type of NSAID that was administered are shown in Table 2. Seven dogs had already received an NSAID upon admission. In the other four dogs, carprofen was administered at the time of anesthesia induction. The anesthesia and surgery time did not significantly differ between both groups (P = 0.65 and P = 0.31, respectively). All dogs of group NP and four out of six dogs from group N needed intraoperative rescue analgesia, consisting of fentanyl (Table 3). No statistically significant difference was found between both groups regarding the intraoperative need for fentanyl (OR: inf, 95% CI: 0.2 – inf, P = 0.18). Two out of six dogs of group NP needed rescue analgesia postoperatively. In group N, all five dogs required postoperative rescue analgesia. The odds ratio was 5.0 (95% CI: 11.4 – 23.7, P = 0.02). The number of times methadone was administered per patient in group N compared to group NP was also significantly different, with an average of 1.8 more rescue analgesia administrations for the dogs of group N (95% CI: 0.2 – 2.8, P = 0.02). The time (twenty hours in total) after surgery itself did not significantly influence the need for postoperative analgesia in either group, taking into account that postoperative pain and consequently the need for analgesia decrease over time (OR: 1.12, 95% CI: 0.9 – 1.5, P = 0.38). The amount of intraoperative fentanyl that was administered, the postoperative short form of the Glasgow Composite Pain Scale scores and the number of rescue analgesia administrations in the postoperative period are summarized in Table 3.

None of the dogs developed serious side effects during the study period. Minor side effects were reported in eight dogs and are summarized in Table 4. There was no significant difference regarding the occurrence of side effects between the two groups (OR: 0.28, 95% CI: 0.004 – 5.9 P = 0.55). All dogs had excellent long-term outcomes and regained ambulation within four weeks after surgery.

DISCUSSION

In this prospective clinical trial, the perioperative analgesic efficacy of paracetamol was evaluated as an adjunct to NSAID and opioid analgesia in dogs that underwent a thoracolumbar hemilaminectomy for the treatment of IVDE. The postoperative pain scores exceeded the threshold for rescue analgesia in dogs from group NP significantly less compared to group N (P = 0.01). The odds of needing postoperative rescue analgesia in dogs that did not receive paracetamol perioperatively were five times higher than those that received additional paracetamol. In a clinical setting, combining an NSAID and paracetamol in dogs undergoing single-site hemilaminectomy seems to provide sufficient postoperative analgesia, without the necessity of an opioid. However, additional intraoperative analgesia still appears necessary.

The positive-controlled clinical study of Pacheco et al. (2020) showed that 33 mg/kg paracetamol/codeine, every eight hours, is an effective perioperative analgesic drug in dogs. In that study, paracetamol/codeine appeared non-inferior to the NSAID meloxicam. In a clinical study by Hernández-Avalos et al.

Table 3. The amount of intraoperative fentanyl, the postoperative SF-GCPS scores and the number of rescue analgesia administrations in the postoperative period to dogs of group N‡ or NP† are shown. Methadone, 0.1 mg/kg IV, was administered with a postoperative SF-GCPS score of more than 5/24 in ambulatory dogs and 4/20 in non-ambulatory dogs (in bold). In case rescue analgesia was required twice during the first eight hours post-extubation period (T0-T8) or once at timepoint T8, 0.1 mg/kg methadone IV was repeated after six hours, at timepoint T14. This is halfway between the pain scoring at timepoint T8 and the last pain scoring at timepoint T20.

Case number	Group	Intraoperative rescue analgesia: fentanyl (total dose in µg/kg)	SF-GCPS (score/total score)†									Number of rescue analgesia administrations during the postoperative period
			T0	T1	T2	T3	T4	T5	T6	T7	T8	T20	Methadone 0.1 mg/kg IV
1	NP	11.2	1/20	2/20	2/20	1/20	1/20	1/24	2/24	2/24	2/24	1/24	0
2	NP	7.8	2/20	4/20	**7/20**	3/20	2/20	**5/20**	4/20	4/20	**5/20**	2/20	4
3	NP	8.7	2/20	3/20	2/20	2/20	1/20	2/20	1/20	1/24	1/24	1/24	0
4	NP	15.5	1/24	3/24	4/24	2/24	4/24	3/24	4/24	3/24	2/24	3/24	0
5	NP	4	3/20	2/20	4/20	3/20	1/20	**6/20**	2/20	1/20	1/20	1/24	1
6	NP	2	1/20	1/20	2/20	1/20	2/20	2/20	3/20	4/20	3/20	4/20	0
7	N	0	2/20	3/20	3/20	4/20	4/20	**6/24**	3/24	2/24	2/24	3/24	1
8	N	4.5	1/20	2/20	3/20	3/20	4/20	4/20	**7/20**	4/20	3/20	**5/20**	2
9	N	0	3/20	2/20	2/20	4/24	**6/24**	4/24	**9/24**	4/24	**8/24**	2/24	4
10	N	2	0/20	**7/20**	**6/20**	2/20	3/20	4/20	4/20	**6/20**	2/20	**7/20**	5
11	N	2	0/20	4/20	**6/20**	**7/20**	**6/24**	3/24	3/24	2/24	**7/24**	2/24	5

NSAID: non-steroidal anti-inflammatory drug; SF-GCPS: short form of the Glasgow Composite Pain Scale; T0-T20: time after extubation in hours; T0: time of extubation;T20: 20 hours post extubation.
† Group NP: NSAID + paracetamol group.
‡ Group N: NSAID + placebo group.

(2019), the use of paracetamol was compared, using a dose of 15 mg/kg IV every eight hours, to the NSAIDs meloxicam and carprofen in dogs undergoing ovariohysterectomy. They demonstrated that paracetamol was as effective as both NSAIDs for postoperative analgesia. Additionally, in a study by Ferrarin et al. (2021), it was shown that methadone as a postoperative drug is not required in dogs that underwent hemilaminectomy for IVDE, when a combination of meloxicam (NSAID) and metamizole (non-opioid analgesic and antipyretic drug) was used for postoperative analgesia. The key finding from this study was that combining paracetamol with an NSAID provides effective postoperative analgesia in dogs undergoing hemilaminectomy to treat intervertebral disc disease and reduces the need for opioid analgesia in the postoperative period. Therapeutic levels of paracetamol have shown adequate analgesic effects with some degree of anti-inflammatory and antipyretic activity in dogs (Fadel et al., 2021). Recommended doses effective for postoperative pain control are generally between 10-20 mg/kg, every 8-12 hours (Serrano-Rodríguez et al., 2019; Fadel et al., 2021; Sartini et al., 2021). In the present study, the dogs received a low dose of paracetamol (10 mg/kg, every 12 hours). The dose used in this study was specifically chosen to determine the effectiveness of paracetamol at the lowest reported dose, since stronger analgesic effects are expected with higher doses. As such, additional studies with higher doses of paracetamol might be of clinical interest.

Methadone was given as part of the premedication for anesthesia to provide pre-emptive surgical analgesia, but was not repeated after the induction of anesthesia. The need for postoperative rescue analgesia was based on the short form of the Glasgow Composite Pain Scale, a composite scale for assessing pain in dogs in a hospital setting on the basis of behavioral observations and response to manipulation of the surgical site (Holton et al., 2001).

No significant differences were found between both groups with regarding the intraoperative need for fentanyl. Fentanyl was chosen as a rescue analgesic intraoperatively, because it is an effective short-acting

pure μ-agonist opioid with a rapid onset, short duration of action and minor cardiovascular effects and therefore suitable for administration as a CRI (Ilkiw et al., 1994; Steagall et al., 2006; Kukanich and Clark, 2012; Skelding et al., 2021).

During the preoperative period, all dogs received methadone and seven dogs had already received an NSAID (six meloxicam, one robenacoxib). Reported preoperative side effects consisted of anorexia (n=6) and regurgitation (n=1). Preoperative anorexia is commonly encountered and can be related to the use of certain drugs (e.g. NSAIDs, opioids), but is also seen with pain and anxiety (Lascelles et al. 2005; Delaney et al. 2006). Two dogs regurgitated intraoperatively, one from group NP and one from group N. The latter regurgitated one hour post methadone administration at induction, but did not show any side effects postoperatively, although the dog received 0.5 mg/kg methadone IV in total during the postoperative period. Four out of six dogs that regurgitated in this study were brachycephalic breeds. Gastrointestinal upset and regurgitation are commonly encountered in those breeds and reported frequently with the use of opioids and NSAIDs (Poncet et al., 2005; Poncet et al., 2006; Lamata et al., 2012; Shaver et al., 2017). Minor postoperative side effects were reported in four out of seven dogs that received postoperative methadone (regurgitation n = 2, hypersalivation n = 1, diarrhea n = 1, vomiting n = 1), and only one of those dogs also received paracetamol. No postoperative side effects were noted in any of the four dogs that did not receive postoperative rescue analgesia with methadone. Side effects as a result of paracetamol treatment are uncommon if a therapeutic dose for a limited period of time is used. Subsequent clinical signs of systemic toxicity are more likely to be seen in doses above 150 mg/kg and include anorexia, abdominal discomfort, vomiting, icterus, facial swelling, respiratory distress and lethargy due to hematological disturbances, hepatic, renal and hemoglobin damage (Omer and Mohammad, 1984; Salem et al., 2010; Serrano-Rodríguez et al., 2019; Fadel et al., 2021). To reduce the incidence of breed-related side effects and since some dogs received corticosteroids at the referring veterinarian (24-48 hours before the start of the study), all dogs received pantoprazole during the study period (Poncet et al., 2005; Poncet et al., 2006; Lamata et al., 2012; Shaver et al., 2017).

Finally, this study had some limitations. Firstly, one dog was excluded from the study because the anesthesia protocol was not followed correctly. Therefore, the sample size did not match the recommended sample size that was calculated with the power analysis; however, this did not significantly influence the results. While the results in this small cohort are already promising, the overall sample size is limited, so further studies in larger cohorts are needed to confirm the findings of the present study. Secondly, anesthesia was performed by different anesthesiologists. To limit interobserver bias, a similar anesthesia protocol was used and the anesthesiologists were blinded for group allocation. Furthermore, the cut-off values for clinical parameters were not standardized (e.g. blood pressure, heart frequency) during anesthesia that would indicate the need for rescue analgesia perioperatively. The administration of fentanyl as rescue analgesia was thus based on the clinical evaluation of nociception at the anesthesiologist's discretion. This might have influenced the results perioperatively. However, fentanyl is a very short-acting drug, so it seems unlikely that its intraoperative administration influenced the postoperative pain scoring, although this cannot be completely ruled out. Finally, throughout the study population, different NSAIDs were used, as the

Table 4. Reported perioperative, preoperative and postoperative side effects.

Case number	Group NP† or N‡	Side effects		
		Perioperative side effects, other than anorexia	Preoperative anorexia	Postoperative anorexia
1	NP	None	Fasted	No
2	NP	Regurgitation (T20)	Yes	No
3	NP	Regurgitation (intraoperative)	No	No
4	NP	None	No	No
5	NP	None	Fasted	No
6	NP	Regurgitation (preoperative)	Yes	No
7	N	None	Yes	No
8	N	Regurgitation (T20)	Yes	No
9	N	Hypersalivation (T6, T8)	No	No
10	N	Diarrhea (T2), vomiting (T20)	Yes	Yes
11	N	Regurgitation (intraoperative)	Yes	No

T2: 2 hours post extubation; T6: 6 hours post extubation; T8: 8 hours post extubation: T20: 20 hours post extubation
† Group NP: NSAID + paracetamol group.
‡ Group N: NSAID + placebo group.

NSAID that had already been started by the referring veterinarian, was continued. This also might have influenced the results.

CONCLUSION

In this study, it is shown that despite multimodal perioperative pain management consisting of a full μ-agonist opioid, an NSAID and paracetamol in dogs undergoing single-site thoracolumbar hemilaminectomy, intraoperative rescue analgesia (e.g. fentanyl) was still required. However, in the postoperative period, the need for opioid-based analgesia was significantly lower in dogs receiving paracetamol than in dogs that did not receive paracetamol intra- and postoperatively. There is supporting evidence that paracetamol is an effective drug for perioperative pain relief and the authors recommend the use of paracetamol in multimodal perioperative analgesia protocols for dogs undergoing hemilaminectomy to treat an intervertebral disc extrusion. Higher doses of paracetamol (e.g. 15 mg/kg every 8-12 hours) are recommended and are possibly needed to replace methadone completely in the postoperative period.

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