Comparison of morphine and carprofen administered alone or in combination for analgesia in dogs undergoing ovariohysterectomy

T B Dzikiti[a*], K E Joubert[a,b], L J Venter[a] and L N Dzikiti[c]

ABSTRACT

In this study the analgesic efficacy of the pure agonistic opioid morphine and the cyclo-oxygenase type-2-selective carprofen were compared since there is no previous specific comparative study for these two common analgesics. Forty-five bitches undergoing elective ovariohysterectomy were randomly assigned to one of three groups; receiving morphine 0.4 mg/kg bodyweight pre-operatively and 0.2 mg/kg every 4–6 hours thereafter (Morphine group), receiving a once-off carprofen 4 mg/kg injection (Carprofen group) or receiving both morphine and carprofen (MorphCarp group). The dogs were premedicated with acepromazine 0.01 mg/kg and induced with either thiopentone 5–10 mg/kg or propofol 4–6 mg/kg. General anaesthesia was maintained with halothane in oxygen. The degree of pain was assessed over a 24-hour period under blinded conditions using a pain scale modified from the University of Melbourne pain scale and the Glasgow composite pain tool. Physiological parameters such as respiratory rate, pulse rate and body temperature were also assessed over the same time period. There was no significant difference in pain-scores and thus analgesia offered by the three analgesia protocols at any assessment point across the three groups, but there were differences within groups across time points. Baseline total pain-scores were lower than scores at all post-operative points within all three groups. Both morphine and carprofen provided good analgesia without any obvious adverse effects. This study indicates that at the dosages indicated above, carprofen administered on its own produces analgesia equal to that produced by morphine and that the two drugs administered together do not produce better analgesia than either drug administered on its own.

Key words: analgesia, balanced analgesia, carprofen, morphine, NSAIDs, opioids, pain.

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INTRODUCTION

All animals undergoing surgical procedures require pain relief after surgery to overcome the deleterious physiological effects of postoperative pain and to address humane and ethical concerns[18,24]. Non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesic agents and local anaesthetic agents are the main drugs used to control postoperative pain in animals[6,15,27]. Opioid analgesics have traditionally been the most widely used analgesics in veterinary practice[31].

The classification of opioid analgesics as controlled drugs, concerns regarding their adverse effects and lack of familiarity with opioids available make veterinarians reluctant to use them for pre-emptive analgesia[6,23]. Moreover, opioids are known to cause cardiopulmonary depression and increase depth of sedation and thus prolong recovery, which can, depending on practice circumstances, be interpreted as undesirable effects of opioid use[20,27]. These negative factors associated with opioid use have resulted in the prominence of NSAIDs in providing perioperative analgesia[31]. Despite the desirable analgesic effects of NSAIDs, their use is associated with inhibition of prostaglandin production and disruption of the processes they participate in, resulting principally in various degrees of renal function impairment and gastrointestinal irritation and ulceration[13,24]. Other adverse effects of NSAIDs include coagulopathy, liver damage and worsening of cardiac failure[19]. The NSAID carprofen (6-chloro-alpha-methyl-carbazole-2-acetic acid) is a particular exception in that it produces little or no side-effects, while at the same time providing good efficacy as an analgesic and anti-inflammatory agent[11]. The exact mode of action of carprofen is not understood. There is , however , evidence from *ex vivo* canine studies that it is cyclo-oxygenase (COX) type 2 selective while some authors suggest that it has limited COX activity[1,31]. With a half maximal inhibitory concentration (IC_{50}) ratio, COX-2/COX-1, of 0.04–0.4, carprofen produces preferential inhibition of COX-2 when compared with most other NSAIDs[3,22]. The products of COX-2 are thought to be responsible for the inflammatory process, while cyclo-oxygenase COX-1, which is produced continuously in small quantities is responsible for production of the homeostatic prostaglandin and thromboxane mediators[28,31]. While the hypothesis developed in 1991 that COX-1 inhibition is associated with side-effects while COX-2 inhibition is associated with therapeutic effects still holds true, it has been modified as a result of recent developments such as the discovery of a third COX isoform, COX-3, and evidence of a role for central nervous system actions of NSAIDs as analgesics and anti-inflammatory agents in addition to their peripheral actions[22]. The injectable form of carprofen has undergone extensive use clinically pre-operatively with good effect and few reported side-effects in cats and dogs[3,19].

Despite the fact that opioids and NSAIDs produce their effects by different mechanisms, it is still reasonable to compare the two since they are both used for relief of pain. It is also of interest to determine how combinations of the two would perform since this approach is thought to provide optimal analgesia rather than use of a single analgesic agent[30]. One clinical trial done in 1994 indicated that carprofen at 4 mg/kg preoperatively provided slightly better pain relief than pethidine at 2 mg/kg preoperatively and 3 mg/kg postoperatively[20]. Pethidine is an opioid, which is 10 times less potent than morphine[9]. A more recent study showed that dogs treated with a combination of 4 mg/kg carprofen and 5 mg/kg pethidine

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had significantly lower visual assessment pain scores (VAS) than those treated with 5 mg/kg pethidine alone, but showed no significant difference from those treated with 4 mg/kg carprofen alone[30].

Currently the main problem with clinical assessment of pain in veterinary patients is the absence of a validated method of pain assessment[4,10]. So far, pain assessment has been based on the use of unidimensional rating scales developed for use in humans, namely the simple descriptive scale (SDS), the numerical rating scale (NRS) and the visual analogue scale (VAS)[14]. These simple scales are subjective, and are only widely used because of their simplicity[33]. A number of composite pain assessment scales have been developed from the three basic ones mentioned above, for example, the 'dynamic' and 'interactive' visual assessment scale (DIVAS) used in a study of the analgesic efficacy of carprofen in dogs[21] and the validated Glasgow Composite Pain Tool[14]. A composite scale modified from the University of Melbourne Pain Scale and the Glasgow Composite Pain Tool was used for assessment of pain in this study. This composite scale has been highly recommended for evaluating pain after routine surgery in dogs and cats. The advantage of this scale is that specific descriptors for individual behaviours are provided, which decreases inter-observer variability[12].

To our knowledge, no studies have been done to compare the analgesic effects of carprofen to those of morphine. The purpose of this study was therefore to determine the efficacy of carprofen and morphine, used alone and in combination, for treating acute postoperative pain in a clinical trial. Morphine is a potent opioid that is extremely popular as a preemptive and postoperative analgesic and one which is commonly taken as the yardstick against which all other analgesics are compared[16,32,35]. The study's aim was to compare these drugs using clinically relevant dosages over a 24-hour period.

Our hypotheses were that carprofen administered on its own produces analgesia equal to that produced by morphine and that the two drugs administered together produce better analgesia than either drug administered on its own.

MATERIALS AND METHODS

A total of 45 normal healthy bitches admitted for elective ovariohysterectomy to the Onderstepoort Veterinary Academic Hospital (OVAH) was used in this study. Permission to use the bitches was obtained from the owners by signing of consent forms. Details of age, weight, duration of anaesthesia and duration of surgery are shown in Table 1. The dogs were assigned randomly to one of three analgesic protocol groups of 15 each.

Table 1: **Descriptive details** (mean ± SD) **of dogs used in the study.**

Group	Age (months)	Body weight (kg)	Anaesthesia time (mins)	Surgery time (mins)
Morphine	21.2 ± 26.2	14.9 ± 10.5	163.1 ± 35.4	121.7 ± 33.1
Carprofen	32.9 ± 33.8	9.2 ± 9.1	155.9 ± 40.2	120.8 ± 37.0
MorphCarp	22.7 ± 20.5	11.4 ± 9.5	190.3 ± 38.5	147.7 ± 37.1

The Morphine group received morphine only for analgesia. The Carprofen group received carprofen only for analgesia. The MorphCarp group received both morphine and carprofen for analgesia. The dogs were starved 10 hours before anaesthesia, while water was withheld from the morning of surgery. All dogs were physically examined before premedication. The dogs were then premedicated with acepromazine maleate (Acevet 2®, Bayer, Isando, South Africa) at a dose of 0.01 mg/kg subcutaneously. The dogs also received either morphine (Morphine sulphate® Fresenius, Bodene, trading as Intramed, Port Elizabeth, South Africa) at 0.4 mg/kg given by subcutaneous injection into the scruff (Morphine group) or carprofen (Rimadyl® injectable, Pfizer Laboratories, Sandton, South Africa) at 4 mg/kg given by subcutaneous injection into the scruff (Carprofen group) or both morphine and carprofen at the same dosages (MorphCarp group) at the time of acepromazine administration. Thirty minutes after premedication, general anaesthesia was induced using thiopentone (Thiopentone Sodium® Fresenius, Bodene, trading as Intramed, Port Elizabeth, South Africa) at a dose of 5–10 mg/kg or Propofol (Propofol 1%® Fresenius, Bodene, trading as Intramed, Port Elizabeth, South Africa) 4–6 mg/kg intravenously, to effect through a catheterised cephalic vein. Placement of an endotracheal tube of appropriate size was done soon after induction and surgical anaesthesia was maintained with halothane (Halothane M-B®, Safeline Pharmaceuticals, Wadeville, South Africa) delivered in oxygen by a Tec 5 vaporiser (Ohmeda Fluotec 5®, BOC Health Care, West Yorkshire, England) *via* a circle breathing circuit. The dogs were allowed to breathe spontaneously. Morphine was subsequently administered every 4–6 hours at a dose of 0.2 mg/kg by subcutaneous injection into the scruff until the following morning (Morphine group and MorphCarp group), while carprofen was only administered once (Carprofen group). The dosages used are based on commonly used clinical dosages and manufacturer's recommendations. The dogs in the Carprofen group also received a subcutaneous injection of normal saline (Intramed Sodium Chloride 0.9%® Fresenius, Bodene, trading as Intramed, Port Elizabeth, South Africa) into the scruff at those 4–6 hourly intervals to standardise the effect of injections across all groups. Ovariohysterectomy was performed through a ventral midline incision after appropriate clipping and surgical preparation of the area. The length of the surgical procedure and anesthetic procedure were recorded. Ringer-Lactate (Intramed Ringer-Lactate® Fresenius, Bodene, trading as Intramed, Port Elizabeth, South Africa) was administered to all the dogs from time of intubation until a few hours post-operatively. The rate of fluid administration was 10 mℓ/kg/h perioperatively and 2.2 mℓ/kg/h postoperatively.

Administration of analgesic drugs was supervised by one anaesthesiologist and the assessment of pain was done by a blinded assessor. Pain assessment was done before sedation (baseline scores), just before induction and at 1 hour, 2 hours, 4 hours, 6 hours and 20 hours after surgery using the pain scale shown in Table 2. As the assessor approached the kennel, he would look at the dog's behaviour and reactions. From outside the dog's kennel questions on posture, activity and vocalisation were answered. Scores ranging from 0 to 4 were then allocated for each of the characteristics. Dogs were then approached, addressed vocally, and the cage door opened. Notes regarding their mental status were then taken. The dogs were then gently handled, encouraged to walk and move around and finally the incision and surrounding area of the abdomen was palpated gently. Scores were then allocated for the dog's willingness to walk and response to firm palpation of the surgical wound. The scores obtained for the component categories of the pain scale were finally summed to form a total pain score. The minimum possible total pain score that could be obtained by use of this scale was 0, while the maximum possible score was 20.

The dogs' temperature, pulse and respiration were recorded at each assessment. Dogs were constantly monitored, and if a dog was found to be in extreme discom-

fort (total pain assessment score above 10), it was excluded from the study and treated with morphine at 0.4 mg/kg medication and would maintain the score at which assessment was terminated for the remainder of the period of study.

This study was approved by both the Animal Use and Care Committee and the Research Committee of the University of Pretoria's Faculty of Veterinary Science.

Statistical analysis of data

Data for pain scores (Table 3) were presented as range (median), while data for physiological parameters were presented as mean ± SD (standard deviation) for analysis. Statistical significance was set at a value of $P < 0.05$. The data were analysed using the R statistical software (R®, The R Foundation for Statistical Computing, Vienna, Austria). Median pain scores were compared between and within groups (Morphine group, Carprofen group and MorphCarp group), at each of the assessment points (presedation, preinduction, 1 hour postoperatively, 2 hours postoperatively, 4 hours postoperatively, 6 hours postoperatively and 20 hours postoperatively). These values were compared using the Kruskal-Wallis rank sum test. It is a nonparametric test for testing the null hypothesis: H_o: location parameters (usually mean or median) are the same in each group versus the alternate H_1: the location parameters differ in at least one group. Where statistical differences were noted, pair-wise comparisons were performed using the pairwise Wilcoxon rank sum test with a Bonferroni adjustment for multiple testing. The same two tests indicated above were used to compare median scores for the component categories of the pain scale (*i.e.* posture, activity, pupil dilation, salivation, vomition, vocalisation, mental status, mobility, and response to touch) at before sedation, just before induction, and at 1, 2, 4, 6 and 20 hours after surgery. Mean age, body weight, duration of anaesthesia, duration of surgery, respiratory rate, pulse rate and body temperature were also compared across the groups.

Table 2: **Pain scale used for pain assessment in dogs** (modified from the University of Melbourne pain scale and the Glasgow composite pain tool).

Category/Expression assessed	Score
Posture	
Normal	0
Rigid	1
Hunched, tense	2
Abnormal (Define...)	3
Guarding affected area	4
Comfort	
Restful, comfortable	0
Restless	1
Uncomfortable	2
Rolling, thrashing	3
Pupils dilated	1
Salivating	1
Vomiting	1
Vocalisation	
Not vocalising	0
Barking (if abnormal)	1
Crying or whimpering	2
Groaning or hissing	3
Screaming	4
Mental status	
Aggressive, obtund, disinterested, nervous/anxious/fearful, happy/content, happy/bouncy or submissive	
Change in mental status	1
Mobility	
Not carried out, will not walk or none of these	0
Stiff or ataxic	1
Lame, slow or reluctant to rise or sit	2
Palpation	
None of these	0
Anxious or looking towards wound	1
Cry or flinch	2
Snap, bite, hiss, growl or guarding wound	3

RESULTS

There were no statistically significant differences between groups in terms of age, body weight, pulse rate, respiratory rate, body temperature, anesthesia time or surgery time. Using the Kruskal-Wallis test, the only statistically significant difference noted between physiological parameters was of body temperature at four hours postoperatively (*P*-value 0.03). When the values were further scrutinised using the Wilcoxon rank sum test for pairwise comparison, the difference appeared to be between the Morphine group and the other two groups, but the *P*-value was not low enough to be statistically significant according to this test.

There were no statistically significant differences between the three groups in terms of median pain scores (Table 3). There were within-group differences in median pain scores. All baseline total pain scores were lower than all postoperative pain scores within all groups, while the 1-hour postoperative total pain score was higher than the 20-hour postoperative pain score within the Carprofen and MorphCarp groups. The box-and whiskers plots of the total pain-scores for the three groups (Figs 1–3) show a clear graphical display of the centring, spread and distribution of these pain-scores.

None of the 45 dogs used in this study had to be excluded from the study for experiencing extreme pain. One of the dogs from the Morphine group was not assessed at 20 hours post-operatively because it had to be taken back to theatre for re-ligation of a bleeding meso-ovarian stump.

DISCUSSION

The animals used in the study were evenly distributed among the three groups as supported by the fact that there were no significant differences between groups in terms of age and body weight. It is also important to note that there were no differences between the three groups in terms of anaesthesia time and surgery time as these could have potentially influenced the pain scores obtained in the post-operative period.

The study was also designed bearing in mind that timing of analgesic intervention may have some influence on postoperative pain[6,8,21,34]. Consequently, the analgesic drugs were administered preemptively. Both morphine and carprofen

Table 3: **Pain scores presented as median (range) for presedation** (baseline) **and preinduction periods as well as for 1, 2, 4 hour, 6 and 20 hour postoperative period for the Morphine group** (M)**, Carprofen group** (C) **and the Morphine-carprofen group** (MC) **in ovariohysterectomy dogs.**

Parameter	Group	Pain scores median (range)						
				Time after surgery (hours)				
		Presedation	Preinduction	1	2	4	6	20
Posture	M	0 (0–0)	0 (0–0)	1 (0–1)	1 (1–2)	1 (1–2)	1 (1–2)	1 (0–1)
	C	0 (0–0)	0 (0–0)	1 (0–1)	1 (0–2)	1 (1–2)	1 (1–2)	1 (0–1)
	MC	0 (0–0)	0 (0–0)	0 (0–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (0–1)
		NS	NS	NS	NS	NS	NS	NS
Comfort	M	1 (0–1)	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)
	C	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)
	MC	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
		NS	NS	NS	NS	NS	NS	NS
Pupil size	M	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
	C	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
	MC	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
		NS	NS	NS	NS	NS	NS	NS
Salivation	M	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
	C	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
	MC	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
		NS	NS	NS	NS	NS	NS	NS
Vomition	M	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
	C	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
	MC	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
		NS	NS	NS	NS	NS	NS	NS
Vocalisation	M	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)
	C	0 (0–0)	0 (0–0)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)
	MC	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)
		NS	NS	NS	NS	NS	NS	NS
Mental status	M	0 (0–0)	0 (0–1)	1 (1–1)	1 (0–1)	1 (0–1)	0 (0–1)	0 (0–1)
	C	0 (0–0)	1 (0–1)	1 (1–1)	1 (0–1)	1 (0–1)	1 (0–1)	0 (0–1)
	MC	0 (0–0)	1 (0–1)	1 (1–1)	1 (1–1)	1 (0–1)	1 (0–1)	0 (0–1)
		NS	NS	NS	NS	NS	NS	NS
Mobility	M	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)
	C	0 (0–0)	0 (0–0)	1 (0–1)	1 (1–1)	1 (0–1)	1 (1–1)	1 (0–1)
	MC	0 (0–0)	0 (0–0)	0 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (0–1)
		NS	NS	NS	NS	NS	NS	NS
Palpation	M	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–1)
	C	0 (0–0)	0 (0–0)	0 (0–2)	1 (0–1)	1 (0–2)	1 (0–1)	0 (0–1)
	MC	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	0 (0–1)
		NS	NS	NS	NS	NS	NS	NS
Total	M	0 (0–3)	1 (0–3)	3 (2–7)*	5 (3–7)*	5 (3–8)*	4 (2–7)*	2.5 (0–5)*
	C	0 (0–1)	1 (0–2)	4 (1–8)*	4 (3–5)*	4 (1–8)*	4 (2–7)*	3 (0–4)*
	MC	0 (0–2)	1 (0–3)	4 (2–9)*	4 (3–8)*	4 (3–7)*	4 (3–7)*	3 (1–5)*
		NS	NS	NS	NS	NS	NS	NS

NS: No significant differences ($P > 0.05$) between groups, *: significantly higher ($P < 0.05$) than baseline (presedation) value.

were administered at dose rates known to provide satisfactory analgesia at the time of designing the research proposal[5,9,22,30] and in a regimen that would be acceptable and easy to apply in veterinary practice. A more recent study that was carried out to assess use of a von Frey device as a mechanical stimulus for evaluation of the antinociceptive effects of morphine in dogs seem to suggest that the dosages of morphine used in our study might be inadequate for achieving effective analgesia. The von Frey device study suggests that a morphine plasma concentration of 30 ng/mℓ provides adequate analgesia. This morphine plasma concentration was obtained with a continuous rate infusion of 0.15 mg/kg/h, 0.5 mg/kg every 2 hours or 1 mg/kg for 3 hours[16,17]. Comparatively, in our study, morphine was administered at a lower dose (0.4 mg/kg) and at less frequent intervals (every 4 hours). This would imply that our morphine administration regimen could have failed to achieve maximal analgesic effect, but the outcome of our study certainly disagrees with this implication.

The pain scores obtained in this study indicate that the three analgesic protocols used in this study offered reliable analgesic efficacy. This is supported by the fact that none of the dogs used in the study required rescue analgesia for experiencing severe unbearable pain at any of the assessment times. The best way to draw a conclusion on the efficacy of analgesia of

the regimens used in this study would have been to include a placebo group as a negative control, but this was deemed unjustifiable on humane grounds. It is now widely accepted that all animals deserve pain relief pre-operatively, peri-operatively and postoperatively[3,25]. Although no records of previous studies comparing analgesic efficacy of morphine and carprofen could be found, similar conclusions on analgesic efficacy of the two drugs have been made in studies where either of these drugs was compared with some other drugs in other comparative analgesia studies[20,21,26,30,32,34]. In previous comparative analgesia studies in dogs, morphine has been compared to buprenorphine and pentazocine, while carprofen has been compared with pethidine and papaveretum[7,26,30,32]. All these studies also reported satisfactory analgesia from both morphine and carprofen.

There was virtually no difference in level of analgesia provided by morphine alone, carprofen alone or morphine and carprofen combined. The similarity in degree of analgesic effects of morphine alone and carprofen alone compare well with findings of most such studies, which also reached the same conclusion when opioid analgesia was compared with NSAID analgesia[2,18,29,30]. It is puzzling that the degree of analgesia obtained with the monoanalgesic regimens was similar to that obtained when morphine and carprofen were administered as a combination. This outcome contradicts the phenomenon of synergism expected when multi-modal or balanced analgesic regimens are used as shown in a study comparing analgesic efficacy of carprofen and pethidine[30].

From the finding that the pain scores at 20 hours postoperatively were still significantly higher than baseline scores in all three groups, it is clear that analgesics should continue to be administered to dogs well beyond this period after an ovariohysterectomy.

There is still no consensus on a validated scale to use in assessing pain in animals[12].

We found the composite scale used in this study to be quite simple and less confusing. The fact that the baseline pain scores were significantly lower than all postoperative pain scores in this study shows that the scale used for assessment of pain is good enough to distinguish animals in pain from the ones that are not in pain.

It is concluded that carprofen administered on its own produces analgesia equal to that produced by morphine and that the two drugs administered together do not produce better analgesia than either drug administered on its own. The importance of morphine as an analgesic agent in clinical practice is well known and this study confirms that. This study also strongly supports the use of carprofen as an analgesic agent in veterinary practice. Further studies are required to verify whether synergism can be obtained with morphine and carprofen using a bigger sample size or using animals undergoing procedures known to be more painful than ovariohysterectomy.

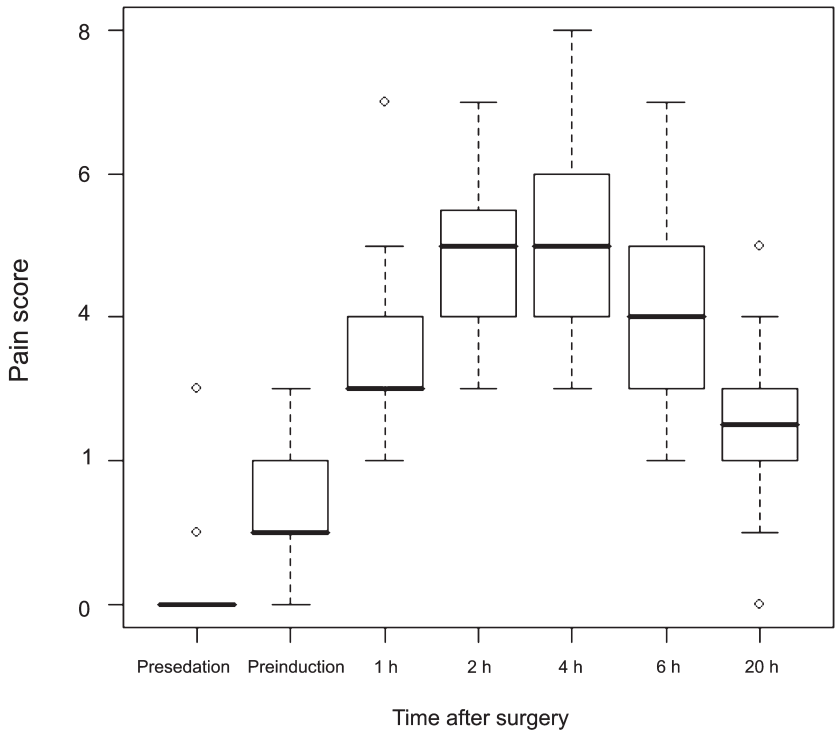

Fig. 1: **Box-and-whisker plot of median total pain scores observed just before premedication** (presedation, baseline), **just before induction** (preinduction), **as well as at 1, 2, 4, 6, 20 hours post-surgical period in dogs treated with morphine for analgesia** (Morphine group). **Each box represents data from the 25th to the 75th percentiles, the bold line represents the median value, and the whiskers represent the range of scores, while the small dots outside the box represent outliers.**

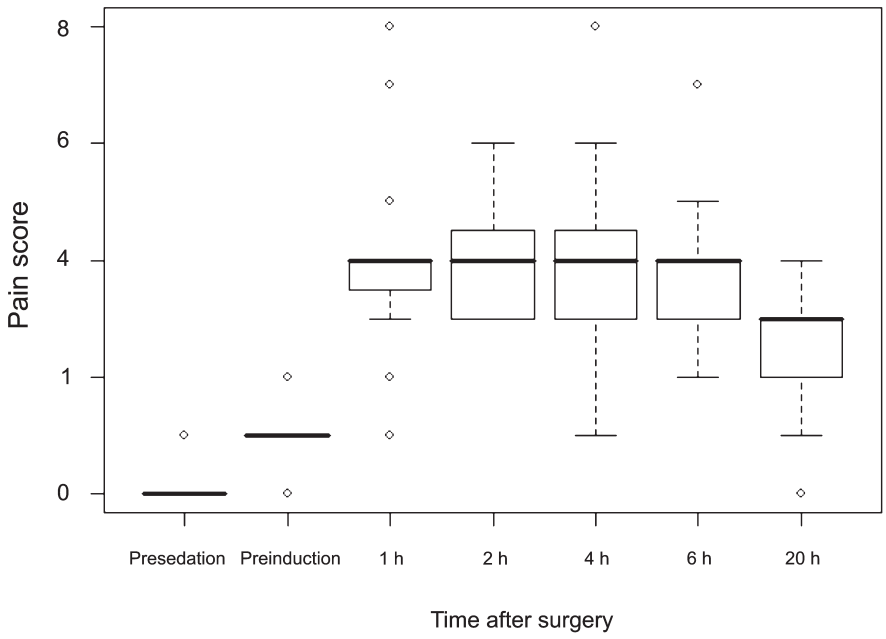

Fig. 2: **Box-and-whisker plot of median total pain scores observed just before premedication** (presedation, baseline), **just before induction** (preinduction), **as well as at 1, 2, 4, 6, 20 hours post-surgical period in dogs treated with carprofen for analgesia** (Carprofen group). **Each box represents data from the 25th to the 75th percentiles, the bold line represents the median value, and the whiskers represent the range of scores, while the small dots outside the box represent outliers.**

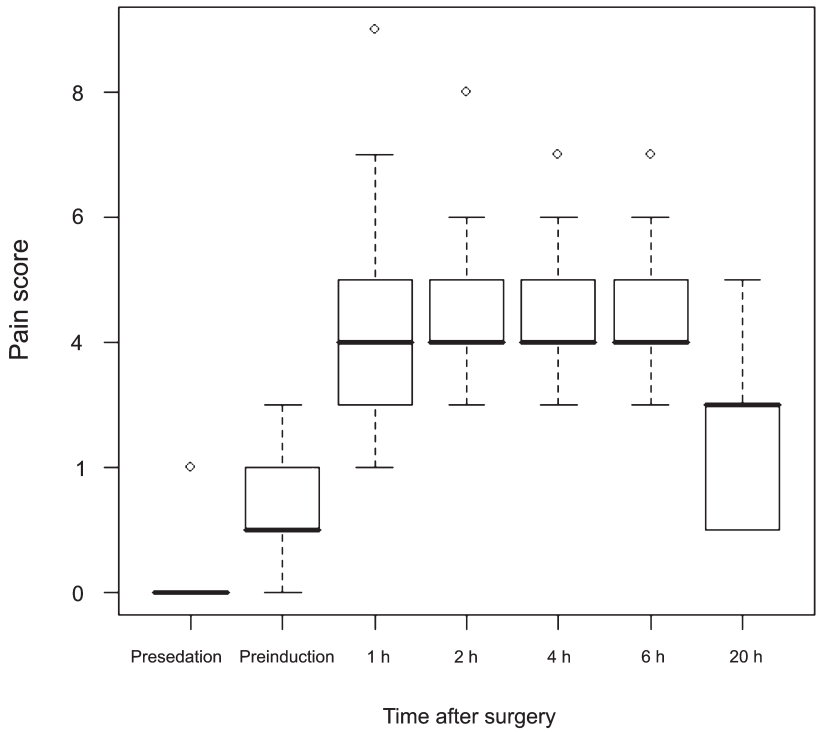

Fig. 3: **Box-and-whisker plot of median total pain scores observed just before premedication** (presedation, baseline)**, just before induction** (preinduction)**, as well as at 1, 2, 4, 6, 20 hours post-surgical period in dogs treated with morphine and carprofen for analgesia** (MorphCarp group)**. Each box represents data from the 25th to the 75th percentiles, the bold line represents the median value, and the whiskers represent the range of scores, while the small dots outside the box represent outliers.**

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