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Comparison of the effects of nefopam and tramadol on postoperative analgesia in dogs undergoing ovariohysterectomy

S. Zhang, J.N. Li, L. Luan, W. Guan, X.Y. Hu, H.G. Fan*

College of Veterinary Medicine, Northeast Agricultural University, Harbin, China

*Corresponding author: fanhonggang2002@163.com

ABSTRACT: Relieving perioperative pain can reduce postoperative suffering and improve recovery from anaesthesia in animals. The aim of this study was to compare the analgesic effects of nefopam and tramadol in dogs undergoing ovariohysterectomy. Twenty-four adult mixed-breed female dogs were randomly divided into three groups (n = 8) and received their respective treatments immediately after surgery: Group T (2 mg/kg tramadol, *i.v.*), Group C (1 mg/kg nefopam, *i.v.*) and Group D (2 mg/kg nefopam, *i.v.*). The heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR) and rectal temperature (RT) were measured and the level of analgesia was assessed using the Glasgow Composite Measure Pain Scale (CMPS-SF). The CMPS-SF was performed at least two days before premedication (baseline), every 2 h for the first 8 h (post-extubation), at 12 h and at 24 h. Results showed that the HR in all groups was significantly ($P < 0.05$) higher at 2 and 6 h than at baseline. The RR in Group T was significantly higher ($P < 0.05$) at 0 and 2 h than at baseline. Rescue analgesia (0.2 mg/kg morphine, *i.v.*) was provided if CMPS-SF pain scores greater than or equal to six. Four dogs required rescue analgesia: one dog in Group T at 2 h and three dogs in Group C at 2 and 6 h. No dogs in Group D required rescue analgesia. The CMPS-SF pain scores of dogs in Group C were significantly higher ($P < 0.05$) than those in Group T at 6, 8 and 12 h. The scores in Group D were significantly lower ($P < 0.05$) than those in Group C at 2, 4, 6, 8 and 12 h. The scores in Group D were significantly lower ($P < 0.05$) than those in Group T at 2 and 4 h. However, the scores in Group D were not significantly different compared with Group T. In conclusion, this study suggests that nefopam at 2 mg/kg *i.v.* produces better postoperative analgesia compared with tramadol at 2 mg/kg *i.v.* or nefopam at 1 mg/kg *i.v.* in dogs undergoing ovariohysterectomy.

Keywords: postoperative analgesia; dogs; nefopam; tramadol; ovariohysterectomy

Dogs undergoing surgery often suffer from postoperative pain. The sequelae of postoperative pain can include reduced appetite, inhibited respiratory function and exacerbated protein catabolism, which may induce central hypersensitivity to noxious stimuli and cardiac arrhythmias (Lorena et al. 2014). Perioperative pain relief is necessary in veterinary clinical practice to reduce postoperative suffering and to improve recovery from anaesthesia (Al-Gizawiy and Rude 2004). To ensure animal welfare and decrease postoperative complications, managing and relieving pain has become increasingly important.

Tramadol, an opioid agonist, engages in complex interactions with opioid, serotonin and adrenergic receptors (Raffa et al. 1992; Sagata et al. 2002). It has been reported to have good postoperative analgesic effects in small animals (Benitez et al. 2015; Karrasch et al. 2015; Sousa and Ashmawi 2015). Tramadol mainly affects the mu receptors, and to a lesser extent, the kappa and delta receptors. Its analgesic effects are mediated through a reduced reuptake of serotonin and norepinephrine (Akbay et al. 2010). The lack of adequate regulatory measures with regard to its use is one of the biggest disadvantages of tramadol compared with other opioids (Lewis and

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Han 1997). In addition, a previous study demonstrated that the seizure threshold can be decreased by tramadol (Akkaya et al. 2009). Although tramadol has been demonstrated to show good postoperative analgesic effects compared with other drugs (Buhari et al. 2012; Davila et al. 2013; Morgaz et al. 2013), the side-effects of tramadol include dizziness, sweating, vomiting, nausea, increased intra-cerebral pressure and anaphylactic reactions. Steps have been taken to limit its use in China (Liu et al. 1999).

The use of opioid analgesics is usually restricted owing to their dependence potentials. Thus, it is necessary to seek alternatives. Nefopam is a centrally acting non-opioid analgesic (Piercey and Schroeder 1981; Durrieu et al. 2007) that has been mainly used to treat cancer pain, visceral smooth muscle cramps and postoperative pain (Mimoz et al. 2001). Nefopam has a particularly good effect on reducing postoperative chronic pain and improving postoperative pain management (Laboureyras et al. 2009). The analgesic effect of nefopam is preferable to morphine during the postoperative period in humans (Alfonsi et al. 2014). Nefopam has approximately one-third to one-half of the potency of oxycodone and morphine (Lu et al. 2013). Nefopam can play a vital role in central analgesia (Guirimand et al. 1999). Its main mechanism of action is inhibition of the mono-amine reuptake system, which has been demonstrated *in vivo* and *in vitro* (Rosland and Hole 1990; Ohkubo et al. 1991). Nefopam is a well-tolerated and safe analgesic. Unlike non-steroidal anti-inflammatory drugs, it does not affect platelet function (Dordoni et al. 1994). It can also inhibit dopamine, norepinephrine, and serotonin reuptake (Piercey and Schroeder 1981). Moreover, nefopam seems to cause minimal respiratory depression, in contrast to opioids (Kapfer et al. 2005). In short, it has great prospects for replacing opioids in many circumstances.

In this study, our purpose was to compare the effect of intravenous (*i.v.*) administration of nefopam and tramadol on postoperative analgesia following ovariohysterectomy in dogs.

MATERIAL AND METHODS

Animals. Twenty-four mixed-breed healthy female dogs were used in the study. Ages ranged from 12 to 18 months, and dogs weighed between 3 and 6 kg. Physical and other examinations, including haematological and biochemical blood tests, ensured that all dogs had no previous analgesic treatment or systemic diseases. The study was approved by the Ethics Committee on the Care and Use of Animals, Northeast Agricultural University, China.

A total of 24 dogs were randomly divided into three treatment groups (n = 8) using a random number table: Group T, Group C and Group D. Dogs in Group T received an *i.v.* injection of tramadol (Grunenthal GmbH, Stolberg, Germany) at a dose of 2 mg/kg. Group C received an *i.v.* injection of nefopam (Heilongjiang Key Laboratory of Anaesthesiology and Intensive Care Research, Harbin, China) at a dose of 1 mg/kg. Group D received an *i.v.* injection of nefopam at a dose of 2 mg/kg.

Anaesthetic and surgical procedures. All dogs were fasted for 12 h for solids and liquids prior to the experiment. Anaesthesia was induced by *i.v.* injection with propofol (Li Bang, Xi'an, China) at 5 mg/kg. A cuffed tube was used for endotracheal intubation. Anaesthesia was maintained with 2% inspiratory isoflurane (Heilongjiang Key Laboratory of Anaesthesiology and Intensive Care Research, Harbin, China) with 100% oxygen using a rebreathing circuit. To keep the vital signs stable, a multiparametric monitor (Datex Ohmeda Cardiotap II, GE Healthcare) was used to monitor the physiological parameters of each dog during surgery. All dogs received *i.v.* lactated Ringer's solution at a rate of 10 ml/kg/h during the surgery.

Ovariohysterectomy is a common surgical procedure performed in small animal practice and it is widely used as a model in analgesic studies in dogs, because it is a surgery that produces moderate or severe postoperative pain. The ovariohysterectomies in our study were performed by the same surgeon with a midline abdominal incision using the 3-clamp principle (Nunamaker et al. 2014). The duration of surgery and extubation time were recorded.

Postoperative assessment. Dogs in all groups were intravenously administered analgesic drugs accurately diluted to the same volume 10 min before the end of the surgery. Repeat doses were given every 6 h for 24 h (medication repeated a total of four times).

After extubation, physiological parameters were monitored using the parametric monitor at baseline, 0 (extubation), 2 (post-extubation), 4, 6, 8 and 24 h. The following parameters were monitored: rectal temperature (RT), respiratory rate (RR), heart rate (HR) and mean arterial pressure (MAP).

The pain scores of all dogs were evaluated using the short form of the Glasgow Composite Measure

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Pain Scale (CMPS-SF; Reid et al. 2007). All pain measurements were performed by one experienced individual (LHY), who was blind to the treatment of the dogs. The CMPS-SF and procedures of pain evaluation are presented in Table 1. A pain assessment was performed at least two days before premedication (baseline), every 2 h for the first 8 h (post-extubation), at 12 h and at 24 h. The postoperative pain behaviours at each time point were measured and the scores were calculated.

Postoperative rescue analgesia. During the study, if a dog scored greater than or equal to six on the CMPS-SF at any time (Morgaz et al. 2013), 0.2 mg/kg morphine *i.v.* was given as a rescue analgesic. If the dog did not respond to that dose, higher doses of morphine were used according to the needs of the dog. Dogs receiving postoperative rescue analgesia were rejected from the next assessment. The number of dogs that required postoperative rescue analgesia was recorded.

Table 1. Short form of the Glasgow composite pain scale

	Descriptor	Score
Category A	(I) quiet	0
	crying or whimpering	1
	screaming	3
	(II) ignoring any wound or painful area	0
	looking at wound or painful area	1
	licking wound or painful area	2
	rubbing wound or painful area	3
	chewing wound or painful area	4
Category B	(III) normal	0
	lame	1
	slow or reluctant	2
	stiff	3
	it refuses to move	4
Category C	(IV) do nothing	0
	look around	1
	flinch	2
	growl or guard area	3
	snap	4
	cry	5
Category D	(V) happy and content or happy and bouncy	0
	quiet	1
	indifferent or non-responsive to surroundings	2
	nervous or anxious or fearful	3
	depressed or non-responsive to stimulation	4
	(VI) comfortable	0
	unsettled	1
	restless	2
	hunched or tense	3
	rigid	4

A = look at dog in kennel, B = put lead on dog and lead out of the kennel, C = if it has a wound or painful area including abdomen, apply gentle pressure 2 in round the site, D = overall

Statistical analysis. The SPSS18.0 (PASW Statistics, Chicago, USA) was used for statistical analyses. Results are presented as the mean ± SD. The physiological parameters (RT, RR, HR, MAP) and pain scores were compared among the three groups at different time points, and were analysed by one-way analysis of variance (ANOVA). Pairwise comparisons analysis based on least significant difference (LSD) methods was used to determine the differences between groups. $P < 0.05$ was considered statistically significant.

RESULTS

All dogs in the study were free of any complications during the surgery, including respiratory depression, hypothermia and hypotension. There were no differences in body weight (T: 4.8 ± 0.5 kg; C: 4.7 ± 0.6 kg; D: 4.9 ± 0.6 kg), age (T: 15.7 ± 3.4 months; C: 16.1 ± 3.2 months; D: 15.5 ± 3.7 months), duration of surgery (T: 36.66 ± 9.06 min; C: 38.82 ± 9.37 min; D: 37.53 ± 8.67 min) or extubation time (T: 8.62 ± 2.26 min; C: 9.37 ± 2.38 min; D: 9.02 ± 2.56 min) among the three groups.

The HR, RR, RT and MAP of dogs among the three groups at baseline, and at 0, 2, 4, 6, 8, 12 and 24 h after extubation are presented in Table 2. The mean heart rates were significantly higher at 2 and 6 h than at baseline for all groups ($P < 0.05$). There were no significant differences between baseline values in MAP or mean temperature scores among the three groups. The mean respiratory rate in Group T was significantly higher ($P < 0.05$) at 0 and 2 h than the baseline values.

The number of dogs that required additional analgesia over time is shown in Table 3. Four dogs required rescue analgesia: one dog in Group T (at 2 h post-extubation) and three dogs in Group C (two at 2 h and one at 6 h post-extubation). No dogs in Group D required rescue analgesia.

The CMPS-SF pain scores of all dogs in each group are shown in Table 4. Compared with Group T, the CMPS-SF pain scores were significantly higher in

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Table 2. Heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), rectal temperature (RT) at baseline, extubation (0), 2, 4, 6, 8, 12 and 24 h after extubation in each treatment group (mean ± SD)

	Group	Time point (h)							
		baseline	extubation	2	4	6	8	12	24
HR(bpm)	T	100 ± 12	107 ± 14	125 ± 20*	108 ± 15	121 ± 20*	107 ± 16	105 ± 16	102 ± 12
	C	103 ± 16	112 ± 16	126 ± 18*	112 ± 18	128 ± 20*	105 ± 15	108 ± 15	106 ± 15
	D	94 ± 13	100 ± 18	116 ± 15*	101 ± 17	119 ± 16*	99 ± 15	98 ± 16	98 ± 14
MAP (mmHg)	T	90 ± 11	96 ± 12	95 ± 12	90 ± 15	88 ± 13	91 ± 16	94 ± 10	95 ± 17
	C	96 ± 17	94 ± 16	97 ± 18	94 ± 16	96 ± 16	91 ± 13	94 ± 15	95 ± 14
	D	100 ± 18	96 ± 12	98 ± 13	95 ± 15	97 ± 17	95 ± 14	101 ± 19	98 ± 15
RR (mpm)	T	26 ± 6	19 ± 5*	20 ± 4*	22 ± 4	25 ± 5	26 ± 4	25 ± 4	26 ± 4
	C	24 ± 4	21 ± 5	24 ± 4	25 ± 4	22 ± 4	24 ± 4	23 ± 4	25 ± 3
	D	22 ± 5	23 ± 5	21 ± 4	23 ± 6	22 ± 4	24 ± 4	23 ± 5	21 ± 4
RT(°C)	T	38.4 ± 0.5	38.0 ± 0.4	38.7 ± 0.5	38.1 ± 0.3	38.4 ± 0.5	38.3 ± 0.3	38.6 ± 0.5	38.3 ± 0.6
	C	38.4 ± 0.5	38.1 ± 0.4	38.8 ± 0.5	38.5 ± 0.3	38.5 ± 0.3	38.5 ± 0.4	38.6 ± 0.3	38.6 ± 0.3
	D	38.6 ± 0.4	38.2 ± 0.4	38.6 ± 0.5	38.7 ± 0.4	38.4 ± 0.6	38.5 ± 0.3	38.4 ± 0.3	38.5 ± 0.3

Group C = 1 mg/kg nefopam, *i.v.*; Group D = 2 mg/kg nefopam, *i.v.*; Group T = 2 mg/kg tramadol, *i.v.*
*Significant differences in each group compared with baseline, $P < 0.05$

Group C ($P < 0.05$) at 6, 8 and 12 h. Compared with Group C, the CMPS-SF pain scores were significantly lower in Group D ($P < 0.05$) at 2, 4, 6, 8 and 12 h. Compared with Group T, the CMPS-SF pain scores were significantly lower in Group D ($P < 0.05$) at 2 and 4 h. However, the CMPS-SF pain scores in Group D exhibited no significant differences from those of Group T ($P > 0.05$) at 6, 8, 12 and 24 h. Dogs in Group C had significantly higher CMPS-SF pain scores C at 2, 4, 8 and 12 h compared with dogs in Group D, but not Group T ($P < 0.05$).

DISCUSSION

Analgesia is usually assessed using the University of Melbourne Pain Scale (UMPS), Visual Analog Scale (VAS), Numeric Pain Intensity Scale (NRS), Glasgow Composite Measure Pain Scale (CMPS-SF) and/or a combination of these. Owing to inter-individual variability and the inability of dogs to verbally communicate pain, it is difficult to recognize and quantify pain in this species. Hence, in some methods of pain assessment, such as the UMPS, researchers have attempted to correlate pain with objective physiological data (Cambridge et al. 2000; Moll et al. 2011). However, this correlation can be influenced by many factors other than pain (Smith et al. 1999). The CMPS-SF is used for assessing postoperative pain, mainly through observation of behaviour, and is one of the best ways to assess the level of pain. In addition, the use of the CMPS-SF has been validated by Murrell et al. (2008). Therefore, we applied the CMPS-SF to assess the level of postoperative pain in dogs undergoing ovariohysterectomy in this study.

Table 3. Dogs that received morphine as rescue analgesia in each group during the study

Group	Time after extubation (h)						
	0	2	4	6	8	12	24
T	0	1	0	0	0	0	0
C	0	2	0	1	0	0	0
D	0	0	0	0	0	0	0

Group C = 1 mg/kg nefopam, *i.v.*; Group D = 2 mg/kg nefopam, *i.v.*; Group T = 2 mg/kg tramadol, *i.v.*

In our study, 2 mg/kg tramadol *i.v.*, was found to have good analgesic effect in dogs after ovariohysterectomy, based on CMPS-SF scores. This result is in agreement with a previous study which concluded that the analgesic effect of 2 mg/kg tramadol *i.v.* is similar to that of 0.2 mg/kg morphine *i.v.* in dogs undergoing ovariohysterectomy (Mastrocinque and Fantoni 2003). In addition, increasing the dose of tramadol or combining it with other analgesics such as dipyrone or meloxicam can produce a good analgesic effect for 24 h, as evaluated by the CMPS-SF or the VAS (Teixeira et al. 2013).

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Table 4. Pain assessment scores for Glasgow Composite Measure Pain Scale (CMPS-SF) in each treatment group (mean ± SD)

Group	Time point (h)						
	baseline	2	4	6	8	12	24
T	0.0 ± 0.0	4.8 ± 1.0*	3.8 ± 0.9*	3.1 ± 0.8*	2.0 ± 0.8*	1.6 ± 0.7*	1.1 ± 0.8*
C	0.0 ± 0.0	5.3 ± 1.2*	4.4 ± 0.9*	4.5 ± 0.8#	3.0 ± 0.8#	2.1 ± 0.8#	1.4 ± 0.7*
D	0.0 ± 0.0	3.9 ± 0.8#	2.9 ± 0.8#	2.8 ± 0.9*	1.6 ± 0.9*	1.3 ± 1.0*	1.0 ± 0.8*

Group C = 1 mg/kg nefopam, *i.v.*; Group D = 2 mg/kg nefopam, *i.v.*; Group T = 2 mg/kg tramadol, *i.v.*
*#Different superscripts within the same line denote significant differences at a given time point, $P < 0.05$

In our study, dogs receiving 1 mg/kg nefopam *i.v.* had significantly higher CMPS-SF scores at 2, 4, 6, 8 and 12 h, and required a greater number of analgesia rescues at 2 and 6 h compared with dogs receiving 2 mg/kg nefopam *i.v.* The analgesic effect of 2 mg/kg nefopam *i.v.* was similar to or better than 2 mg/kg tramadol *i.v.* in dogs undergoing ovariohysterectomy. These results indicate that 2 mg/kg nefopam *i.v.* can provide a better and safer analgesic effect. Moreover, nefopam *i.v.* was described to harbour robust anti-nociceptive properties, with an ED_{50} value of 2.56 ± 0.38 mg/kg observed in the mouse writhing abdominal test (Girard et al. 2008).

The reported side-effects of nefopam include tachycardia, dry mouth, nausea, vomiting, lightheadedness and nervousness (Gregori-Puigjane et al. 2012). In our study, restlessness was observed during the 8–12 h period (post-extubation) in the dogs receiving 2 mg/kg nefopam *i.v.* and 2 mg/kg tromadol *i.v.*, but no respiratory depression was observed in the dogs receiving 2 mg/kg nefopam *i.v.* In postoperative epidural analgesia, administration of nefopam with fentanyl significantly ameliorated the adverse effects of fentanyl, including respiratory depression, pruritus and urinary retention. Our study showed that the use of 2 mg/kg nefopam *i.v.* or 2 mg/kg tramadol *i.v.* yields better analgesia than 1 mg/kg nefopam *i.v.* in the early postoperative period for dogs undergoing ovariohysterectomy, as shown by lower CMPS-SF values. The analgesic efficacy of each treatment can be measured by evaluating CMPS-SF scores, the number of animals needing rescue, as well as objective parameters. In this study, the CMPS-SF pain scores in dogs receiving 2 mg/kg nefopam *i.v.* and 2 mg/kg tramadol *i.v.* were lower than those in dogs receiving 1 mg/kg nefopam *i.v.* at each time point. Taken together with the smaller number of animals needing rescue and the decreased number of side-effects, 2 mg/kg nefopam *i.v.* can be considered as a good postoperative analgesic in dogs undergoing ovariohysterectomy.

In conclusion, nefopam and tramadol can be used for analgesia in dogs undergoing ovariohysterectomy. Nefopam at 2 mg/kg *i.v.* produces better postoperative analgesia compared with tramadol at 2 mg/kg *i.v.* or nefopam at 1 mg/kg *i.v.*

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