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Scientific Article

Effects of tramadol, morphine or their combination in dogs undergoing ovariohysterectomy on peri-operative electroencephalographic responses and post-operative pain

K Kongara*§, JP Chambers* and CB Johnson*

Abstract

AIM: To compare the peri-operative electroencephalogram (EEG) responses and post-operative analgesic efficacy of pre-operative morphine or tramadol with a combination of low-dose pre-operative morphine and post-operative tramadol, in dogs undergoing ovariohysterectomy.

METHODS: Dogs undergoing routine ovariohysterectomy were treated with either pre-operative morphine (0.5 mg/kg S/C, n=8), or tramadol (3 mg/kg S/C, n=8), or pre-operative low-dose morphine (0.1 mg/kg S/C) and post-operative tramadol (3 mg/kg I/V, n=8). All dogs received routine pre-anaesthetic medication, and anaesthesia was induced with I/V thiopentone to effect and maintained with halothane in oxygen. Respiratory rate, heart rate, end-tidal halothane tension (EtHal) and end-tidal CO_2 tension ($EtCO_2$) were monitored throughout surgery. The EEG was recorded continuously in a three electrode montage. Median frequency (F50), total power (Ptot) and 95% spectral edge frequency (F95) of the EEG power spectra were compared during different 100-second periods of surgery: prior to and during skin incision, ligation of each ovarian pedicle, ligation of uterine body and skin closure. Post-operatively, pain was assessed using the short form of the Glasgow composite measure pain scale (CMPS-SF).

RESULTS: There was no difference in F50 or Ptot of the EEG between baseline and noxious surgical events within each treatment group, or between the three groups ($p>0.05$). The mean F95 was higher during the first three periods of surgery for dogs administered tramadol and low-dose morphine than those that received 0.5 mg/kg morphine ($p=0.001$). Dogs that received low-dose morphine and tramadol had lower CMPS-SF pain scores after ovariohysterectomy than those that received either tramadol or morphine alone ($p=0.001$). There was no difference in pain scores between dogs in the latter two groups.

CONCLUSION AND CLINICAL RELEVANCE: Tramadol and morphine administered pre-operatively provided an equal degree of post-operative analgesia in dogs after ovariohysterectomy. A combination of pre-operative low-dose morphine and post-operative tramadol produced better post-operative analgesia than either drug administered alone pre-operatively. Administration of analgesics pre- and post-operatively could result in improved post-operative well-being of ovariohysterectomised dogs.

KEY WORDS: *Morphine, tramadol, dogs, ovariohysterectomy, analgesic efficacy*

Introduction

Opioids are the mainstay analgesics for management of post-operative pain in small animals. Morphine is the gold standard μ-opioid and the most commonly used peri-operative analgesic, despite side effects such as vomiting, respiratory depression and others (Hall and Clark 2001). Tramadol is a centrally acting analgesic with several mechanisms of action including μ-opioid receptor affinity, but it is devoid of the typical μ-receptor-specific side effects in humans (Raffa *et al*. 1992). Inhibition of serotonin (5-hydroxy tryptamine, 5-HT) and noradrenalin reuptake by central neurons is another mechanism of action of tramadol in addition to weak μ-receptor affinity (Raffa *et al*. 1992). Both serotonin and noradrenalin are the nociceptive modulatory transmitters in the descending inhibitory pathway (Millan 2002). Ovariohysterectomy is a routine surgical procedure in small animal practice. This surgery causes marked post-operative pain in dogs (Lascelles *et al*. 1998; Gayner and Muir 2002). As it is performed routinely on healthy and pain-free animals the efficacy of test drugs can be reliably assessed, assuming all post-operative pain resulted from surgery only (Slingsby *et al*. 2006).

The electroencephalogram (EEG) is a record of the spontaneous electrical activity of the cerebral cortex. It is well established that the cerebral cortex participates in the processing of afferent nociceptive input that results in conscious pain perception. Correlation of EEG spectral frequency changes with behavioural responses to nociceptive stimulus in conscious sheep (Ong *et al*. 1997) supports this. Changes in the EEG power spectrum, specifically, median frequency (F50) and total power of the EEG

CMPS-SF	Short form of the Glasgow composite measure pain scale
EEG	Electroencephalogram(s)/electroencephalographic
EtHal	End-tidal halothane tension
$EtCO_2$	End-tidal CO_2 tension
F50	Median frequency of EEG
F95	95% spectral edge frequency of EEG
Ptot	Total power of the EEG
VAS	Visual analogue scale

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(Ptot), have also been used to objectively quantify nociception and to evaluate the anti-nociceptive efficacy of drugs against noxious electrical and surgical stimuli in rats, dogs and horses (Murrell and Johnson 2003; Murrell *et al*. 2005; 2007; Kongara *et al*. 2010). In dogs, ovariohysterectomy was demonstrated to cause quantitative changes in various frequency bands of the EEG power spectrum recorded intra-operatively (Trucchi *et al*. 2003). There has been no report of studies that used intra-operative EEG to assess the anti-nociceptive efficacy of analgesics in dogs undergoing ovariohysterectomy.

Subjective assessment of post-operative pain using different pain scales, including the visual analogue scale (VAS), numerical rating scale and simple descriptive scale, has been practised in clinical trials of analgesics in dogs (Lascelles *et al*. 1997; Slingsby *et al*. 1998; Lemke *et al*. 2002). Though these scales provided a reliable subjective appraisal of acute pain, lack of linearity and specificity with descriptive pain behaviours were claimed as drawbacks (Holton *et al*. 1998; Hansen 2003). Recently, the short form of the Glasgow composite measure pain scale (CMPS-SF) has been introduced for assessment of acute pain in a clinical setting (Reid *et al*. 2007). The CMPS-SF has the benefit of been designed for quick assessment of acute clinical pain (Morton *et al*. 2005; Reid *et al*. 2007). VAS has been reported to be satisfactory to measure sedation in dogs undergoing surgery (Lascelles *et al*. 1998; Slingsby *et al*. 2001; 2006).

The aim of the present study was to compare the EEG changes and analgesic efficacy of morphine (0.5 mg/kg) or tramadol (3 mg/kg) or a combination of low-dose morphine (0.1 mg/kg) and tramadol (3 mg/kg) in dogs undergoing ovariohysterectomy. The study was designed firstly to compare changes in the peri-operative EEG of dogs administered morphine or tramadol or low- dose morphine pre-operatively, and secondly to compare the efficacy of morphine or tramadol administered alone pre-operatively with that of a combination of low-dose morphine administered pre-operatively and tramadol administered post-operatively, using the CMPS-SF.

Materials and methods

Animals

Twenty-four mixed-breed dogs undergoing ovariohysterectomy were recruited for the trial. The mean body weight of the dogs was 19.3 (SD 3.9, min 4.5, max 34.5) kg. Age of the dogs ranged from 6 months to 6 years with a mean of 1.9 (SD 0.9) years. All dogs were clinically normal. This study complied with the requirements of the New Zealand Animal Welfare Act 1999 and Massey University's Code of Ethical Conduct for the Use of Live Animals for Research, Testing and Teaching.

Pre-anaesthetic medication

After routine physical examination, each dog was assessed for the presence of pain, using the CMPS-SF. They received 0.05 mg/kg acepromazine maleate and 0.04 mg/kg atropine S/C as pre-anaesthetics, 30–45 minutes before induction of anaesthesia. This is the standard pre-anaesthetic medication for dogs at the Massey University Veterinary Teaching Hospital.

Analgesia

Dogs were randomly allocated to one of the three treatment groups. Dogs in the morphine group (n=8) received 0.5 mg/kg morphine (Morphine Sulphate Inj., MaynePharma Private Ltd., Victoria, Australia) S/C; those in tramadol group (n=8) received 3 mg/kg tramadol (Tramal 100; Grunenthal GmbH, Aachen, Germany) S/C; and dogs in combination group (n=8) received 0.1 mg/kg morphine S/C at the same time as pre-anaesthetic medication. Also, dogs in the combination group received 3 mg/kg tramadol I/V at extubation post-operatively. The sedation of each dog was assessed using the VAS just prior to induction of anaesthesia, by observing the dog's posture, mental alertness, and its ability to stand and walk. At each assessment, a mark was made on a 100-mm scale, on which 0 corresponds to "no sedation" and 100 corresponds to "fast asleep" (Lascelles *et al*. 1994). The distance from 0 to the marked point on the scale was later converted to numerical form for statistical analysis.

Anaesthesia

Anaesthesia was induced with I/V thiopentone sodium (Pentothal; Boehringer-Ingelheim, Sydney, Australia) (mean 2.9 (SD 1.1) mg/kg) to effect and maintained with halothane (Halothane-Vet; Merial NZ Limited, Manukau City, NZ) delivered in 100% oxygen (BOC, Palmerston North, NZ) via a circle breathing system (VMS Anaesthesia Machine; Matrix Medial Inc, New York, USA). The concentration of halothane was adjusted to keep the dog at a suitable plane of surgical anaesthesia. As soon as the dog was anaesthetised and its airway, breathing and circulation had been checked, a pulse oximeter (Pulse Ox-Fisher & Paykel Healthcare Ltd, Auckland, NZ) and Doppler transducer with cuff (Doppler flow detector, Parks Medical Electronics Inc, Aloha OR, USA) was attached to monitor arterial haemoglobin oxygen saturation and blood pressure non-invasively. All dogs received Hartmann's solution (Baxter Healthcare Ltd, Toongabbie, Australia) I/V at the rate of 10 mL/kg/hour to maintain systolic arterial blood pressure above 100 mmHg throughout the anaesthetic period. Intra-operatively, 1 μg/kg fentanyl (Fentanyl injection; 500 μg in 100 mL; Mayne Pharma Pty Ltd, Victoria, Australia) was administered I/V by the anaesthetist as needed, to control any tachycardia and tachypnoea which occurred in response to surgery. Respiratory rate, heart rate, end-tidal halothane tension (EtHal) and end-tidal CO_2 tension ($EtCO_2$) of each dog were also monitored using an anaesthetic agent monitor (Hewlett Packard M1025B; Hewlett Packard, Hamburg, Germany). All these parameters, and the signs of depth of anaesthesia, were recorded every 5 minutes until the end of surgery.

EEG recording

Three 27 SWG stainless steel needle electrodes (Medlec, Radiometer, Auckland, NZ) were placed S/C with the non-inverting electrode over the zygomatic process of the frontal bone, the inverting electrode over the mastoid process and the ground electrode caudal to the occipital process. The EEG recording was started as soon as the dog was stabilised under anaesthesia. The EEG was recorded with a sample rate of 1 kHz and a pass band of 0.5–400 Hz using an amplifier and analogue to digital converter (Alert System, Medlec, Surrey, UK) and stored on a personal computer. During ovariohysterectomy, EEG data from 100-second blocks were taken at six stages of surgery: the 100-second block immediately preceding the skin incision was the baseline period, the 100-second block during the skin incision was the skin incision period, the 100-second blocks following clamping through ligation of the suspensory ligament of each ovary were the ovary 1 and ovary 2 periods, the 100-second block of data following clamping through ligation of the body of the uterus was the uterine body period, the 100-second

block during skin closure was the skin closure period. EEG recording was stopped at the end of anaesthesia.

The raw EEG was analysed after completion of each experiment, using the Spectral Analysis Program (SAP, Chris Jordan, Northwick Park Hospital, Herts, UK). A 30-Hz digital low pass filter was applied and Fast Fourier Transformation was carried out on each 2.048 second epoch using a 10% raised cosine window function. Median frequency (F50), total power (Ptot) and 95% spectral edge frequency (F95) of the EEG power spectra were used for statistical comparison.

Surgery

Final year veterinary students under the supervision of a veterinary surgeon performed the ovariohysterectomy using a routine ventral midline approach.

Post-operative pain assessment

Before recovery from anaesthesia dogs were moved to a cage in the recovery ward and the endotracheal tube was removed when their laryngeal reflexes were restored. Each dog was assessed using the CMPS-SF, at 1, 3, 6 and 9 h post-operatively. The CMPS-SF includes six behavioural categories: vocalisation, attention to wound, mobility, response to touch, demeanour and posture/activity, each with four to six ranked pain descriptors. The numerical rank of each descriptor increases with the intensity of pain (Reid *et al*. 2007). The CMPS-SF score is the sum of the rank scores which were assigned by an observer as best describing the behaviour of the dog, within each category. The maximum score is 24 and the recommended score for analgesic intervention is six. If any dog appeared to be in an unacceptable pain (CMPS-SF score $\geq$6), morphine (0.3 mg/kg I/M) or fentanyl (1 μg/kg I/V) was administered as rescue analgesia. Sedation was assessed using VAS at the same post-operative time as pain assessment.

Statistical analysis

The distribution of the EEG data was tested for normality (Shapiro-Wilk, Kolmogorov-Smirnov, Anderson-Darling and Cramér-von Mises tests) and residuals of data were found to be normally distributed. A linear mixed model was used for comparing the treatment groups and included the fixed effects of time, treatments, and random effects of animals. The covariance error structure for repeated measures over different surgical periods within animals within group was determined using Akaikes information criterion. A first-order auto-regressive model was found to be the most appropriate error structure. The difference of means among treatment groups was tested using a *t*-test adjusted for number of comparisons.

Pre-operative pain scores were all zero and so not considered further for statistical analysis. Post-operative scores at each of the recorded times were categorised into three classes, as class 1 (pain score 0–2; mild/no pain), class 2 (pain score 3–5; moderate pain) and class 3 (pain score $\geq$6; severe pain). The pooled numbers of dogs within each pain class were used to compare the between-treatment-group differences in pain scores, employing a Wilcoxon-Mann-Whitney odds macro (O'Brien and Castelloe 2006). The three treatment groups were compared in three combinations of two each.

Pre- and post-operative sedation scores were classified into four classes based on level of sedation, as class 1 (score 0–24) class 2 (score 25–49), class 3 (score 50–74) and class 4 (score 75–100). The VAS sedation scores were analysed and compared in similar way as that of pain scores, except that they were classified into four classes.

Heart rate, respiratory rate, EtHal and EtCO2 of the dogs recorded at 5-minute intervals during surgery were analysed as repeated measures employing linear mixed model analysis. The model included fixed effects of treatment, time and their interaction, and random effects of animal.

Results were considered significant if $p<0.05$. All analyses were conducted using SAS v9.1 (SAS Institute Inc Cary NC, USA).

Results

Mean surgery time was 87.9 (SD 6.7) minutes. Pre-operatively, vomiting and defecation were noticed in 5/8 dogs administered morphine at 0.5 mg/kg. None of the dogs that received morphine at 0.1 mg/kg or tramadol vomited or defecated. Four dogs in the morphine group, four dogs in the tramadol group and two dogs in the combination group received I/V fentanyl (1 μg/kg) intraoperatively. Four of eight dogs in each of the morphine and tramadol groups needed rescue analgesia as early as 1-h post-surgery, while only one dog in the combination group required rescue analgesia by 6-h post-surgery.

There was no change in F50 and Ptot between treatment groups or interaction of treatment with time for these outcomes during ovariohysterectomy ($p>0.05$). Within each treatment group, there were no differences in F50 and Ptot between baseline and different surgical periods ($p>0.05$, Tables 1 and 2).

Mean F95 was higher during the baseline, skin incision and ligation of first ovary periods for dogs administered tramadol and low-dose morphine than those that received morphine (0.5 mg/kg) pre-operatively ($p=0.001$; Figure 1). There were no differences in mean F95 during the ligation of the second ovary or uterine body between treatment groups ($p>0.05$).

The mean EtHal of dogs administered morphine (0.87 (SD 0.58)%) was lower at 10, 40 and 60 minutes after intubation than those administered tramadol (1.17 (SD 0.9)%; $p=0.015$) and low-dose morphine (1.08 (SD 0.6)%; $p=0.024$). There were no differences between morphine, combination and tramadol groups in overall mean respiratory rate (12.9 (SD 0.9), 16 (SD 1.3) and 13.7 (SD 0.8) breaths per minute, respectively); heart rate (115.9 (SD 1.2), 118 (SD 1.4) and 120.7 (SD 1.1) beats per

Table 1. Mean (±SD) median frequency (Hz) of electroencephalograms recorded during ovariohysterectomy at different surgical periods, for dogs (n=8 per group) treated pre-operatively with morphine (0.5 mg/kg, S/C), tramadol (3mg/kg S/C) or low-dose morphine (0.1 mg/kg S/C).

Treatment group	Baseline (Hz)	Skin incision (Hz)	Ovary 1 ligation (Hz)	Ovary 2 ligation (Hz)	Uterus ligation (Hz)	Skin closure (Hz)
Morphine (0.5 mg/kg)	11.9±0.9	11.5±1.0	11.0±0.7	11.4±1.0	11.2±0.7	11.1±0.8
Tramadol (3 mg/kg)	12.0±0.6	11.3±1.1	12.4±0.5	12.3±0.9	12.8±0.4	11.9±0.9
Morphine (0.1 mg/kg)	12.0±0.8	10.6±0.9	11.2±0.7	11.4±0.9	11.8±0.5	11.4±0.5

Table 2. Mean (±SD) total power (Hz) of electroencephalograms recorded during ovariohysterectomy at different surgical periods, for dogs (n=8 per group) treated pre-operatively with morphine (0.5 mg/kg, S/C), tramadol (3 mg/kg S/C) or low-dose morphine (0.1 mg/kg S/C) pre-operatively.

Treatment group	Baseline (Hz)	Skin incision (Hz)	Ovary 1 ligation (Hz)	Ovary 2 ligation (Hz)	Uterus ligation (Hz)	Skin closure (Hz)
Morphine (0.5 mg/kg)	170.8±1.4	178.1±1.0	154.2±1.7	166.7±1.0	159.2±0.7	156.08±1.2
Tramadol (3 mg/kg)	168.9±2.1	169.4±1.1	177.7±1.5	168.3±1.9	164.7±0.4	161.8±1.0
Morphine (0.1 mg/kg)	170.2±1.8	165.6±1.5	178.2±1.8	162.7±2.1	171.8±0.5	178.3±1.5

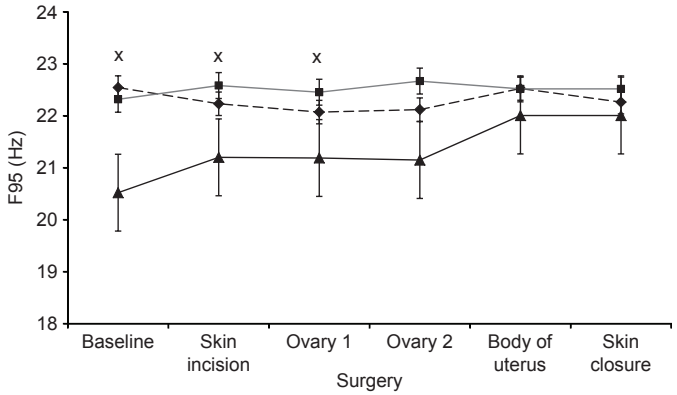

Figure 1. Mean (±SD) 95% spectral edge frequency (F95%, Hz) of electroencephalograms recorded during ovariohysterectomy immediately before (baseline) and during skin incision, during ligation of the first (ovary 1) and second ovary (ovary 2), ligation of the body of the uterus, and skin closure for dogs (n=8 per group) treated pre-operatively with morphine (■ 0.5 mg/kg, S/C), tramadol (▲ 3 mg/kg, S/C) or low-dose morphine (◆ 0.1 mg/kg, S/C). [x]Significant difference between dogs administered tramadol and low-dose morphine and dogs administered morphine (0.5 mg/kg) (p=0.001).

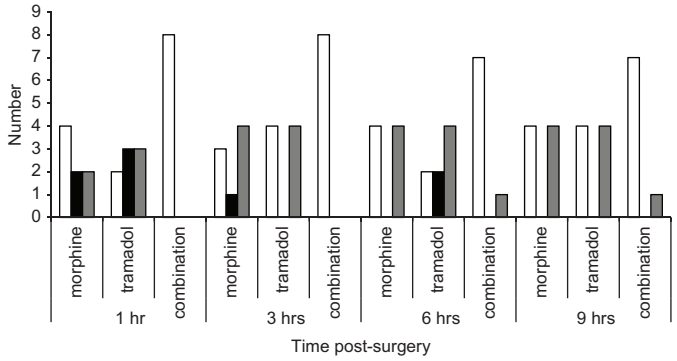

Figure 2. Number of dogs categorised as having mild/no pain (□), moderate pain (▩), or severe pain (■) at 1, 3, 6 and 9 h after ovariohysterectomy that were treated pre-operatively with morphine (0.5 mg/kg, S/C) or tramadol (3mg/kg, S/C) or a combination of pre-operative morphine (0.1 mg/kg, S/C) and post-operative tramadol (3 mg/kg, I/V).

minute, respectively) or $EtCO_2$ (52 (SD 0.9), 48 (SD 1.2) and 54 (SD 1.1) mmHg, respectively) (p>0.05).

The number of dogs in pain class 3 (pain score ≥6; severe pain) was higher for those administered morphine (0.5 mg/kg) or tramadol than for those administered the combination, at 3, 6 and 9 h post-operatively. The number of dogs in pain class 1 (pain score 0–2; mild/no pain) was higher in the combination group at all post-operative times than for the morphine or tramadol groups (Figure 2). There was no significant difference in the overall median class of pain score between morphine (2 (min 1, max 3)) and tramadol (2 (min 1, max 3)) groups. The overall median class of pain score of dogs administered a combination of morphine and tramadol was lower (1 (min 1, max 3); p=0.001) than the other two treatment groups.

Pre-operatively, the median sedation score category of dogs administered morphine (3.5 (min 1, max 4)) was higher than that of tramadol (1 (min1, max 2); p<0.001) and low-dose morphine (1; p<0.001). Post-operatively, morphine (median 2 (min 1, max 4)) produced more sedation than tramadol (1 (min 1, max 2); p=0.01). There was no difference in the level of sedation produced by the combination of morphine and tramadol and tramadol.

Discussion

The aim of this study was to compare peri-operative EEG responses and post-operative analgesic efficacy of morphine or tramadol administered pre-operatively, with a combination of low-dose morphine administered pre-operatively and tramadol administered post-operatively in dogs undergoing ovariohysterectomy.

No changes in F50 and Ptot between baseline and noxious surgical events within each treatment group or between the three treatment groups, were found in the current study. Previously, significant changes in intra-operative EEG frequency spectra have been reported during ovariohysterectomy in dogs (Trucchi *et al.* 2003). Studies in horses, red deer (*Cervus elaphus*) and calves have demonstrated that surgical stimuli produce significant changes in F50 and Ptot (Murrell and Johnson 2003; Johnson *et al.* 2005; Gibson *et al.* 2007), and pre-operative lignocaine (administered I/V and as ring block) blocked the changes in these two EEG variables. Also, experiments in halothane-anaesthetised, unstimulated ponies, revealed that drugs of well-known analgesic efficacy caused a reduction in F50 (Johnson 1996; Johnson and Taylor 1999; Johnson *et al.* 2000). Collectively, results from these studies suggest that changes in F50 and Ptot may be predominantly linked to nociception. However, the EEG correlates of nociception vary with experimental conditions such as depth of anaesthesia, type of anaesthetic agent and severity of noxious stimulation (Murrell and Johnson 2006). In addition, use of agents for stabilising intra-operative haemodynamic variables (e.g. mean arterial blood pressure and heart rate) may influence the EEG responses (Miller *et al.* 1995; Murrell *et al.* 2000).

There are a few possible explanations for not finding differences in EEG indices of nociception/anti-nociception between the three treatment groups in the present study. Difference in the

EtHal between the treatment groups might have influenced the EEG responses generated by the cerebral cortex. Another confounding factor could be administration of fentanyl during surgery. Dogs in all the three treatment groups received I/V fentanyl intra-operatively. Fentanyl is a potent μ-opioid receptor agonist and has been demonstrated to alter the amplitude and frequency of the EEG in un-stimulated dogs (Wauquier *et al*. 1981). In addition, anaesthesia was induced with I/V thiopentone in dogs of all treatment groups in the current study and this drug has been shown to alter EEG variables in ponies (Murrell *et al*. 2000). The terminal elimination half-life of thiopentone (20 mg/kg) in dogs after I/V administration was said to be 6.9 (SD 2.1) h (Anonymous 1999). In the present study, EEG was recorded 10–15 minutes after anaesthetic induction with I/V thiopentone in all dogs and it is likely that thiopentone affected the EEG responses of dogs.

An important limiting factor in the current study was the lack of an untreated control group for comparison with the three treatments. Morphine has been described as a well-known yard stick for efficacy comparison (Brodbelt *et al*.1997), but it is unclear whether the lack of difference in the EEG indices of nociception between the treatment groups, including low-dose morphine, was because of the diverse experimental conditions or equal efficacy of tramadol and morphine (in both dose rates). A negative control group was not included on ethical grounds as this surgery is likely to cause severe pain.

Ovariohysterectomy induces a distinct viscero-somatic nociception in rats and dogs (Lascelles *et al*. 1997; Gonzalez *et al*. 2000). Procedures such as skin incision, body wall incision and skin closure are presumably associated with somatic nociception, whereas ligation of ovaries is predicted to be associated with visceral nociception (Gayner and Muir 2002). In the present study, EEG data were taken during baseline, skin incision, and skin closure, and from clamping through ligation of both ovaries and uterine body with the view of comparing changes in EEG spectral frequencies that may specify the nociception/anti-nociception. However, the confounding experimental factors described above may have obtunded the generation of significant EEG responses between the treatment groups.

The F95 of the EEG power spectrum showed differences between tramadol and morphine groups. This component of the EEG power spectrum reflects more about general central nervous system depression than nociception (Johnson and Taylor 1999; Murrell and Johnson 2003; Kongara *et al*. 2010). Differences in EtHal (during both anaesthesia and surgery) between treatment groups may have been associated with F95 changes, but this study was not designed to examine the linear relationship between F95 and EtHal changes and no attempt was made to compare these statistically.

Immediate and appropriate assessment of post-operative pain is important for evaluation of analgesic efficacy that also aids in optimal pain control (Lascelles *et al*. 1994). Use of changes in non-interactive behaviour of undisturbed animals coupled with responses to handling of the animal and its surgical site (interactive behaviour) has been reported to be the most effective clinical tool for rapid evaluation of post-operative pain (Waterman and Kalthum 1989; Lascelles *et al*. 1994). The combination of non-interactive and interactive behavioural changes serves as a basic template for constructing different pain scales. Because of its reported ease of use and quick applicability in the clinical setting, the CMPS-SF was chosen to score the pain-related dog behaviours that indirectly measure the efficacy of test drugs in the present study. Also, the CMPS-SF is the only method that has any validation data at present (Morton *et al*. 2005; Reid *et al*. 2007).

The statistical analyses of pain and sedation scores were complicated by dogs receiving rescue analgesia as early as 1-h post-surgery in both pre-operative morphine and tramadol groups. Keeping the sample size in view (n=8), we used the ''pain score categorisation'' method suggested by Slingsby *et al*. (2006) to analyse the treatment effects instead of removing the dogs which received rescue analgesia at 1-h after surgery. Though this kind of statistical analysis let us assess the overall effect of the treatments, it may not allow for comparison of treatment effects at different post-operative times. In the current study, the dogs treated with a combination of morphine and tramadol had a lower overall pain score than the dogs treated with either pre-operative morphine or tramadol alone. Clinically, the difference between pre-operative analgesia just covering the intra-operative period and immediate post-operative analgesia covering the early post-operative period has been demonstrated previously in dogs undergoing ovariohysterectomy (Lascelles *et al*. 1997).

There was no difference in the overall mean pain score between pre-operative morphine and tramadol. Four dogs in each group required fentanyl intraoperatively. Inclusion of another group of dogs with no treatment would have more clearly demarcated the efficacy of morphine or tramadol in its own right. This was not possible because of ethical concerns.

To date there have been no dose titration studies of morphine in dogs (Kukanich *et al*. 2005). The recommended dose of morphine ranges from 0.05 to 2 mg/kg I/V or I/M or S/C every 2–6 h (Carroll 1999; Wagner 2002). This range has been recommended based on clinical impressions or subjective visual assessment of analgesia or pain, that appears to be significantly variable (Kukanich *et al*. 2005). Also, no dosage recommendations are available for tramadol in dogs as it has not been investigated extensively in this species; therefore the dose rates of the morphine and tramadol used in the present study were chosen based on their experimental or clinical use in animals and humans.

The occurrence of side effects such as respiratory depression, nausea and vomiting increases with increase in dose of pure agonist opioids like morphine (Hall and Clarke 1991). In the current study, we chose to administer morphine at a lower dose (0.1 mg/kg) pre-operatively, in combination with tramadol (administered post-operatively) to determine whether it can produce safer and better analgesia than morphine administered singly at a higher dose (0.5 mg/kg), which is frequently associated with remarkable side effects. The dogs treated with 0.1 mg/kg morphine showed no side effects in contrast to those that received 0.5 mg/kg morphine.

In the present study, inclusion of the treatment group comprising pre-operative morphine and post-operative tramadol aided in revealing the best pain management strategy for this surgical procedure, though pre-operative tramadol and morphine (administered alone) produced similar degree of analgesia. Use of another treatment group, which received post-operative treatment only, would have more clearly demarcated the benefit of administration of analgesics pre- and post-operatively. Availability of dogs, EEG recording equipment and time were the factors that restricted the inclusion of a post-operative analgesic group.

In previous studies, pre-operative tramadol showed efficacy equal to morphine and superior to butorphanol in dogs undergoing ovariohysterectomy (Mastrocinque and Fantoni 2003; Paolo *et al*.

2004). In those studies, and the present one, tramadol had been given I/V, I/M and S/C, respectively. It appears that tramadol can produce analgesia in dogs administered by any of these routes. In this study it was noted that S/C drug administration along with routine pre-anaesthetic medication (administered S/C) had the benefit of ease of administration as it did not require additional (stressful) handling of dogs.

In conclusion, this study demonstrated that both tramadol (3 mg/kg) and morphine (0.5 mg/kg) administered pre-operatively, provides an equal degree of post-operative analgesia in ovariohysterectomised dogs. A combination of pre-operative low-dose morphine (0.1 mg/kg), that caused no side effects, and post-operative tramadol (3 mg/kg) produced better post-operative analgesia after ovariohysterectomy than either drug administered alone pre-operatively. Stable intra-operative experimental conditions are required to find a significant difference in EEG indices of nociception/anti-nociception, between different treatment groups. The CMPS-SF was used satisfactorily to evaluate the efficacy of different classes of analgesics in the post-operative period. Further studies are required with a large dog population to compare the efficacy of these two analgesics administered at different dose rates and times of surgery, for better post-operative analgesia.

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