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A comparison between methadone and buprenorphine for perioperative analgesia in dogs undergoing ovariohysterectomy

Summary

Objective: To investigate whether preoperative methadone provides superior perioperative analgesia compared to buprenorphine in dogs undergoing ovariohysterectomy.

Methods: Eighty female dogs were recruited to an assessor-blinded, randomised, clinical trial. Dogs received a premedication of 0.05 mg/kg acepromazine or 10 µg/kg medetomidine combined with either 0.3 mg/kg methadone or 20 µg/kg buprenorphine intramuscularly. Anaesthesia was induced with propofol and maintained with isoflurane. Pain was assessed using two scoring schemes (a dynamic interactive visual analogue scale and the short form of the Glasgow Composite Pain Scale) before premedication, 30 minutes later and every hour for 8 hours after premedication. If indicated, rescue analgesia was provided with methadone. Meloxicam was administered after the final assessment. The area under the curve for change in pain scores over time, and the requirement for rescue analgesia, were compared between groups.

Results: Groups premedicated with buprenorphine had significantly higher pain scores than those premedicated with methadone. There was no interaction between opioid and sedative for any outcome measure. Rescue analgesia was required by significantly more dogs premedicated with buprenorphine (45%) than methadone (20%).

Clinical significance: At the doses investigated, methadone produced superior postoperative analgesia compared to buprenorphine in dogs undergoing ovariohysterectomy.

Keywords

Pain, methadone, buprenorphine, analgesia, ovariohysterectomy.

Introduction

Ovariohysterectomy remains one of the most frequently performed procedures in primary care veterinary practice. It has been shown to have the potential to cause moderate to severe acute postoperative pain in dogs (Hardie et al., 1997, Lascelles et al., 1999, Coleman and Slingsby, 2007) and provision of sufficient analgesia is essential for patient welfare. Perioperative analgesia is considered to be the most effective method of reducing postoperative pain (Katz et al., 2011). It incorporates analgesia throughout the pre-, intra-, and postoperative phases and aims to prevent the establishment of altered central pain pathways as a result of noxious afferent inputs (Dahl and Kehlet, 2011). Opioids are effective perioperative analgesics and commonly used for this purpose in veterinary medicine. The two most widely used in the UK for pain resulting from surgery are buprenorphine and methadone (Hunt et al., 2015).

The pharmacology of buprenorphine is complex and has recently been the subject of scientific scrutiny (Pergolizzi *et al.* 2010). Buprenorphine has a high affinity for the mu (μ) opioid receptor and although previously considered a partial μ -receptor agonist, it is now considered to have the ability to produce a full analgesic effect in animal models, although this is dependent on the intensity of the stimuli. Recent radio-labelling studies in humans have also shown that full analgesia can be produced at less than 100% occupancy of the μ -receptor, which is the definition of a full μ -agonist opioid (Greenwald *et al.* 2003). The dose of buprenorphine that is currently widely used in veterinary practice in the UK is between 10 and 20 $\mu\text{g}/\text{kg}$. Slingsby and colleagues showed that an increase in buprenorphine from 20 to 40 $\mu\text{g}/\text{kg}$ caused no changes in physiological parameters and did not increase analgesia in dogs that had undergone ovariohysterectomy (Slingsby et al., 2011). However, this may be due to insensitivities in pain scoring because a ceiling effect in analgesia for buprenorphine has been discounted in animal studies (Raffa *et al.* 2005).

Methadone is a full μ -receptor agonist and has been licensed for use in dogs since 2011. It is available as a racemic mixture of two isomers. The analgesic effect is attributed to

the L-isomer, which principally binds to the μ -receptor. The D-isomer acts as an antagonist of the N-methyl D-aspartate receptor (NMDAR) (Davis and Inturrisi, 1999). Activation of NMDARs after tissue injury facilitates hyperexcitability and plasticity of nociceptive neurones, therefore antagonism of NMDARs gives methadone the potential to prevent central sensitisation and secondary hyperalgesia. Since methadone is a full μ -agonist, it produces a maximal response at full saturation of receptor binding sites (Inturrisi, 2002) and is effective for moderate to severe pain. It also has a dose-dependent action making it easy to dose to effect.

Recent studies investigating buprenorphine have shown that it provides adequate analgesia for ovariohysterectomy in dogs (Shih et al., 2008, Slingsby et al., 2011, Hunt et al., 2013b). However, there have been limited studies directly comparing buprenorphine and methadone with respect to analgesia. Recently, Hunt and colleagues (2013b) compared buprenorphine and methadone in dogs undergoing orthopaedic surgery. They found that premedication with methadone in combination with acepromazine had significantly better analgesic efficacy compared to buprenorphine and acepromazine (Hunt et al., 2013a).

In 2013 the proportion of practices stocking methadone in the UK was 57.3% compared to 98.9% stocking buprenorphine (Hunt *et al.* 2015). A possible explanation for the reduced use of methadone is unfamiliarity with dosing, safety and potential adverse reactions. **The current study aimed to address these concerns by investigating methadone and buprenorphine in combination with the common sedative drugs acepromazine and medetomidine and provide evidence for their effectiveness and practicality to aid clinicians in their decision-making regarding opioid choice for moderate to severely painful procedures. We hypothesised that methadone would provide superior analgesia to buprenorphine in dogs premedicated with either acepromazine or medetomidine and undergoing ovariohysterectomy.**

Materials and methods

Design

An assessor-blinded, randomised, prospective clinical trial was conducted. The study protocol was approved by a local ethical review group (VIN/15/023) and was carried out under an Animal Test Certificate-S issued by the Veterinary Medicines Directorate.

Sample size

No formal power calculation was conducted, but a similar study in dogs undergoing orthopaedic surgery by Hunt and colleagues was able to show a difference between methadone and buprenorphine with 18 dogs per group (Hunt et al., 2013a). Similar outcome measures were used in the present study and the study of Hunt *et al.* (2013b), and a similar difference in Glasgow Composite Pain Score between groups of 3 points was accepted as being clinically relevant for the two studies. Given that all ovariohysterectomies would be carried out by the same qualified veterinary surgeon, 20 animals per group was similarly predicted to be sufficient to see a difference in outcome measures in the present study.

Enrolment and inclusion

Eighty dogs undergoing routine ovariohysterectomy were recruited. Written, informed consent for inclusion in the study was obtained for all dogs before surgery. All dogs underwent a pre-anaesthetic examination and only those falling within the American Society of Anaesthesiologists (ASA) physical status classification category 1 or 2 were included. Exclusion criteria included dogs which had received analgesia, anaesthesia, or sedation within the previous 7 days, or that were not amenable to handling.

Randomisation

Dogs were block-allocated to receive medetomidine or acepromazine. The first 20 animals received acepromazine, the second 20 medetomidine and this was repeated. Dogs were randomly allocated to receive either buprenorphine or methadone (random

number generator; www.random.org) within the two sedative groups separately, to ensure an equal number of animals ($n = 20$) in each of the four groups: 1. acpBUP (acepromazine and buprenorphine), 2. acpMET (acepromazine and methadone), 3. medBUP (medetomidine and buprenorphine), 4. medMET (medetomidine and methadone). This method of randomisation was chosen for practical reasons because it would have been more difficult to run an efficient surgery list if dogs were completely randomised to the four groups.

Pre-anaesthetic assessments

Dogs were fasted for a minimum of 8 hours before anaesthesia but were provided with water until time of premedication. Baseline parameters for heart rate (HR), respiratory rate (f_R), sedation, pain and mechanical nociceptive threshold (MNT) at the site of surgery were measured by the same assessor who was blinded to the treatment group. All assessments were carried out in this same order with a short break (1-2 minutes) between assessments of sedation, physiological parameters, pain and MNT. Heart rate and f_R were measured manually by palpation of pulse and observation of breathing. Sedation was measured using a simple descriptive scale (SDS) (Table 1) and a dynamic interactive visual analogue scale (DIVAS_{sed}). Pain was measured using the short form of the Glasgow Composite Pain Scale (SF-GCPS) and a DIVAS (DIVAS_{pain}). DIVAS uses a 100mm scale where 0 represents no sedation or pain and 100 represents maximal sedation or the worst possible pain for the procedure. Animals were assessed undisturbed from outside the kennel. They were then approached, spoken to and encouraged to walk and move. Finally, the incision and surrounding area of the abdomen were palpated.

The MNT was measured as an indicator of secondary mechanical hyperalgesia using a pressure onset device (PRoD) manufactured by Topcat Metrology. A 2mm probe was placed approximately 3 cm from the incision site and pressure applied at a rate of 2 Newtons per second. Testing was terminated when a positive response was seen, such as deliberate movement away from the probe, guarding against the probe, looking

around towards the probe, snapping or biting. A cut-off of 20 N was applied to prevent the risk of tissue damage should higher forces be applied to the skin. A baseline value was obtained by taking an average of three measurements at the same site along the proposed incision site. At all other timepoints a single measurement was taken, this measurement could be from anywhere adjacent to and along the length of the surgical incision site.

Administration of test drugs

Premedication consisted of either 0.05 mg/kg acepromazine (ACP 2 mg/mL; Novartis Animal Health) or 10 µg/kg medetomidine (Sedator 10 mg/mL; Dechra Veterinary Products) combined with 20 µg/kg buprenorphine (Buprenodale 0.3 mg/mL; Dechra Veterinary Products) or 0.3 mg/kg methadone (10 mg/mL Comfortan; Dechra Veterinary Products). Drugs were drawn up in the same syringe by the surgeon (not blinded to the treatment) and administered intramuscularly into the quadriceps muscles. The assessor was not present when premedication was administered. Thirty minutes were allowed to elapse for the premedication drugs to have a sedative effect before further measurements were taken.

Induction

Pre-induction parameters for HR, f_R , temperature (T), sedation and the MNT were recorded at the 30-minute time point. An intravenous (IV) catheter was placed into the cephalic vein and anaesthesia induced by IV injection of propofol to effect (Propoflo 10mg/mL; Zoetis). Jaw-tone and palpebral reflexes were monitored until the level of anaesthesia was adequate for orotracheal intubation with a cuffed endotracheal tube. The dose of propofol used was recorded.

Anaesthesia maintenance

Anaesthesia was maintained with isoflurane (ISO) vaporised in oxygen delivered with a T-piece breathing system for animals <10 kg bodyweight, and a circle system in animals >10kg bodyweight. Depth of anaesthesia and physiological parameters were monitored

continuously by a Registered Veterinary Nurse (RVN). The ISO concentration was recorded as the vaporiser dial setting. The vaporiser was not calibrated before the start of the study. Physiological parameters were measured using a multi-parameter monitor (PM9000 multiparameter monitor; Burtons) and included HR, f_R , non-invasive blood pressure (NIBP), arterial haemoglobin saturation with oxygen (SpO_2) and end tidal carbon dioxide concentration ($PE'CO_2$). Measurements were recorded every 5 minutes and at the following time points: incision, ligation of right and left ovarian pedicle, ligation of cervix, final sutures. All surgeries were carried out by the same experienced veterinary surgeon. Isoflurane administration stopped at the end of surgery and the dog was taken back to its kennel for recovery.

Reversal and Recovery

Medetomidine was antagonised with atipamazole (Atipam 5 mg/mL; Dechra Pharmaceuticals). A dose volume equivalent to the volume of medetomidine previously administered was given intramuscularly into the lumbar muscles at the point of extubation. The orotracheal tube was removed when the swallowing reflex returned. Patients were placed in a kennel and covered with padded incontinent sheets or reflective blankets. Body temperature was measured until normal ($>37^\circ\text{C}$). Time taken from extubation to head lift, sternal recumbency, and standing was recorded. Quality of recovery was evaluated using a SDS scale (Table 1).

Postoperative assessments and pain management

Heart rate, f_R , sedation, pain and the MNT were assessed 2, 3, 4, 5, 6, 7 and 8 hours after the administration of premedication in the same order unless the animal was still anaesthetised, as previously described.

A second dose of the allocated test opioid was scheduled to be administered at 5 hours post premedication in all dogs. This was drawn up by the surgeon carrying out the surgery and given intramuscularly. The assessor remained blinded to the second administration of analgesia. However, a SF-GPCS score of $\geq 5/20$ in non-ambulatory

dogs or $\geq 6/24$ in ambulatory dogs was an indication for additional (rescue) analgesia (methadone 0.3 mg/kg, IM). The assessor was not blinded to administration of rescue analgesia. Pain was assessed 30 minutes later and if required another dose of 0.3 mg/kg methadone given IM. If additional analgesia had been necessary after a second dose of methadone the assessor would have administered an NSAID (rescue NSAID) (Meloxicam (Metacam®; Boehringer-Ingelheim) 0.2 mg/kg subcutaneously). Dogs that required rescue analgesia before or at the 5-hour time-point did not receive the scheduled second dose of test opioid. Unless received earlier as rescue, all dogs were administered meloxicam at 0.2 mg/kg subcutaneously (Metacam®; Boehringer-Ingelheim) after assessments were completed 8 hours post-surgery. Any adverse events seen pre, intra or post operatively were noted. Adverse events included hypersalivation, vomiting, sedation or apnoea.

Statistical methods

Data were assessed for normality both by visual inspection of histograms and the Shapiro-Wilk test and appropriate parametric and non-parametric techniques used (SPSS Statistics Version 23; IBM Corporation). Postoperative pain (SF-GCPS and DIVASpain) and MNT assessments were analysed using a general linear regression model (GLM) in which the area under the curve (AUC) for each parameter was used to analyse the overall effect of sedative and opioid and the interaction between the two on postoperative parameters. The SF-GCPS was scored out of 24 as all dogs were ambulatory at the 2 hour time point. Postoperative MNT scores for each individual were converted to percentage change from baseline values to account for the variation in pain threshold between individuals. Baseline values were given a value of 100%. The proportion of dogs in each group requiring rescue analgesia or experiencing adverse events was compared using a Chi-squared test. A Cox-regression survival curve was used to analyse the effect of sedative and opioid on the requirement of rescue analgesia. Postoperative sedation scores were compared between groups using a Kruskal Wallis test. DIVASpain scores were analysed as raw data. In dogs receiving rescue analgesia,

recorded scores were included in the analysis rather than using the last observation carried forward technique. P values of < 0.05 were considered statistically significant unless multiple comparisons were performed when a Bonferroni correction was applied. Results of parametric tests are reported as mean \pm SEM or \pm SD and results of nonparametric tests are reported as median \pm range (minimum – maximum). The 95% confidence intervals (95%CI) are reported for the mean/median difference.

Results

Demographic data

Demographic data for dogs in the four groups are shown in Table 2.

Post-operative pain

Rescue analgesia was required by significantly more dogs premedicated with buprenorphine (45%, 18/40 dogs) compared to methadone (20%, 8/40 dogs) (Chi squared test, $p = 0.017$). Of these dogs that required rescue analgesia, 88% (six dogs in the methadone group and 16 dogs in the buprenorphine group) required additional analgesia before the scheduled second dose of analgesia 5 hours post premedication, and 12% (two dogs in the methadone group and two dogs in the buprenorphine group) required it after 5 hours but before 8 hours after premedication. No dogs required administration of meloxicam earlier than the 8-hour time point after assessments were completed. A Cox regression survival analysis showed methadone resulted in a decreased requirement for rescue analgesia compared to buprenorphine, $p = 0.02$. Choice of sedative ($p = 0.413$) or the interaction between opioid and sedative ($p = 0.107$) did not affect rescue analgesia requirement.

Overall SF-GCPS and **DIVASpain** scores were lower in methadone groups compared to buprenorphine groups. Mean \pm SEM area under the curve for SF- GCPS scores were significantly greater in the **buprenorphine groups** (23 ± 1.2) compared to the

methadone groups (15.1 ± 1.2) ($p < 0.0001$) with a difference of 7.9 ± 1.44 [95% CI 4.90-11.0]. The choice of sedative ($p = 0.729$) or the interaction between sedative and opioid ($p = 0.370$) had no effect on SF-GCPS pain scores. Mean \pm SEM area under the curve for DIVASpain scores were also significantly greater in the buprenorphine groups (13.0 ± 0.65 cm) compared to methadone groups (10.0 ± 0.65 cm) ($p = 0.01$) with a difference of 3.02 ± 0.97 cm [95% CI 1.18-4.86] cm). The choice of sedative ($p = 0.579$) or the interaction between sedative and opioid ($p = 0.593$) had no effect on DIVASpain scores. Change in SF-GCPS and DIVASpain scores over time in all four groups are shown in Figures 1 and 2 respectively.

Mechanical Nociceptive Thresholds

There was no difference in the overall postoperative MNT scores between dogs receiving methadone and buprenorphine ($p = 0.25$). Choice of sedative ($p = 0.09$) and interaction between sedative and opioid ($p = 0.9$) did not have a statistically significant effect on MNT (Figure 3).

Post-operative sedation

There was no significant difference in SDS or DIVASsed postoperative sedation scores at any time-point with respect to opioid. However, dogs premedicated with acepromazine showed significantly higher SDS (Figure 4) and DIVASsed (Figure S1) scores 2, 3 and 4 hours post-premedication compared to the medetomidine groups ($p < 0.001$ at each timepoint).

Adverse effects

The frequency of adverse effects was low overall and those observed during the study included hypersalivation, vomiting, sedation and apnoea during anaesthesia. Each adverse effect was compared among all four groups (Table 3). Only hypersalivation on recovery showed a significant difference between groups. This difference occurred between medetomidine and acepromazine groups, being significantly higher in dogs that received medetomidine ($p = 0.03$), and there was no difference with respect to opioid

($p=1.00$) or interaction between sedative and opioid ($p=1.00$). There was no significant difference among groups for any other adverse effect.

Data relating to physiological parameters and isoflurane requirements for maintenance of anaesthesia and recovery times are provided in the Supplementary materials available online (Tables S1 and S2). Physiological parameters were within normal clinical limits in all dogs during anaesthesia and surgery. Although there were no differences between opioid groups, dogs administered medetomidine required significantly less propofol ($p<0.01$) for induction and required less overall ISO (measured as dialled vapouriser setting) ($p<0.01$). Dogs administered medetomidine also had lower HRs ($P<0.01$) and higher systolic ($p=0.014$), mean ($p<0.01$) and diastolic ($p>0.01$) arterial pressures intraoperatively. Recovery times were shorter in dogs that received medetomidine compared to dogs that received acepromazine.

Discussion

Dogs that received 0.3 mg/kg methadone had significantly lower SF-GCPS and **DIVASpain** scores and required significantly less rescue analgesia compared to groups that received 20 $\mu\text{g}/\text{kg}$ buprenorphine. This supports our hypothesis that methadone produces superior perioperative analgesia compared to buprenorphine for ovariohysterectomy in dogs.

The experience of pain incorporates physiological, emotional and cognitive components making it subjective to each individual and difficult to evaluate, especially in animals. Assessing pain in animals relies on behavioural, and to some extent, physiological, observation. However, external environmental or situational factors can also affect a patient's response to pain and confound pain behaviours. For this reason, the present study used two different methods for evaluating pain postoperatively. The primary measure for pain was the SF-GCPS since this pain scale has been validated for acute pain in dogs in a clinical setting. Requirement of rescue analgesia was based on the

validated intervention level of the SF-GCPS (Reid *et al.* (2007)). The **DIVASpain** scale was used as an additional measure of pain since more than one assessment tool is commonly used to help measure pain more accurately. **DIVASpain** has been used in many veterinary pain studies (Lascelles *et al.*, 1998, Stanway *et al.*, 2002, Leece *et al.*, 2005, Slingsby *et al.*, 2011, Bortolami *et al.*, 2013, Slingsby *et al.*, 2015) and using it here may also allow better comparisons with other studies. Both SF-GCPS and **DIVASpain** are interactive scales and assess the patient at rest and during movement to ensure relevant behavioural aspects of pain are assessed.

When evaluating SF-GCPS and **DIVASpain** scores data were not corrected for rescue analgesia (*i.e.* the last observation before administration of additional methadone in dogs that required rescue analgesia was not carried forward for the remaining time points). The last observation carried forward method prevents artificial lowering of pain scores as a result of rescue analgesia, thereby increasing the ability of tests to discriminate between the two drugs. However, in the present study both SF-GCPS and **DIVASpain** scores showed significant differences between methadone and buprenorphine groups regardless of analysing uncorrected data.

In contrast to the DIVAS pain scale, the SF-GCPS is a validated composite scale and aims to assess the affective and emotional components of pain. It has been designed using psychometric principles to produce a set of specific questions with defined behaviours (Holton *et al.*, 2001). This reduces subjectivity, and variability in interobserver and intraobserver interpretation (Reid *et al.*, 2007, Murrell *et al.*, 2008, Sharkey, 2013). However, a degree of clinical reasoning is still needed to evaluate other factors that may confound pain behaviours such as temperament, sedation and environment. The SF-GCPS also has a validated intervention criterion (Reid *et al.* 2007). For this reason, the SF-GCPS score was used when determining the requirement of additional rescue analgesia.

To minimise variability all assessments were carried out by a single assessor. The disadvantage of this is that scores for a subjective test are based on one opinion and it is

difficult to measure an assessor's sensitivity to pain against others. This could have an impact when comparing the results of different pain studies.

Experience has been shown to have an impact on pain assessment (Holton et al., 1998). In the present study, the assessor received training in using the SF-GCPS and **DIVASpain** before beginning data collection. It is possible that increased experience throughout the study resulted in increased sensitivity to pain, although there was no evidence to support a general drift in pain scores (either becoming higher or lower) over time. However, the effect of experience was also minimised by the short duration of the study since data collection was completed over 3 months. Any shift in scoring based on experience would have applied equally to both the SF-GCPS and **DIVASpain** and dogs in all treatment groups would have been equally affected.

Previous studies investigating the use of buprenorphine in dogs undergoing ovariohysterectomy have found it provides adequate analgesia. Hunt *et al.* (2013a) showed 20 µg/kg buprenorphine combined with 25 µg/m² dexmedetomidine or 0.03 mg/kg acepromazine provided suitable analgesia in dogs and cats undergoing mild to moderate elective surgeries including ovariohysterectomy. However, perioperative meloxicam was also administered, likely decreasing postoperative pain scores. Furthermore, dogs undergoing castration were also included in this population. Castration is less painful than ovariohysterectomy (Slingsby *et al.* 2011) and inclusion of associated pain scores may have decreased overall pain scores. Slingsby *et al.* (2011) found 20 µg/kg buprenorphine combined with 0.03 mg/kg acepromazine resulted in a mean **DIVASpain** score of 40mm suggesting adequate analgesia, however 92% (11/12) dogs required rescue analgesia within 5 hours. Our study found that 45% (18/40) of dogs administered 20 µg/kg buprenorphine required rescue analgesia. The disparity between the studies may be a result of different observers showing different sensitivities to pain behaviours and that different outcome measures were used to determine the requirement for rescue analgesia.

While our study shows overall pain scores were low in the buprenorphine group, dogs administered methadone had even lower pain scores and required significantly less rescue analgesia. This suggests that methadone is the more efficacious analgesic in ovariohysterectomy and this is likely to be true for other moderate to severely painful surgeries. These findings are mirrored by the results of Hunt *et al.*'s study (2013) which show that methadone is superior to buprenorphine in dogs undergoing orthopaedic surgery.

In the population of dogs that required rescue analgesia, the number of additional methadone administrations *per* rescue did not differ, despite initial premedication opioid. This suggests that previous administration of buprenorphine did not antagonise the clinical analgesic effect of methadone. Previous studies in dogs have found contradictory results when investigating the interaction between buprenorphine and pure μ -agonists. One study found that pre-treating dogs undergoing ovariohysterectomy with buprenorphine reduced the analgesic efficacy of the full μ -opioid sufentanil (Goyenechea Jaramillo *et al.*, 2006), whereas other studies, similar to the present study, found no antagonistic effects of buprenorphine on subsequent administration of postoperative methadone (Hunt *et al.*, 2013a) or intra-operative fentanyl (Taylor and Walsh, 2002). Recent findings in human medicine have also found that buprenorphine does not antagonise the analgesic efficacy of morphine (Oifa *et al.*, 2009). Therefore, irrespective of preoperative opioid choice methadone can still be given to painful patients postoperatively if necessary.

Of the dogs that received rescue analgesia, 88% needed treatment before the scheduled second dose of test opioid at 5 hours, *i.e.* before the expected duration of action of both drugs (Brodbelt *et al.* 1997, Ingvast-Larsson *et al.* 2010). This illustrates individual variation in response to opioids and highlights the need for regular postoperative pain assessments. Five hours was chosen as the time for the second dose of test opioid as it incorporated the expected duration of action of both methadone and buprenorphine. Therefore, the difference in requirement of rescue analgesia between methadone and

buprenorphine groups is a result of inadequate analgesic efficacy and unlikely to be due to pharmacokinetic differences between the two drugs.

The mechanical nociceptive threshold (MNT) was measured against baseline values as percentage change. It was hypothesised that dogs that received methadone would exhibit less hyperalgesia postoperatively than those treated with buprenorphine since methadone is also an NMDA antagonist. Variability in MNT data post-operatively was large but overall mean MNT decreased in the different treatment groups at all time points demonstrating that OVH resulted in secondary hyperalgesia. However, no difference was detected in MNT values between groups. This limited the usefulness of the test and may be because the level of hyperalgesia was not sufficient to distinguish between the two drugs, or that MNT is less discriminatory than the two pain scales that were used concurrently in the present investigation. The most painful aspect of OVH is usually the pulling and tearing of the suspensory ligament and there is little trauma around the incision site. Incisions are relatively small and the muscle layer remains intact since the incision is made through the linea alba which has few nociceptors and blood vessels (Grint et al., 2006). In addition, it was noted that sedation may have confounded MNT scores at the early measurement time points after surgery and that some animals became distracted, and possibly conditioned to the uncomfortable stimulus from the PRoD, making it difficult to accurately judge the point at which the animal felt discomfort.

The dose of methadone used in the present study (0.3mg/kg) was lower than the 0.5-1 mg/kg dose stated in the Summary of Product Characteristics (SPC). This lower dose is widely recommended since it anecdotally provides good analgesia and eliminates some of the dose-dependent adverse reactions such as vomiting, respiratory depression and bradycardia seen at higher doses (Maiante et al., 2009, Credie et al., 2010). The results of the present study demonstrate that the lower dose of 0.3mg/kg of methadone provides good analgesia and is well tolerated. The incidence of each adverse effect reported was similar between groups. A significant difference was shown in

hypersalivation on recovery between acepromazine and medetomidine groups. However, this was most probably caused by the administration of atipamazole to antagonise medetomidine on recovery, since hypersalivation is a possible adverse effect of atipamazole.

The aim of this study was to provide clinical evidence to help veterinarians in their decision-making regarding opioid use. Using methadone at a lower dose may dispel worries about analgesic efficacy, dose unfamiliarity and drug safety - factors which were identified by a recent survey as influencing clinicians when choosing an opioid for perioperative analgesia (Hunt et al., 2015).

In conclusion, our results support the hypothesis that methadone provides superior perioperative analgesia compared to buprenorphine in dogs undergoing ovariohysterectomy. Methadone resulted in lower postoperative pain scores and a reduced necessity for additional analgesia, and should be considered for the premedication of dogs undergoing ovariohysterectomy and other moderate to severely painful surgeries. Despite this, our results indicate that individual response to opioid analgesia is variable and regular postoperative pain assessments are fundamental for good pain management. It is also important to note that although this study did not administer non-steroidal analgesics during premedication a multi-modal approach to analgesia is recommended.

References:

- Bortolami, E., Murrell, J. C., & Slingsby, L. S., (2013) Methadone in combination with acepromazine as premedication prior to neutering in the cat. *Veterinary Anaesthesia and Analgesia* **40**, 181-93.
- Brodbelt, D., Taylor, P.M., Benson, G.J., (1997) A comparison of preoperative morphine and buprenorphine for post operative analgesia for arthrotomy in dogs. *Journal of Veterinary Pharmacology and Therapeutics* **20**, 284-289.
- Coleman, D. L., & Slingsby, L. S., (2007) Attitudes of veterinary nurses to the assessment of pain and the use of pain scales. *Veterinary Record* **160**, 541-544.
- Credie, R. G., Teixeira Neto, F. J., Ferreira, T. H., *et al.* (2010) Effects of methadone on the minimum alveolar concentration of isoflurane in dogs. *Veterinary Anaesthesia and Analgesia* **37**, 240-9.
- Dahl, J. B., & Kehlet, H., (2011) Preventive analgesia. *Current Opinion in Anaesthesiology*, **24**, 331-8.
- Davis, A. M., & Inturrisi, C. E., (1999) d-methadone blocks morphine tolerance and n-methyl-d-aspartate induced hyperalgesia. *Journal of Pharmacology and Experimental Therapeutics* **289**, 1048-1053.
- Goyenechea Jaramillo, I. A., Murrell, J. C., & Hellebrekers, L. J., (2006). Investigation of the interaction between buprenorphine and sufentanil during anaesthesia for ovariectomy in dogs. *Veterinary Anaesthesia and Analgesia* **33**, 399-407.
- Greenwald, M.K., Johnson, C.E., Moody, D.E., *et al.* (2003) Effects of buprenorphine maintenance dose on μ -opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* **28**, 2000-2009.
- Grint, N. J., Murison, P. J., Coe, R. J., *et al.* (2006) Assessment of the influence of surgical technique on postoperative pain and wound tenderness in cats following ovariohysterectomy. *Journal of Feline Medicine and Surgery* **8**, 15-21.

- Hardie, E. M., Hansen, B. D., & Carroll, G. S., (1997). Behavior after ovariohysterectomy in the dog: what's normal? *Applied Animal Behaviour Science* **51**, 111-128.
- Holton, L., Pawson, P., Nolan, A., *et al.* (2001) Development of a behaviour-based scale to measure acute pain in dogs. *Veterinary Record* **148**, 525-531.
- Holton, L. L., Scott, E. M., Nolan, A. M., *et al* (1998). Comparison of three methods used for assessment of pain in dogs. *Journal of the American Veterinary Medical Association* **212**, 61-6.
- Hunt, J. R., Attenburrow, P. M., Slingsby, L. S. *et al.* (2013b) Comparison of premedication with buprenorphine or methadone with meloxicam for postoperative analgesia in dogs undergoing orthopaedic surgery. *Journal of Small Animal Practice* **54**, 418-24.
- Hunt, J. R., Grint, N.J., Taylor, P. M., *et al* (2013a). Sedative and analgesic effects of buprenorphine, combined with either acepromazine or dexmedetomidine, for premedication prior to elective surgery in cats and dogs. *Veterinary Anaesthesia and Analgesia* **40**, 297-307.
- Hunt, J. R., Knowles, T. G., Lascelles, B. D., *et al.* (2015) Prescription of perioperative analgesics by UK small animal veterinary surgeons in 2013. *Veterinary Record* **176**, 493.
- Ingvast-Larsson, C., Holgersson, A., Bondesson, U., *et al.* (2010) Clinical pharmacology of methadone in dogs. *Veterinary Anaesthesia and Analgesia* **37**, 48-56.
- Inturrisi, C. E., (2002). Clinical pharmacology of opioids for pain. *Clinical Journal of Pain* **18**, S3-13.
- Katz, J., Clarke, H., & Seltzer, Z. E., (2011) Preventive analgesia: quo vadimus? *Anesthesia & Analgesia* **113**, 1242-1253.
- Lascelles, B. D., Cripps, P. J., Jones, A., *et al* (1998) Efficacy and kinetics of carprofen, administered preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. *Veterinary Surgery* **27**, 568-82.

- Lascelles, B. D. X., Capner, C. A., & Waterman Pearson, A. E., (1999) Current british veterinary attitudes to perioperative analgesia for cats and small mammals. *Veterinary Record* **145**, 601-604.
- Leece, E. A., Brearley, J. C., & Harding, E. F., (2005) Comparison of carprofen and meloxicam for 72 hours following ovariohysterectomy in dogs. *Veterinary Anaesthesia and analgesia* **32**, 184-92.
- Maiante, A. A., Teixeira Neto, F. J., Beier, S. L., *et al.* (2009) Comparison of the cardio-respiratory effects of methadone and morphine in conscious dogs. *Journal of Veterinary Pharmacology and Therapeutics* **32**, 317-28.
- Murrell, J. C., Psatha, E. P., Scott, E. M., *et al.* (2008) Application of a modified form of the glasgow pain scale in a veterinary teaching centre in The Netherlands. *Veterinary Record* **162**, 403-408.
- Oifa, S., Sydoruk, T., White, I., *et al.* (2009) Effects of intravenous patient-controlled analgesia with buprenorphine and morphine alone and in combination during the first 12 postoperative hours: a randomized, double-blind, four-arm trial in adults undergoing abdominal surgery. *Clinical Therapeutics*, **31**, 527-41.
- Pergolizzi, J, Aloisi, A.M., Dahan, A., *et al.* (2010) Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Practice* **10**, 428-450.
- Raffa, R., Rawls, S., Beysarov, E.P., Netter's Illustrated Pharmacology. Belmont, CA: Saunders; 2005.
- Reid, J., Nolan, A. M., Hughes, J. M., *et al.* (2007) Development of the short-form glasgow composite measure pain scale (CMPS-SF) and derivation of an analgesic intervention score. *Animal Welfare* **16**, 97-104.
- Sharkey, M., (2013) The challenges of assessing osteoarthritis and postoperative pain in dogs. *American Association of Pharmaceutical Scientists Journal* **15**, 598-607.
- Shih, A. C., Robertson, S., Isaza, N., *et al* (2008) Comparison between analgesic effects of buprenorphine, carprofen, and buprenorphine with carprofen for canine ovariohysterectomy. *Veterinary Anaesthesia and Analgesia* **35**, 69-79.

Slingsby, L. S., Bortolami, E., & Murrell, J. C., (2015) Methadone in combination with medetomidine as premedication prior to ovariohysterectomy and castration in the cat. *Journal of Feline Medicine and Surgery* **17**, 864-72.

Slingsby, L. S., Taylor, P. M., & Murrell, J. C., (2011) A study to evaluate buprenorphine at 40 µg kg⁻¹ compared to 20 µg kg⁻¹ as a post-operative analgesic in the dog. *Veterinary Anaesthesia and Analgesia* **38**, 584-593.

Stanway, G. W., Taylor, P. M. & Brodbelt, D. C., (2002) A preliminary investigation comparing pre-operative morphine and buprenorphine for postoperative analgesia and sedation in cats. *Veterinary Anaesthesia and Analgesia* **29**, 29-35.

Taylor, P. & Walsh, C., (2002) Does buprenorphine premedication affect the action of fentanyl during surgery in dogs. Meeting abstracts proceedings of the Association of Veterinary Anaesthetists Spring Meeting, **2002**. 31.

The Glasgow Composite Pain Scale is from

<http://www.newmetrica.com/wpcontent/uploads/2016/09/Reid-et-al-2007.pdf>,
accessed 24th August 2017)

Atipamezole data can be accessed from

<https://www.zoetisus.com/products/dogs/antisedan-atipamezole.aspx>, accessed
1st September 2017).