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Objectives: To investigate analgesic efficacy of methadone compared to buprenorphine, within the QUAD protocol for anaesthesia in cats undergoing ovariohysterectomy.

Methods: One hundred and twenty cats were recruited to an assessor-blinded, randomised, clinical trial. Cats received either methadone (5mg/m^2) or buprenorphine (180µg/m^2) combined with ketamine, midazolam and medetomidine intramuscularly. Anaesthesia was maintained with isoflurane in oxygen. Atipamezole was administered at extubation. Pain was assessed using the feline Composite Measure Pain Scale (CMPS-F), a dynamic interactive visual analogue scale (DIVAS) and mechanical nociceptive threshold (MNT). Sedation, pain, heart rate, and respiratory rate were measured prior to QUAD administration, before intubation, and 2, 4, 6 and 8 hours post QUAD administration. If indicated by the CMPS-F, rescue analgesia was provided with 0.5mg/kg of methadone administered intramuscularly. Meloxicam was administered after the last assessment. Differences in pain scores between groups were compared using a two way repeated measures ANOVA and requirement for rescue analgesia was compared using a Chi-squared test.

Results: Cats administered methadone had lower CMPS-F scores over time ($p=0.04$). Eighteen cats out of 60 required rescue analgesia in the methadone group compared with 29 out of 60 in the buprenorphine group ($p=0.028$). All cats that received rescue analgesia required it within 6 hours post QUAD administration. There were no differences between groups in MNT or pain measured using the DIVAS.

Conclusions and relevance: Methadone produced clinically superior post-operative analgesia for the first eight hours after neutering compared to buprenorphine when used within the QUAD protocol.

Introduction

Neutering is one of the most common surgical procedures performed in cats in veterinary practice. There is often limited monitoring equipment in these situations and a safe but effective and relatively rapid anaesthetic and analgesic regime is important. The QUAD protocol comprises medetomidine, ketamine, midazolam and buprenorphine. It was developed at the RSPCA Greater Manchester Animal Hospital (GMAH) to provide safe anaesthesia and analgesia for neutering in cats, particularly young cats, by providing a multimodal technique and dosing on the basis of body surface area[1].

Neutering, particularly ovariohysterectomy, has been shown to cause acute post-surgical pain. Pain in cats has historically been under-treated compared to other species[2-3]. This is most likely because cats tend to mask signs of pain and pain behaviours are often subtle, probably because cats are a solitary prey species[4]. However, the importance of adequate pain relief and pain assessments in feline patients is becoming increasingly recognised.

Opioids are currently the cornerstone of acute pain treatment and the two most commonly used opioids for surgical pain in the UK are buprenorphine and methadone[5]. Buprenorphine is considered a partial μ agonist as well as a kappa and delta receptor antagonist, however recent studies have shown it can produce a full analgesic effect and behave as a full μ agonist in a clinical setting[6]. Methadone is a full μ receptor agonist producing a maximal response at full saturation of receptor binding sites[7]. Additionally, it is licenced as a racemic mixture formed of two isomers. The L-isomer binds to the μ receptor and provides analgesia,

while the D-isomer acts as an N- methyl D- aspartate (NMDA) receptor[8]. This gives methadone the potential to prevent central sensitisation and hyperalgesia.

Both methadone and buprenorphine have been shown to provide adequate analgesia for feline ovariohysterectomy[9-13]. However, there is some controversy over opioid efficacy in cats. No difference in postoperative analgesia following neutering (OVH and castration) was found between methadone, buprenorphine and butorphanol, when combined with acepromazine[12] or medetomidine[13]. In contrast, buprenorphine[10] and methadone[14] have been shown to be superior to butorphanol in cats undergoing ovariohysterectomy. There are a limited number of studies which have directly compared methadone and buprenorphine, and to the authors' knowledge, none have compared the two drugs in the context of the QUAD or triple combination (medetomidine, buprenorphine, ketamine) protocols. In order to compare methadone and buprenorphine more accurately within the QUAD protocol we chose not to administer a NSAID pre-operatively which may have otherwise masked differences between treatment groups. This mimics common clinical practice where the NSAID is administered during the recovery period to minimise the risk of renal complications should hypotension occur during anaesthesia.

We hypothesised that methadone would provide superior analgesia compared to buprenorphine in cats undergoing ovariohysterectomy when incorporated in the QUAD protocol.

Material and Methods

Study Design

An assessor blinded, randomised, prospective clinical trial was conducted at the Greater Manchester RSPCA Animal Hospital. The study protocol was approved by the University of Bristol Ethical Review Group (VIN/15/023) and was carried out under an Animal Test Certificate-S issued by the Veterinary Medicine Directorate. Figure 1 provides an overview of the study protocol.

Sample size

In the study by Polson and colleagues[11], pain scores were not significantly different between groups but were greatest at the 4 hour time point after surgery. At this point the mean DIVAS (SD) score in the buprenorphine group was 12 (19) mm[11]. A reduction in DIVAS pain score by 10 mm was considered clinically relevant, therefore a reduction in pain score by 10 mm was considered to be the clinically relevant difference for the methadone group. Therefore, taking into account an α value of 0.05 and power of 0.8, the number of animals in each group needed to detect a difference between opioids was 58.

Enrolment and inclusion

One hundred and twenty cats undergoing routine midline ovariohysterectomy were recruited. Written, informed consent for inclusion in the study was obtained prior to surgery. All cats underwent a pre-anaesthetic examination and only those classified as American

Society of Anaesthesiologists (ASA) category 1 or 2 were included. Exclusion criteria comprised cats under 4 months of age, cats which had received analgesia, anaesthesia, or sedation within the previous 7 days, and cats that were not amenable to handling.

Randomisation

Cats were randomly allocated by random number generator (www.random.org) to receive either of the two opioids within the QUAD protocol to generate two groups of 60 individuals.

Assessments

Assessments throughout the study period were conducted by the same assessor who was blinded to the treatment group. Assessments included heart rate (HR), respiratory rate (f_R), sedation, pain and mechanical nociceptive threshold (MNT) and were measured in the same order at each time point. HR and f_R were measured manually by counting the number of heart beats or breaths over a 15 second period. Sedation was measured using a simple descriptive scale (SDS)[13] (Table 1) and dynamic interactive visual analogue scale (DIVASsedation). Pain was measured using the validated Composite Measure Pain Scale-feline (CMPS-F)[15] and DIVASpain. DIVAS uses a 10 cm scale where 0 represents no sedation or pain and 10 represents maximal sedation or the worst possible pain for the procedure[16]. Cats were assessed from a distance before the assessor approached the kennel and response to verbal interaction and stroking was assessed. Finally, the assessor gently palpated the wound. Secondary hyperalgesia surrounding the surgical wound was measured as the mechanical nociceptor threshold (MNT) using a pressure onset device

(ProD) by Topcat Metrology®. The ProD tip (2 mm diameter) was placed 2 centimetres away from the incision wound and pressure applied at a rate of 2N per second. Maximum pressure applied was 15N, above which there was a risk of tissue damage. If no response was noted prior to the cut off, a score of 15N was given.

Pre-operative Assessments

Baseline parameters were measured prior to QUAD administration. Parameters were also measured ten minutes after QUAD administration, prior to intubation.

Administration of test item

The anaesthetic drugs were drawn up in the same syringe by the veterinary surgeon carrying out surgery and administered intramuscularly into the quadriceps muscles. Premedication comprised of 600 μg/m^2 medetomidine (Sedator 10mg/mL; Dechra Pharmaceuticals), 60 mg/m^2 ketamine (100mg/mL Anesketin; Dechra Pharmaceuticals), 3mg/m^2 Midazolam (5mg/mL Hypnovel; Roche) and either 5mg/m^2 methadone (Comfortan 10mg/mL; Dechra Pharmaceuticals) or 180μg/m^2 buprenorphine (Buprenodale 0.3mg/mL; Dechra Pharmaceuticals).

Heart rate, f_R, sedation and MNT were measured once the cat was fully sedated and non-responsive. The larynx was then sprayed with lidocaine hydrochloride (Intubeaze ® 20mg/mL, Dechra Veterinary Products) to prevent laryngeal spasm and an appropriately sized non-cuffed endotracheal tube was placed.

Anaesthesia maintenance

Anaesthesia was maintained with isoflurane (ISO) vaporised in oxygen delivered with a T-piece breathing system. Depth of anaesthesia and physiological parameters were monitored continuously. Physiological monitoring comprised measurement of HR, f_R, non-invasive blood pressure (NIBP), haemoglobin saturation with oxygen (SpO_2), end tidal carbon dioxide concentration (ET[CO_2]) using a multi-parameter monitor (PM9000 multiparameter monitor; Burtons, UK). Measurements were recorded prior to the first surgical incision and then at the following important time points: skin incision, ligation of right and left ovarian pedicles, ligation of cervix, placement of the final skin sutures. All surgeries were carried out by the same experienced veterinary surgeon. Surgical time was defined as the time from first skin incision to last skin suture.

Recovery

Medetomidine sedation was antagonised with atipamazole at a dose of half the volume of administered medetomidine (Atipam® 5mg/mL; Dechra Pharmaceuticals) at the point of extubation. The endotracheal tube was removed when it was clear that the cat was making effective ventilatory movements and was maintaining an oxygen saturation of >95% when inhaling room air. Time from extubation to head lift, sternal recumbency, and standing were recorded. Quality of recovery was evaluated using a SDS scale (Table 1). Rectal temperature was measured until it was >37°C.

Post-operative assessments

Heart rate, f_R, sedation, pain and MNT were assessed 2, 4, 6 and 8 hours after QUAD administration. A post-operative CMPS-F score equal or greater than 4 out of 16 was considered to indicate the requirement for additional rescue analgesia. Methadone at a dose of 0.5 mg kg^{-1} was administered intramuscularly as rescue analgesia. The assessor was not blinded to rescue analgesia. Pain was assessed 30 minutes later and if required another dose of 0.5 mg kg^{-1} methadone given IM. All cats were administered meloxicam at 0.3 mg kg^{-1} subcutaneously (Metacam®; Boehringer-Ingelheim) after assessments were completed at 8 hours post-surgery.

Statistical methods:

Data were assessed for normality by visual inspection of histograms and using the Shapiro-Wilk test and appropriate parametric and non-parametric techniques used (SPSS Statistics Version 23; IBM Corporation). Means of normal data were compared between the treatment groups using a t-test. The means of nonparametric data were compared using a Mann-Whitney U test. A mixed between-within group (two-way) ANOVA was used to compare repeated measures over time and between groups. MNT was analysed as a percentage change from baseline, with baseline values given a scores of 100%, to account for the variation in pain threshold between individuals. Pain scores were corrected for rescue analgesia, where the score awarded before rescue analgesia administration was carried forward. The proportion of cats in each group requiring rescue analgesia or experiencing adverse events was compared using a Chi-squared test. P values of ≤ 0.05 were considered

statistically significant unless multiple comparisons were performed, when a Bonferroni correction was applied. Parametric data are reported as mean ± standard deviation and nonparametric data are reported as median (range).

Results:

Demographic data:

Mean ± SD age was 13.3 ± 9.46 months in the methadone group and 16.2 ± 14.4 months in the buprenorphine group ($p = 0.13$). Mean ± SD weight not significantly different between groups ($p=0.99$) (2.5 ± 0.6 and 2.5 ± 0.5 kg in the methadone and buprenorphine groups respectively). Body surface area was also very similar between groups (0.18 ± 0.07 and 0.18 ± 0.06 m^2 in the methadone and buprenorphine groups respectively). Surgery time in the methadone group was 14.9 ± 2.4 minutes and 14.8 ± 2.5 minutes in the buprenorphine group and this was not statistically significantly different between groups ($p=0.94$).

Physiology

Baseline HR and f_R were within normal limits and did not differ between groups ($p = 0.13$ and 0.26 respectively). Ten minutes post QUAD administration, both HR and f_R were significantly lower compared to baseline in both groups ($p < 0.001$). There was no significant difference in HR ($p = 0.79$) or f_R ($p = 0.97$) between cats that received methadone and those that received buprenorphine post QUAD administration.

Intra-operative physiological parameters (HR, RR, SBP, DBP, and MBP) were analysed as percentage change from baseline values measured prior to the point of incision and showed no significant difference between groups overtime or at any timepoint. There was no significant difference between groups with respect to ISO concentration, measured as the dialled vaporiser setting, ET[CO_2] or SpO_2 (Table 2).

Sedation

Sedation was increased in all groups post premedication ($p < 0.0001$) (MET: SDS 3(3-3), DIVAS 9.98 (9 – 10) cm; BUP: SDS 3 (3-3), DIVAS 10 (10 – 10) cm) compared to baseline (SDS 0, DIVAS 0). There was no significant difference in SDS or DIVAS sedation scores post-premedication between groups.

Post-operatively, SDS and DIVASsedation scores showed no significant difference in sedation at any time-point with respect to opioid.

Pain

Pain scores, measured using DIVAS and CMPS-F were 0 in all cats at baseline and following QUAD, with no significant differences between groups.

Post-operatively, although with post hoc testing the difference in pain scores between groups was not significant at any one particular time point, the methadone group had significantly lower CMPS-F pain scores compared to the buprenorphine group overtime ($p = 0.04$) (Figure 2).

Post-operatively there was no significant difference in DIVASpain scores between groups overtime ($p = 0.06$) (Figure 3).

MNT

Mechanical nociceptive threshold values were not significantly different between groups at baseline ($p = 0.66$), but significantly increased post QUAD administration in both groups ($p < 0.001$). There was no significant difference in MNT score post premedication compared to baseline values with respect to opioid ($p = 0.71$). Post-operatively there was no significant difference in MNT data between groups over time ($p = 0.47$) (Figure 4).

Recovery

Recovery quality was generally good in all cats and there was no significant difference in recovery quality at extubation ($p = 0.313$), head lift ($p = 0.750$), sternal recumbency ($p = 0.810$) or standing unaided ($p = 0.775$). There was also no significant difference in the time taken between removal of endotracheal tube and head lift ($p = 0.603$), sternal recumbency ($p = 0.729$) and standing between groups ($p = 0.743$) (Table 3).

Intervention analgesia

Eighteen of 60 cats in the methadone groups required rescue analgesia compared to 29 of 60 in the buprenorphine group ($p = 0.04$). No cats required more than one dose of rescue analgesia. All cats that received rescue analgesia required it within 6 hours post QUAD administration. CMPS-F scores one hour after rescue analgesia were significantly lower than scores before rescue analgesia ($p<0.0001$). A Kaplan Meier survival graph was plotted using the number of cats requiring rescue analgesia at each time point. The two curves differed significantly ($p = 0.028$) with time (Figure 5).

Adverse effects

The frequency of adverse effects was low. Three cats in the methadone group and four cats in the buprenorphine group vomited after QUAD administration. Two cats in the methadone group showed lip licking post QUAD administration. Two cats in the buprenorphine group showed lip licking post administration of rescue analgesia (0.5 mg kg^{-1} methadone administration). There was no significant difference between groups for any of the adverse effects observed during the study.

Discussion

The aim of the study was to compare postoperative analgesia between methadone and buprenorphine within the QUAD protocol in cats undergoing ovariohysterectomy. Our results showed that cats administered methadone pre-operatively had lower overall CMPS-F and required less rescue analgesia postoperatively than those administered buprenorphine.

There is some controversy over the optimum handling of pain score data in clinical studies. Pain scores can be analysed as raw data or corrected for rescue analgesia by carrying forward the score at the time of rescue analgesia administration to maintain the expected pain scores if additional analgesia had not been given. This increases the sensitivity of data analysis to discriminate between two interventions. We chose to analyse data using the last observation carried forward method for DIVAS, CMPS-F and MNT since although it was hypothesised that methadone would provide superior analgesia compared to buprenorphine, overall pain scores were predicted to be low. Pain was assessed after administration of the QUAD protocol but before surgery. This assessment time point was not ideal because cats were effectively anaesthetised and therefore it was not meaningful to assess pain at this point.

There is some disparity in the results of studies that have compared methadone and buprenorphine in cats. The discrepancy between studies evaluating different opioids may be attributable to the difference in study protocols (dose of opioid, type of surgery, surgery technique, and experience of surgeon) as well as the sensitivity of pain scoring systems used. Assessing pain in animals relies largely on behavioural observation of the sensory and affective aspects of pain[17-18]. The inability to verbally communicate makes pain assessment in animals difficult. Until recently there have been no validated pain scoring systems for cats and most opioid comparison studies have used an interactive visual analogue scale (IVAS). Although more sensitive than other forms of pain assessment such as the simple descriptive

scales, IVAS is very subjective and influenced by factors such as experience and perception of 'worst possible pain'[17]. In order to overcome this, the same assessor is needed to carry out all pain scores, however, the lack of specific anchor points on the scale can still result in variability and is likely the reason for the different outcomes of DIVAS and CMPS-F scores in the present study. Despite this criticism, the authors included DIVAS pain scoring to allow better comparison of the present study to previous studies.

The CMPS-F has been shown to reduce intra and inter-assessor variability by using defined behaviours weighted by severity[15,19]. The psychometric design helps to reduce subjectivity and also provides a validated set intervention criterion. Therefore, the requirement of rescue analgesia was based on the CMPS-F score.

Methadone was hypothesised to limit secondary hyperalgesia at the site adjacent to the surgical wound due to its ability to antagonise NMDA receptors. However, secondary hyperalgesia occurred in all cats with no significant difference in MNT scores between the two groups over time or at any time point in either raw or corrected data. These results are similar to previous studies[10,11,13]. In contrast, Bortolami et al. (2013)[12] reported that cats administered methadone in combination with acepromazine prior to ovariohysterectomy showed no significant variation in MNT scores over time compared to baseline scores, supporting the potential anti-hyperalgesia action of methadone. However, OVH was carried out using a flank approach whereas the midline approach was used in the present study. The flank technique has been shown to cause greater wound tenderness because it

damages muscle tissue, which has a greater number of nociceptors connecting to Aδ and C fibres compared to the connective tissue linea alba which is incised in the midline technique[20]. In addition, ketamine is also a non-competitive NMDA receptor antagonist and may have reduced the ability to detect differences in MNT between methadone and buprenorphine. It is possible that a more invasive surgery may have resulted in more apparent differences in MNT between groups.

A large number of cats in both the methadone and buprenorphine groups required rescue analgesia which may be due in part to the delayed administration of the NSAID until the end of the assessment time period. However this also illustrates the importance of pain scoring after ovariohysterectomy, particularly if animals are not administered a NSAID until the recovery period. An alternative explanation may be the short duration of time between administration of the test drugs in the QUAD protocol and the start of surgery, which was approximately 20 -25 minutes. In a thermal threshold model peak effects of buprenorphine have been shown to occur 90 minutes after IV drug administration with a significant hysteresis between plasma drug concentration and effect[21]. In contrast the peak effect of methadone on thermal threshold after IM administration has been shown to occur slightly earlier at 60 minutes after administration[22]. The relatively slow onset of action times of methadone and buprenorphine may have prevented the administration of pre-emptive analgesia to these cats undergoing surgery, driving upregulation of the pain pathways and increased pain sensation, including secondary mechanical hyperalgesia, in the postoperative period. However this mimics routine clinical practice with the QUAD protocol

where surgery is performed rapidly after drug administration in order to capture the peak effects of the sedative drugs in the combination.

Once rescue analgesia had been administered the assessor was no longer blinded to treatment group, however no cats required administration of a second dose of rescue analgesia.

The QUAD protocol doses drugs on the basis of body surface area (BSA) rather than bodyweight because it was a protocol developed for small kittens where dosing on bodyweight can lead to dosing inaccuracies due to their greater body surface area to mass ratio[1]. A freely downloadable App has been developed for the QUAD protocol to allow calculation of drug doses using BSA based on inputting the bodyweight of the cat. The calculation to derive BSA from bodyweight uses a constant of 10.4 for all bodyweight cats. However it has been suggested that this relationship only holds true for cats <2.5 kg bodyweight[23], therefore it is possible that there were dosing in accuracies in the present study where the mean weight of the cats was 2.5 kg. However weights were similar between groups indicating that any inaccuracies would have also been similar between groups.

Vomiting occurred in a small number of cats after administration of the QUAD protocol, likely attributable to the administration of medetomidine[24]. Lip licking, thought to indicate nausea, was also noted in a minority of animals. Due to their low frequency these adverse events were not considered to be clinically significant by the authors.

This study aimed to differentiate between the analgesic efficacy of methadone and buprenorphine. For this reason NSAIDs were not included within the protocol and only administered once observations were complete. However, it is possible that the addition of an NSAID may have reduced the differences seen between the two opioids by providing additional analgesia. In normal clinical settings, a multi-modal approach to analgesia is recommended. Future studies should focus on the evaluation of opioids with NSAIDs given at the time of surgery.

In conclusion, the results of this study support the hypothesis that overall methadone provides superior analgesia compared to buprenorphine at the doses used in the QUAD protocol, and this may extend to the triple combination protocol. However, the action of opioids in human individuals is variable and it is likely that this is also the same cats. Factors such differences in cytochrome P450 mediated metabolism and variance in the μ1 opioid receptor (OPRM1) gene have been reported to play a role in the individual variability in the clinical effect and tolerability of opioid analgesics in man[25]. Therefore it is important that regular pain assessments are undertaken in the post-operative period regardless of opioid choice. A multi-modal approach including the use of a pre-operative NSAID is also recommended.

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Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and /or publication of this article.

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Figure legends

Figure 1: Graphical representation of the timeline of the study

Figure 2: Mean postoperative Feline Composite Measure Pain Scale (CMPS-F) scores over time for methadone and buprenorphine groups. Methadone groups had significantly lower pain scores over time, $p = 0.04$. Error bars indicate SD.

Figure 3: Mean postoperative Dynamic Interactive Visual Analogue Scale (DIVAS) pain scores over time in the methadone and buprenorphine groups. Error bars indicate SD.

Figure 4. Mean postoperative Mechanical Nociceptive Threshold (MNT) scores over time in the methadone and buprenorphine groups. Values are presented as percentage change from baseline. Error bars indicate SD.

Figure 5: A Kaplan-Meier survival graph showing survival as the proportion of cats not requiring rescue analgesia at each timepoint postoperatively. * denotes a significant difference between the two curves ($p = 0.028$).