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Effect of Buprenorphine and Butorphanol for Postoperative Analgesia Following Ovariohysterectomy in Cats

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Buprenorphine, Butorphanol, Cats, Analgesia, Postoperative, Ovario-hysterectomy

ABSTRACT

The majority of anesthetic combinations that are used frequently do not offer adequate postoperative analgesia. Postoperative pain can cause stress and delay the healing of the surgical site. Opioids are the drug of choice for analgesia. This study was designed to compare the analgesic efficacies of buprenorphine and butorphanol following ovariohysterectomy in cats. This study selected 12 clinically healthy cats. The cats were divided into 2 equal groups (A and B), with 6 cats in each group. Group A was treated with buprenorphine, and Group B was treated with butorphanol. The efficacy of both opioids was evaluated based on subjective and objective parameters of postoperative analgesia, which are pain assessment scores, glucose level, and serum cortisol level. In glucose levels, there was a significant difference between the groups at 3, 6, and 9 h postoperatively, as the group treated with butorphanol had more glucose levels in comparison with the buprenorphine group. In serum cortisol levels, there was a significant difference between both groups at 3 and 6 h postoperatively, as the cortisol level was low in the buprenorphine-treated group. In objective parameters of pain assessment, there was a significant difference between the groups in food intake, reaction on palpating the surgical site, and movement of the cat postoperatively ($p < 0.05$). Buprenorphine provides better and longer analgesia in comparison with butorphanol after ovariohysterectomy in cats up to 9 h postoperatively.

INTRODUCTION

Cats, *Felis catus* is believed to have been first domesticated by Egyptians around 4000 years ago (Anonymous, 2008). Later on, cats were relocated to Europe and other countries across the world. There are different breeds of cats that are being kept as companion animals in Pakistan. Besides these cats, there are many feral and stray cats in Pakistan and there is a dreadful need to control their population. The best and most effective way to control their population is Trap-neuter-return (Swarbrick and Rand, 2018). Whenever cats undergo any kind of surgical procedure, they experience postoperative pain like humans. It is concluded by many veterinary surgeons that when cats undergo ovariohysterectomy, they experience postoperative pain (Lascelles *et al*., 1999). But to relieve postoperative pain in cats is not in practice as it should be. So, it would be humane to avoid postoperative pain in cats that undergo ovariohysterectomy (Ansah *et al*., 2002). Besides its welfare aspect, postoperative pain may also eventually increase postoperative complications such as delayed wound healing, and wound interference and may ultimately lead to chronic pain (Orskov, 2010). The evaluation of pain and its management in cats has increased in recent times.

Pain is a demonstrative and sensory event and mostly in the case of animals, they are unable to express their suffering. So, it's a bit challenging to evaluate pain in animals. Especially in the case of cats as it is quite difficult to recognize whether they are in pain or not. The signs of pain in cats are very subtle. Pains cause stress, affect feeding, and metabolic activity, suppress the immune system, alter the normal physiological behavior of

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animals, and ultimately lead to chronic pain which may eventually affect the healing of the surgical site (Lascelles and Pearson, 1997; Taylor, 2003). The best way to analyze whether the cat is in pain or not is through a combination of blood values, interaction with animals, and behavioral examination (Hammond *et al*., 2008).

The primary duty of a veterinary surgeon is to relieve the suffering of animals that are in their care. So, veterinary surgeons should try their level best to minimize their pain before, during, and after anesthesia (Slingsby and Pearson, 1998). Opioids are used for pain management in animals. Opioids produce their effects by binding to their receptors in the central nervous system (CNS). The most important opioid-specific receptors are mu (μ), delta (δ), and kappa (κ). Opioids are usually classified as pure agonists, partial agonists, mixed agonist-antagonists, and antagonists (Welsh, 2009). Only a few opioid analgesic drugs are approved to control postoperative pain in cats; this includes buprenorphine, a partial opioid agonist, and butorphanol, an opioid agonist (Slingsby and Pearson, 1998).

Buprenorphine is a semisynthetic, lipophilic, and partial opioid agonist at μ receptors. In small animals, buprenorphine is majorly used as an analgesic drug to control mild to moderate pain (Plumb, 2008). Buprenorphine, when used in combination with full agonist opioids such as morphine, antagonizes their action (Lutfy and Cowan, 2004). It produces a longer duration of action due to its slow dissociation from μ receptors (Hammond *et al*., 2008). Buprenorphine is well tolerated by cats, causes minimal sedation, and has less risk of respiratory depression. It has very few side effects in the case of cats (Steagall *et al*., 2009).

Butorphanol is a centrally acting opioid agonist at κ receptors and an antagonist at μ receptors. It's a synthetic opioid that is being used in many veterinary species. Initially, it was used as an antitussive agent in dogs, but nowadays it is used as an analgesic agent in canines, equines, and felines. It produces its analgesic effect by blocking the transmission of nociceptive stimulus in the spinal cord's dorsal horn and also decreases the rate of release of neurotransmitters in the spinal cord (Schnellbacher, 2010). It is used to treat moderate to severe pain. Usually in cats, dogs, and horses, it is used in sedative combinations with α2-agonists and to produce mild analgesia. Butorphanol, when used as a sole agent in dogs, produces mild sedation in dogs, but not in cats (Hammond *et al*., 2008).

As, the analgesic activity of most of the anesthetic drugs is limited and in order to avoid any deleterious postoperative complication, due to pain and for the sake of animal welfare it is necessary to provide postoperative analgesia to animals following any invasive surgery. So, this research is designed to compare the efficacies of buprenorphine and butorphanol for postoperative analgesia.

MATERIALS AND METHODS

Cats

Twelve adult, clinically healthy female cats (1-2 years of age) divided into two groups (Group A and Group B) with 12 adult female cats in each group. In group A, cats were anesthetized using a combination of xylazine-ketamine- and Atropine sulfate. Xylazine was given at a dose rate of 0.6 mg/kg, Ketamine at 6mg/kg, and Atropine sulfate at 0.02mg/kg. The anesthetic cocktail was administered intramuscularly and buprenorphine was also administrated intramuscularly at a dose rate of 0.02mg/kg but separately.

In group B, cats were given the same anesthetic cocktail as in group A at the same dose rate. However, butorphanol was given at a dose rate of 0.4 mg/kg separately.

Surgical procedure

All cats were physically examined and weighed on an electronic weighing balance before surgery. The cats were kept fasting for 10 h before surgery, and clinical parameters temperature, heart rate, and respiratory rate were recorded in all cats. After administration of the anesthetic cocktail, the cats were restrained in dorsal recumbency. The surgical site and surrounding area were clipped and scrubbed with 30% povidone-iodine solution.

An incision was given on the ventral side of the body caudal to the umbilicus on the skin. After incising through subcutaneous tissue and fat, the linea alba was exposed. Linea alba was grasped, pulled outward, and with the help of a surgical blade, a stab incision was made on it. The incision was extended in both directions cranially and caudally with mayo scissors. The right uterine horn was located caudal to the right kidney with the index finger and confirmed by tracing it back to the ovary and uterine bifurcation. A suspensory ligament was identified at the proximal edge of the ovary and broke manually. A slit was made in the meso-ovarium caudal to the ovarian pedicle. The ovarian pedicle is triple-clamped and served between the clamp closest to the ovary and the middle clamp. Ligatures were placed with absorbable suture material, 2/0 polyglactin 910, at the groove made by the third clamp, the most distant one from the ovary. The vessel was held with a small hemostatic clamp and observed for any bleeding. Traced the uterine body with the help of the uterine horn and identified the other uterine horn and ovary. The same procedure was repeated for this side's ovary and ovarian pedicle. Then the uterine body is elevated with the help of both uterine horns, and three clamps are placed at the uterine body cranial to the cervix in order to place ligatures. Uterine arteries were ligated just caudal to the most caudal clamp, and the uterine body was severed between the proximal and middle clamp. The uterine body was ligated with absorbable suture material, 2/0 polyglactin 910. The uterine pedicle was grasped with small hemostatic forceps and observed for any bleeding. The clamp was removed, and the pedicle was placed back in the abdomen gently. Linea alba was closed with absorbable suture material, 2/0 polyglactin 910, in a simple interrupted pattern. Subcutaneous tissue was closed with absorbable suture material, 2/0 polyglactin 910, in a continuous intradermal pattern (Fossum, 2013; Slatter, 2003).

Parameters for assessment of pain: Behaviour: Normal, 0; Scared, 1; Aggressive, 2. Vocalization: None, 0; Intermittent, 1; Continuous, 2. Food intake: Normal, 0; Less food intake, 1; No food intake, 2. Posture: Relaxed, 0; Tense, 1; Crouched, 2. Movement: Calm, 0; Restless, 1; Violent, 2. Reaction on palpation of surgical site: Relaxed, 0; Tensing abdomen on palpation, 1; Growling, 2. Respiratory pattern: Normal respiration, 0; Mild abdominal respiration, 1; Marked abdominal respiration, 2. Temperament: Friendly, 0; Restless, 1; Aggressive, 2.

Blood collection procedure

A blood sample was collected in a non-heparinized and heparinized vacutainer before surgery. This sample was collected to evaluate the serum cortisol level before surgery in each cat. For the observation of serum cortisol level, a sample of blood was collected preoperatively and at 3 h, 6 h, and 9 h postoperatively in non-heparinized vacutainers. The serum was separated and used for estimation of blood glucose level and serum cortisol level 3 h, 6 h, and 9 h, postoperatively.

Statistical analysis

The results of blood glucose level and serum cortisol level were statistically analyzed using repeated measures test with a significant level of 0.05% ($p < 0.05$) on statistical analysis software SPSS 20.0 version, and parameters of pain assessment were statistically analyzed using the mann-whitney test with a significant level of 0.05% ($p \leq 0.05$) on statistical analysis software SPSS 20.0 version.

RESULTS

Table I shows the effect of buprenorphine and butorphanol after xylazine-ketamine-atropine sulfate anesthesia on blood glucose and serum cortisol level in cats following ovariohysterectomy. The normal glucose concentration in cats and dogs is 70-120 mg/dL (National Research Council *et al*., 2006). The mean blood glucose level of cats in both groups was within normal range. The mean blood glucose level in group A was within the normal range at all h (0, 3, 6, and 9), postoperatively. The mean blood glucose level of group B started to increase 3 h postoperatively and continued to increase up to 6 h postoperatively. After that, it started to decline at 9 h, postoperatively.

Table I. Effect of buprenorphine (0.02 mglkg) and butorphanol (0.4 mg/kg) administered intramuscularly after xylazine-ketamine-atropine sulfate anesthesia on the blood glucose and serum cortisol level following ovariohysterectomy in cats.

Time	Buprenorphine Group A (n= ?)	Butorphanol Group B (n=?)
Blood glucose level		
0 h	111.7 ± 6.84	113.2 ± 9.25
3 h	119.5 ± 5.21	128 ± 9.62
6 h	117 ± 8.51	122.5 ± 9.88
9 h	117.5 ± 6.13	119.2 ± 2.62
Serum cortisol level		
0 h	4.02 ± 0.29	4.13 ± 1.14
3 h	1.95 ± 0.40	5.29 ± 1.40
6 h	3.11 ± 0.82	10.33 ± 0.94
9 h	4.53 ± 0.55	11.46 ± 1.09

In overall comparison, there was a significant difference between both groups at 3 and 6 h postoperatively as $p < 0.05$. However, there was no significant difference between both groups at 0 and 9 h, postoperatively.

The mean serum cortisol level of cats of group A (buprenorphine) before surgery was 4.02 ± 0.29. At 3 h postoperatively, the mean serum cortisol level in group A decreased to the lowest point and then started to increase and continued to do so up to 9 h postoperatively.

The mean serum cortisol level of cats of group B (butorphanol) before surgery was 4.13±1.14. The mean serum cortisol level in group B started to increase 3 h postoperatively and continued to do so up to 9 h postoperatively.

There was a significant difference between the groups at 3, 6, and 9 h postoperatively. However, there was no significant difference between the groups at 0 hr postoperatively, and in overall comparison, there was a significant difference between both groups as $p > 0.05$.

Objective parameters of pain assessment were also evaluated in both groups at 0, 3, 6, and 9 h postoperatively. There was no significant difference between the groups at any h in behavior, vocalization, posture, respiratory pattern, and temperament ($p > 0.05$). However, there was a significant difference between the groups in food intake, reaction on palpating the surgical site, and movement of the cat at 9 h postoperatively ($p < 0.05$).

DISCUSSION

The analgesic effect of buprenorphine was found to be superior to that of butorphanol when both were compared after ovariohysterectomy up to 9 h postoperatively in cats. Cats, *Felis catus,* are one of the most popular pets. One of the most common surgical procedures that are performed nowadays in veterinary practice is elective ovariohysterectomy in cats (Gassel *et al*., 2005). The analysis of postoperative pain is quite difficult in cats due to many reasons. As they are not that much expressive in their pain-associated behavior. Additionally, there are very few analgesic drugs available in the market for cats, and there are more side effects associated with them. But recently more work has been done in the field of postoperative analgesia in cats. Postoperative pain can lead to many complications that ultimately hinder the healing of the surgical incision site (Lascelles and Pearson, 1997). The best way for the assessment of postoperative pain in cats is through the combination of behavioral indicators and blood values (Slingsby and Pearson, 1998). Veterinary professionals are usually reluctant to use analgesic drugs because of the side effects produced by them, and most of the potent analgesics are controlled drugs. The major options for the provision of analgesia are non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetic drugs (Gassel *et al*., 2005). Most of the NSAIDs are usually avoided in the case of cats as they cause major renal side effects. Two different opioid analgesics, buprenorphine, and butorphanol, were used in this study to check their efficacy for postoperative analgesia after ovariohysterectomy in cats.

The present study was clinic-oriented, as all the cats that were included in this study were owned by different clients. The anesthetic protocol used in this study was according to the normal practice of small animal veterinary surgery in Pakistan: xylazine and ketamine. Immediately after surgery, it was quite difficult to differentiate analgesia from sedation as all cats were still under the effect of anesthesia. The high sedation scores were recorded in both groups up to 2 h postoperatively.

In the present study, physiological parameters, such as temperature, pulse rate, respiratory rate, blood glucose concentration, and serum cortisol concentration, along with behavioral parameters, were tested for their relationship with pain. In many species, only serum cortisol concentration is measured as an indicator of pain (Anil *et al*., 2006). However, the levels of serum cortisol can be altered by anesthesia, fear, stress, or manipulation during surgery. Based on these factors, only objective assessment can predict pain alone in cats. For this reason, behavioral parameters were also added in this study. The behavioral indicators of feline pain that were added in the present study were published by Hansen (1997), Mathews (2000), and Merola and Mills (2016). In the present study, the serum cortisol level, palpation of the surgical site, and interactive behavior of the animal were found to be good indicators for the evaluation of postoperative analgesia. Similar findings were reported by Cambridge *et al*. (2000) that interaction with animals and palpation of the surgical site were found to be the most reliable indicators of pain.

In the present study, the temperature, pulse, and respiration rate (TPR) were recorded at different intervals and found to be within the normal range. However, there were minor differences in TPR in both groups. A decrease in respiratory rate was observed in both groups, which could be due to the effect of anesthesia. It was also reported by Dahan and Teppema (2003) that anesthesia can cause respiratory depression to some extent. So, a slight depression in respiratory rate wasn't alarming. Overall, no noticeable change was observed in TPR in both groups.

Buprenorphine is a potent opioid with a slow onset of action, a prolonged duration of analgesia, and fewer side effects. It provides adequate analgesia without producing major respiratory depression (Steagall *et al*., 2014). It was reported by Inagaki and Kuzukawa (1997) that the preoperative administration of buprenorphine has an anesthetic-sparing effect; it produces euphoria with little or no sedation. However, in the present study, buprenorphine was used postoperatively and reduced the pain effectively. Similar findings were also reported by Steagall *et al.* (2007) that buprenorphine reduces postoperative pain more efficiently in comparison with other NSAIDs. It was reported by Shih *et al*. (2008) that buprenorphine is a better analgesic drug in comparison with carprofen when its analgesic activity was compared, even after up to 8 h post-administration. Similarly, it was reported by Slingsby and Pearson (1998) that buprenorphine provides better postoperative analgesia in cats after ovariohysterectomy in comparison with ketoprofen.

The route of administration of buprenorphine can affect its efficacy. The best results are produced when it is administered via the intramuscular or intravenous route (Steagall *et al*., 2014). So, in the present study, the intramuscular route was used to evaluate its analgesic activity. Buprenorphine is one of the safest opioids in terms of side effects and produces the least respiratory depression in comparison with other opioids (Dahan *et al*., 2010). The analgesic activity of buprenorphine is much better and longer (Stanway *et al*., 2002). It was reported by Steagall *et al*. (2009) that dysphoria and vomiting are the most common side effects associated with opioids. However, in the present study, only one cat demonstrated dysphoria.

Opioids are the analgesics of choice, with butorphanol being most commonly used in both dogs and cats (Dohoo and Dohoo, 1996). Butorphanol is an opioid agonist at κ receptors and a partial antagonist at μ receptors (Aarnes and Muir, 2011). It provides moderate pain relief. The sedative and analgesic properties of butorphanol are due to its agonist property at κ receptors (Deutsch *et al*., 2017). Butorphanol also reduces the doses of other drugs if used in combination with it for induction and maintenance of anesthesia. As it was reported by Ansah *et al*. (2002) butorphanol provides better analgesia postoperatively in cats that undergo ovariohysterectomy when compared with medetomidine for analgesic activity. It also produces a moderate type of sedation postoperatively, which allows adequate muscular activity and prevents vigorous reaction at the same time. However, in the present study, the combinations of butorphanol with other drugs were not studied.

In the present study, butorphanol provided short-term pain relief; this could be due to its shorter half-life. Similar findings were also reported by Taylor *et al*. (2010) that the onset of butorphanol is rapid and the duration of action is relatively shorter in comparison with other opioids. Similarly, it was reported by Niedfeldt and Robertson (2006), that butorphanol is a partial agonist at kappa receptors; it rapidly reaches a ceiling effect and also has a short half-life. Similar findings were also reported by Gellasch *et al*. (2002) that the analgesic activity of butorphanol is relatively shorter and requires multiple doses at different intervals to lengthen its analgesic efficacy. Because of its shorter duration, the blood concentration of glucose can be increased in cats receiving butorphanol postoperatively due to pain and stress. As it was reported by Rand *et al*. (2002) acute stress can be seen in cats that undergo surgical manipulation and hyperglycemia can be observed when they are under acute stress. Similar findings were also recorded in the present study, as the blood glucose level was high in the butorphanol group. This increase in glucose level could be due to the stress associated with pain. As it was reported by Semick *et al*. (2018) cats are prone to developing stress-associated increased glucose levels. Moreover, the postoperative increase in glucose level could also be due to stress, which triggers the release of glucagon and reduces the secretions of insulin (Semick *et al*., 2017). It was also reported by Szabo *et al*. (2000) that an increase in glucose levels was observed in cats after ovariohysterectomy. Additionally, pain can change several neuroendocrine axes, which can result in an increase in serum cortisol levels as well as glucose levels.

The measurement of serum cortisol levels is used as an indicator of pain in many species (Heo *et al*., 2018). Cortisol stimulates tissue protein breakdown, increases the production of glucose, and increases the sensitivity of blood vessels toward adrenaline, which results in increased blood pressure and heart rate (Kamgang *et al*., 2023). The concentration of glucose and cortisol is a major indicator of pain due to surgical trauma (Freeman *et al*., 2010). The concentration of cortisol starts to increase at the start of surgery and continues to do so as it reaches its peak levels at 4-6 h postoperatively. It was reported by Taylor *et al*. (2010) that cats treated with buprenorphine had lower pain scores in comparison with butorphanol at 2 and 24 h postoperatively. Similar findings were also recorded in the present study, as cortisol levels as well as the behavioral parameter scores were low in cats treated with buprenorphine in comparison with butorphanol. Similarly, it was reported by Dobbins *et al*. (2002) that buprenorphine showed low serum cortisol levels and cumulative pain scores after sterilization in cats.

In the present study, the need for rescue analgesia was also used to evaluate the efficacy of postoperative analgesia. The cumulative pain score of 6 or greater is used to determine the need for rescue analgesia. It was demonstrated that butorphanol doesn't provide proper postoperative analgesia following ovariohysterectomy in cats and requires rescue analgesia. However, the pain scores were lower in cats treated with buprenorphine even after 9 h of ovariohysterectomy. So, buprenorphine provided better and longer postoperative analgesia than butorphanol. Similar findings were also reported by Taylor *et al*. (2010) that buprenorphine provides better and longer analgesia in comparison with butorphanol. There were some limitations of this study, such as a small sample size, a short surgical procedure, and the absence of measurement of thermal threshold level.

CONCLUSION

In conclusion, the outcome of this study shows that the postoperative pain after ovariohysterectomy in cats can be reduced by using a postoperative analgesic, and in cats that are undergoing any surgical procedure, buprenorphine can be used to control postoperative pain.

DECLARATIONS

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IRB approval

The study protocol was approved in accordance with institutional guidelines by ethical review committee of University of Veterinary and Animal Sciences (UVAS), Lahore.

Ethical considerations

This study was approved by the ethical committee, Directorate of Advanced Studies, UVAS Lahore.

Generative AI and AI-assisted technology statement

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

Statement of conflict of interest

The authors have declared no conflict of interest.

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