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Comparison of analgesic effects of medetomidine and meloxicam in pain control after ovariectomy in cats

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Abstract

In small animal practice, various medications are used for postoperative pain management, with NSAIDs and alpha-2 adrenergic drugs being commonly employed. This study aimed to compare the efficacy of these medications in relieving postoperative pain following ovariectomy in cats. In this study, eleven healthy adult female cats were anesthetized for traditional midline ovariectomy and randomly administered either 0.2 mg/kg of IV Meloxicam (MLX) or 20 µg/kg of IV medetomidine (MED). Parameters including serum cortisol and glucose levels, pain scores using the Unesp-Botucatu Multidimensional Pain Scale (UMPS) method, anesthesia duration, blood pressure, and hemoglobin oxygen saturation (SpO_2) were measured before the surgery and at 1, 2, 4, 6, and 24 hours post-surgery. All cats experienced pain, with the highest pain score recorded 3 hours post-surgery. Although the median pain score at this time point was higher in the MLX group than in the MED group, the difference was insignificant. The median serum glucose level peaked at two hour-post-surgery, significantly correlating with UMPS pain scores. Anesthesia duration was significantly lower in the MLX group, and the serum cortisol level in the MED group was significantly higher than in the MLX group at the 2-hour mark post-surgery. No significant difference in SpO_2 changes was observed between the two groups. In conclusion, both Meloxicam and medetomidine are equally effective in alleviating post-ovariectomy pain in cats. However, due to their shorter anesthesia duration, Meloxicam may be the preferable choice for pain management in ovariectomy surgery. Furthermore, blood glucose levels can serve as a reliable pain indicator in cats, along with other biochemical markers.

1. Introduction

Surgery is known as an effective treatment method in many diseases and complicated disorders in veterinary medicine (Venugopalan 2020). However, this method can act as a double-edged sword and lead to provoking a series of cellular and immunological reactions in the body, which ultimately cause pain (Steagall et al. 2021). Upon surgery, the body experiences tissue damage which triggers the release of histamine and inflammatory mediators, including peptides (*e.g.* bradykinin), lipids (*e.g.* prostaglandins), neurotransmitters (*e.g.* serotonin), and neurotrophins as nerve growth factor (Venugopalan 2020). The release of these mediators activates peripheral pain receptors, leading to the perception of pain in the affected animal. If the pain is not relieved, it can result in self castigation. Post-operative pain, which is categorized as acute pain, can have various negative effects on the body, such as delaying in the wound healing process, increasing the risk of wound infection and tumor metastasis, and the elevated tissue metabolism. Altogether, these consequences can prolong the post-operative recovery period for the patient (Dugdale et al. 2020).

The significance of pain control post-surgery is underscored in scientific writings, emphasizing the necessity of a suitable analgesic plan in pre-anesthesia protocols, including pre-emptive analgesia, which aims to minimize pain perception and enhance overall recovery by administering analgesics before the onset of surgical pain. It is considered advantageous to prescribe a combination of medications from different pharmacological classes for anesthesia induction. This strategy not only ensures pain relief during and after the surgical procedure but also aids in decreasing the amount of anesthetic drugs needed, thereby lowering the potential side effects associated with anesthesia (Lee et al. 2015; Raayat Jahromi et al. 2016). Various methods and medications are employed to alleviate post-operative pain, including local anesthetics, steroidal anti-inflammatory drugs (SAIDs), non-steroidal anti-inflammatory drugs (NSAIDs), alpha-2 receptor agonists, and narcotic analgesics. Each of these pain-relieving agents carries the potential for specific and limited pain relief. Narcotic painkillers known as opioids are currently recognized as the most potent pain relievers in veterinary medicine, commonly utilized for both acute and chronic pain management (Sandilands and Bateman 2016). Nevertheless, the use of these drugs is associated with side effects such as respiratory depression, hypotension, and abnormal behavior in certain species, leading to restrictions in their prescription (Bley et al. 2004; Robertson and Taylor 2004; Tavakoli et al. 2012). Consequently, there is a continuous endeavor to explore alternative drug classes to mitigate these limitations.

In veterinary medicine, NSAIDs are widely used as analgesic drugs, particularly cyclooxygenase 2 (COX-2) inhibitors (Borer et al. 2017; Knych 2017; Monteiro-Steagall et al. 2013). This subgroup is favored for its more precise action and reduced risk of gastrointestinal and renal complications, compared to other subgroups within this drug family (Borer et al. 2017). Recent researches have highlighted the role of the COX-2 enzyme in inflammatory processes, without involvement in the production of prostaglandins (PGs) essential for physiological functions, unlike the COX-1 enzyme (Esmaeeli et al. 2016). Meloxicam (MLX), a COX-2 inhibitor, is recognized for its potent anti-inflammatory properties, which inhibit the synthesis of PGs responsible for pain and inflammation, with well-established efficacy in dogs and cats (Borer et al. 2017; Mathews et al. 2015; Merema et al. 2017; Vesal and Foroud 2015). Alpha-2 adrenergic receptor agonist drugs are commonly used in pre-anesthesia protocols for their sedative and hypnotic properties. By targeting these receptors in the brain cortical layer, brainstem, and spinal cord, these medications also provide analgesic effects. Medetomidine (MED), a novel drug in this class, exhibits a stronger and more specific binding to alpha-2 receptors compared to older sibling, xylazine (Talukder and Hikasa 2009). This enhanced affinity makes MED a preferred choice over xylazine in small animal medicine, particularly when combined with other agents such as ketamine for inducing sedation or pre-anesthesia in dogs, cats, and even exotic species like rabbits and African lions (Semjonov et al. 2017; Weiland et al. 2017). Furthermore, apart from the aforementioned benefits associated with the above drug categories, the inappropriate utilization of NSAIDs may result in adverse reactions including vomiting, diarrhea, loss of appetite, fatigue, and dark feces (Monteiro-Steagall et al. 2013). Similarly, investigations have indicated that the administration of MED may be occasionally linked to unfavorable side effects such as pulmonary edema (in felines), bradycardia, hypotension, heightened cardiac output, and diminished body temperature (Schaer 2022; Sinclair 2003).

Ovariectomy, a frequently performed surgical procedure in female animal species, induces a level of mild to moderate postoperative pain. This surgical technique is commonly employed in research settings to elicit consistent and measurable postoperative pain in various animals (Katic and Dupre 2017). The present study aimed to investigate the potential superiority, for clinical administration, of two drugs, namely MED as an Alpha-2 adrenergic receptor agonist and MLX as a NSAID drug after ovariectomy surgery in cats and the induction of moderate pain relief.

2. Materials and Methods

2.1. Preparation of animals before surgery

A group of 11 mixed-breed female DSH cats were selected and relocated to a specialized housing facility in the Faculty of Veterinary Medicine, Islamic Azad University, Garmsar Branch. Following a comprehensive examination, no health issues were detected in any of the subjects. To ensure the successful adaptation of the cats to the new environment and to minimize stress factors that could potentially bias the research data, a 2-week acclimatization period was implemented before the initiation of the surgical procedures. During this period, the cats were provided with comfortable bedding, regular interactions with caregivers, and a stable and quiet environment to promote their well-being. Additionally, gradual exposure to handling and socialization techniques was employed to help the cats become accustomed to human presence. At the time of surgery, the abdominal surface of the animals was clipped, and a venous catheter was inserted.

2.2. Measurement of vital parameters and data collection

Pain intensity following surgery was assessed utilizing the Unesp-Botucatu Multidimensional Pain Scale (UMPS) technique in this investigation. The UMPS method involves evaluating various physiological and behavioral indicators of animals both pre- and post-surgery. These indicators include pupil status, heart rate, respiration rate, body temperature, salivary flow, alterations in behavior, physical state of the animal post-surgery, and the animal's response to contact with the surgical site. Subsequently, a score was assigned based on the degree of change in each indicator, yielding a pain intensity score ranging from 3 to 21. The study aimed to investigate the impact of MED and MLX on the cardiovascular system of cats by measuring blood pressure parameters and hemoglobin oxygen saturation percentage (SpO_2). Blood pressure was assessed using an indirect method and a digital sphygmomanometer, while SpO_2 was measured with a handheld pulse oximeter (Solaris Medical Technology, US). Prior to transferring the cats to the surgical department, a blood sample was taken and relevant physiological data were collected at baseline to mitigate stress. Also, blood samples were collected from cats at various time points post-surgery to assess serum glucose and cortisol levels. Each sample (3 ml) was drawn from the cephalic vein. The samples were then transferred to glass test tubes without anticoagulant and left undisturbed for 13 minutes at room temperature to allow clot formation. Subsequently, the test tubes were centrifuged (1113 rpm, 11 min) to separate the serum. The separated sera were then aliquoted into 2 ml microtubes, labeled, and stored in a freezer. For further analysis, the samples were sent to the Razi medical diagnosis laboratory. The results obtained were documented in the pre-designed forms. A limited number of personnel were employed throughout the study to ensure consistency and accuracy of results, which were then recorded systematically.

2.3. Anesthetizing the cats

After weighing, a pre-anesthesia protocol was followed for each cat involving the intramuscular (IM) administration of acepromazine (1.13 mg/kg). Prophylactic antibiotics were administered with 1 g cefazolin (22 mg/kg) in all cats undergoing surgery, and the antibiotic treatment was discontinued one week after the surgery. Anesthesia induction was achieved through IV administration of ketamine (6.5 mg/kg) and midazolam (0.2 mg/kg), with the time of induction being documented in a specialized form. The cats undergoing surgery were randomly assigned to either the MLX or MED groups. Following anesthesia induction, MLX (1.2 mg/kg) and MED (21 μg/kg) were administered intravenously to the respective groups at the time of surgery during the study.

2.4. Ovariectomy surgical operation

Following the administration of anesthesia, the animal undergoing surgery was positioned on the operating table in a supine orientation. The surgical site on the abdomen was initially disinfected with betadine scrub solution and dried using a sterile swab. Subsequently, the area was stained and prepped with an 11% betadine solution. The primary surgical procedure was executed utilizing the midline approach. Initially, a scalpel blade number 15 was employed to create a cutaneous incision (20 to 25 mm) on the skin surface, slightly posterior to the umbilical scar. Subsequently, the linea alba was incised using curved metzenbaum scissors, followed by cutting the peritoneal membrane, enabling access to the peritoneal cavity. Using a specialized sterile hook, each uterine horn was initially located and then ovaries were taken out from the abdominal cavity. By cutting the associated suspensory ligament, the ovary was exposed. Subsequently, an incision was made in the broad uterine ligament near the base of the ovary. Hemostat forceps were employed, and the vessels were ligated using an absorbable synthetic polyglycolic acid thread No. 2, suitable for the average body weight of the cats (approximately 4 kg), and the base was then cut using scissors. Moving forward, the connection between the ovary and the uterine horn was ligated with the same suture thread, ensuring the complete removal of the ovary. After confirming the absence of any bleeding at the base of the ovary and the uterine horn, they were carefully returned to the abdominal cavity.

Following the removal of all ovarian structures and associated tissues from the abdominal cavity, the surgical incision was meticulously closed in three layers, as described below: The muscular layer was precisely sutured using polyglycolic acid 1-1, an absorbable synthetic thread, using a simple continuous pattern. Subsequently, the subcutaneous layer was closed with polyglycolic acid absorbable synthetic thread No.1-3 by a simple continuous pattern. Finally, the skin was sutured with non-absorbable nylon synthetic suture 1-3, employing a simple interrupted pattern. The end of surgery time was recorded upon the final skin suture and a specialized elastic dressing was applied to cover the surgical wound. Post-surgery, the cat was kept in a specific location and closely monitored until complete recovery. Upon the onset of voluntary movements trying to reach the sternal posture, the time was recorded and the duration of anesthesia was determined. Subsequent evaluations were carried out 1-hour, 2-hour, 4-hour, 6-hour, and 24-hour after the surgery. After regaining consciousness, the animal was returned to the holding place and only water was given until 24 hours after the operation to prevent any disturbances in the results of the glucose measurement. After collecting the data from all 11 examined cats in specific forms, it was subjected to descriptive statistical analysis and ANOVA test.

3. Results

3.1. Pain score evaluation

Among experimental groups, the calculated pain score in MLX group was evaluated as statistically non-significant between 2 and 6 hours ($P = 0.5640$), and significant for 2 and 4 h ($P = 0.0361$), 2 and 24 h ($P = 0.0160$), as well as zero and 2 h ($P = 0.0160$) post-operation. In MED group, the estimated pain score was statistically significant between zero and 2 ($P = 0.0080$), zero and 4 ($P = 0.0088$), zero and 6 ($P = 0.0086$), as well as 6 and 24 h post-operation ($P = 0.0439$). Examination of the pain score in the cats studied demonstrated that the cats experienced the highest pain score based on the UMPS method 2 hours post-operation. Despite the higher pain score in the MLX group compared to the MED group at this time, statistical analysis using the Mann-Whitney test indicated that the difference in pain scores between the two groups was not statistically significant. In the comparison of pain score in other hours, no significant difference was observed between the two groups (Fig. 1).

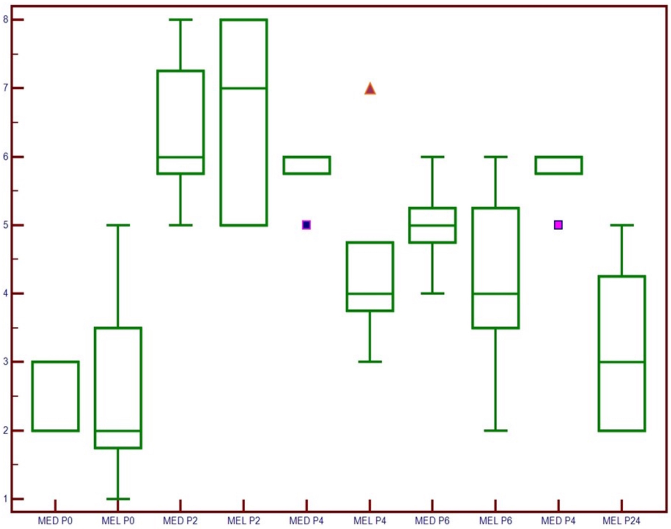

Fig. 1. Comparison of mean pain scores between the two groups

3.2. Heart rate evaluation

A statistically significant association was found in heart rate changes in MLX and MED groups between 2 hours post-operation and 0, 4, 6, and 24 hours after surgery. Moreover, a remarkable correlation was demonstrated between zero and 4 hours after ovariectomy in MED group. Examination of heart rate fluctuations in the cats examined indicated that the most pronounced changes in heart rate, as determined by the UMPS method, were observed six hours after the surgical procedure. While heart rate changes were more prominent in the MED group than the MLX group at this time point, statistical analysis disclosed that the difference in heart rate changes between the two groups was not statistically significant (Fig. 2).

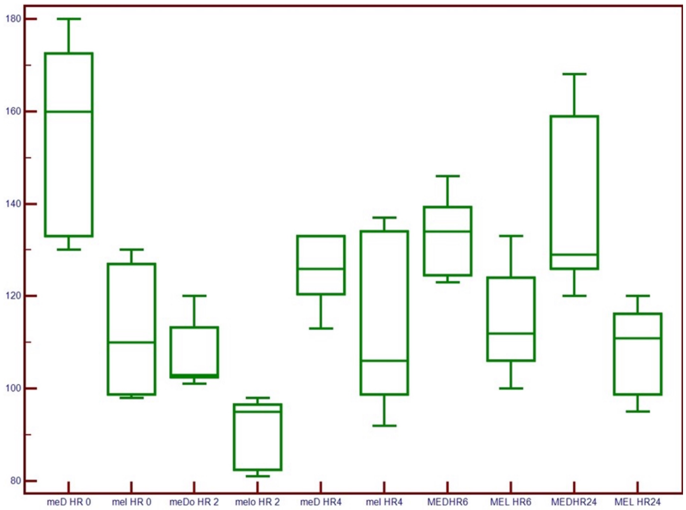

Fig. 2. Comparison of mean heart rate changes between the two groups

3.3. Serum cortisol hormone assessment

The results pertaining to the serum cortisol concentration in both groups indicated that the highest changes in cortisol levels were observed 2 hours after the surgery (Fig. 3). However, the MED group exhibited higher serum cortisol levels than the MLX group at this time, a statistical comparison revealed that the difference was not statistically significant ($P = 0.4647$). Additionally, there were no significant variations in cortisol levels between the two groups at other time intervals ($P > 0.05$).

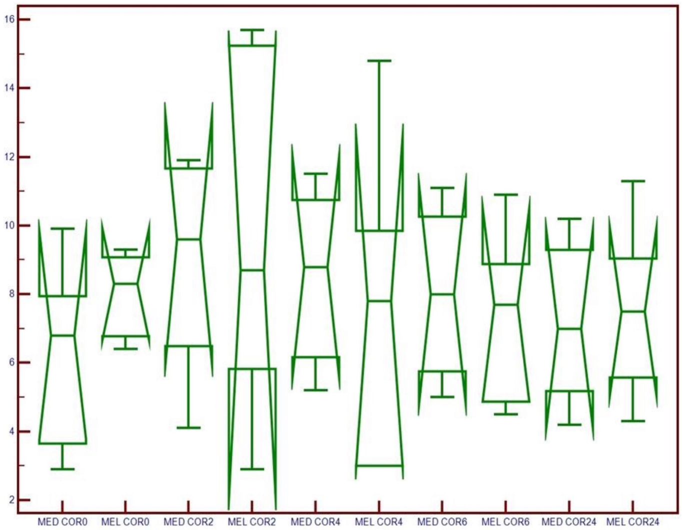

Fig. 3. Comparison of mean serum cortisol concentration between the two groups

3.4. Serum glucose assessment

The inter-group comparison highlighted that the serum glucose concentration peaked two hours after the operation in both groups (Fig. 4). A higher serum glucose concentration was detected in the MED group than in the MLX group 2 hour after operation, while the glucose concentration was not deemed significantly different between the groups ($P = 0.5309$).

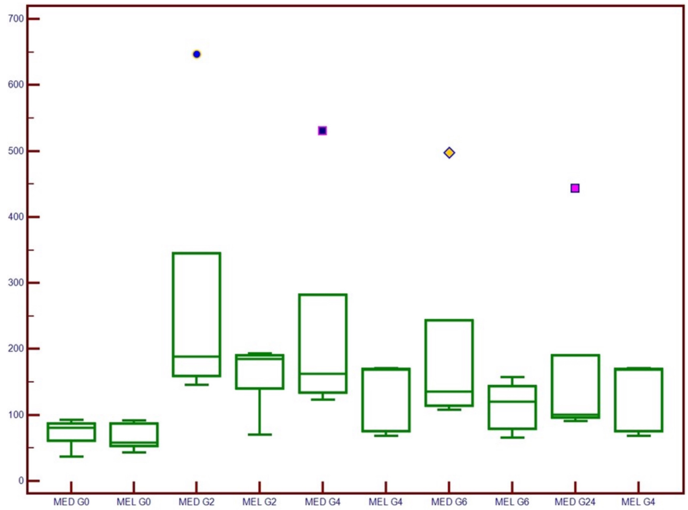

Fig. 4. Comparison of mean glucose concentration between the two groups

3.5. Blood pressure changes

The comparison of groups indicated that the blood pressure changes were most evident in both groups 24 hours following the operation. During this period, alterations in the blood pressure in both groups mirrored each other, showing statistically significant changes, whereas in other time periods changes were not statistically significant ($P = 0.9035$).

3.6. Changes in hemoglobin oxygen saturation percentage

At 2 hours after the operation, the lowest recorded SpO2 levels for the MLX and MED groups were 96% and 87%, respectively. Overall, measuring SpO2 at different time points and comparing the two groups did not indicate any noteworthy change ($P > 0.05$).

3.7. Duration of anesthesia

In this study, the duration of anesthesia was assessed by determining the time interval between the administration of the anesthetic drug and the animal's placement in the sternal position. The results demonstrated a noteworthy difference in the duration of anesthesia between both groups (Fig. 5). The mean duration of anesthesia was significantly longer in the MED group (mean time: 150 minutes) compared to the MLX group (mean time: 90 minutes) ($P = 0.03$).

3.8. Correlation between different parameters

The studies conducted revealed a significant relationship between changes in pain levels and blood glucose levels in the

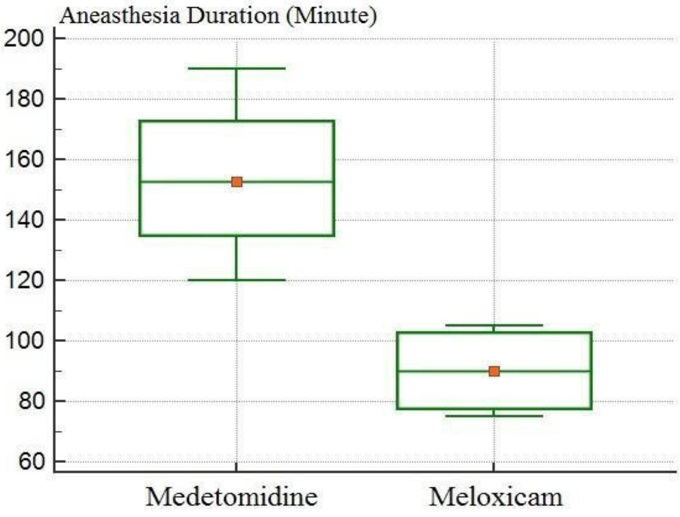

Fig. 5. Comparison of mean duration of anesthesia between the two groups

MLX group (P = 0.04), while it was not evident in the MED group (P = 0.2099). Additionally, it was determined that changes in pain levels exhibited a significant correlation with the SpO_2 in the MLX group (P = 0.01), whereas no such correlation was found in the MED group (P = 0.6885).

4. Discussion

Postoperative pain is an indispensable feeling due to any surgical intervention, with varying intensity based on the extent of tissue damage. Neglecting to manage this pain could result in a range of undesirable consequences compromising the patient's mental and physical health, including delayed wound healing, increased susceptibility to wound infection, enhanced potential for tumor metastasis, disturbances in the cardiovascular system, alterations in tissue metabolism, and ultimately protracted recovery duration. Appropriate sedatives with maximum efficiency and minimum side effects seem to be necessary in pain postoperative pain control (Beckman 2013). In the present study, the analgesic effect against pain induced by ovariectomy surgery in 11 domestic cats in Tehran was investigated by MLX and MED drugs.

A non-steroidal anti-inflammatory drug, MLX, is often recommended for managing post-surgical pain in small animals due to its ability to reduce pain and fever. This medication performs by inhibiting the COX enzyme, playing a crucial role in converting arachidonic acid to prostaglandin H_2, the initial step in the synthesis of inflammatory mediators known as PGs (Charlton et al. 2013). Another used drug of alpha-2 adrenergic compounds group is a racemic compound of two isomers (dexmedtomidine and levomedtomidine) named MED having proper sedative effects at dose rate of 1-2 μg/kg only. The recommended dose for a single injection in cats is 1-20 μg/kg by IM or IV injection (Ansah et al. 2002; Cullen 1996). The reliable assessment of pain in small animals often involves measuring the concentration of serum cortisol, as any induced stress causes the activation of the hypothalamus-pituitary-adrenal axis (Sinclair 2003; Tallant et al. 2016). This activation leads to a significant increase in the secretion of cortisol hormone from the adrenal cortex. The UMPS method was invented initially in 1955 at the University of Melbourne and its adequacy in measuring animal pain has been accepted (Afshar et al. 2017). Considering that acepromazine, ketamine, and midazolam drugs were used only once in all cats for anesthesia induction, it was expected that they might have similar results in the two studied groups without any involvement in visceral analgesics.

In the current investigation, a comparison was made between the pain scores obtained from measuring pain in two distinct groups using the UMPS method. Based on the findings, 2 hours post-operation, the cats in the MED group exhibited lower pain scores compared to the MLX group, however, differences were statically non-significant. Consequently, it could be inferred that both drugs possessed comparable analgesic effects in controlling pain after ovariectomy in cats. The highest pain score was experienced by cats 2 hours after surgery, similar to the previous studies (Slingsby and Waterman-Pearson 2000; Tavakoli et al. 2012). Different time intervals (2, 4, and 6 hours post-operation) for both groups were used to evaluate serum cortisol hormone. The highest serum cortisol concentrations were recorded 2 hours post-operation in both MLX and MED groups; in addition, in both study groups, the level of cortisol hormone 24 hours following operation was not significantly different from the baseline level, suggesting that along with the significant reduction in pain score after 24 hours, no significant pain was sensed by cats after this period. In total, the MED group exhibited higher serum cortisol levels compared to the MLX group, which could be attributed to the distribution of alpha-2 receptors in the endocrine glands. The administration of MED has caused the stimulation of alpha-2 receptors in the cortical part of the adrenal gland and this has caused an increase in the amount of cortisol in the MED group.

The normal blood glucose level in cats is 110-120 mg/dL using the glucose oxidase method. Cortisol is a glucocorticoid with potent effects on the metabolism of carbohydrates and promoting liver gluconeogenesis. Both of these processes ultimately increase blood sugar and hyperglycemia occurs (Barbarossa et al. 2017). Therefore, due to the increase in cortisol hormone following the presence of pain, it was expected that the subsequent increase in blood sugar could also be used as a pain measurement index. The highest glucose levels were detected in sera of the examined cats in Tehran 2 hours following surgery, particularly in MED group, while no significant difference was observed between groups. Similar trend was shown in other time periods. This could be due to the effect of MED on alpha-2 receptors in the pancreatic beta cells and inhibition of insulin secretion (Sinclair 2003; Tallant et al. 2016).

The correlation evaluation revealed a very significant association between glucose level changes and pain score in MLX group. Both parameters reached peak at 2 hours post-surgical intervention, suggesting that measuring blood glucose levels can serve as a suitable indicator for evaluating pain after ovariectomy in cats. In contrast to the results of this study, Tavakoli et al. (2012) did not find a significant correlation between glucose changes and pain score using the VAS method in cats. The examination of blood pressure changes in both groups showed no significant difference in both groups. The normal range of SpO_2 in cats is typically between 95% and 100%, with levels below 90% indicating potential hypoxia. In the present study, most of the cats experienced SpO_2 levels below 90%, with some even dropping to levels indicating mild to moderate hypoxia, with no statistically remarkable difference between groups. This finding emphasized that both drugs caused a decrease in hemoglobin oxygen level in spite of their analgesic properties. During periods of pain, alterations in the animal breathing pattern lead to changes in the SpO_2 levels, resulting in the patient experiencing varying degrees of hypoxia. Ko et al. (2000) showed that administration of a combination of ketamine and MED did not significantly reduce respiratory rate or depth, thus providing an effective sedative. Similarly, Weiland et al. (2017) demonstrated that the use of ketamine and MED for anesthesia induction in rabbits was successful and did not pose any complications to the vital organs. It was observed that the combination of MED and ketamine resulted in slower anesthesia induction and recovery, as well as reduced cardiac and respiratory fluctuations compared to the midazolam and ketamine combination. In this study, the MED group displayed a significantly longer duration of anesthesia compared to the MLX group. This finding could be attributed to the impact of MED on alpha-2 receptors in the central nervous system, which results in a reduction in norepinephrine release and subsequently leads to sedation and drowsiness. However, it was important to note that there is a lack of specific research comparing the duration of anesthesia between MED drug and NSAIDs.

5. Conclusions

Based on the findings, the pain score 2 hours post-operation in the MLX group slightly exceeded that of the MED group; however, not statistically significant, especially when considering the shorter time periods post-surgery. The duration of anesthesia in the MLX group was significantly different compared to the MED group. Furthermore, the reduced impact of MLX on the heart rate fluctuations in contrast to MED, along with the comparable risk of respiratory complications and hypoxia between the two drugs, suggests that MLX may be the preferred choice. Nevertheless, the overall results suggested that both MED and MLX drugs exhibited similar efficacy in managing pain following ovariectomy surgery in female mixed-breed cats in Tehran, Iran.

Declarations

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