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Comparison of Postoperative Analgesic Effects of Medetomidine-Ketamine, Isoflurane and Medetomidine-Butorphanol, Isoflurane Combinations in Anesthesia for Ovariohysterectomy in Cats

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Abstract
Mild to moderate pain occurs after spaying in cats. Pain is a condition that must be treated. Analgesics can be used alone or in combination to achieve more effective results. The aim of this study is to compare the postoperative analgesic effects of combinations of medetomidine, ketamine, isoflurane, meloxicam and medetomidine, butorphanol, isoflurane, meloxicam in cats undergoing ovariohysterectomy surgery. The study material consisted of healthy female cats (n=20) of various breeds and at least 6 months of age. All cats received pre-anesthetic medetomidine at a dose of 80 µg kg^{-1} intramuscularly, with the first group receiving ketamine 0.5 mg kg^{-1} subcutaneously as an analgesic, and the second group receiving 0.4 mg kg^{-1} subcutaneously of butorphanol. Anesthesia induction (5%) and maintenance (2%) were provided by inhalation anesthesia (isoflurane). The incision was made in the middle third of the area, divided into three parts between the navel and the pubis. To measure the differences in pain between the groups formed after the operation, the heart rate, respiratory rate, and body temperature of the cats were measured at postoperative 0, 1, 2, 3, 4, 6, and 12 hours, and their body language was evaluated according to the 'Colorado State University Feline Acute Pain Scale'. Pain scores were found to be higher in the butorphanol group than in the ketamine group at postoperative hours one and two. While heart rate and body temperature values between the groups were similar, respiratory rates differed among the groups. These findings suggest that subanesthetic/analgesic doses of ketamine are more potent in postoperative pain management of infertility compared to analgesic doses of butorphanol.

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1. Introduction

The ovariohysterectomy operation in cats is generally performed by laparotomy, where the ovaries and uterus are removed, and the incision is closed with several layers of sutures (Murugesan et al., 2020). Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Animals experience sensory experiences that alter their biochemistry, physiological parameters, and behaviors in response to painful stimuli, and they try to avoid such stimuli in the future (Landa, 2012). According to studies on pain, pain has negative effects on animals, such as increasing susceptibility to infection and slowing wound healing. Therefore, recognizing pain is extremely important (Hekman et al., 2012). Objective measurements such as heart rate, arterial blood pressure, plasma cortisol, and catecholamine levels have been associated with acute pain; however, it should be noted that stress, fear, and anesthetic drugs affect these measurements. Therefore, pain assessment is primarily subjective and based on behavioral signs (Mathews et al., 2014). Ketamine is used in acute pain conditions including traumatic injury and surgical interventions to increase the analgesia provided by traditional analgesics, reduce relaxation and central sensitization, and potentially reduce the development of chronic pain conditions (Egger et al., 2013). The dose range of ketamine that can be used as an analgesic for cats is 0.1-1 mg kg^{-1} subcutaneously, intravenously, and intramuscularly (Lamont, 2002). Ketamine is most effective when administered before nociceptive stimulation and continued throughout the duration of the stimulus (Nagasaka et al., 2000). Ketamine does not block acute nociceptive input, but prevents the formation of central stimulation. Ketamine provides analgesia in the postoperative period as a bolus or constant-rate infusion and has no side effects at subanesthetic doses (Bell et al., 2006). Before presenting any discussion on different pain control models, it should be discussed how to assess the pain level of patients. Today, there are many assessment methods available, and none are perfect. Different tolerances and expectations regarding patients' pain experiences exist, and a pain level of 5 out of 10 generally has different effects for different people, making pain assessment in animals much more challenging than in humans. Therefore, understanding how animals show pain is crucial for knowing when and how to treat the patient (Fossum, 2012). To perform proper pain management, it is essential to observe patients behaviorally along with examination results such as body temperature, respiratory pattern, and pulse rate. It is reasonable to assume that cat-friendly approach techniques and a quiet, clean, and warm environment may help improve the emotional aspect of pain. The cognitive aspect of pain arises from previous experiences or knowledge. For these reasons, accurately assessing pain in cats is difficult. Monitoring cortisol concentrations due to increased pain is not always practical in a clinical setting. Pain assessment in cats is generally done by observing subjective behavioral changes. Dynamic and interactive responses to the cat (response to palpation) can provide the best assessment. However, resting cats should not be disturbed for pain assessment. Distinguishing between pain and dysphoria in cats can be challenging. Dysphoria is often associated with high doses of opioids. An analgesic intervention can be applied to differentiate between pain and dysphoria; a decrease in observed behaviors indicates the presence of pain, while no change or worsening of behaviors suggests dysphoria (Steagall, 2019). The Colorado State University Acute Pain Scale is designed as a user-friendly scale with verbal and visual descriptions. It is the first scale designed to address the feline population. It is a numerical scale from 0 to 4 and includes both observational and applied sections. A section is also included to assess body tension (Fossum, 2012). Palpation of the incision area is known to be a significant indicator in assessing pain (Al-Gizawiy and Rude, 2004). The Colorado State University Acute Pain Scale includes a section on palpation of the incision area, which distinguishes it from most other pain scales.

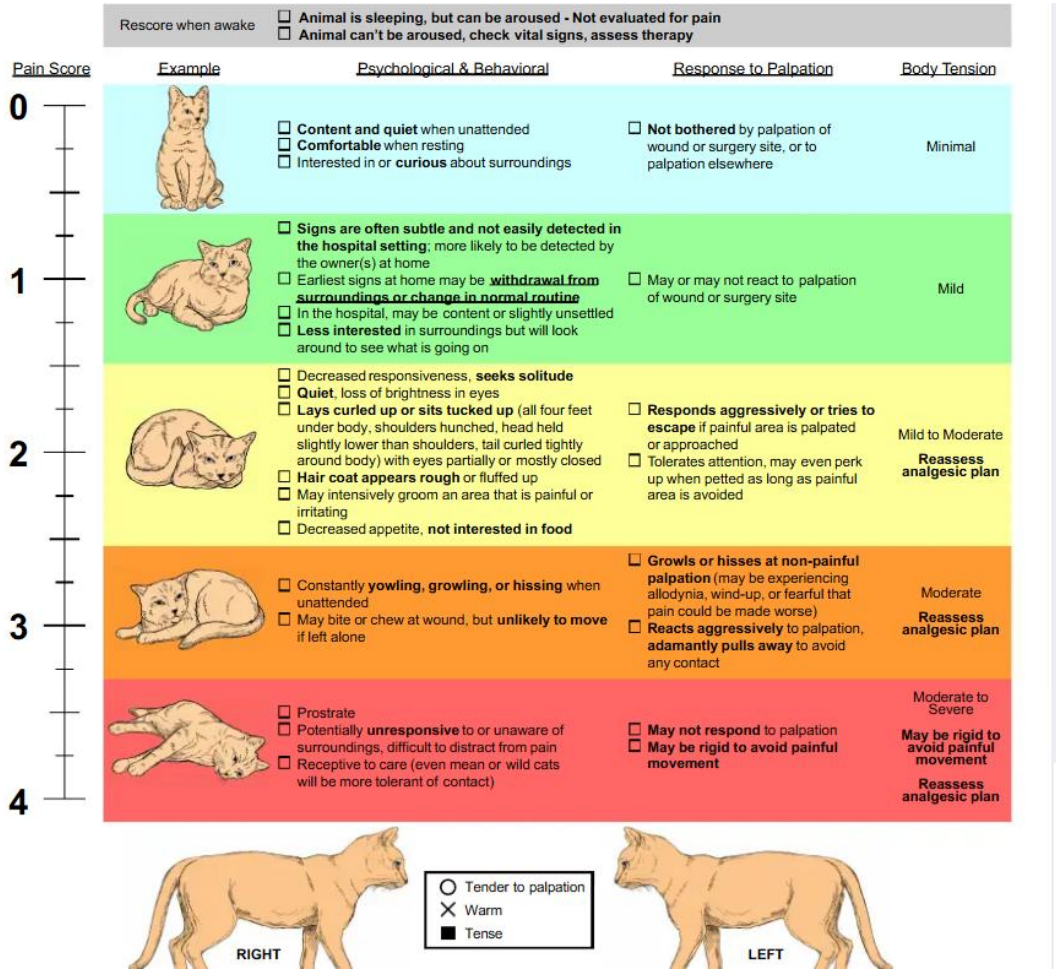

Figure 1. Colorado State University Medical Center Cat Acute Pain Scale (Gaynor, 2015).

2. Material and Methods

In the first group (n=10), medetomidine (80 µg kg^{-1}) (Zoetis, Domitor 1 mg ml^{-1}) was administered intramuscularly for premedication, followed by induction (5%) (mask) and maintenance (2%) (endotracheal intübation) of anesthesia using inhalation anesthesia (isoflurane), and butorphanol (0.4 mg kg^{-1}, subcutaneous) (Richterpharma, Butamidor 10 mg ml^{-1}) was administered as an analgesic (Slingsby, 2000). In another group, medetomidine (80 µg kg^{-1}) was administered intramuscularly, and induction (5%) (mask) and maintenance (2%) (endotracheal intübation) of anesthesia were provided using inhalation anesthesia (isoflurane), with ketamine (0.5 mg kg^{-1}, subcutaneous) (Richterpharma, Ketasol 100 mg ml^{-1}) administered to perform the ovariohysterectomy operation (Mathew, 2014; Koç, 2021). Cats were placed in a dorsal recumbent position for the operation. The length of the ventral midline abdominal incision depends on the size of the animal. The distance between the navel and the pubis is divided into three parts. The incision is made from the middle third. However, the length of the incision must be sufficient to visualize intra-abdominal structures and perform the procedure safely. The ovaries are usually removed without the need to rupture the suspensory ligament. The uterus is located by using a uterine hook or a finger and is exteriorized. The uterus is followed cranially to locate the ovaries. A double ligature is placed on the cranial artery and ligament of the ovary. The tissue is cut caudal to the ligatures, and the procedure is repeated for the other horn. The uterus is followed to locate the cervix, which is ligated, and the uterus and ovaries are completely removed. The linea

alba, subcutaneous tissues, and skin are closed with appropriate sutures, and meloxicam (Bavet, Meloxicam, 5 mg ml^{-1}) is administered subcutaneously at a dose of 0.2 mg kg^{-1} as an analgesic (Monnet, 2013). During the operation, the cats' pulse, oxygen saturation and body temperature values were monitored with the HASVET 838 PM bedside monitor. In order to measure the differences in postoperative pain between the groups, the cats' heart rate, respiratory rate and body temperature will be measured at 0, 1, 2, 3, 4, 6 and 12 hours postoperatively, and their body language will be evaluated by the same veterinarian according to the 'Colorado State University Feline Acute Pain Scale'. The veterinarian assessing pain scores was blinded to the treatment groups (double-blinded assessment) to eliminate observer bias.

2.1 Statistical analysis

The obtained results will be analyzed using Kruskal Wallis for intergroup differences, and the statistics of the differences between hours within groups will be analyzed using Analysis of Variance (ANOVA) (IBM SPSS Statistics 26). Data will be presented in table format as mean (standard deviation) ($\bar{x}$ ($S\bar{x}$)). Results with ($P<0.05$) in tests conducted within and between groups will be interpreted as significant (Er, 2019). Since ovariohysterectomy is known to be a painful procedure requiring analgesia, a negative control group was not included in the study for ethical reasons (Warne, 2014).

3. Results and Discussion

No patient responded to palpation; there was no abdominal defense. Only a patient in the butorphanol group (patient 3) was squinting its one eye at postoperative hours 1 and 2 and displayed passive-aggressive behavior by not wanting to allow examination; however, there was no abdominal defense or sensitivity in the suture area. In the ketamine group, patients 12 and 13 had such a high level of fear that efficient observation could not be conducted. Observations made before and after the operation indicated that the pain level might be too low to be clinically understood. In the butorphanol group, patient 1 attempted to escape from the observer and examination at postoperative hour 1, trying to hide the wound area, but there was no sensitivity or response during palpation of the abdominal defense or suture area.

3.1. Pain scores difference between hours

The differences in pain scores within the butorphanol group are significant ($P<0.05$). Significantly more pain was observed in the postoperative first hour compared to other hours ($P<0.05$). There was no significant difference between other hours ($P>0.05$). Pain scores of patients in the postoperative first and second hours were significantly different from those in other hours. Ketamine provided better analgesia compared to butorphanol in the first ($P=0.34$) and second ($P=0.31$) hours.

Table 1. Interpretation of Pain Degree Intra-Group and Inter-Group Statistics Results

	Pain Scores							
	Post op 0. h	Post op 1. h	Post op 2. h	Post op 3. h	Post op 4. h	Post op 6. h	Post op 12. h	P time
Butorphanol Group	- (-)	0.4 $(0,51)^{Aa}$	0.1 $(0,31)^{Aab}$	- (-)	- (-)	- (-)	- (-)	0.037
Ketamin Group	- (-)	0.2 $(0.42)^{B}$	- $(-)^{B}$	- (-)	- (-)	- (-)	- (-)	0.052
P group	1.0	0.34	0.31	1.0	1.0	1.0	1.0	

Data are presented as mean (standard deviation) ($\bar{x}$ ($S\bar{x}$)).
A, B: Means with different letters in the same column are statistically significant ($P<0.05$).
a, b, c: Means with different letters in the same row are statistically significant ($P<0.05$).

3.2. Heart rate per minute difference between hours

It was determined that the heart rate per minute for both the butorphanol and ketamine groups showed a significant increase from the postoperative zero hour to the twelfth hour (P=0.000). However, there was similarity in heart rate per minute between the groups (P>0.05).

Table 2. Interpretation of ıntra-group and ınter-group statistical results of pulse rate

	Heart Rate							
	Post op. 0. h	Post op 1. h	Post op 2. h	Post op 3. h	Post op 4. h	Post op 6. h	Post op 12. h	P time
Butorphanol Group	99.70 (16.34)^{a}	110.60 (34.79)^{ab}	138.80 (33.93)^{c}	154.60 (21.78)^{d}	178.20 (19.73)^{e}	183.20 (9.27)^{e}	182.10 (10.81)^{e}	0
Ketamin Group	110.50 (20.76)^{a}	111.80 (28.37)^{a}	138.90 (26.67)^{b}	163.70 (22.14)^{c}	176.70 (15.42)^{cd}	175.70 (12.10)^{cde}	187.90 (23.77)^{e}	0
P Group	0.19	0.49	0.88	0.36	0.82	0.19	0.34	

Data are presented as mean (standard deviation) ($\bar{x}$ ($S\bar{x}$)).
A, B: Means with different letters in the same column are statistically significant (P<0.05).
a, b, c: Means with different letters in the same row are statistically significant (P<0.05).

3.3 Respiratory rate difference between hours

No difference was observed between groups in terms of respiratory rates at the same hours (P>0.05). However, within-group evaluations showed that in both groups, the respiratory rates of patients significantly increased from the postoperative zero hour to the twelfth hour (P<0.05).

Table 3. Interpretation of intra-group and inter-group statistical results of respiratory rate

	Respiratory Rate							
	Post op 0. h	Post op 1. h	Post op 2. h	Post op 3. h	Post op 4. h	Post op 6. h	Post op 12. h	P time
Butorphanol Group	37.70 (10.85)^{a}	40.00 (9.59)^{b}	40.00 (4.76)	40.50 (6.11)	41.60 (6.68)^{abc}	42.40 (4.32)^{abd}	46.20 (3.73)^{abe}	0.045
Ketamin Group	38.10 (7.09)^{ac}	39.60 (6.48)^{bc}	41.50 (7.50)^{c}	40.80 (5.97)^{abce}	44.00 (4.66)^{cd}	45.20 (5.13)^{def}	45.60 (6.43)^{cdf}	0.028
P Group	0.65	0.64	0.64	0.64	0.34	0.20	0.64	

Data are presented as mean (standard deviation) ($\bar{x}$ ($S\bar{x}$)).
A, B: Means with different letters in the same column are statistically significant (P<0.05).
a, b, c: Means with different letters in the same row are statistically significant (P<0.05).

3.4 Body temperature (°C) difference between hours

A significant increase in respiratory rate was observed in the butorphanol group from the postoperative zero hour to the first hour and from the fourth hour to the twelfth hour (P<0.05). In the ketamine group, a significant increase was observed from the postoperative zero hour to the twelfth hour (P<0.05). The difference between groups was insignificant (P>0.05). Significant differences in body temperatures were observed in the first, fourth, and fifth measurement times (P<0.05). Both groups showed significant increases in body temperatures until the twelfth hour after the operation.

Table 3. Interpretation of intra-group and inter-group statistical results of body temperature values

	Bodey Temperature (°C)							
	Post op 0. h	Post op 1. h	Post op 2. h	Post op 3. h	Post op 4. h	Post op 6. h	Post op 12. h	P time
Butorphanol Group	36.52 (0.78)^{aA}	36.38 (0.42)^{ab}	36.89 (0.48)^{ac}	37.37 (0.38)^{dA}	37.83 (0.30)^{eA}	38.14 (0.31)^{f}	38.53 (0.34)^{g}	0.000
Ketamin Group	37.44 (0.61)^{aB}	36.88 (0.64)^{b}	37.19 (0.61)^{ac}	37.73 (0.33)^{adB}	38.25 (0.45)^{eB}	38.38 (0.36)^{e}	38.41 (0.34)^{e}	0.000
P Group	0.01	0.06	0.36	0.04	0.02	0.20	0.42	

Data are presented as mean (standard deviation) ($\bar{x}$ ($S\bar{x}$)).
A, B: Means with different letters in the same column are statistically significant (P<0.05).
a, b, c: Means with different letters in the same row are statistically significant (P<0.05).

Currently, ketamine, one of the commonly used anesthetics, is a derivative of dissociative anesthetics and barbiturates. It is preferred due to its advantages, such as providing deep analgesia, not irritating tissues, and maintaining airway patency without endotracheal intubation because it does not eliminate laryngeal and pharyngeal reflexes. However, it also has disadvantages, including increasing heart rate, blood pressure, intracranial and intraocular pressure, causing diplopia and nystagmus, lack of an antagonist, seizures, postoperative delirium, and salivation. It should not be used in patients with hypertrophic cardiomyopathy or in cats with impaired renal function (Koç et al., 2021). However, when used in sub-anesthetic doses, ketamine does not show side effects (Bell et al., 2006), and it has a good analgesic effect when administered before nociceptive stimulation (Nagasaka et al., 2000). For these reasons, the aim is to use the sub-anesthetic dose of ketamine along with isoflurane and medetomidine to achieve the highest level of analgesia with the least side effects.

Butorphanol is a synthetic opioid agent. Initially used as a cough suppressant in veterinary medicine, it is now included in multimodal anesthesia procedures as a pre-anesthetic and analgesic. Its analgesic effect lasts approximately 1 hour. Although it may be relatively insufficient for orthopedic pain in cats and dogs, it is a safe and effective analgesic for mild to moderate pain, particularly cranial and abdominal pain (Koç et al., 2021). In surgeries where the analgesic properties of butorphanol are utilized, inhalation anesthesia can be employed to maintain anesthesia. Inhalation anesthesia is a method used to provide general anesthesia. One of the volatile anesthetic agents known to have similar properties today is isoflurane (Skarada et al., 1996; Steffey, 1996). Functional or pathological kidney disorders do not occur with isoflurane anesthesia. Therefore, it can be easily used in patients with kidney diseases. Due to its lesser effects on the liver compared to other anesthetic agents, it is indicated for use in patients with liver failure (Düzgün and Perk, 1998; Hall and Clark, 1999; Ko et al., 2000; Perk and Yücel, 1994). In a study aimed at reducing minimum alveolar concentration through premedication with medetomidine and propofol before gas anesthesia, the use of medetomidine as a premedicant allowed for less sevoflurane usage (De cramer et al., 2017). In light of all these studies, the goal during the neutering of cats is to provide the safest anesthesia while achieving the highest analgesic effect by using medetomidine as a premedicant, isoflurane as a maintenance anesthetic, and meloxicam along with sub-anesthetic doses of subcutaneous butorphanol or ketamine. Additionally, the antidepressant effects of ketamine administered in sub-anesthetic doses become apparent with significant clinical improvement 2-4 hours post-administration (Vlerick et al., 2019). A single sub-anesthetic dose of ketamine provides effective but short-acting analgesia, and preoperative administration is more advantageous than postoperative administration (Slingsby, 2000). Another study reported that the analgesic effect of ketamine continued for hours postoperatively after administration in sub-anesthetic doses. Although the analgesic efficacy of ketamine for acute postoperative

pain varies depending on the type of surgery, dosing regimen, and accompanying medications, it is comparable to an opioid when administered alone. In the study, 0.3 mg kg^{-1} of ketamine was defined as an equivalent analgesic to 0.7 mg kg^{-1} of pethidine (Chizh, 2007). Based on this research, a comparison was made between ketamine and butorphanol, comparing doses of 0.5 mg kg^{-1} of ketamine with 0.4 mg kg^{-1} of butorphanol. After neutering with medetomidine, propofol, isoflurane, and butorphanol or buprenorphine, all cats in the butorphanol group required analgesic supplementation within the first 360 minutes. However, cats in the buprenorphine group did not need additional analgesia (Warne, 2014). Despite the application of butorphanol with meloxicam in our procedures, a significant difference in pain levels occurred between the ketamine and butorphanol groups, with pain occurring in the first and second postoperative hours in the butorphanol group, followed by a significant decrease in the third hour. No signs of pain were observed in the ketamine group. Neither group required additional applications. No significant difference was found in pulse measurements between the groups. In another study, heart rates and blood pressures were measured in cats sedated with dexmedetomidine alone and in combination with ketamine or butorphanol. In all groups, heart rates significantly decreased after injections; however, the decrease following the administration of dexmedetomidine and butorphanol was more pronounced compared to the other groups. Additionally, there was no significant difference in blood pressures. The pulse rates in the group using butorphanol were lower than those in the group using ketamine, despite ketamine not being used in sub-anesthetic doses (Selmi, 2003). The reason we did not observe a decrease in pulse levels in this study may be due to the lack of preoperative measurements. In the ketamine group, respiratory rates significantly increased over time in a directly proportional manner within the group. However, the respiratory rate in the butorphanol group showed a slight increase during the first hour post-operation, then entered a plateau phase and did not increase until the fourth hour. This situation may have been influenced by the sedative effect of butorphanol (Egger et al., 2013). Additionally, although pain scores were significantly different, no significant difference was observed in respiratory rates between the groups. Physiological changes, such as heart and respiratory rates and pupil size, are poorly correlated with acute pain in cats. This is because anxiety, stress, and fear can affect these variables, particularly in a clinical setting. Therefore, pain assessment in cats is generally performed by observing subjective behavioral changes. Dynamic and interactive responses from the cat (such as response to palpation) can provide the best assessment. However, resting cats should not be disturbed for pain evaluation (Steagall, 2019). Shy or fearful and aggressive behaviors in cats can serve as challenging criteria for distinguishing whether patients are truly in pain or whether their behavior affects pain assessment (Buisman, 2017). It is now known that the UNESP-Botucatu MCPS pain scale is affected by the implementation of ketamine-based protocols. Specifically, ketamine creates a confusing effect on the 'psychomotor' subscale, which can lead to false increases in pain scores. This may potentially result in inappropriate additional analgesic support being administered to pain-free cats (Buisman, 2017). In our second group, since ketamine was used, the UNESP-Botucatu MCPS pain scale was not preferred, despite it containing a broader survey compared to the Colorado Cat Pain Scale.

4. Conclusion

In this thesis study, the analgesic effects of subcutaneous administration of ketamine and butorphanol in cats subjected to the same anesthesia protocol were compared using pain scales. This data was interpreted alongside measurable values such as pulse, respiration, and body temperature. The differences in pain levels within the butorphanol group between the hours are significant. Significantly more pain was observed during the first postoperative hour compared to the other

hours. There was no significant difference between the other hours. The pain levels of patients during the first and second postoperative hours were significantly different from those in the other hours. Ketamine provided better analgesia than butorphanol during the first and second postoperative hours. Although the neutering operation involves abdominal pain, the preference for ketamine over butorphanol in subcutaneous analgesic doses may be more appropriate for pain management. The Colorado Cat Pain Scale may not be sufficient for observing the behaviors of fearful and asocial cats. In future research, cats to be included in the study should be previously observed to determine whether they are comfortable in a clinical environment. There is a need for studies aimed at developing existing scales to reduce their disadvantages. No significant difference was found between the groups in terms of pulse rates. Within the group, pulse rates significantly increased in a directly proportional manner over time. The sub-anesthetic dose of ketamine used subcutaneously eliminates its cardiovascular effects and may be a good option for analgesia in patients with cardiovascular problems. In the butorphanol group, the respiratory rate showed a slight increase during the first postoperative hour but remained stable until the fourth hour. This may have been due to the minimal respiratory system effects of butorphanol or its sedative effect. In the ketamine group, however, the increase in respiratory rate continued steadily, indicating that ketamine had no effect on respiration. The significant increase in body temperatures in all patients until the measurement taken at the twelfth hour after the operation indicates that ketamine and butorphanol have no different effects on body temperature.

Declaration of Author Contributions

The authors declare that they have contributed equally to the article. All authors declare that they have seen/read and approved the final version of the article ready for publication.

Declaration of Conflicts of Interest

All authors declare that there is no conflict of interest related to this article.

Ethical Committee Approval

This study was approved by the Balıkesir University Animal Experiments Local Ethics Committee, Balıkesir, Türkiye (Approval no: 2023/2-8).

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