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Sedative, Analgesic, Behavioral Effect of Xylazine-Ketamine-Nalbuphine induction Anesthesia in Cats Subjected to Median Celiotomy

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ABSTRACT

This study was conducted to evaluate the effect of intramuscular (IM) administration of xylazine- ketamine -nalbuphine compared to xylazine-ketamine combination in cats subjected to median Celiotomy. Six clinically healthy adult castrated male cats (aged between 1-2 years and body weight about 1.8 to 2.6 kg) were randomly allocated into two groups; anesthesia was IM induced with xylazine-ketamine-nalbuphine combination (XKN group; $n = 3$), and xylazine-ketamine alone (XK group; $n = 3$). Following induction, cats underwent ventral median Celiotomy. Basic physiological parameters, analgesic and sedative scores were recorded at 5, 10, 15, 20, 30, 60, 90, and 120 min postoperatively (PO). Post-operative pain-related behaviors were also assessed. The XKN group showed shorter times to lateral and sternal recumbency and longer times to first head lift and standing position than XK group ($P \leq 0.05$). Sedation score revealed a significant ($P \leq 0.05$) difference between both groups at 20, 30, 60 and 120 min PO. Cats in the XKN group exhibited lower post-operative pain -related behavior than those in the XK. Nalbuphine improves sedation and postoperative analgesia of xylazine-ketamine combination in cats.

1. INTRODUCTION

Anesthesia is a reversible technique that aims to provide a quick, safe, effective, and affordable means of chemical restraint so that medical or surgical procedures can be carried out with the least amount of stress, pain, discomfort, and hazardous side effects to patients or anesthetists (Haque and Lucky, 2019). For successful surgical procedures, anesthesia is required to establish desired sedation, analgesia, and muscular relaxation (Nesgash et al., 2016). To achieve a speedy and safe recovery, an ideal anesthetic protocol for such procedures requires the administration of an anesthetic combination having minimum cardiopulmonary depressive effects (Kreisler et al., 2020). Ketamine hydrochloride is a dissociative anesthetic with sympathomimetic action in the central nervous system (CNS). When administered alone, it causes insufficient muscular relaxation and a persistent pain reflex. Muscle hypertonicity, myoclonus, convulsions, and a dose-dependent decrease of heart function are all possible side effects (Mahmud et al., 2014).Therefore, ketamine is usually administered in combination with other medication classes such as benzodiazepines and $alpha_2$ adrenergic agonists to reduce these undesirable and restrictive effects (Özkan et al., 2010). $Alpha_2$-adrenergic agonists are commonly used in animals for its sedative, analgesic, and muscle relaxant properties. Their actions were exerted via stimulation of alpha2-adrenergic receptors located in presynaptic and postsynaptic locations in the CNS. Once $alpha_2$ adrenergic receptors are activated, the release of catecholamine and dopamine neural conduction was inhibited. During anesthetic procedures, xylazine is commonly used as a premedication adjunct to ketamine (Haque and Lucky, 2019; Nesgash et al., 2016; Yohannes, 2018). The choosing of anesthetic protocol for achieving acceptable induction and recovery as well as lessening post-operative pain in animals is gaining more interest in practitioners and increasingly becoming a hot research topic for researchers. The combination of $alpha_2$-adrenergic agonists and opioids provides a multimodal pain management with superior analgesia, considerable opioid sparing, fewer side effects, and overall patient satisfaction (Peng et al., 2015). Nalbuphine is an agonist-antagonist opioid, which possesses analgesic efficacy equivalent to morphine when given intravenously at the same dose. Nalbuphine could be used to relieve mild to severe painful conditions in humans (Liang et al., 2020). Nalbuphine has recently been shown to increase analgesic outcomes in horses (Kulkarni et al., 2015) and camels (Khalil et al., 2019). Administration of nalbuphine has been reported to have minimal cardiorespiratory effects in dogs (Sawyer et al., 1982).

In bellicose animals like cats, surgical interventions necessitates a sufficient anesthesia with adequate sedation and postoperative pain control while minimizing the risk of overdosing (Lee et al., 2016). It may be challenging to acquire such features with a single anesthetic agent (Brown et al., 2018). Multimodal analgesia is defined as the concept of simultaneous administration of two or more analgesics of various classes to provide the most effective analgesia (Robertson and Taylor, 2004). For intramuscular (IM) anesthetic induction, pre-mixed combinations of an opioid, dissociative, and $alpha_2$-adrenergic agonist (often referred to as "kitty magic") are commonly used (Kreisler et al., 2020).

Behavioral signs are the most important indicators for surgical pain in different animal species (Moberg, 1987). Post-operative pain assessment in cats has been investigated using a range of techniques, including behavioral and physiological changes (Benito et al., 2013). There are many reliable behaviors associated with pain in cats as activity, grooming, wound contact, crouching, abnormal gait, standing, resting etc. (Merola and Mills, 2016a; Rütgen et al., 2011; Waran et al., 2007).

To our knowledge, no scientific studies have been reported to use nalbuphine in combination with xylazine and ketamine in cats. Therefore, the goal of this study was to determine, anesthetic, post-operative analgesic, behavioral and cardiorespiratory effects of nalbuphine-xylazine-ketamine to xylazine-ketamine alone in cats.

2. MATERIALS AND METHODS

2.1. Animals

Six healthy adult castrated stray Mau male cats aged 1-2 years and weighted 1.8 to 2.6 kg were enrolled in this study. All cats were captured, weighed, and kept in experimental research division under the same environment. The cats were submitted to a comprehensive clinical examination, complete blood count and serum biochemical profile to ensure their health status. Two weeks before the experiment, the animals were acclimatized to the environmental conditions. Food was withheld for eight hours, but water was allowed prior to the experiment. This study was approved by the Ethical Committee for Institutional Animal Use and Care of the College of Veterinary Medicine, Benha University (BUFVTM-01-05- 2021).

2.2. Experimental design

A total of six cats were randomly assigned into two equal-sized groups (3 cats each) in a prospective randomized, blinded design. In the XK group, a mixture of xylazine (Xylaject, Adwia Co., Cairo, Egypt, 1 mg/kg) and ketamine (ketamine 100, Pantex, Holland, 10 mg/kg) was given IM for induction of anesthesia. Anesthesia in the XKN group was induced using a mixture of xylazine (Xylaject, Adwia Co., Cairo, Egypt, 1 mg/kg) and ketamine (ketamine 100, Pantex, Holland, 10 mg/kg), and nalbuphine (Nalufin, 20 mg-ml, Pharmacia, Ammon, Egypt, 0.5 mg/kg).

Prior to experiment, ventral abdomens in cats were aseptically prepared using a standard technique. Following induction, the cats were placed in dorsal recumbency and ventral median celiotomy of 3 cm in length was performed and closed by an experienced surgical team using a standard technique.

2.2.1. Basic physiological parameters

Heart rate (HR; beats/ min), respiration rate (RR; breaths/min), rectal temperature (RT; ^{o}C) were recorded at 5, 10, 15, 20, 30, 60, 90, and 120-min post-induction. Auscultation with a stethoscope placed over the left side of the chest and counting abdomen movements were used to determine HR and RR. A digital thermometer was used to measure RT.

2.2.2. Sedation and recovery quality assessment

Sedation score (SC) was among the anesthetic measures. The degree of sedation and anesthesia in cats was scored by an examiner who unaware of the drugs given for each group using a modified numerical rating scale (Rodrigo-Mocholí et al., 2016).Poor sedation (0–2), light sedation (4–5), moderate sedation (6–9), and severe sedation (10). Anesthesia was defined as a total score of 12 or higher (Table 1). Times to sternal recumbency (SR), lateral recumbency (LR), initial head lift (HL), standing position (SP) were recorded after the end of administration of the drugs (T 0).

2.2.3. Post-operative observation of pain indicator behaviors

The frequency of post-operative pain related behaviors was recorded after recovery until the entire period of the experiment (120 min). The recovered cats were carefully observed by an observer blinded to the treatments to record behavioral signs. Each cat behavioral patterns were observed using focal observation. The examiner stood a suitable distance from the animals to make a good observation. The observer focused on body care, ataxia (abnormal gait), crouching, and wound contact which considered as pain-related behaviors (Merola and Mills, 2016b). The most observed behaviors were described as the following: Body care, including licking and cleaning the body by tongue or scratching some body parts by legs (Waran et al., 2007); Ataxia: Abnormal gait, prayer position in which cat sitting or standing in crouching position and wound contact: cat head was directed toward the site of operation (Rütgen et al., 2011).

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM Armonk, NY, USA) and JMP Pro 13 (SAS Institute Inc., NC, USA). Data were presented as means ± standard error of the means (SEM). Normality of the data distribution was evaluated by the Shapiro-Wilk test. Comparisons between were performed using independent t-test. Significance was set at ($P \leq 0.05$).

3. RESULTS

3.1. Basic physiological parameters

Non-significant difference was detected in HR, RR and RT between the two groups at the different time points following induction, except at 120 min, RT was higher in the XKN group than the XK group ($p < 0.05$) (Table 2).

3.2. Sedation and recovery quality assessment

Sedation score was higher in the XKN group than XK group. A significant ($P \leq 0.05$) difference was found between both treatments at 20, 30, 60 and 120 min post-induction. The XKN group had the highest sedation score. The highest sedation score (15/15) was observed in the XKN at 20 min post-induction (Table 3). Induction of anesthesia was calmer and quicker in the XKN group than the XK group. Times to SR and LR revealed a non-significant difference ($P > 0.05$) between the groups; however, they were lower in the XKN group than in the XK group (1.76 ± 0.14 and 2.10 ± 0.15 min; 3.50 ± 0.28 and 3.80 ± 0.20 min, respectively). Cats in the XKN group had a prolonged recovery time than those in the XK group. Time to HL was significantly longer ($p < 0.05$) in XKN group than the XK group (63.33 ± 1.85 and 45.33 ± 2.60 min, respectively). Additionally, a longer time ($p < 0.05$) to SP was observed in the XKN group compared to the XK group (79.66 ± 1.45 and 55.66 ± 1.20 min, respectively) (Table 4).

3.3. Behavioral post-operative pain assessment

Cats in the XKN group showed a lower incidence of post-operative pain-related behaviors than those in the XK group. Body care and ataxia were significantly observed in in XK group ($P < 0.05$) than the XKN group. Both treatments did not affect significantly on praying position and wound contact, however, cats in the XK group exhibited higher frequency of these behaviors than those in the XKN group (Table 5).

Table 1. Modified numerical rating scale (range from 0 = low value to 4 = high value) of five independent parameters used for scoring the degree of sedation and anesthesia in cats.

parameter	Description	Score
Spontaneous position	Able to stand and walk	0
	Sedated but standing or sitting	1
	Lying down but able to react quickly or stand up	2
	Lying down, but reacting slowly and having difficulty in standing up	3
	Lying down and unable to stand up	4
Resistance to lateral recumbency	Strong resistance	0
	Moderate resistance	1
	Slight resistance	2
	No resistance	3
Response to noise	Normal response	0
	Listens and moves	1
	Listens and ear moves	2
	Hardly perceives	3
	No response	4
Jaw relaxation	Normal	0
	Slightly reduced	1
	Greatly reduced	2
Eyelid reflex	Normal 0	0
	Depressed reflex	1
	No reflex	2
		15

The sedation was judged to be poor (total score 0–2), mild (total score 4–5), moderate (total score 6–9) and deep (total score 10 ≤) as modified after (Rodrigo-Mocholí et al., 2016).

Table 2. Basic physiological parameters following induction of anesthesia with xylazine-ketamine-nalbuphine (XKN) and xylazine-ketamine (XK) alone in cats undergoing median celiotomy.

parameter	Treatment	
	XK	XKN
RT (ºC)		
5 min	37.53 ± 0.18[a]	37.76 ± 0.23[a]
10 min	37.30 ± 0.11[a]	37.53 ± 0.21[a]
15 min	36.96 ± 0.13[a]	37.16 ± 0.24[a]
20 min	36.50 ± 0.11[a]	36.73 ± 0.32[a]
30 min	36.20 ± 0.15[a]	36.33 ± 0.38[a]
60 min	36.10 ± 0.10[a]	36.36 ± 0.35[a]
90 min	36.36 ± 0.27[a]	36.66 ± 0.17[a]
120 min	35.93 ± 0.08[b]	36.90 ± 0.11[a]
RR (breaths/ min)		
5 min	30.33 ± 2.18[a]	31.66 ±1.33[a]
10 min	28.33 ± 1.66[a]	29.66 ± 2.60[a]
15 min	29.33 ± 1.66[a]	29.66 ± 2.60[a]
20 min	25.66 ± 0.66[a]	27.00 ± 0.57[a]
30 min	24.66 ±1.45[a]	25.00 ± 1.15[a]
60 min	24.33 ± 1.20[a]	23.66 ± 0.88[a]
90 min	24.00 ± 0.57[a]	21.00 ± 1.52[a]
120 min	24.00 ± 0.57[a]	20.66 ± 1.20[a]
HR (beats/min)		
5 min	97.66 ± 1.20[a]	98.33 ± 240[a]
10 min	96.33 ± 0.88[a]	96.33 ± 1.85[a]
15 min	94.66 ± 0.33[a]	95.00 ± 1.52[a]
20 min	94.00 ± 0.57[a]	94.00 ± 1.52[a]
30 min	92.00 ± 1.73[a]	93.33 ± 2.84[a]
60 min	91.33 ± 0.88[a]	90.33 ± 2.96[a]
90 min	92.00 ± 0.57[a]	88.66 ± 2.72[a]
120 min	92.66 ± 0.88[a]	88.00 ± 2.08[a]

Least square means (± SEM) at the same row with different superscript letters are significantly different at $P \leq 0.05$

Table 3. Sedation score following induction of anesthesia with xylazine-ketamine-nalbuphine (XKN) and xylazine-ketamine (XK) alone in cats undergoing median celiotomy.

Sedation score	Treatment	
	XK	**XKN**
5 min	7[a]	11[a]
10 min	10[a]	11[a]
15 min	10[a]	12[a]
20 min	11[b]	15[a]
30 min	12[b]	14[a]
60 min	8[b]	12[a]
90 min	6[a]	9[a]
120 min	4[b]	7[a]

Least square means at the same row with different superscript letters are significantly different at $P \leq 0.05$.

Table 4. Induction and recovery times [Time to sternal recumbency (SR), time to lateral recumbency (LR), time to first head lift (HL) and time to standing position (SP)] following induction of anesthesia with xylazine-ketamine-nalbuphine (XKN) and xylazine-ketamine (XK) alone in cats undergoing median celiotomy.

Group	SR	LR	HL	SP
XK	2.1 ± 0.26 [a]	3.8 ± 0.36 [a]	45.33 ± 4.51 [b]	55.67 ± 2.08 [b]
XKN	1.77 ± 0.25 [a]	3.5 ± 0.5 [a]	63.33 ± 3.21 [a]	79.67 ± 2.52 [a]

Least square means (± SEM) at the same column with different superscript letters are significantly different at $P \leq 0.05$.

Table 5. Frequency of some pain related behaviors following induction of anesthesia with xylazine-ketamine-nalbuphine (XKN) and xylazine-ketamine (XK) alone in cats undergoing median celiotomy.

Treatment	Frequency of the behavioral patterns			
	Body care	**Ataxia**	**Praying position**	**Wound contact**
XK	3.33 ± 0.33[a]	12.00 ± 1.15[a]	2.33 ± 0.33 [a]	3.00 ± 1.00 [a]
XKN	0.66 ± 0.33[b]	4.66 ± 0.33[b]	1.66 ± 0.33 [a]	1.33 ± 0.33[a]
P-value	0.005	<0.001	0.2	0.1

Least square means (± SEM) at the same column with different superscript letters are significantly different at $P \leq 0.05$.

4. DISCUSSION

In this current study, induction of anesthesia with IM administration of a mixture of nalbuphine (0.5 mg/kg), xylazine (1 mg/kg mg/kg), and ketamine (10 mg/kg) provided adequate sedative, analgesic, behavioral effects in cats undergoing median celiotomy. Although the xylazine and ketamine combination is one of the most used injectable anesthetic protocols for cats, dose-dependent cardiorespiratory issues may be encountered when try to achieve a desired level of sedation and analgesia by dose repetition (Brodbelt et al., 2007; Dittmar et al., 2004). Multimodal regimen by combining a tranquillizer and an analgesic in optimal doses is the method of choice to produce the greatest sedative and opioid action with the fewest adverse effects can solve the problem (Steagall and Monteiro-Steagall, 2013). The current study looked at the effects of nalbuphine when administered intramuscularly with xylazine-ketamine. It found that nalbuphine speeds up the onset of Xylazine-Ketamine anesthesia and provides greater long-term sedation and analgesia than the XK group. In the treatment of severe pain, nalbuphine hydrochloride is effective and can attain a maximum analgesic efficacy (Eisele and Steffey, 1984; Kay, 1985; Romagnoli and Keats, 1980). Nalbuphine treatment is known to produce a lot of sedation (Costa et al., 2021). Opioids, like nalbuphine, have a strong calming effect because they effectively relieve postoperative restlessness and pain, because an unseated cat might be restless and react aggressively to pain or stress following surgery, inflicting harm to itself, adequate sedation is critical (Bhalla et al., 2018). It is not only a worry for the animal's welfare when pain is not adequately handled, but it may also have a variety of negative effects that can hinder the patient's rehabilitation (Orskov, 2010). Our findings are consistent with current research on preemptive analgesia for pain management (Goodwin, 1998; Reichert et al., 2001). Preemptive analgesia is a novel method to postoperative pain management that seeks to avoid or minimize pain before it starts (Kien et al., 2019).

The greater sedative and analgesic impact of KXN is attributed in this study to a synergistic multimodal interaction between sedative (xylazine hydrochloride) and opioids (Nalbuphine hydrochloride). With consistent with our findings, the combination of xylazine and butorphanol (an opioid) has better analgesic results than butorphanol alone (Brunson and Majors, 1987). Nalbuphine hydrochloride combination with xylazine or xylazine and acepromazine for horse premedication provided a better quality analgesia and decrease the additional doses of ketamine required to maintain anesthesia (Kulkarni et al., 2015). In camels, the administration of a nalbuphine-xylazine combination improved the sedative and analgesic onset and duration, as well as behavioral scores and both heart and respiration rates, as compared to xylazine alone (Khalil et al., 2019). The nalbuphine-xylazine combination in dog caused deep sedation and analgesia (Torad and Hassan, 2018). In cats, dexmedetomidine in combination with butorphanol or ketamine produced more adequate sedation without clinically significant cardiovascular effects than dexmedetomidine alone (Selmi et al., 2003).

Qualitative behavior assessment can be reliable and repeatable under controlled experimental conditions (Wemelsfelder and Lawrence, 2001). Activity, grooming, wound contact, and prayer position were used to evaluate the post-operative pain in cats undergoing ovariohysterectomy (Rütgen et al., 2011). After Median Celiotomy, cats in the XK group had a higher frequency of body care, ataxia, wound contact, and prayer position than cats in the XKN group. Because all these behaviors are linked to pain, cats in the XK group experienced more post-operative pain than cats in the XKN group and attempted to alleviate it by the expression of these behaviors. When nalbuphine is added to xylazine-ketamine combination the analgesic time is extended and the pain sensation is reduced which is beneficial to animal welfare. In the same line with the current study, (Merola and Mills, 2016b) reported that abnormal gait (ataxia) and crouching (prayer position) were frequently observed in high level pain in cats.

Non-a moderate reduction in HR and RR were found over the whole trial period in both XKN and XK combinations, which were clinically relevant findings. Furthermore, no significant changes between the two therapies were found. As a result, xylazine administration has been linked to these results. Because of its central sympatholytic action, xylazine induces bradycardia and a drop in blood pressure, as well as a drop in RR due to direct respiratory depression (Abouelfetouh et al., 2021; Dzikiti et al., 2007) . The usage of ketamine hydrochloride raises the heart rate, blood pressure, and cardiac output (Verstegen et al., 1991). The depressant effects of xylazine, on the other hand, were not counterbalanced by the pressor effects of ketamine. Heart rate drops considerably in cats given romifidine-ketamine combination and likewise in cats given medetomidine-ketamine combination (Cruz et al., 2000). In this investigation, nalbuphine in the XKN combination had no effect on cardiorespiratory measures when compared to XK alone. Previous research found that nalbuphine has little cardiorespiratory effects, which supported this conclusion (Sawyer et al., 1982). Previous research has shown that nalbuphine is an agonist-antagonist opioid analgesic with cardiovascular stability and a lower capping impact on respiratory depression in humans (Kiran et al., 2011) camels (Khalil et al., 2019). In patients undergoing cardiac surgery, nalbuphine's cardiopulmonary protective action makes it safe and offers greater hemodynamic stability than morphine during the early postoperative period (Solanki et al., 2015).Cardiovascular stability was seen in (Pugh and Drummond, 1987) study, as it had been in previous investigations (Fahmy, 1980; Lake et al., 1982). The ventilatory rate did not change as the nalbuphine plasma concentration increased, indicating that respiratory depression was not a common side effect (Romagnoli and Keats, 1980). The hypothermia was most likely caused by the alpha2 agonist-induced depression of thermoregulatory circuits, decreased metabolic rate, and increased muscular relaxation (PONDER and CLARK, 1980; Selmi et al., 2003). Because it induces less respiratory depression at greater dosages than full agonists, nalbuphine may have an advantage over them (Romagnoli and Keats, 1980).

5. CONCLUSIONS

It is concluded that intramuscular injection of a combination of xylazine, ketamine, and nalbuphine produces a multimodal anesthesia with adequate sedative, analgesic, behavioral, and clinical effects in cats undergoing median Celiotomy.

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