Comparative study on the efficacy of ketamine-xylazine-buprenorfine and ketamine-xylazine-nalbufine in rabbits undergoing castration

Comparatieve studie naar de efficiëntie van ketamine-xylazine-buprenorfine en ketamine-xylazine-nalbufine bij castratie van konijnen

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ABSTRACT

The current clinical study was designed to evaluate the anesthetic effects of a combination of xylazine-ketamine-buprenorphine (KXB) and of xylazine-ketamine-nalbuphine (KXN) in rabbits undergoing castration. The study was conducted in twelve adult male rabbits aged between six months and one year and weighing between 4 and 5 kg. The rabbits were divided into two groups, each comprising six rabbits. Each rabbit in group A was administered a ketamine-xylazine-buprenorphine combination. Each rabbit in group B was given a ketamine-xylazine-nalbuphine combination. Various intraoperative and postoperative anesthetic effects were evaluated. The data were analyzed using a t-test with a repeated measure design and Mann-Whitney test. In this study, the anesthetic combination used in group A (KXB) resulted in a slightly longer anesthetic duration with better postoperative analgesia than in group B (KXN). However, all other parameters showed no significant differences between both groups. It was found that the use of a aketamine-xylazine-buprenorphine combination provides a slightly longer anesthetic duration and better postoperative analgesia than a ketamine-xylazine-nalbuphine combination.

SAMENVATTING

In deze klinische studie werden de anesthetische effecten van een combinatie van xylazine-ketamine-buprenorfine (KXB) en van xylazine-ketamine-nalbufine (KXN) vergeleken tijdens castratie van konijnen. De studie werd uitgevoerd bij twaalf volwassen mannelijke konijnen (tussen de zes maanden tot één jaar oud, met een lichaamsgewicht van 4-5 kg). De konijnen werden in twee groepen van elk zes dieren verdeeld. Elk konijn in groep A kreeg de KXB-combinatie toegediend, de konijnen in groep B kregen de combinatie KXN. Verschillende intra- en postoperatieve effecten werden geëvalueerd. Voor de statistische analyse werden een t-test en een Mann-Whitney-test gebruikt. De KXB-combinatie resulteerde in een iets langere anesthesieduur met betere postoperatieve analgesie dan de KXN-combinatie. Voor de andere parameters werden echter geen significante verschillen vastgesteld. Uit de studie blijkt dat het gebruik van KXB een iets langere anesthesieduur en betere postoperatieve analgesie geeft, dan het gebruik van de KXN-combinatie.

INTRODUCTION

As in other domestic animals, castration is a routine procedure in rabbits. It is mostly performed to control the reproduction of pets and stray animals, as well as to prevent unwanted sexual behavior and sex hormone-induced aggression (Kaiser et al., 2023). Other terms for castration include desexing or gonadectomy. Furthermore, many other diseased conditions, such as cryptorchidism, testicular hypoplasia, severe testicular traumas, testicular neoplasia, testicular torsion, perineal hernia and prostate cancer may require castration (Urfer and Kaeberlein, 2019).

Rabbits are also frequently used as animal models for various experimental surgeries. A balanced anesthesia protocol is strongly recommended in rabbits (Akter et al., 2023). Properly administered balanced inhalation anesthesia in rabbits can be used effectively (Omowumi et al., 2022). However, an anesthesia machine may not always be available, but safe anesthesia for shorter procedures can also be achieved with injectable anesthetics.

Ketamine is one of the most commonly used dissociative anesthetic drugs for the induction and maintenance of anesthesia in experimental animals, including rabbits. The main advantage of this anesthetic agent is that it does not cause major cardiovascular depression (Atalanet al., 2019). Other functions of ketamine include pain relief, sedation and muscle relaxation during anesthesia (Green et al., 2011).

Xylazine is an α2 agonist with pronounced sedative, mild analgesic and skeletal muscle relaxing properties. It is used in premedication or sedation protocols in several species. It causes longer sedation than analgesia (Papudesi et al., 2023).

Opioids are the most effective analgesics and are the treatment of choice during pain in veterinary medicine. They are found in both natural and synthetic form, primarily used for their analgesic activity. Despite a wide range of side effects, they are the most effective analgesics used in systemic treatment of acute pain in many species (Allweiler, 2016).

A mixed therapy with opioids and α2 agonists provides deep analgesia and sedation due to their synergistic effect in both small and large animals (Allweiler, 2016). Adequate pain management should always be provided. In the case of rabbits, opioids are the preferred analgesic medication (Wenger, 2012).

Buprenorphine, a semi-synthetic opioid, and a derivative of morphine alkaloid, is widely used to provide adequate analgesia, sedation and preanesthetic medication. It is rapidly absorbed after intramuscular injection (Kumar et al., 2023). In rabbits, its onset is 15-30 minutes and the duration of effect is up to 8-10 hours (Cooper et al., 2009).

Nalbuphine, a comparatively new morphine-like drug and a potent analgesic with fewer side effects, has an onset of action within 2-3 minutes after IV injection at a dose of 2 mg/kg in rabbits. Its duration of effect is 6 hours, with fewer adverse effects than other opioids, making it an attractive analgesic for animals (Cruz et al., 2022). The current study was designed to evaluate the effects of a combination of xylazine and ketamine with either buprenorphine or nalbuphine and to provide field veterinarians with a balanced and economical cocktail of anesthesia and analgesia in rabbits.

MATERIALS AND METHODS

This clinical study was conducted in twelve adult male rabbits aged between six months and one year old, with weights ranging from 4 to 6 kg. The rabbits were divided into two groups, each comprising six rabbits. They were housed in an experimental shed at the Department of Clinical Surgery and Pet Sciences, the University of Veterinary and Animal Sciences (UVAS) in Lahore (Pakistan). The study was conducted under the ethical guidelines approved by Ethical Review Committee (ERC), UVAS, Lahore, Pakistan, with reference no. 219/2018.

All rabbits were fasted for at least two hours prior to surgery. The health status of the rabbits was assessed through clinical examinations, including body temperature, heart rate, respiration rate (RR), capillary refill time (CRT) and dehydration. All the rabbits were manually restrained by gently gripping the scruff. Xylazine was administered as premedication in both groups at a dose of 0.4 mg/kg intramuscularly to facilitate ear vein catheterization. Ten minutes after injecting xylazine as a sedative, a 24-gauge catheter (Rabbit ear vein catheter®, SAI Infusion Technologies, USA) was placed in the marginal ear vein and used to induce general anesthesia (Holve et al., 2013).

For general anesthesia, each rabbit in group A was administered a combination of ketamine-xylazine-buprenorphine (KXB). The dose rate of xylazine (Xylaz®, Farvet pharmaceuticals) was 3mg/kg body weight, ketamine (Batamine®, Bajwa Pharmaceuticals, Pakistan) 25mg/kg and buprenorphine (Segesic® Saydon pharmaceutical, Pakistan; 0.05mg/kg (Plumb, 2005). Each rabbit in group B was administered a combination of ketamine-xylazine-nalbuphine. Xylazine and ketamine were dosed likewise as in group A. The dose rate of nalbuphine (Kinz®, Sami pharmaceutical, Pakistan) was 0.1 mg/kg (Plumb, 2005). All anesthetic agents were mixed in a single syringe before being injected into the ear vein catheter.

All the animals were positioned in dorsal recumbency for castration. The surgical site was prepared by clipping the hair and using a 30% povidone iodine solution as an antiseptic. A prescrotal skin incision was made. The skin, subcutaneous tissues and testicular layers (tunica vaginalis and tunica albugenia) were incised. The testis was exteriorized, and ligation of the spermatic cord was done using chromic gut 2.0 absorbable suture material. The testis was excised distal to the ligature. Skin suturing was not done and healing of the wound was left to occur through secon-

Table 1. Simple descriptive analgesia scale.

Score	Description	Behavior
0	No pain	Normal posture, no response to wound palpation
1	Mild pain	Slightly abnormal appearance e.g. hunched posture/coat
2	Moderate pain	Staring and response to gentle wound pressure
3	Sever pain	Miserable appearance and wound palpation is not possible

dary intention. A similar procedure was performed for the second testis (Miller et al., 2022).

The rabbits of both groups were evaluated for the following parameters: sedative effects including onset of anesthesia (in seconds), duration of anesthesia (in minutes), recovery from anesthesia (in minutes) and duration of surgery (in minutes). These parameters were defined based on the duration of anesthesia and recovery stages. The onset of anesthesia was defined as the moment when the animals were laterally recumbent with a relaxed jaw, no clamp response, and their eyes were in the ventromedial position without any corneal reflex. The end of anesthesia was confirmed when they moved their limbs and attempted to lift their head. The end of the recovery period was defined as the moment where the animals were standing without any signs of ataxia. Rectal temperature (^{o}C), heart rate (bpm) and respiration rate (per minute) and reflexes (eye reflex, pedal withdrawal reflex, ear pinch reflex and toe pinch reflex (Rachel, 2018; Dunville et al., 2002) were measured at 0, 15, 30, 45 and 60 minutes. Hematological parameters (WBCs count, RBCs count and hemoglobin), liver function tests (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) andrenal function tests (serum creatinine and blood urea nitrogen) were measured at 0, 30 and 60 minutes. All blood samples were processed as mentioned by Benjamin (1983). A scoring scale for analgesia was used to evaluate postoperative pain. The analgesia was recorded at 0, 3, 7 and 10 hours after recovery. The analgesia scale included score numbers of 0, 1, 2, and 3, indicating no pain, mild pain, moderate pain, and severe pain, respectively (Anekaret al., 2023) (Table 1).

A Shapiro-Wilk test was used to confirm that the duration of the different phases of anesthesia and recovery, as well as the monitored values during anesthesia and the hematobiochemical parameters followed a normal distribution. These variables were compared between both groups using a-test and are represented as mean ± SD (Tables 2 and 3). The postoperative analgesia scores were compared between both groups using a Mann-Whitney U test, and are represented as median and range (Table 4). All body reflexes were measured by physical methods (Table 5). All results were analyzed with a significance level of 0.05% ($p \leq 0.05$), using the statistical analysis software version SPSS 20.0 (Daniel, 2010).

RESULTS

All results are shown in Tables 2, 3, 4 and 5. There were no significant differences between the groups regarding the onset of anesthesia, duration of surgery, and recovery time ($p \geq 0.05$). However, there was a significant difference between the groups regarding the duration of anesthesia ($p \leq 0.05$). The mean duration of anesthesia was found to be significantly different, with 51.50±6.50 minutes in the KXB group and 43.17±5.49 in the KXN group.

There was no difference between the KXB and KXN groups in terms of body temperature and heart rate. However, a significant difference was observed in relation to the respiratory rate. The respiratory rate in group B (KXN) was slightly higher than in group A (KXB). However, the respiratory rates of both groups were within the reference range.

At 0 minute of anesthesia, eye reflex, pinch reflex, pedal withdrawal reflex and ear pinch reflex were present in all rabbits of group A (KXB) and group B (KXN). At 60 minutes of anesthesia, all reflexes were restored in all rabbits.

The hemato-biochemical parameters, such as WBCs, RBCs, Hb, ALT, AST, ALP, serum creatinine, and BUN were not significantly different between the KXB and KXN groups. However, the postoperative analgesia scale was significantly different between both groups. Group A (KXB) showed less pain at various time intervals compared to group B (KXN).

DISCUSSION

The efficacy of two anesthetic combinations, KXB and KXN, was evaluated in rabbits. To the best of the authors' knowledge, these unique combinations of anesthesia have not been compared to each other before in rabbits or any other animal species undergoing castration.

Statistically, there was a non-significant difference in the onset of anesthesia, duration of surgery, and recovery time between both groups. The onset of induction was 15 seconds, and all reflexes were absent 15 minutes after intravenous injection. In a study by Murphy et al. (2010), it was indeed observed that buprenorphine in combination with ketamine and medetomidine induces smooth induction within ten min-

Table 2. Comparative mean values of physiological and hemato-biochemical parameters of group A (ketamine, xylazine, buprenorphine) and group B (ketamine, xylazine, nalbuphine) in rabbits (n=12) undergoing castration.

Body temperature (°C) Time (mins)	**Group A**	**Group B**	**P-value**
0	39.3±0.6	39.2±0.8	0.487
15	38.7±0.4	38.3±0.4	0.319
30	38.3±0.5	37.7±0.3	0.223
45	38.5±0.5	37.1±0.6	0.212
60	37.3±0.4	36.7±0.4	0.201
Heart rate (Beats per min)			
0	227.8±31.8	238.1±32.9	0.593
15	212.3±33.5	218.8±31.4	0.736
30	195.6±29.7	199.1±32.5	0.850
45	177.5±30.1	182.1±30.5	0.795
60	178.3±28.5	174.8±25.5	0.828
Respiratory rate (Breaths per min)			
0	54.3±6.40	61.0±5.5	0.042
15	43.6±6.18	50.8±3.7	0.036
30	36.5±6.15	43.5±5.3	0.033
45	29.5±2.88	37.3±7.3	0.035
60	23.1±3.37	36.0±3.4	0.000
WBCs (10^9/L)			
0	**8.2±0.9**	**8.2±0.9**	0.977
30	**8.0±0.9**	**8.0±1.0**	0.986
60	**8.1±0.9**	**7.9±1.0**	0.767
RBCs (10^{12}/L)			
0	**6.3±0.6**	**6.4±0.7**	0.781
30	**6.2±0.6**	**6.2±0.6**	0.980
60	**6.2±0.6**	**6.2±0.6**	0.918
Hemoglobin (%)			
0	**12.2±1.3**	**12.4±1.3**	0.790
30	**11.7±1.4**	**11.7±1.4**	0.984
60	**11.8±1.4**	**11.5±1.4**	0.701
ALT (U/l)			
0	**57.6 ±4.3**	**58.3±5.5**	0.821
30	**83.6±5.3**	**87.5±7.3**	0.327
60	**77.6±3.9**	**109.3±8.5**	0.226
AST (U/l)			
0	**78.0±9.5**	**79.5±11.5**	0.811
30	**110.1±9.7**	**120.1±8.2**	0.684
60	**128.0±9.0**	**151.8±10.4**	0.522
ALP (U/l)			
0	**44.1±11.7**	**45.3±11.3**	0.864
30	**57.8±10.7**	**65.8±11.1**	0.235
60	**75.8±12.5**	**98.8±13.9**	0.213
Serum creatinine (mg/dl)			
0	**1.0±0.3**	**1.0±0.2**	0.927
30	**1.3±0.3**	**1.5 ±0.3**	0.360
60	**1.1±0.3**	**1.7±0.4**	0.333
BUN (mg/dl)			
0	**39.0±5.0**	**43.1±6.3**	0.238
30	**57.5±3.7**	**68.5±5.5**	0.232
60	**60.0±4.7**	**81.5±6.7**	0.128

Table 3. Comparative mean values of anesthetic parameters of group A (ketamine, xylazine, buprenorphine) and group B (ketamine, xylazine, nalbuphine) in rabbits (n=12) undergoing castration.

Parameters	Group A (Mean± S.D)	Group B (Mean± S.D)	P-value
Onset of anesthesia (sec)	14.1±2.4	15.1±3.0	0.248
Duration of anesthesia (min)	51.5±6.5	43.1±5.4	0.037
Recovery time (min)	7.8±1.7	9.1±1.9	0.237
Duration of surgery	31.2±5.7	29.1±2.1	0.061

Table 4. Comparative mean values of analgesic parameters of group A (ketamine, xylazine, buprenorphine) and group B (ketamine, xylazine, nalbuphine) in rabbits (n=12) undergoing castration.

	Group A		Group B	
Time (Hour)	Median	Range	Median	Range
0	0	0-0	0	0-0
3	0	0-1	2	1-2
7	0.5	0-1	2	1-2
10	1	0-1	2	1-2

Table 5. Comparison of various body reflexes of group A (ketamine, xylazine, buprenorphine) and group B (ketamine, xylazine, nalbuphine) in rabbits (n=12) undergoing castration. Values for individual animals are shown for group A (animals A1-A6), and group B (animals B1-B6). Presence of reflex Y=Yes, Absence of reflex N=No

Eye reflex	Group A						Group B					
Time (Min)	A1	A2	A3	A4	A5	A6	B1	B2	B3	B4	B5	B6
0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	N	N	N	N	N	N	N	N	N	N	N	N
30	N	N	N	N	N	N	N	N	N	N	N	N
45	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y
60	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Toe pinch reflex												
0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	N	N	N	N	N	N	N	N	N	N	N	N
30	N	N	N	N	N	N	N	N	N	N	N	N
45	N	N	N	N	N	Y	Y	Y	Y	Y	Y	Y
60	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Pedal withdrawal reflex												
0	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	N	N	N	N	N	N	N	N	N	N	N	N
30	N	N	N	N	N	N	N	N	N	N	N	N
45	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
60	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ear pinch reflex												
0		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15		N	N	N	N	N	N	N	N	N	N	N
30		N	N	N	N	N	N	N	N	N	N	N
45		N	Y	N	N	Y	Y	Y	Y	Y	Y	Y
60		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

utes after intravenous injection.

There was a significant difference in the duration of anesthesia between both groups. Similar results were observed in a study by Steagall et al. (2009) in cats, in which the duration of effect was between twenty and thirty minutes using buprenorphine alone, similar to the KXB group. Buprenorphine has a complex mode of action and can be used at a dose rate of 0.01 to 0.04 mg/kg to induce analgesia between 20 and 30 minutes (Steagall et. al. 2009). Statistically, there was no significant difference in recovery time after anesthesia between both groups. The combination of xylazine, ketamine and buprenorphine produced a longer duration of anesthesia, analgesia, and smooth recovery with significant hypotension when compared with xylazine, ketamine and acepromazine in mice (Buitrago et al., 2008). Buprenorphine alone had a good post-operative analgesia in mice (Jirkof et al., 2015). Also, in mice, it was found that buprenorphine with carprofen has a recovery time between 30 and 45 minutes (Adamson et al., 2010). In goats, nalbuphine with xylazine and ketamine had a shorter recovery time of 38 minutes, time to first movement 34 minutes, and time to standing 55 minutes compared to a xylazine and ketamine combination with a recovery time of 47 minutes, time to first movement of 37 minutes, and time to standing of 38 minutes in goats. However, there was no significant difference between both groups associated with induction time and surgery duration (Abouelfetouh et al., 2022).

The difference in body temperature and heart rate of both groups was non-significant. Buprenorphine did not cause any change in blood pressure, nor in the heart rate of rabbits (Shafford and Schadt, 2008). In a study by Pathak et al. (2012), there was no significant change in the heart rate and rectal body temperature when buprenorphine with ketamine was used in buffalos during spinal analgesia.

A statistically significant decrease in respiratory rate was observed in group A (KXB) compared to group B(KXN). Buprenorphine alone caused a moderate decrease in the respiratory rate in rabbits, but this respiratory depression may be more reflective of sedation rather than true respiratory depression (Schroeder and Smith, 2011). In the study by Pathak et al. (2012), buprenorphine with ketamine resulted in a significant decrease in the respiratory rate from 5 to 15 minutes postinjection during spinal analgesia in buffalo calves. Ketamine and medetomidine following buprenorphine provided better analgesia than pentobarbitone with no respiratory distress. It has also prolonged the recovery time up to 60 minutes in rats (Roughan et al., 1999).

In the present study, there was a significant difference in analgesia of both groups. Group A exhibited more postoperative analgesia than group B. In a study by Paugh et al. (1987), buprenorphine demonstrated superior analgesic activity compared to nalbuphine in humans with a strong affinity at μ receptors and slow dissociation from receptors. The analgesic effects of buprenorphine alone can be observed within 30 minutes after intravenous injection (Steagall et al. 2014). In a study by Reifenrath et al. (2022), buprenorphine produced effective analgesia following orthopedic surgery in rats. However, some rats showed side effects such as depression and pica-behavior. Better postoperative analgesia has been observed in rats when the dose of buprenorphine increased from 0.01 mg/kg to 0.05 mg/kg via the subcutaneous route (Curtin et al., 2009). Buprenorphine alone produces a long-lasting analgesia in rats undergoing laparotomy. However, observed side effects include disturbed circadian rhythm, increased activity and behavioral changes (Jirkof et al., 2015). Subcutaneous administration of buprenorphine can induce mild postoperative analgesia compared to the intravenous or intramuscular routes in rabbits. The subcutaneous route may be useful to sustain analgesic serum levels in rabbits after achieving efficient pain relief (Askar et al., 2020). Nalbuphine has shown to provide good analgesia in a long-term rat model of sepsis (Jeger et al., 2017). However, it leads to a significant decrease in heart rate, respiratory rate and arterial pressure during the anesthesia stage. In the study by Jeger et al. (2017) on awake septic rats, the heart rate was not affected by nalbuphine infusion. Nalbuphine plasma concentrations remained stable between 4 and 24 hours of continuous infusion in the septic rats. In a study by Coetzee et al. (2014), nalbuphine alone reduced pain related behavior in calves after castration.

In a study by Staffieri et al. (2009), buprenorphine with lidocaine produced longer-lasting analgesia compared to xylazine with lidocaine in goats. Intrathecal buprenorphine alone produces prolonged postoperative analgesia compared to nalbuphine in lower limb orthopedic surgeries in humans (Kaushal et al., 2021). In a study by Pathak et al. (2012), buprenorphine with ketamine had an onset of analgesia at four minutes and a duration of analgesia of more than 180 minutes during spinal analgesia in buffalo calves. Nalbuphine with lidocaine has no significant impact on heart rate, body temperature, respiratory rate and liver enzymes (Ragab and Fathy, 2018). All parameters were within the normal range at the end of a 180-minutes' trial (Ragab and Fathy, 2018).

In the present study, there was no significant difference in liver enzymes, i.e. alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. Buprenorphine was shown not to be related to an increased level of liver enzymes. In humans, an increase in liver enzymes may be related to other factors, such as stress and chronic disease (Rezaei et al., 2022). Nalbuphine alone has no significant impact on liver enzymes in healthy humans (Gao et al., 2022). However, the half-life, volume of distribution and mean residence time of nalbuphine are prolonged in human patients with liver dysfunction (Gao et al., 2022).

In the present study, serum urea nitrogen and creatinine levels revealed a non-significant difference in both groups. However, there was a slight elevation of serum urea nitrogen and creatinine. In a study by Grag et al. (2013), an increase in serum urea nitrogen and creatinine was seen during anesthesia and might have been due to transient and mild depression of the kidney function with a decrease of renal blood flow and a consequent decrease in the glomerular filtration rate. In a study by Cooper et al. (2009), there was no postoperative effect of buprenorphine and meloxicam on blood urea nitrogen (BUN) and serum creatinine profile in rabbits. In a study by Ragab and Fathy (2018), serum creatinine and BUN were within the reference range at the end of 180 minutes of a clinical trial using nalbuphine with lidocaine in bucks.

In the present study, there was a non-significant decrease in red blood cells, white blood cells and hemoglobinin in both groups. In mice, postoperative use of buprenorphine alone has no significant impact on the hematology profile including RBCs, WBCs and Hb (Traul et al., 2015).

CONCLUSION

The results of this study suggest that the use of a KXB combination provides a better outcome in terms of duration of surgery and postoperative analgesia than a combination of KXN. When comparing the anesthetic and analgesic effects of the two cocktails, the KXB combination was shown to provide slightly more promising results than the KXN combination. Therefore, the KXB combination for anesthesia might be preferred over the KXN combination in terms of postoperative analgesia in rabbits.

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