J Vet Sci. 2019 Sep;20(5):e55
https://doi.org/10.4142/jvs.2019.20.e55
pISSN 1229-845X·eISSN 1976-555X

Journal of Veterinary Science JVS

Original Article

Anesthesiology & Pain Medicine

Sedative, analgesic, behavioral and clinical effects of intravenous nalbuphine-xylazine combination in camels (*Camelus dromedarius*)

Ahmed H. Khalil[1], **Atef S. Abd Al-Galil**[2], **Ahmed A. Sabek**[3,*], **Mohamed M. Zeineldin**[4], **Seham Y. Abo-Kora**[5]

[1]Department of Veterinary Surgery, Anaesthesiology and Radiology, Faculty of Veterinary Medicine, Benha University, Moshtohor, Kalyobiya 13736, Egypt
[2]Department of Veterinary Surgery, Anaesthesiology and Radiology, Faculty of Veterinary Medicine, Menofiya University, Shebin El-Kom, Egypt
[3]Department of Veterinary Hygiene and Management, Faculty of Veterinary Medicine, Benha University, Moshtohor, Kalyobiya 13736, Egypt
[4]Department of Animal Medicine, Faculty of Veterinary Medicine, Benha University, Moshtohor, Kalyobiya 13736, Egypt
[5]Department of pharmacology, Faculty of Veterinary Medicine, Benha University, Moshtohor, Kalyobiya 13736, Egypt

Received: Jun 3, 2019
Revised: Jul 21, 2019
Accepted: Aug 20, 2019

***Corresponding author:**
Ahmed A. Sabek
Department of Veterinary Hygiene and Management, Faculty of Veterinary Medicine, Benha University, Moshtohor, Kalyobiya 13736, Egypt.
E-mail: ahmedsabek1987@gmail.com

ORCID iDs
Ahmed H. Khalil
https://orcid.org/0000-0001-6843-8867
Ahmed A. Sabek
https://orcid.org/0000-0003-2776-4150

Conflict of Interest
The authors declare no conflicts of interest.

Author Contributions
Conceptualization: Khalil AH, Abd Al-Galil AS.
Data curation: Khalil AH, Sabek AA, Zeineldin

ABSTRACT

This study examined the sedative, analgesic, behavioral, and clinical effects of a combination of xylazine (XY) and nalbuphine-xylazine (NA-XY) in camels. A total of five adult camels were used in a prospective randomized cross-over design with a wash out period of two weeks. Camels were allocated randomly to two treatment groups: the XY group (xylazine, 1.1mL/100 kg IV) and the NA-XY group (xylazine, 1.1mL/100 kg IV and nalbuphine, 1 mg/kg IV). The sedative, analgesic, behavioral, and clinical effects of XY and NA-XY combination were evaluated prior to administration (baseline) and at 5, 15, 30, 45, 60, 75, 90, and 120 minutes post-administration. The results showed that the NA-XY combination accelerates the onset of sedation and analgesia and prolongs the durations of both sedation ($p < 0.001$) and analgesia ($p < 0.01$). The behavioral parameters showed higher scores with a NA-XY combination than xylazine alone. Although a XY injection resulted in a significant decline in the heart and respiratory rate, the NA-XY combination group revealed a non-significant change in both clinical parameters compared to the baseline. In conclusion, the use of a NA-XY combination in camels improved the sedative and analgesic onset and duration with an improved outcome in the behavioral scores, as well as in both the heart and respiratory rates compared to XY alone.

Keywords: Analgesia; behavior; camel; nalbuphine-xylazine combination; sedation

INTRODUCTION

Injectable anesthetic drugs for deep sedation in camels are commonly used in clinical practice [1]. Alpha-2 adrenergic agonist drugs (xylazine, romifidine, detomidine, and medetomidine) have been used widely for animal restraint, analgesia, muscle relaxation, minor surgery, and diagnostic procedures [2]. The administration of such agents provide an average intra-operative duration of approximately 60 and 40 minutes for sedation and

MM. Formal analysis: Sabek AA, Abo-Kora SY. Methodology: Khalil AH, Abd Al-Galil AS, Sabek AA, Zeineldin MM. Writing - original draft: Khalil AH, Abd Al-Galil AS, Abo-Kora SY. Writing - review & editing: Zeineldin MM, Sabek AA.

analgesia, respectively [3]. While multiple injections are needed to maintain a certain level of sedation, the higher risk for developing serious complications and cardiopulmonary depression has limited the clinical application of α-2 adrenergic agents. Therefore, an effective and safe drug combination is needed to handle and restrain animals as well as achieve a faster onset and longer duration of sedation and analgesia. In camels, several drug combinations, such as xylazine-ketamine [2], xylazine-propofol-diazepam and xylazine-propofol [4], have been used successfully in clinical settings.

Recently, the analgesic effects of morphine and nalbuphine, a synthetic opiate with mixed agonist-antagonist actions, have been reported [5,6]. As a novel opioid κ receptor agonist-antagonist, nalbuphine, can agitate the κ receptors to achieve a superior analgesic effect and antagonize the μ receptors to reduce the incidence of adverse reactions [7,8]. The intravenous administration of nalbuphine in dogs has been reported to affect all behavioral scoring parameters [9]. Previous studies reported the effects of combinations of xylazine and other analgesic drugs on the locomotion and movement of sheep [10] and ponies [11]. The nalbuphine-xylazine combination showed effective analgesic and sedative outcomes with cardiovascular stability in calves [7], dogs [12] and horses [13]. However, the nalbuphine-xylazine combination has not been used in camels. Therefore, this study was designed to evaluate the sedative, analgesic, behavioral, and clinical effects of a nalbuphine-xylazine combination in camels.

MATERIALS AND METHODS

The study procedures were conducted in compliance with the recommendations of the guidelines for the care and use of animals at the college of Veterinary Medicine, Benha University. The protocol was approved by the Ethical Committee for Institutional Animal Use and Care of the College of Veterinary Medicine, Benha University (BUFVTM 01-04-2019).

Animals and study design

A total of five adult dromedary camels (two males and three non-pregnant females) with an average body weight of 385 ± 15.3 kg, aged between 4–5 years were used randomly in a crossover design. All camels were housed in a single pen, fed grass (hay) supplemented with concentrate, and given access to water *ad libitum*. Prior to enrollment, each camel was subjected to a complete physical examination to ensure that they were clinically healthy. Food and water were withheld for 24 and 12 h before the experiments, respectively. The camels were assigned to receive one of two intravenous anesthesia protocols, with a wash-out period of two weeks. First, xylazine (XY group) (Xylaject 20%, Adwia Co., Egypt) was injected IV at a dose of (1.1mL/100 kg) for each camel. After two weeks, the same camels were injected IV with the nalbuphine-xylazine combination (NA-XY group) at a dose of xylazine (1.1mL/100 kg) (Xylaject 20%, Adwia Co) and nalbuphine (1 mg/kg) (Nalufin, 20 mg-mL, Pharmacia, Egypt). The injections were carried out in the left jugular vein using a 20-gauge catheter (Int. Comp. Med. Nec., Egypt). All injections were performed while the camels were secured and laid down on a sternal recumbency with both the fore and hind limbs tied together. After the injections, they were allowed to stand up immediately. The study was performed outdoors in a quiet environment with natural daylight and an ambient temperature between 22°C–25°C. On all occasions, the person assigned to evaluate the analgesic agents was completely blinded to the anesthetic protocol.

Treatment evaluations

Sedative and analgesic evaluation

The evaluation was done before injecting the drugs at the baseline (0 min) and at 5, 15, 30, 45, 60, 75, 90, and 120 min after injection. The onset and depth of analgesia were recorded each minute after the injection by recording the response of the animal to pinching with a hemostat clamp (closed to the first ratchet). Pinching was applied to both sides of the shoulder, flank area, thigh, perineum, and dorsal fetlock of the hind limb. The forceps were kept in place for 5 sec or until a response appeared. The animal's eyes were covered at the time of pinching to avoid any visually motivated response. A positive pain response was defined as the purposeful avoidance movements of the head, neck, trunk, limbs and tail, attempts to kick and bite, and turning of the head toward the stimulus site. As soon as the camel showed one of the defined responses, the investigator removed the clamp as described elsewhere [14]. The degree of sedation was evaluated by monitoring of the changes in body language as the distance between the ear tips, ataxia, which is defined as a change in locomotion expressed through the abduction of the hind limbs, and distance between the camel head and ground. The time between the appearance and disappearance of sedation and analgesia was considered as the duration of sedation and analgesia, respectively. The depth of sedation and analgesia was graded on a scoring system from 0 to 3, as described elsewhere (**Table 1**).

Behavioral evaluation

The examiner who was unaware of the injected drugs estimated the behavioral scoring parameters, such as head deviation, tongue protrusion, and salivation on a scale from 0 to 3 (**Table 2**). The examiner stood a suitable distance from the animals to make a good observation. By scan observation, the examiner observed the head deviation, tongue protrusion, and salivation at the baseline and at each time point post injection.

Heart and respiratory rate evaluation

The clinical parameters, including heart rate and respiratory rate, were also evaluated at the baseline (0 min) and then at 5, 15, 30, 45, 60, 75, 90, and 120 min after injection. The heart rate was assessed by palpation of the middle coccygeal and femoral artery, and is expressed as beats/minute. The respiratory rate was measured by an inspection of the respiratory movements and by auscultation of the trachea and is expressed as breaths/minute.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM Armonk, USA). The normality of the data distribution was evaluated using a Shapiro-Wilk test. Data analysis

Table 1. Description of sedative and analgesic scores

Score	Sedation		Analgesia	
	Criteria	Description	Criteria	Description
0	No sedation	Normal movement, head and neck carriage, normal distance between the ears, tongue inside the mouth and no salivation	No analgesia	Strong response to noxious stimulus
1	Mild sedation	Mild change in movement, mild head dropping or deviation to one side, mild increase in the distance between the ears, mild protrusion of the tongue and mild salivation	Mild analgesia	Weak response at all times of noxious stimulus
2	Moderate sedation	Moderate change in movement, moderate head dropping or deviation to one side, moderate increase in the distance between the ears, moderate protrusion of the tongue and moderate salivation	Moderate analgesia	Very weak occasional response
3	Sever sedation	Severe change in movement, severe head dropping or deviated and rest on the back, severe increase in the distance between the ears, severe protrusion of the tongue (whole tongue out of mouth) and severe salivation (excessive salivation)	Severe analgesia	No response to noxious stimulus

Journal of Veterinary Science

Table 2. Behavioral scoring parameters

Parameter	Score	Description
Head deviation	0	No deviation
	1	Mild deviation to one side
	2	Moderate deviation to one side
	3	Severe deviation, head rest on the back
Tongue protrusion	0	Tongue inside the mouth, no protrusion
	1	Small part of tongue get out from one side of the mouth
	2	Large part of tongue get out from one side of the mouth
	3	The whole tongue is outside the mouth
Salivation	0	No salivation
	1	Little drops get out from the mouth
	2	Much drops get out from the mouth
	3	Excessive salivation, like strand hanged from the mouth

was performed using an Analysis of variance (ANOVA) and non-parametric Wilcoxon/Kruskal-Wallis Tests where relevant. Significance was set to $p < 0.05$ and all values are presented as the mean ± standard error of mean.

RESULTS

The results showed that the NA-XY combination had a significant effect on sedative, analgesic, clinical, and behavioral parameters in camels, which are represented by a significant increase in the duration of sedation and analgesia. In addition, it caused a significant change in all recorded behavioral parameters, as well as non-significant change in both the heart and respiratory rates compared to the XY group. An intravenous injection of NA-XY combination resulted in rapid onset of apparent sedative effects (5.40 ± 0.24 and 4.8 ± 0.37) min for the XY group and NA-XY group, respectively. The sedative effects persisted for 44.00 ± 2.44 and 90.00 ± 2.60 min for the XY group and NA-XY group, respectively (**Table 3**).

Intravenous injection of NA-XY combination resulted in rapid onset and prolonged analgesic duration than XY alone. The onset of the analgesic effect for the XY group and NA-XY group were 9 ± 0.58 and 7.20 ± 0.37 min, respectively. The analgesic durations for the XY group and NA-XY group were 28.4 ± 1.68 and 55.00 ± 7.4 min, respectively (**Table 3**).

The post-administration sedative effect was evaluated through a change in body language. The results showed that the NA-XY combination increased the distance between the ear tips significantly throughout all time points post injection. The highest significant difference occurred at T30, where the distance between the ear tips was 20.6 ± 0.81 and 29.2 ± 1.59 cm for both XY and NA-XY groups, respectively (**Table 4**). The degree of ataxia was also recorded through monitoring the abduction of the hind limbs (distance between the hind limbs), which showed significant changes after injection of NA-XY combination. The maximum

Table 3. Onset and duration of sedation and analgesia after IV injection of xylazine and nalbuphine-xylazine combination

Treatment	Sedation		Analgesia	
	Onset	Duration	Onset	Duration
XY	5.40 ± 0.24	44.00 ± 2.44^{b}	9 ± 0.58^{a}	28.4 ± 1.68^{b}
NA-XY	4.8 ± 0.37	90.00 ± 2.60^{a}	7.20 ± 0.37^{b}	55.00 ± 7.4^{a}
p value	0.2	< 0.001	< 0.05	< 0.01

Means (± SE) with different superscript letters in the same column are significantly different.
XY, xylazine; NA-XY, nalbuphine-xylazine.

https://doi.org/10.4142/jvs.2019.20.e55

Table 4. Body language change of camels before and after IV injection of xylazine and nalbuphine-xylazine combination

Item	Treatment	Pre-treatment	Post-treatment							
		T0	T5	T15	T30	T45	T60	T75	T90	T120
Ear tips distance	XY	18.4 ± 1.36	20 ± 1.58	21 ± 1.14	20.6 ± 0.81^{b}	19.25 ± 0.72^{b}	19.33 ± 0.73	19.6 ± 0.74	20 ± 1.37	20.6 ± 1.06
	NA-XY	18.2 ± 0.86	21.4 ± 1.53	22 ± 1.26	29.2 ± 1.59^{a}	23.4 ± 0.92^{a}	20.2 ± 1.59	20.4 ± 1.60	22.6 ± 1.16	21.4 ± 1.13
Abduction of hind limbs	XY	5.6 ± 2.58	48.8 ± 2.15^{b}	24 ± 1.70^{b}	32.6 ± 2.50^{b}	34.2 ± 0.24	32.4 ± 2.50	26.8 ± 1.98^{b}	25 ± 1.58^{b}	25.8 ± 1.60^{b}
	NA-XY	5.4 ± 2.35	66.6 ± 1.86^{a}	37.8 ± 2.61^{a}	38.2 ± 2.41^{a}	36 ± 1.87	35 ± 1.58	39.6 ± 1.63^{a}	36.4 ± 1.86^{a}	36.8 ± 1.52^{a}
Head to ground distance	XY	212.4 ± 2.50	190 ± 1.63	176.8 ± 0.86^{b}	188.6 ± 2.42^{a}	174 ± 2.21^{a}	181.4 ± 2.73^{a}	192.4 ± 2.50^{a}	198.2 ± 2.59^{a}	200.4 ± 2.07^{a}
	NA-XY	212.4 ± 2.50	189 ± 1.70	185.8 ± 1.68^{a}	96.2 ± 2.15^{b}	122.4 ± 2.50^{b}	122 ± 2.54^{b}	118 ± 1.37^{b}	115.8 ± 1.68^{b}	118.2 ± 1.08^{b}

Means (± SE) with different superscript letters in the same column with different treatments are significantly different.
XY, xylazine; NA-XY, nalbuphine-xylazine.

distance recorded at T5 post administration as the distance between the hind limbs was 48.8 ± 2.15 and 66.6 ± 1.86 cm for XY group and NA-XY group, respectively (**Table 4**). The distance between the head and ground was significantly lower in the NA-XY group than the XY group at all times after the injections except at T15, in which the distance was 176.8 ± 0.86 and 185.8 ± 1.68 for the XY group and NA-XY group, respectively. The most obvious head dropping was observed in T30 in the NA-XY group; the distance between the head and ground was 96.2 ± 2.15 cm compared to 188.6 ± 2.4 cm for the XY group at the same time point (**Table 4**).

As shown in **Table 5**, the behavioral scoring parameters were affected at different treatment time points as the head deviation degree was significantly higher in the NA-XY group than the XY group, particularly at T30, T45, and T60 post administration. The degree of tongue protrusion was higher in the XY group than in the NA-XY group at T15 post administration. In contrast, at T60, T75, and T90 post injection, the degree of tongue protrusion was higher in the NA-XY group than the XY group. The degree of salivation was significantly higher in the NA-XY group than the XY group from T30 until T90 post administration.

A clinical assessment of the camels showed that XY administration decreased both the heart and respiratory rates significantly at different time points compared to the baseline. The NA-XY combination showed non-significant changes in both the heart and respiratory rates at different time points compared to the pretreatment baseline (T0), as shown in (**Table 6**).

Table 5. Behavioral scoring parameters of camels before and after IV injection of xylazine and nalbuphine-xylazine combination

Item	Treatment	Pre-treatment	Post-treatment							
		T0	T5	T15	T30	T45	T60	T75	T90	T120
Head deviation	XY	0	0	1	1^{b}	1	0^{b}	0	0	0
	NA-XY	0	0	2	3^{a}	2	2^{a}	1	1	0
Tongue protrusion	XY	0	0	2^{a}	1	1	1	0^{b}	0^{b}	0
	NA-XY	0	1	1^{b}	1	1	3^{a}	2^{a}	2^{a}	1
Salivation	XY	0	0	1	0^{b}	1	0^{b}	0^{a}	0^{b}	0
	NA-XY	0	0	1	2^{a}	2	3^{a}	2^{a}	2^{a}	1

Variables with different superscript letters in the same column with different treatments are significantly different.
XY, xylazine; NA-XY, nalbuphine-xylazine.

Table 6. Clinical evaluation of camels before and after IV injection of xylazine and nalbuphine-xylazine combination

Item	Treatment	Pre-treatment	Post-treatment							
		T0	T5	T15	T30	T45	T60	T75	T90	T120
Heart rate	XY	58.8 ± 0.96	52 ± 1.04^{b}	46.8 ± 0.58^{b}	41.6 ± 0.52^{b}	42.8 ± 0.73^{b}	46.4 ± 0.60^{b}	46.6 ± 0.50^{b}	49.8 ± 0.37^{b}	52.4 ± 0.35^{b}
	NA-XY	59.2 ± 0.66	56.6 ± 0.50^{a}	54.6 ± 0.50^{a}	51.6 ± 0.74^{a}	49.2 ± 1.01^{a}	51 ± 0.44^{a}	52 ± 0.31^{a}	54 ± 0.44^{a}	56.8 ± 0.39^{a}
Respiratory rate	XY	30.2 ± 0.86	24.6 ± 0.50^{b}	21.4 ± 0.60^{b}	19.2 ± 0.73^{b}	19.4 ± 0.50^{b}	20 ± 0.70^{b}	20.6 ± 0.60^{b}	22.6 ± 0.92^{b}	23.4 ± 0.25^{b}
	NA-XY	30 ± 1.09	28.2 ± 0.96^{a}	26 ± 0.94^{a}	25.2 ± 0.96^{a}	25.4 ± 0.81^{a}	26.6 ± 0.87^{a}	27.2 ± 0.96^{a}	27.2 ± 0.91^{a}	28.8 ± 0.30^{a}

Means (± SE) with different superscript letters in the same column with different treatments are significantly different.
XY, xylazine; NA-XY, nalbuphine-xylazine.

Journal of Veterinary Science

DISCUSSION

This study indicates that the intravenous administration of a nalbuphine (1 mg/kg) and xylazine (1.1mL/100 kg) combination had great sedative, analgesic, behavioral, and clinical effects on camels. The maximum duration of sedation and analgesia after administering the α-2 agonist is 55 to 65 and 37 to 46 minutes for sedation and analgesia, respectively [14-16], which may be insufficient during long lasting operations. Combinations of α-2 agonist and opioids have been reported to decrease the number of side effects and improve the sedation and analgesia durations compared to individual drug injections [17,18]. Such combinations of an α-2 agonist and opioids have been used previously in camels as xylazine-tramadol [19] and midazolam-propofol [20]. Nalbuphine is an appealing opioid with a low cost and wide safety margin. The drug appears to be safe for enhancing the neuroleptanalgesic effects with xylazine and possibly other α-2 agonists [12]. The selected dose of nalbuphine in the present study (1 mg/kg) was calculated based on the fact that nalbuphine is considered to be one-fifth as potent as butorphanol when administered parenterally [21]. The safe analgesic dose of butorphanol in camels has been reported to be 0.2 mg/kg IV [22].

Sedation and analgesia

While previous studies have reported the safe and efficient effects of a NA-XY combination in different species [7,12,13], the effects of this combination in camels have not been recorded. Similar to previous studies, the results of the current study showed that a combination of nalbuphine with xylazine resulted in the rapid onset and prolonged duration of sedation and analgesia compared to xylazine alone [23]. Numerous studies in pets and horses have reported improved effects on sedation and analgesia when an α-2 agonist was administered in combination with an opioid due to the synergistic effects of sedatives and opioid drugs [24-27]. Similarly, Coetzee et al. [7] reported that nalbuphine accelerates the onset and extends the duration of both sedation and analgesia in calves. Moreover, the combination of nalbuphine hydrochloride and medetomidine yielded good quality sedation with 50 min of muscular relaxation and acceptable physiological parameters [28,29]. The current study recommended the following body language indicators to assess the degree of sedation: distance between the ear tips, abduction of the hind limbs as an ataxia indicator and distance between animal's head and ground as an indicator for muscle relaxation. The increase in the distance between the ear tips and a decreased distance between the head and ground post injection may be attributed to the muscle relaxation and reduction of awareness caused by the sedative effects of the drugs. These results agree with previously published studies [14,15].

Ataxia is considered one of the most important indicators of abnormal locomotion. In the current study, the camels were allowed to stand up after drug administration. The distance between the hind limbs was measured as an indicator of ataxia. After xylazine and nalbuphine-xylazine combination injection, the abduction between the hind limbs increased, leading to slow motion or no motion, particularly in the NA-XY group. Coetzee et al. [7] recorded a decrease in the number of steps taken after castration in calves with less pain-associated behaviors due to the sedative effects after nalbuphine administration. The frequency of all recorded adverse behaviors in dogs was less when nalbuphine was combined with xylazine. Nalbuphine-xylazine combination also improved the onset of both sedation and analgesia, decreased the animal movement, and kept the animal calm during the recovery period [12].

Behavioral scoring parameters

The behavioral indicators, such as head deviation, tongue protrusion and salivation, were affected significantly by different treatments. After administration, the behavioral parameters increased, particularly in the NA-XY group due to the CNS excitation produced by the drugs. These results agree with Dhanjal et al. [30] who reported that the use of tramadol as opioids in horses leads to head deviation. Seo et al. [31] also reported that tongue protrusion and salivation increased after administration of a xylazine-tramadol combination.

Heart and respiratory rate

In the XY group, the camels showed a significant decrease in both heart and respiratory rates in all time points post-injection compared to baseline values. Cardiopulmonary suppression is a common concern after an injection of α-2 adrenoceptor agonists because of the central stimulation mediated through the vagus nerve and a decrease in sympathetic tone [32]. Previous studies [33,34] in camels reported a significant reduction in heart and respiratory rates after intravenous administration of xylazine. On the other hand, the cardiopulmonary stability was the main feature observed after intravenous administration of NA-XY combination. No significant differences in heart rate and respiratory rate were observed in the NA-XY-treated camels compared to the baseline values. This is consistent with the literature and supports the observation that nalbuphine is an agonist-antagonist opioid analgesic with cardiovascular stability and a smaller capping effect on respiratory depression in humans [35] and calves [7]. The cardiopulmonary protective effect of nalbuphine makes it safe and provides better hemodynamic stability during the early postoperative period compared to morphine in patients with cardiac surgery [36].

In conclusion, nalbuphine is capable of producing an additive-synergistic effect when added to IV xylazine. This effect is evidenced in camels by the rapid onset, greater intensity, and longer duration of sedation and analgesia. An additional discernible feature of this combination is the consequential cardiopulmonary stability. The nalbuphine-xylazine combination also affects the behavioral parameters The changes in the response of these behavioral parameters indicate a state of deep sedation and analgesia with no agitation and calm recovery.

ACKNOWLEDGMENTS

The authors wish to acknowledge the time and effort of the workers at an animal farm, College of Veterinary medicine, Benha University for their contribution in conducting this study.

REFERENCES

1. Abrahamsen EJ. Chemical restraint, anesthesia, and analgesia for camelids. Vet Clin North Am Food Anim Pract 2009;25:455-494.
PUBMED | CROSSREF
2. Al-Mubarak AI, Abdin-Bey M, Ramadan RO. A retrospective clinical evaluation of xylazine-ketamine total intravenous anaesthesia (TIVA) in dromedary camels. J Camel Pract Res 2008;15:201-203.
3. Ismail ZB. A review of anaesthetic drugs used for premedication, sedation, induction and maintenance in camels (*Camelus dromedarius*) in field situations. J Camel Pract Res 2016;23:207-211.
CROSSREF

4. Mohamed GA, Sanhouri AA, Ramadan RO, Almubarak AA. The effects of different anaesthetic regimes using propofol and different sedatives on the concentration of plasma cortisol and glucose in camels (*Camelus dromedarius*). J Camel Pract Res 2013;20:295-298.
5. Frazílio FO, DeRossi R, Jardim PH, Marques BC, Martins AR, Hermeto LC. Effects of epidural nalbuphine on intraoperative isoflurane and postoperative analgesic requirements in dogs. Acta Cir Bras 2014;29:38-46.
PUBMED | CROSSREF
6. Verma D, Naithani U, Jain DC, Singh A. Postoperative analgesic efficacy of intrathecal tramadol versus nalbuphine added to bupivacaine in spinal anaesthesia for lower limb orthopaedic surgery. J Evol Med Dent Sci 2013;2:6196-6206.
CROSSREF
7. Coetzee JF, Lechtenberg KF, Stock ML, Kukanich B. Pharmacokinetics and effect of intravenous nalbuphine in weaned Holstein calves after surgical castration. J Vet Pharmacol Ther 2014;37:169-177.
PUBMED | CROSSREF
8. Yang L, Wu J, Li T. The application of nalbuphine in patient-controlled intravenous analgesia for patients undergoing subtotal gastrectomy. Exp Ther Med 2018;15:1910-1913.
PUBMED
9. Faisal AT, Elham AH. Sedative, analgesic and behavioral effects of nalbuphine-xylazine and nalbuphine-midazolam combinations in dogs. J Vet Behav 2018;28:40-45.
CROSSREF
10. Borges LP, Nishimura LT, Carvalho LL, Cerejo SA, Auckburally A, Mattos-Junior E. Behavioral and cardiopulmonary effects of dexmedetomidine alone and in combination with butorphanol, methadone, morphine or tramadol in conscious sheep. Vet Anaesth Analg 2016;43:549-560.
PUBMED | CROSSREF
11. Costa GL, Cristarella S, Quartuccio M, Interlandi C. Anti-nociceptive and sedative effects of romifidine, tramadol and their combination administered intravenously slowly in ponies. Vet Anaesth Analg 2015;42:220-225.
PUBMED | CROSSREF
12. Lester PA, Gaynor JS, Hellyer PW, Mama K, Wagner AE. The sedative and behavioral effects of nalbuphine in dogs. Contemp Top Lab Anim Sci 2003;42:27-31.
PUBMED
13. Kulkarni H, William BJ, George RS, Kannan TA. Analgesic and adjunct actions of nalbuphine hydrochloride in xylazine or xylazine and acepromazine premedicated horses. Indian J Anim Res 2015;49:699-703.
14. Marzok M, El-Khodery S. Sedative and analgesic effects of romifidine in camels (*Camelus dromedarius*). Vet Anaesth Analg 2009;36:352-360.
PUBMED | CROSSREF
15. El-Maghraby HM, Al-Qudah K. Sedative and analgesic effects of detomidine in camels (*Camelus dromedarius*). J Camel Pract Res 2005;12:41-45.
16. Khamis Y, Fouad K, Sayed A. Comparative studies on tranquilization and sedation in *Camelus dromedarius*. Vet Med Rev 1973;4:336-345.
17. LeBlanc PH. Chemical restraint for surgery in the standing horse. Vet Clin North Am Equine Pract 1991;7:521-533.
PUBMED | CROSSREF
18. DeRossi R, Jorge TP, Ossuna MR, Carneiro RP, Alves OD, Zanenga NF. Sedation and pain management with intravenous romifidine-butorphanol in standing horses. J Equine Vet Sci 2009;29:75-81.
CROSSREF
19. Al-Taher AY, Zabady MK, Almubarak AI, Ismail M, Ramadan RO. Clinical use of tramadol and xylazine in dromedary camel undergoing soft tissue surgeries. J Anim Vet Adv 2014;13:206-208.
20. Palecha S, Gahlot TK, Bishnoi P. Efficacy of midazolam-propofol combination anaesthesia in dromedary camels (*Camelus dromedarius*). J Camel Pract Res 2015;22:217-222.
CROSSREF
21. Pallasch TJ, Gill CJ. Butorphanol and nalbuphine: a pharmacologic comparison. Oral Surg Oral Med Oral Pathol 1985;59:15-20.
PUBMED | CROSSREF
22. Al-Mubarak AI. Sedative, analgesic and biochemical effects of butorphanol in camels (*Camelus dromedarius*). J Camel Pract Res 2013;20:23-27.
23. Edmondson MA, Duran SH, Boothe DM, Stewart AJ, Ravis WR. Pharmacokinetics of tramadol and its major metabolites in alpacas following intravenous and oral administration. J Vet Pharmacol Ther 2012;35:389-396.
PUBMED | CROSSREF

24. Selmi AL, Mendes GM, Lins BT, Figueiredo JP, Barbudo-Selmi GR. Evaluation of the sedative and cardiorespiratory effects of dexmedetomidine, dexmedetomidine-butorphanol, and dexmedetomidine-ketamine in cats. J Am Vet Med Assoc 2003;222:37-41.
PUBMED | CROSSREF

25. Leppänen MK, McKusick BC, Granholm MM, Westerholm FC, Tulamo R, Short CE. Clinical efficacy and safety of dexmedetomidine and buprenorphine, butorphanol or diazepam for canine hip radiography. J Small Anim Pract 2006;47:663-669.
CROSSREF

26. Monteiro ER, Figueroa CD, Choma JC, Campagnol D, Bettini CM. Effects of methadone, alone or in combination with acepromazine or xylazine, on sedation and physiologic values in dogs. Vet Anaesth Analg 2008;35:519-527.
PUBMED | CROSSREF

27. Cardoso CG, Marques DR, da Silva TH, de Mattos-Junior E. Cardiorespiratory, sedative and antinociceptive effects of dexmedetomidine alone or in combination with methadone, morphine or tramadol in dogs. Vet Anaesth Analg 2014;41:636-643.
PUBMED | CROSSREF

28. Wolfe LL, Lance WR, Smith DK, Miller MW. Novel combinations of nalbuphine and medetomidine for wildlife immobilization. J Wildl Dis 2014;50:951-956.
PUBMED | CROSSREF

29. Wolfe LL, Miller MW. Using tailored tranquilizer combinations to reduce stress associated with large ungulate capture and translocation. J Wildl Dis 2016;52 (2 Suppl):S118-S124.
PUBMED | CROSSREF

30. Dhanjal JK, Wilson DV, Robinson E, Tobin TT, Dirikolu L, Dirokulu L. Intravenous tramadol: effects, nociceptive properties, and pharmacokinetics in horses. Vet Anaesth Analg 2009;36:581-590.
PUBMED | CROSSREF

31. Seo JP, Son WG, Gang S, Lee I. Sedative and analgesic effects of intravenous xylazine and tramadol on horses. J Vet Sci 2011;12:281-286.
PUBMED | CROSSREF

32. Argoff CE, Viscusi ER. The use of opioid analgesics for chronic pain: minimizing the risk for harm. Am J Gastroenterol Suppl 2014;2:3-8.
PUBMED | CROSSREF

33. Bolbol AE, Hassanein A, Ibrahim H. some studies in the camel after sedation with Rompun. Vet Med Rev 1980;1:55-60.

34. White RJ, Bali S, Bark H. Xylazine and ketamine anaesthesia in the dromedary camel under field conditions. Vet Rec 1987;120:110-113.
PUBMED | CROSSREF

35. Kiran K, Vyas V, Patil S. Comparative efficacy and safety of intravenous tramadol and nalbuphine for pain relief in postoperative patients. Indian J Pain 2018;32:96.
CROSSREF

36. Solanki RN, Gosai ND, Joshi GM, Patel BM, Modi HV, Jain R. A comparative study of intravenous nalbuphine HCl and tramadol HCl for post- operative pain relief following orthopaedic surgeries. Asian Pac J Health Sci 2015;2:153-158.
CROSSREF