

Anesthetic impact assessment of nefopam, xylazine, ketamine, propofol combination in local donkeys

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Abstract

Anesthesia is used in animals to relieve pain during surgical interference or other procedures which were likely causing pain. Safe, effective, and reversible anesthesia requires selecting proper anesthetic agents. This study aimed to evaluate the qualitative and quantitative aspects of total intravenous anesthesia (TIVA) induced by using nefopam/xylazine/ ketamine and propofol combination in local breed donkeys. Nefopam/xylazine/ ketamine and propofol anesthetic combination was evaluated for pain management by using nefopam to provide the maintenance of the anesthetic stage. The onset and duration of anesthetic induction, time of maintenance, and period of recovery were recorded. Furthermore, heart rate, respiratory rate, body temperature, and blood picture were analyzed before and after administration of the combination. Our findings revealed that administration of Nefopam/ xylazine/ ketamine and propofol combination led to a smooth induction with rapid onset within one minute. The anesthetic effect was maintained for approximately 31 minutes after continuous infusion of propofol for standard deviation (19 ± 2 minutes). This was followed by a smooth recovery within approximately 48 minutes after induction of anesthesia. It concluded that nefopam/xylazine/ketamine and propofol infusion is considered satisfactory for pain management and provide satisfactory anesthesia for short surgical procedures in donkeys.

Keywords: Donkeys; Ketamine; Nefopam; Total intravenous anesthesia; Propofol; Pain Management

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Introduction

There is no anesthetic drug available today that can deliver adequate anesthesia on its own. As a result, sedative-anesthetic combos have been widely used in animal practice. The anesthetic combination should combine many qualities, such as appropriate sedation and a deeply unconscious state, without significantly altering the patient's physiologic parameters (Burnham et al., 2022). Certain surgical procedures require general anesthesia because they cannot be performed under regional or local anesthesia (Joubert et al., 1999). The first recorded anesthetic combination was xylazine/ketamine, which is now the standard field anesthetic method in North America (Muir, 1991).

Nefopam is a powerful analgesic with a novel structure and distinct physiological features that provide immediate and significant pain relief in conditions such as trauma, wounds, post-operation, cancer, skeletal muscle, as well as dental pain, prolapsed intervertebral disc, and neurogenic pain (Sivananthan et al., 2012).

Furthermore, Matei et al. (2018) stated that the drug is free from many complicated factors that are related to narcotic analgesic treatment. Nefopam is not recommended in case of seizures or a heart attack. It is a centrally acting analgesic distinct from other analgesics or narcotics such as morphine, codeine, and pentazocine. The drug doses cannot produce drug dependence on the narcotic type (Engbang et al., 2021).

In contrast to propofol, donkeys pre-medicated with ketamine and xylazine showed quick induction, extended duration, smooth recovery, and adequate anesthesia (Fathy, 2018).

However, Molinaro Coelho et al. (2014) found that utilizing propofol infusion can mitigate its adverse effects.

The current study was designed to analyze the anesthetic impact and pain management during and after injection of nefopam/ xylazine/ ketamine and propofol combination in donkeys.

Materials and methods

Ethical Statement

The experimental study was carried out according to the animal ethical committee of the Faculty of Veterinary Medicine, South Valley University, Qena (Approval No, VM/SVU/23(2)-25).

Drugs Nopain[®] (nefopam hydrochloride 20 mg/ml) was purchased from MUP-Egypt, Xyla-ject[®] 2% (Xylazine HCL 20 mg/ml) was purchased from ADWIA co.10th of Ramadan city. Egypt, ketamine[®] (Ketamine HCL 50 mg/ml) was purchased from Sigma-Tec pharmaceutical Industries – Egypt, and Diprifan[®] 10% (Propofol 100 mg/ml) was purchased from B.Braun Melsunges AG Germany.

Experimental animals

The experiment was performed on five healthy local donkeys of age ranging from 5-8 years and 95 ± 59 kg body weight. The donkeys were housed in the Teaching farm of the Faculty of Veterinary Medicine, South Valley University, Qena, Egypt. The donkeys were fed on green fodder, hay and supplemented with concentrates, and water was freely accessed. The animals were kept for two weeks for acclimatization before the experiment. The donkeys were examined clinically before and throughout the experiment.

The site of IV injection was clipped, shaved, and aseptically prepared, and 18-gauge intravenous catheters were inserted at a 30-45° angle in the jugular vein and

used for intravenous (IV) injection of drugs and collection of blood samples. The catheter was fixed without using local anesthetic which provides the efficiency of controlling pain in the case of using nefopam. A normal saline 500 ml and micro-dropper set was used for continuous infusion for 19 ± 2 minutes.

Throughout 9 pilot studies; Nopain[®] was injected intramuscularly at a dose of 0.2-0.5 mg/kg before injection of pre-anesthetic anesthesia within 30 minutes with Xyla-ject[®] 2% that was administered

intravenously at a dose of 0.5- 1.1 mg/kg 5 minutes before induction of anesthesia (Zero time). Ketamine[®] was injected intravenously at a dose of 2-2.5 mg/kg. Diprifan[®] 10% was administered intravenously at a dose of 2-4 mg/kg as a continuous infusion (drip). The best dose and anesthetic combination which proved good anesthetic criteria was selected for further experimental investigation (Table 1).

Table (1): Composition, doses, and time of administration of the anesthetic combinations:

	Drug	Dose	Time
Combination	Nefopam HCL (0.1 %)	0.4 mg/kg I/M	30 minutes prior to induction of anesthesia
	Xylazine HCl (20mg/ml)	1.1 mg/kg I/V	starting time
	Ketamine HCl (50 mg/kg)	2.2 mg/kg I/V	5 minutes following xylazine administration.
	Propofol (10mg/ml)	2 mg/kg (Administered as continuous infusion in normal saline)	5 minutes following ketamine administration.

Monitoring the clinical effects of the anesthetic drugs

Following the injection of xylazine, animals were monitored for observing the signs appeared after pre-anesthetic medicine injection, induction, and maintenance by anaesthetic drug infusion.

Criteria for scoring the quality of induction, muscle relaxation, and recovery

Scoring the quality of induction, muscle relaxation, and recovery were assessed against criteria used by Ghurashi et al. (2016), such as induction score, sedation score, analgesic score, muscle relaxation score, and recovery score.

Induction score

Score	Quality	Character
1	Smooth	Gradual falling to the ground with no paddling and no stiffness of limbs
2	Fair	Gradual falling to the ground with mild paddling and no stiffness of limbs
3	Rough	Gradual falling with vigorous paddling and stiffness of limbs

Sedation score (Valverde et al., 2004)

Grade (0): no sedation.

Grade (1): mild sedation: less alert but still active.

Grade (2): moderate sedation drowsy: recumbent but can stand and walk.

Grade (3): deep sedation very drowsy: recumbent and unable to walk.

Analgesic score (Torad et al., 2009)

Grade (0) normal: Response to pointed stimulus.

Grade (1) mild analgesia: Depressed reaction to a painful stimulus.

Grade (2) moderate analgesia: No response to skin pricks.

Grade (3) complete analgesia: No response to muscle pricks.

Assessment of the depth of anesthesia was judged by certain tests, including the presence or absence of reflex responses, in the anesthetized subject to stimuli, among these reflexes: tongue reflex, palpebral reflex, corneal reflex, swallowing reflex, pedal reflex, anal reflex, and tail reflexes. They represented by the following plus system:

+++	Normal reflex
++-	Sluggish reflex
+--	Very sluggish reflex
---	Abolished reflex

Reflexes

The following reflexes were monitored closely, and remarks were recorded immediately for assessment of anesthetic depth as the following:

Muscle relaxation score

Score	Quality	Character
1	Excellent	Complete relaxation (jaws, neck, abdomen, and limbs)
2	Good	Relaxation of neck, abdomen, and limbs
3	poor	Rigidity in muscles of jaws, neck, abdomen, and limbs

Tongue reflex

It was assessed by pulling the tongue outside the mouth. When the animal retracts its tongue into the mouth, the reflex was considered positive (Nuha, 2004).

Palpebral reflex

Its reflex was assessed by digital touch on the canthus or eyelashes, if a purposeful motor reflex was observed, the reflex was considered positive (Batoul, 1990).

Corneal reflex

It was assessed positively when blinking induced by a gentle touch of the cornea and it is usually lost after the palpebral reflex (Tranquilli et al., 2013).

Swallowing reflex

External digital pressure on the larynx was used to assess the swallowing reflex. The positive response was considered when swallowing or laryngeal movements were observed (Rawlings and Kolat, 1983).

Pedal reflex

Pedal reflex was assessed by pinprick on the coronary band of the digit. If the animal moves its leg or leg muscle, the reflex was considered positive (Williams and Wyatt, 2007).

Anal reflex

Anal reflex was assessed by inducing tension of the anal sphincter with two fingers. The positive response was considered when the movement of the anal sphincter was noticed (Subjective).

Recovery score

Score	Quality	Character
1	Smooth	Donkey capable of standing at first attempt-mild ataxia
2	Fair	Donkey remained calm and needed two-three attempts to stand- clear ataxia
3	Poor	Donkey remained calm but was assisted to stand
4	Very poor	Donkeys' excitement during recovery - assisted and supported

Anesthetic Phases**Induction phase**

It is the time calculated as the elapsed period between the end of an anesthetic injection and the beginning of recumbency.

Duration of lateral recumbency

It was measured as the duration between the beginning time of lateral recumbency and when the animal exhibited sternal recumbency (Ghurashi et al., 2008).

Duration of sternal recumbency

It is a period between starting of sternal recumbency without returning to lateral recumbency till the beginning of the unaided standing of the donkey (Ghurashiet al., 2008).

Duration of standing

It is a time between the unaided standing of the donkey till walking for a few steps (Ghurashi et al., 2007).

Total anesthetic time

It is the duration between the beginning of anesthesia till complete recovery (animal walking) (Nuha, 2004).

Physiological parameters

Respiratory rate (breaths/min), heart rate (beats/min) and rectal temperature (°C) were monitored and recorded before premedication and at 15, 30, 45- and 60-minutes interval using standard methods (Kelly, 1984).

Biochemical analysis

Two blood samples (with and without anticoagulant) were collected from the jugular vein before the premedication, at 15, 30, 45 and 60 min and after complete recovery of general anesthesia to evaluate

the effect of the anesthesia on blood picture, the liver and kidney functions.

Blood picture

The samples were collected in centrifuge tubes with and without anticoagulant using standard technique. Then subjected to the following examinations which described by Fawcett and Scott (1960); Barham and Trinder, (1972) and Reitman and Frankel (1957).

1) Liver function tests: by colorimetric determination of serum transaminases using reagent kits (M/S Transasia Biomed Pvt Ltd, India):

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Kidney function tests:

a) Serum creatinine determination: by colorimetric method.

b) Serum urea determination: by enzymatic method according to calorimetric methods described by Fawcett and Scott (1960); Reitman and Frankel (1957) and Barham and Trinder (1972).

Clinical observation

Study animals were undergone close visual examination during full period of the experiment for monitoring and detecting any signs related to the study protocol.

Statistical analysis

The data were analyzed by One Way Analysis of Variance (ANOVA) using SPSS Version 16.00. The results were expressed as Mean \pm Standard error and a value of $p \leq 0.05$ was considered statistically significant.

Results

Efficiency of the anesthetic combination

A dose of 2.2 mg/kg b.w.t of ketamine hydrochloride was sufficient to produce a smooth induction within one minute of starting ketamine administration in 3 donkeys and providing mild sedation in one donkey while the 5th showed moderate

sedation. A dose of 2 mg/kg b.w.t of Propofol administration by infusion provided anesthesia for 31±1.85 minutes, with a duration of ketamine induction of 11±3.83 minutes.

A period of 48.33±3.10 minutes was required for unaided standing with a smooth recovery (Table 2).

Table (2): Anesthetic efficiency of the proposed combinations:

Group	Onset of anesthesia (Seconds)	Quality of induction (min)	Duration of induction (min)	Duration of maintenance (min)	Duration of recovery (min)
Combination	66 ±6 .53	Smooth	11 ±3.83	31 ±1.85	48.33±1.10 smooth recovery

Values are Means±SE.

Following ketamine injection, all the studied donkeys showed moderate to deep sedation (very drowsy, recumbent, and unable to walk), and complete analgesia was encountered in 4 donkeys with moderate analgesia in one donkey. After induction and during the maintenance period, complete analgesia was demonstrated in all donkeys.

With regards to the depth of anesthesia, pedal and palpebral reflexes showed a slight depression in all donkeys

with normal swallowing, and anal reflexes, while corneal, and tongue reflexes were sluggish in 3 donkeys.

Muscle relaxation was evident in all donkeys. After ketamine induction, the moderate plane of anesthesia was achieved with a good degree of muscle relaxation.

On Propofol infusion, deep anesthesia was maintained with very good muscle relaxation in 2 donkeys and good relaxation in 3 donkeys (Table 3).

Table (3): Influences of administration of the proposed drug combinations on analgesia, body reflexes and muscles

Group	Stage	Analgesia grade	Body reflexes				Corneal reflex	Muscle relaxation
			Palpebral	Pedal	Anal	Swallowing		
Combination	Zero time	2	0	0	0	0	0	----
	After induc 15 min	2-3	2	2	2	2	2	2

	30 min	3	3	3	3	3	3	1-2
	45 min	3	3	3	3	3	3	1
	60 min	2	0	0	1	1	0	2
	After recovery	0-1	0	0	0	0	0	-----

With regards to the heart rate induction, xylazine/ ketamine/ propofol combination induced a slight decrease in heart rate after injection of Propofol within normal saline compared with the recorded data compared after induction, this increase occurred for heart rate was evident.

The respiratory rate showed a significant decrease from the beginning of the entire observation period.

Concerning the changes in body temperature, an insignificant decrease after induction was noticed but after injection of Propofol, a significant decrease was recorded during the observation periods (Table 4).

Table (4): Changes in heart rate, respiratory rate, and body temperature following administration of the anaesthetic combinations

Group	Stage	Heart rate	Respiratory rate	Body temperature	
Combination	Zero time	48 ± 0.65	26.90 ± 0.45	38.49 ± 0.44	
	After induction	15 min	47.35 ± 1.89	23 ± 1.80*	37.23 ± 0.23
		30 min	47 ± 3.22	23.23 ± 1.18	37.32 ± 0.37
		45 min	46 ± 1.45	24.05 ± 0.90	37.67 ± 0.18
		60 min	47 ± 0.52	23.65 ± 0.40	37.77 ± 0.11
	After recovery	48.02 ± 1.50	25.86 ± 0.40	38.05 ± 0.45	

Values are Means ± SE *p< .05.

A significant change in AST activity levels was recorded at 15 min. while in combination serum urea showed non-significant changes at any recorded time. While Creatinine levels showed a significant increase at 45 min (p=0.001) during the entire observation period.

Serum ALT showed a significant increase at 45 min (p=0.026) of the entire observation period while AST activities showed insignificant decreases along the observation periods (p=0.015).

On RBCs, WBCs, and HB values, a non-significant increase in these variables

was recorded after induction while these parameters showed a non-significant increase at 30 and 60 minutes following Propofol injection (No statistical differences were found).

With regards to the effect of the combination on leukogram, the obtained

results revealed a significant increase in lymphocytes at 60 minutes after induction ($p=0.049$). On the contrary, the monocyte counts significantly decreased only at 15 min ($p=0.01$) during the whole experimental period (Table 5).

Table (5): Blood picture before and after administration of combination

Time		RBcs ($\times 10^6/\mu\text{l}$)	HB (gm/dl)	WBcs ($\times 10^3/\mu\text{l}$)	Lymphocyte ($\times 10^3/\mu\text{l}$)	Monocyte ($\times 10^3/\mu\text{l}$)	Platelets ($\times 10^3/\mu\text{l}$)
Zero time		4.55 \pm 0.50	8.94 \pm 0.09	13.48 \pm 0.17	52.23 \pm 1.45	20.03 \pm 0.03	133.67 \pm 0.89
After induction	15 min	4.53 \pm 0.07	8.9 \pm 0.20	11.34 \pm 0.19	52.21 \pm 0.24	17.22 \pm 0.02*	128.28 \pm 0.69
	30 min	4.57 \pm 0.11	8.85 \pm 0.11	11.10 \pm 0.45	55.41 \pm 0.78	19.35 \pm 0.33	130.35 \pm 0.31
	45 min	4.88 \pm 0.22	8.89 \pm 0.11	12.54 \pm 0.54	56.55 \pm 0.05	19.04 \pm 0.01	130.55 \pm 1.61
	60 min	4.76 \pm 0.15	9.17 \pm 0.21	12.26 \pm 0.62	60.76 \pm 0.21*	19.56 \pm 0.02	132.69 \pm 0.58
After recovery		4.60 \pm 0.13	8.89 \pm 0.04	13.55 \pm 0.05	53.15 \pm 0.01	20.23 \pm 0.33	133.17 \pm 1.49

Values are Means \pm SE * $p < .05$

Clinical observation

All donkeys showed no signs of pain during the injection. During the recovery period, one donkey urinated while standing from recumbency. All donkeys recovered smoothly with lateral and sternal positions from 6 up to 10 minutes. The voluntary swallowing returned during the recovery period and the sternal recumbency was observed in 3 donkeys.

Discussion

Following nefopam and xylazine premedication, all the studied donkeys showed moderate to deep sedation with complete analgesia. In previous studies, a smooth rapid recovery was observed in propofol-administered animals (Branson and Gross, 1994; VanNatta and Rex, 2006;

Branson, 2011) that is consistent with our findings that revealed a very good muscle relaxation in all donkeys. An excellent smooth recovery was encountered in all animals subjected to a combination regimen of general anesthesia. In addition, propofol reduces the cardiac output and the total peripheral resistance despite unchanged or increased heart rate (Fusellier et al., 2007). Xylazine induction and the addition of propofol in normal saline minimized the occurrence of depression in case of using ketamine and propofol alone. Also, nefopam has been shown no significant circulatory or respiratory depression (Al-hussainy et al., 2022).

On the other hand, it was reported that injected animals with xylazine-propofol showed a distinct increase in heart rate and the marked decrease in respiratory rate which were observed with using propofol as a general anesthetic in equines (ElSayad, 2006).

Concerning the body temperature, there was a slight decrease in body temperature after induction in all animals but after injection of propofol, a significant decrease was recorded during the observation periods. Meanwhile, Sinclair (2003) reported that α_2 agonists were better for the maintenance of body temperature which may be attributed to their peripheral vasoconstriction action along with the central redistribution of blood with subsequent reduction in the cutaneous temperature.

The hematological results of RBCs, WBCs, and HB values after induction and following propofol administration were increased. On the contrary, Atalan et al. (2002) reported a significant decrease in hematocrit percentage in dogs subjected to anesthesia by xylazine–ketamine.

Moreover, TLC increased due to the increased blood flow through the microcirculation and redistribution of white blood cells which is considered responsible for this increase after induction of ketamine as was also stated by Greene (2001); Latimer (2011) except monocyte count significantly decreased only at 15 min. The data of serum biochemical assays implicated a significant increase in serum ALT activities and creatinine along the entire recorded periods and this agreed with Short and Bufalari (1999) who mentioned that, Propofol was rapidly metabolized with minimal body accumulation which was considered a factor suitable for maintenance of

anesthesia. Similar results were reported by Sano et al. (2003) who said that Propofol is a drug of choice essential for induction and maintenance of general anesthesia in small animals.

Serum biochemical parameters (urea levels) showed no significant changes at any recording time. These results agreed with Fusellier et al. (2007) who reported that there was no change in GFR during anesthetic episodes of Propofol (6 mg/kg).

Ketamine is a dissociative anesthetic agent, when used in combination with xylazine or diazepam for induction of anesthesia produces a good degree of muscle relaxation and a good score of sedation and analgesia with a relatively prolonged anesthetic stage. Moreover, ketamine prevents respiratory depression which was seen when propofol was given alone (Clarke et al., 2014).

Conclusion

It could conclude that Nefopam/xylazine/ketamine and propofol combination was more suitable for the reduction of pain as a result of a short surgical interference with regards to the improvement of their anesthetic effects and counteracting some of their depressants effects on vital, hematological, and biochemical parameters.

The current study showed that nefopam/xylazine/ketamine and propofol combination was of an improved anesthetic effect. Also, the depressants effects of single use of the studied agents were unnoticeable in our study via evaluating the vital, hematological, and biochemical parameters.

Authors' contributions

ASS and AAA conceived and designed the study. KMA carried out the experimental procedures; KMA wrote, edited, and reviewed the manuscript. All

authors have read and agreed to the published version of the manuscript.

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