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Comparison of Dexmedetomidine-Nalbuphine combination Vs. Dexmedetomidine alone on clinical, behavioral and biochemical investigations in goat received total intravenous anesthesia via Ketofol

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ABSTRACT

The quality of sedation and analgesia on behavioral, cardio-pulmonary, and biochemical effects of a novel pre-anesthetic medication, consisting of dexmedetomidine (DEX) alone Vs dexmedetomidine-nalbuphine combination (DEX-NAL) in bucks undergoing total intravenous anesthesia (TIVA) using ketamine and propofol (Ketofol) for induction and maintenance, respectively. Six clinically healthy bucks were randomly assigned into two groups. The first group was subjected to an intravenous injection of DEX (3 µg/kg BW), and the second one was injected with DEX-NAL (DEX 3 µg/kg BW & nalbuphine 0.5 mg/kg BW). Anesthesia was induced by intravenous ketamine (5 mg/kg BW) and maintained through intermittent bolus of propofol (2 mg/kg BW). Sedative, analgesic, behavioral, cardio-pulmonary, and biochemical effects of DEX and DEX-NAL were evaluated before any treatment (s) (baseline), after premedication, after induction and at 5, 15, 30, 45, 60, 75, 90 and 120 minutes after drug administration. The use of DEX-NAL combination provided a deeper, potent, rapid onset, smooth induction and recovery, prolonged sedation, anesthesia, and total recovery time than DEX alone. There were higher scores of behavioral parameters, and significant hemodynamic and cardiovascular stability in DEX-NAL group than DEX group. This study concluded that adding NAL to DEX, a novel pre-anesthetic regimen, before TIVA induced by Ketofol improves the quality of anesthesia and recovery with acceptable cardiopulmonary and biochemical outcomes in goats.

1. INTRODUCTION

Goats have been used as animal models in several investigations, particularly in medical, chemotherapeutic, orthopedic, cardiovascular, reproductive, laparoscopic intervention, and psychological practice. (Zhang et al., 2020; El-Kasapy, 2023). The urgent need to attain of satisfactory anesthetic protocol for those investigations or other surgical interventions is gaining much attention (Abouelfetouh et al., 2022).

The balanced anesthetic protocol is a combination of medications that generate general anesthetic effects while having minimal adverse effects on cardiopulmonary function as compared to using one drug alone (Straticò et al., 2021).

Multimodal anesthesia is the use of different anesthetic agents to achieve at least approximately each of the separate characteristics of the anesthetic state (Brown et al., 2018). The idea behind Multimodal anesthesia is that the combined medications will work in harmony and minimize the side effects by producing anxiolysis, smooth induction, optimal analgesia, hypnosis, and muscular relaxation, and lowering dose requirements for anesthetic agents (Abouelfetouh et al., 2021).

The development of anesthetic combinations with selective opiate receptor activation has resulted in improved analgesia while minimizing respiratory depression and excitatory effects (Helal et al., 2024).

Alpha2 adrenergic agonists, opioids, and ketamine have been used and act synergically to produce multimodal analgesia in different animals (Sabek et al., 2021; Abouelfetouh et al., 2022 and Helal et al., 2024). In a clinical setting, an opioid and a tranquilizer or sedative are commonly chosen to provide neuroleptic analgesia, thus creating a calmer patient who is not aroused during induction (Weil & Baird 2020). Furthermore, the addition of opioids to the general anesthesia regimen is beneficial for postoperative pain and myoclonus (Ju et al., 2020).

NAL is an opioid agonist-antagonist and has been progressively used for postoperative analgesia over the last decade (Singh et al., 2024) . Recently, NAL has been an important element of multimodal anesthesia and used as a pain-relieving medication for moderate, severe conditions and gynecological interferences (Amin et al., 2020). NAL has been used in veterinary practice in parenteral

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administration and achieving an amazing result in cats (Kreisler et al., 2020), in dogs (Torad and Hassan 2018), in donkeys (Helal et al., 2024), and in camels (Khalil et al., 2019).

DEX is the most selective for the α2-adrenergic receptor and the most potent member of the α2-agonists available (Di Franco et al., 2023). It has analgesic effects with minimal cardiovascular responses both intraoperatively and postoperatively (Naddaf et al., 2015) and owing to minimal respiratory depression (Gerlach et al., 2009). DEX causes manageable bradycardia, a decrease in cardiac output, and an initial elevation in systemic arterial blood pressure (BP) followed by hypotension. In total intravenous anesthesia, premedication with DEX-NAL produces excellent quality anesthesia, analgesia, sedation, and muscle relaxation. Furthermore, it produces a longer duration of anesthesia, sedation, and analgesia (Helal et al., 2024).

Ketamine is a dissociative anesthetic agent that is considered the chief component in anesthesia management for small ruminants, it can be used for anesthesia in sheep and goat without the fear of causing convulsion (Berry 2015).

Propofol (2, 6-diisopropyl phenol) is a non-barbiturate, non-dissociative, and non-cumulative intravenous anesthetic agent that belongs to the alkyl phenol group (Hall et al., 2001). Propofol is the most popular maintenance agent with its favorable characteristics of short acting, rapid and smooth induction and recovery, and rapid elimination from the blood circulation, making the drug potentially useful in ruminants in which these features are particularly desirable. (*Prassinos et al., 2005)*. However, despite these advantages, it carries risks of respiratory depression and hemodynamic instability (Hall et al., 2001). It is recommended to combine propofol with an analgesic agent, opioid or alpha-2-adenoreceptor agonist, for painful procedures to improve muscle relaxation and reduce the required dose of ketamine and propofol and maintain haemodynamic and cardiopulmonary stability (Kathy et al., 2012).

Ketofol combination, which means using ketamine for induction and propofol for maintenance of general anesthesia, provides satisfactory induction and muscle relaxation with a longer anesthetic period and smoother recovery, which seemed due to the synergistic effect exerted by the mixture (Naddaf et al., 2015).

This study hypothesized that the addition of Nalbuphine to dexmedetomidine pre-medication would enhance TIVA achieved by Ketofol combination using ketamine induction and propofol maintenance with no hazard on cardiopulmonary and hemodynamic stability in bucks.

To knowledge, the combination of DEX-NAL in one regimen has been used before in donkeys (Helal et al., 2024), but has not been applied in goats; therefore, the current study was conducted to evaluate the cardio-pulmonary, behavioral, and biochemical effects of DEX-NAL combination Vs DEX alone on TIVA of bucks using ketamine for induction and propofol for maintenance.

2. MATERIAL AND METHODS

The study was conducted after approval from the institutional animal ethics committee of the faculty of veterinary medicine, Benha University, Egypt, and provided approval number (BUFVTM 07-01-024).

2.1 Animals and management

Six apparently healthy native adult male goats (bucks) aged 2.0 - 2.5 years with an average body weight of 20.00±3.57 kg were used in this study. All bucks were dewormed and kept in a group pen at Faculty of Veterinary Medicine, Benha University in June 2023, for two weeks before the experiment for acclimatization. The animals were fed with a constant mixture of alfalfa hay and corn 15 kg per head, supplemented with minerals and fresh water also provided. The bucks were allocated to two groups according to the anesthetic protocols. The bucks were fasted from food and water for 12 and 8 hrs, respectively, prior to anesthetic induction. On the day of the experiment, skin over the left jugular vein was clipped, scrubbed with povidone-iodine and cannulated in the jugular vein using 20- gauge cannula for drug injections.

2.2. Drugs used

2.2.1. Atropine sulfate 1% solution (2 ml ampoule (Atropine®; Sigma Tec Pharma., Egypt).

2.2.2. Dexmedetomidine 4 µg/ml (Medrelaxmidine®; Arabcomed Arab co., Cairo, Egypt).

2.2.3. Nalbuphine Hydrochloride 20 mg/ml (Nalufin®; Amoun Pharm, Egypt).

2.2.4. Ketamine 50 mg/ml (Ketamine®; Sigma Tec Pharm., Egypt)

2.2.5. Propofol 10 mg/mL (Lipuro®; B. Braun Melsungen AG, Melungeon, Germany).

2.3 Experimental design

Six bucks were allocated into two groups (3 animals/group). Both groups received atropine sulfate at a dose of 0.05 mg/kg by slow IV injection per 2 minutes (Sahay & Dass 2005). Two minutes later, preanesthetic medication achieved by DEX alone in group 1(G1) at a dose of 3 µg/kg BW by slow IV injection per 2 minutes (Di Franco et al., 2023) and DEX-NAL combination in group 2 (G2) at a dose of 3 µg/kg and 0.5 mg/kg BW for DEX and nalbuphine, respectively (Abouelfetouh et al., 2022) by slow IV injection in one syringe per 2 minutes. Ten minutes later, the induction of anesthesia was achieved by Ketamine HCl at a dose of 5 mg/kg BW by slow IV injection per 2 minutes (Celestine et al., 2014). Anesthesia maintenance was achieved through a total maintenance dose of propofol was 2 mg/kg BW (Njoku 2015). The total dose was divided into 4 equal doses; each one was given as a bolus rapidly after reaching to score 2 pedal reflexes.

2.4 Assessment of anesthesia

The anesthetic effect of both protocols was evaluated depending on clinical, behavioral, physiological, echocardiographic and hematobiochemical analysis.

2.4.1 Clinical examination: depends on the following parameters:

a. Onset of sedation: it was recorded by measuring the interval between injection of the drug and appearance of the first signs of relaxation.

b. Duration of sedation: it was considered as the interval from the appearance of the first signs of relaxation to the time point of standing up and walking normally without ataxia.

c. The onset of anesthesia: it was recorded by measuring the interval between the injection of the drug and the absence of reflexes.

d. Duration of anesthesia: it was considered as the interval from the absence of reflexes and return of reflexes.

e. Total recovery period: it was estimated as the interval from the absence of reflexes until the animal stood.

f. Quality of induction and recovery was recorded and classified according to Abouelfetouh et al. (2022) as good, fair, and poor induction or recovery as followings:

=== Induction ==	*Good*	Induction was smooth, rapidly returned to the recumbent position, and absence of any excitement
	Fair	Induction was slightly prolonged, excitation was mild, and swallowing reflex was present
	Poor	Excitement was obvious, animal jumped or attempted to stand after recumbence, and full swallowing reflex was present
===== Recovery ======	*Good*	Recovery was smooth, the animal easily returned to alertness, sternal position recurred, stood up within a short time, and walked with less ataxia
	Fair	Transient excitation or movement of the whole body, some struggling was observed, excessive response that disappeared as soon as animal stood up unaided, and with moderate ataxia
	Poor	Stereotype behavior as circular movement, premature trials to stand, and struggling was prolonged

g. The depth of sedation and analgesia was recorded each minute post-injection and graded on a scoring system from 0 to 3, as described in Table (1) as modified from Ragab et al. (2022) for sedation and Halfaya (2017) for analgesia.

h. The onset and depth of analgesia were evaluated by "pin prick test" recording the response of the animal to pinching with a sterile needle and hemostat clamp (closed to the first ratchet). A positive pain response was defined as the purposeful avoidance movements of the limbs, attempts to kick, and turning of the head toward the stimulus site. As soon as the goat showed one of the defined responses, the clamp was removed. The anesthetized animals were then positioned on the right side; their heads were elevated to allow free drainage of saliva.

Several reflexes, such as jaw relaxation, palpebral and pedal reflexes, were scored on a scale system from 0-3 according to Negi et al. (2024) (Table 1).

2.4.2 Behavioral evaluation

The examiner, who was unaware of the injected drugs, stood a suitable distance from the animals to make a good observation, estimated the body language and scaled on behavioral scoring parameters at each point post-injection, such as head deviation, tongue protrusion, and salivation at the baseline on a scale from 0 to 3 (Table 2) as modified from Khalil et al. (2019) and Ragab et al. (2022).

2.4.3 Physiological parameters:

Heart rate (HR, beats/min), respiratory rate (RR, breaths/min), rectal temperature (RT, °C), non-invasive arterial blood pressure (mmHg) and Systolic arterial pressure (SAP) (mmHg), mean arterial pressure (MAP) (mmHg) , diastolic arterial pressure (DAP) (mmHg), and hemoglobin oxygen saturation (SpO2) (%) were recorded using a multiparameter electrocardiogram monitor (PM-9000 Express, Mindray Co., Ltd., Shenzhen, China) (Abouelfetouh et al., 2021). These parameters were recorded at 0 min (baseline) and subsequently after premedication, induction, and at 5, 15, 30, 45, 60, 75, 90, and 120 minutes after drug administration.

2.4.4 Biochemical parameters:

a. Blood sampling

Blood samples were taken from bucks at 0 (baseline) then after premedication, after induction and then after 5, 15, 30, 45, 60, 75, 90 and 120 minutes from drug administration and divided into two parts: one put into fluoride tube for glucose analysis, and the other part put in plain tube to obtain the serum after centrifugation at 3000 rpm for 15 minutes. The clear serum was collected and stored at -20°C till biochemical analysis of ALT, AST (liver enzymes) and LDH, CpK (cardiac enzymes), as well as cortisol analysis.

b. Biochemical analysis

The concentration of glucose was determined as described by Caraway and Watts (1987), and the activities of ALT, AST according to Young (1997), using JENWAY 6051 Colorimeter U.K device with its specific Spectrum GmbH Company kits (CAT. NO. 250001; 264001; 260001, respectively). The activities of LDH and CpK were evaluated as described by Friedman and Young (1997), using Sphera (Italy), with the manufacturer-recommended reagent kit (Autobio Diagnostics Co., LTD), CAT. NO. 12580; 11790, respectively. The concentration of cortisol was determined using Auto Lomo A1000 (China), with the recommended reagent kit (Autobio Diagnostics Co., LTD), CAT. NO. CMD0302, (Levine et al., 2007). Blood urea nitrogen (BUN) (mg/dl) was estimated by the enzymatic colorimetric method (Chaney and Marbach 1962). Creatinine was estimated, and values were expressed by mg/dl through enzymatic method by using Creatinine colorimetric assay kit reagent according to Prabhu et al.,(2022).

Table 1 Description of sedative scores (Ragab et al., 2022), analgesic scores (Halfaya, 2017), body reflexes (Negi et al., 2024).

Score		Sedation	Analgesia	Body reflexes		
				Jaw relaxation R.	Palpebral R.	Pedal R.
0	No	Goat revealing the initial attitude	noxious Strong response to stimulus	Not permitting jaw opening	Intact and robust (rapid blink)	Intact and powerful (potent withdrawal)
1	Mild	Low head carriage, "droopy eyelid," ptyalism, and diminished reaction to external stimuli	Weak response at all times of noxious stimulus	The animal resists opening and closes its jaw rapidly	Intact but weak (slow response)	Intact but weak (animal response slowly)
2	Moderate	Head lowers toward the ground, swaying of hind legs and attempts to lie down but aroused with stimulation	Very weak occasional Response	The animal has less resistance to opening its jaw and wrapping it slowly	Intact but very light (slow and occasionally response)	Intact but very light (slow and occasional response)
3	Sever	Recumbence and impassive to external stimuli	No response to noxious stimuli	There is no resistance and the jaw still opens	Abolished completely	Abolished completely

Table 2 Behavioral scoring parameters (Khalil et al., 2019).

Clinical parameter	Score			
	0	1	2	3
Head deviation	No deviation	Mild deviation to one side	Moderate deviation to one side	Severe deviation, head rest on the back
Gait	Normal gait	Mild sedation causes mild ataxia (abnormal movement)	Moderate ataxia	Severe ataxia and the buck may fall while walking
Tongue protrusion	Tongue inside the mouth, no protrusion	Small part of tongue gets out from one side of the mouth	Large part of tongue gets out from one side of the mouth	The whole tongue is outside the mouth
Salivation	No salivation	Little drops get out from the mouth	Many drops get out from the mouth	Excessive salivation, like a rope hanging from the mouth

2.5 Statistical analysis

Data analysis was done using SPSS version 22. An Independent *t*-test was used to assess the data. A Shapiro-Wilk test was used to determine if the distribution of the data was normal. The data were presented as means and standard errors. The difference in the data was defined as P≤ 0.05.

3. RESULTS

3.1. Clinical parameters:

Onset of sedation (sec), duration of sedation (min), onset of anesthesia (sec), time from induction till maintenance (min), maintenance period (min), total time of anesthesia (from beginning of induction until the end of maintenance), total recovery time (min), sedation quality and analgesia Quality were estimated and recorded in Table (3).

Sedation (time and score)

The sedative effects of intravenous injection of DEX-NAL combination as a premedication revealed that the mean values of onset of sedation and duration of sedation were (3.00±0.57 sec and 100.02±0.88 min), respectively. The sedative effects of intravenous injection of DEX alone revealed that the mean values of onset of sedation and duration of sedation were (8.33±0.88 sec and 84.66±0.88 min), respectively. These results asserted that DEX-NAL group showed a significantly (P ≤ 0.05) rapid onset of sedation and longer duration of sedation than DEX group.

Regarding the quality of sedation, severe sedation was predominant in all animals of DEX-NAL group score 3, while DEX group revealed a mild to moderate sedation score 2. Snoring sound and vocalization were clear in DEX group throughout the entire sedation period, while in DEX- NAL group it was absent. The results showed that premedication using intravenous injection of DEX- NAL combination produced significantly (P ≤ 0.05) profound sedation than using ~~of~~ DEX alone.

Induction (time and Quality)

Concerning the anesthetic effects of each group after induction by IV injection of ketamine, DEX-NAL significantly (P ≤ 0.05) hasten (4.00±1.15 sec) the onset of anesthesia than DEX alone (9.00±0.57). Moreover, DEX-NAL significantly (P ≤ 0.05) prolonged the duration of anesthesia from induction till injection of the first bolus of propofol from 16.00±0.57 min in DEX group to 24.00±0.57 min in DEX-NAL group.

Following the administration of ketamine, good induction was observed in all bucks that received DEX- NAL combination, and there was a smooth induction; the animal quickly transitioned to recumbent position with the absence of any excitement. Whereas among those that received DEX alone, the quality of induction ranged from fair to good, with more prolonged induction and mild excitation.

Analgesia score

The quality of analgesia was remarkably enhanced in the DEX-NAL group. DEX-NAL group exhibited severe analgesia (score 3) without any response to external painful stimuli after premedication until T75, moderate analgesia (score 2) at T90, and no analgesia (score 0) at T120. However, at DEX group analgesic score fluctuated from moderate (score 2) after premedication, severe (score 3) after induction up to T45, moderate (score 2) at T60, mild (score 1) at T75, and no analgesia (score 0) at T90.

Recovery (time and quality)

The total recovery period and the quality of recovery were significantly (P ≤ 0.05) improved in DEX-NAL group than in DEX group. All bucks in DEX-NAL group revealed good recovery and transited from lateral recumbence to sternal recumbence and then standing position without any excitement, whereas most goats in DEX group exhibited good to fair recovery, with some struggling but standing up unassisted with moderate ataxia. DEX-NAL treated bucks needed a total recovery period of 9.66±0.33 min while DEX treated bucks needed a total recovery period of 18.00±0.57 min to transition from lateral recumbence after the return of reflexes to the standing up position.

Estimation of Reflexes according to Numerical scoring system.

Each group displayed a characteristic reflex score fluctuation, which supported the fact of deeper sedation and smoother recovery in DEX-NAL group when compared with DEX group alone. DEX-NAL group reached the highest score rapidly, which lasted for an adequate period and decreased gradually to return to score 0 at T120. DEX group reached the highest score later and decreased sharply to return to score 0 at T90. In DEX group, score 2 jaw relaxation reflex was recorded after premedication till T60 and sharply returned to score 0 at T90. Whereas DEX-NAL exhibited score 3 after premedication till T75 and then gradually returned to score 2 at T90 then score 0 at T120. Palpebral reflex score in DEX group scored 2 up to T30, scored 3 at T45 and T60, then sharply returned to score 0 at T90. Whereas in DEX-NAL. group Scored 3 after premedication till T60 and then gradually returning to scored 2 at T75 and T90 and reach score 0 at T120. Animals receiving DEX- NAL revealed a centrally fixed eyeball during the entire period of induction, which means the animal was in complete deep anesthesia; however, in DEX group eyeball was fixed downward. In DEX group, pedal reflex scored 2 after premedication till T15, scored 3 at T45 and T 60 then sharply returned to score 0 at T90, whereas DEX-NAL group recorded score 3 after premedication till T60 and gradually returned to score 0 at T120 (Table 4).

3.2 Evaluation of Behavioral Parameters

The post-administration sedative effect was evaluated through a change in body language such as gait scoring, head-to-ground distance, tongue protrusion, head deviation, and salivation. The degree of ataxia was recorded through monitoring the gait scoring; DEX-NAL group exhibited a significantly higher score (score 2) than DEX group (score 1) after premedication. At T90, the gait score in DEX group was mild (score 1) and returned to normal at T120 (score 0).

Table 3 Results of the onset of sedation (sec), duration of sedation (min), onset of anesthesia (sec), time from induction till maintenance (min), maintenance period (min), total recovery time (min), sedation quality and analgesia quality for DEX group (G1) and DEX- NAL group (G2).

Parameters	G1 (DEX)	G2 (DEX-NAL)
Onset of sedation (sec)	8.33±0.88*	3.00±0.57
Duration of sedation (min)	84.66±0.88	100.02±0.88*
Onset of anesthesia (sec)	9.00±0.57*	4.00±1.15
Time from induction till Maintenance (min)	16.00±0.57	24.00±0.57*
Maintenance period (min)	48.66±5.23	50.66±2.33
Total time of anesthesia (from beginning of induction until the end of maintenance) (min)	64.00±4.72	74.66±2.96*
Total recovery time (min)	9.66±0.33	18.00*±0.57*
Sedation quality	2.00±0.00	3.00±0.00*
Analgesia quality	2.00±0.00	3.00±0.00*

Mean (± SE) with a star symbol "*" in the same row is significantly different at p≤ 0.05.

While DEX-NAL group still recumbent at T90 and returned to normal gait at T120. The distance between the head and ground showed a lower value after premedication with a significant change than in DEX group-. However, there's no significant difference in head ground between the two groups at T90 and T120. In DEX group Tongue was mildly protruded after premedication up to T75 (score 1) and remained inside the mouth at T90 (score 0). However, In DEX-NAL group, tongue protrusion was moderate after premedication up to T90 (score 2) and returned to normal at T120 (score 0). Head deviation in DEX group was moderate after premedication (score 2), and no deviation was recorded at T90 (score 0). However, In DEX-NAL group Head deviation was severe after premedication (score 3), moderate at T90 (score 2) and returned to normal at T120 (score 0). DEX group revealed mild salivation after premedication up to T75 (score1), however DEX–NAL. The group revealed moderate salivation after premedication up to T60 (score2) and mild salivation at T75 (score1). Salivation was absent at T90 in both groups (score 0) (Table 4).

Table 4 Different reflexes (Jaw relaxation, palpebral reflex and pedal reflex) and body languages (Head ground distance, gait score, tongue protrusion, head deviation and Salivation) in DEX group (G-1) and DEX- NAL group(G-2) at baseline (before treatment), after premedication (A-P), after induction (A-I) and at 5, 15, 30, 45, 60-, 75-, 90- and 120-minutes post induction.

	G	T0	A-P	A-I	T5	T15	T30	T45	T60	T75	T90	T120
Jaw relaxation	G-1		2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	1±0.00	0	0
	G-2		3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00*	2.00±0.00*	0
Palpebral reflex	G-1		2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	3±0.00	3.00±0.00	1.00±0.00	0	0
	G-2		3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	2.00±0.00	2.00±0.00*	0
Pedal reflex	G-1		2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	1.00±0.00	0	0
	G-2		3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	3.00±0.00	2.00±0.00	2.00±0.00*	0
Head ground distance	G-1	73.00±2.30	39.33±2.02				Recumbence				68.66±0.88	73.00±2.30
	G-2	68.66±1.85	35.00±1.15*				Recumbence					68.66±1.85
Gait	G-1	0	1.00±0.00				Recumbence				1.00±0.00*	0
	G-2	0	2.00±0.00*				Recumbence					0
Tongue protrusion	G-1	0	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	0	0
	G-2	0	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	0
Head deviation	G-1	0	2.00±0.00				Recumbence				0	0
	G-2	0	3.00±0.00*				Recumbence				2.00±0.00*	0
Salivation	G-1	0	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	0	0
	G-2	0	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	2.00±0.00*	1.00±0.00	0	0

Means (± SE) with a star "*" in the same column are significantly different at p≤0.05.

3.3 Basic Physiological Parameters

Basic physiological parameters for each group (DEX and DEX-NAL groups), including HR, R.R, SpO2, RT, SAP, MAP, and DAP were recorded in Table (5). DEX group revealed a bradycardia after premedication, T15, 30, 45, and T60, and the heart rate was significantly lower than that in DEX-NAL group at the same time. Mean systolic BP revealed a dramatic decrease in DEX group and nearly touched half of the normal value at T30 and then gradually increased to reach the normal value at T120, while in DEX-NAL group, the Mean systolic BP remained stable within the normal value and showed significant higher results as compared with those in DEX group. Mean BP and Diastolic BP in DEX group revealed a sharp decrease after premedication to reach near the half-normal values after induction until T75 and return to normal at T120, However, DEX-NAL group revealed a mild decrease at most times of the study but remained significantly higher than in DEX group. Changes in respiratory rate were mild around the normal value in both groups, except at T5 and T15 when the respiratory rate showed a significantly higher value in DEX group compared to DEX-NAL group. Significant changes were obvious between the two groups regarding the SpO2%. DEX-NAL group showed a significantly higher value after induction until the end of the study. The lowest SpO2% value in DEX group was 84.33 ±0.33 and recorded just after induction, while in DEX-NAL group it was 94.66±0.33 and recorded at T15. Additionally, no clinical complications were observed, and oxygen supplementation was not required. There was no significant difference in rectal temperature between the two groups at all time points.

Table 5 Physiological parameters (H.R, SAP, DAP, MAP, R.R, SpO2 and R.T) in DEX group (G-1) and DEX- NAL group (G-2) at baseline (before treatment), immediately after premedication, immediately after induction and at 5, 15, 30, 45, 60-, 75-, 90- and 120-minutes post induction).

Parameters		T0	A-P	A-I	T5	T15	T30	T45	T60	T75	T90	T120
H.R (beats/min)	G-1	72.00	67.00	72.33	72.66	71.66	69.66	70.66	70.33	73.00	74.66	72.66
		±0.57	±1.15	±0.74	±3.17	±0.65	±3.92	± 3.48	±6.17	±7.00	±5.17	±0.33
	G-2	72.00	74.33	72.66	73.33	75.00	74.00	75.00	76.66	74.00	73.66	73.00
		±0.57	±0.33*	±2.18	±0.88	±2.08*	±1.00*	±1.00*	±2.02*	±1.00	±0.66	±0.57
SAP (mmHg)	G-1	100.02	68.66	70.00	67.66	61.00	58.33	61.33	64.33	72.33	88.33	100.02
		±1.45	±1.85	±6.24	±4.80	±2.51	±4.40	±3.48	±2.40	±6.35	±2.40	±1.15
	G-2	100.03	100.01	100.01	100.00	100.03	100.02	99.66	100.00	100.04	100.03	100.55
		±0.88	±0.88*	±0.88*	±0.00*	±0.88*	±1.20*	±0.88*	±1.45*	±1.55*	±0.88*	±0.33
DAP (mmHg)	G-1	84.66	57.00	30.33	37.66	28.33	29.33	30.00	32.00	35.00	62.00	84.00
		±1.20	±0.57	±3.84	±3.69	±2.40	±3.75	±3.05	±2.08	±0.57	±1.52	±0.57
	G-2	84.66	81.00	84.33	71.00	72.33	72.00	67.00	72.00	77.66	82.33	84.66
		±1.20	±3.21*	±2.60*	±4.50*	±2.84*	±3.51*	±2.51*	±3.60*	±2.84*	±1.20*	±0.33
MAP (mmHg)	G-1	90.00	66.66	41.00	47.66	38.33	39.00	41.33	45.33	47.66	71.33	89.66
		±0.57	±2.51	± 4.50	±5.69	±3.38	±5.77	±4.66	±3.38	±5.69	±0.66	±0.33
	G-2	90.00	89.66	89.66	85.33	89.00	89.33	84.33	86.00	89.66	89.66	92.33
		±0.57	±1.45*	±1.45*	±4.17*	±0.57*	±1.85*	±4.63*	±2.51*	±0.3*	±0.33*	±0.66*
R.R (breaths/min)	G-1	30.00	24.33	26.00	37.66	34.00	31.33	32.33	29.66	28.33	27.33	28.00
		±0.57	±2.02	±1.52	±4.33*	±3.78*	±1.85	±2.90	±1.85	±1.66	±0.88	±1.00
	G-2	30.00	25.66	24.00	23.33	26.00	29.33	28.00	26.33	24.66	24.3	27.66
		±0.57	±0.33	±0.57	±0.33	±0.57	±0.88	±0.57	±1.33	±2.33	±1.20	±1.45
SpO2 (%)	G-1	99.00	95.66	84.33	84.66	86.66	86.33	87.66	87.66	88.66	91.33	92.00
		±0.57	±0.88	±0.33	±1.45	±2.33	±0.21	±0.33	±1.33	±0.66	±0.88	±0.57
	G-2	99.00	98.00	96.66	96.33	94.66	97.66	97.33	97.33	96.33	98.00	98.66
		±0.57	±0.57	±0.33*	±0.21*	±0.33*	±1.45*	±0.88*	±0.33*	±0.66*	±1.15*	±0.33*
R.T (°C)	G-1	38.33	38.13	38.00	38.83	38.80	38.56	38.53	38.26	38.50	38.33	38.26
		±0.08	±0.16	±0.26	±0.23	±0.17	± 0.26	±0.26	±0.16	±0.00	±0.06	±0.03
	G-2	38.33	38.33	38.33	38.36	38.33	38.26	38.26	38.36	38.36	38.33	38.36
		±0.08	±0.08	±0.08	±0.08	±0.03	±0.08	±0.13	±0.08	±0.06	±0.06	±0.06

Means (± SE) with a star symbol * are significantly different at p≤0.05 with the correlated mean at the other treatment in the same column

3.4. Biochemical parameters

CPK markedly decreased in DEX group from T5 till the end of the study and showed significantly lower results from T5 till T90 as compared with DEX-NAL group, which showed nearly normal values. Lactate dehydrogenase (LDH) showed non-significant changes between both groups and remained within the normal value at all time points of the study. AST and ALT were affected by an increase after premedication till the end of the study; both showed significantly higher result in DEX group than DEX-NAL after induction, at T15 till the end of the study. Cortisol level showed significantly higher results in DEX group as

compared to DEX-NAL group at all times of the study. The cortisol level showed subnormal values in DEX-NAL group at all times of the study; however, in DEX group, cortisol values exceeded the normal range and reached their peak after induction, at T5 and T15. The mean glucose value was in both groups at all times of the study but recorded a significantly higher result in DEX group than DEX-NAL group after premedication, at T15 and T30. Regarding urea and creatinine, there were no significant changes between both groups at the entire time during the study (Table 6).

Table 6 Biochemical (CPK, LDH, AST, ALT, Cortisol, Glucose, Urea and Creatinine) parameters in DEX group (G-1) and DEX- NAL group (G-2) at baseline (before treatment), immediately after premedication, immediately after induction and at 5, 15, 30, 45, 60-, 75-, 90- and 120-minutes post induction).

Parameters		T0	A-P	A-I	T5	T15	T30	T45	T60	T75	T90	T120
CPK (U/L)	G-1	173.33	124	125	79	71	77	75	68.67	80	76	94
		±3.33	±3.45	±2.54	±2.4	±2.56	±2.66	±2.23	±2.44	±2.42	±2.9	±2.46
	G-2	205.67	166.67	148.33	141	147	142	144.33	143.33	173.67	166.33	157
		±2.03	±2.83	±2.15	±2.53	±2.98*	±2.12*	±1.98*	±2.05*	±3.76*	±3.21*	±2.67
LDH (U/L)	G-1	298.33	230.67	253.33	249±	262.33	258	262	283.67	280.33±	272	263.67±
		±5.03	±2.57	±3.41	2.65*	±3.09	±3.27	±3.05	±1.74	3.22	±3.88	3.26
	G-2	393.67	264	273.33	307.33	293.67	296.33	294.33	300.67	303.67±	311	306±
		±5.33	±0.58	±0.88	±2.54	±6.17	±8.97	±6.36	±7.33	3.16	±1.64	3.1
AST (U/L)	G-1	13.0	19.00	27.00	36.00	34.33	29.66	27.00	24.33	20.66	19.66	17.33
		±3.00	±0.00	±0.00	±2.88	±1.66	±1.33	± 2.30	±2.66	±2.33	± 3.33	±3.84
	G-2	16.0	19.00	31.33	36.00	41.33	39.66	37.66	43.33	30.00	27.33	24.33
		±3.00	±0.00	±2.60*	±2.88	±3.17*	±3.66*	±1.66*	±3.33*	±3.00*	±4.33*	±3.52*
ALT (U/L)	G-1	7.33	10.66	13.00	16.00	15.00	13.00	13.00	11.66	10.66	10.00	9.00
		±1.33	±0.33	±0.00	±1.00	±1.52	±1.51	±2.08	±1.76	±1.45	±1.73	±1.73
	G-2	8.66	11.00	15.00	17.33	17.33	17.66	17.00	15.33	14.33	13.00	12.00
		±1.33	±0.0*	±0.57*	±0.88	±1.45*	±2.40*	±1.15*	±1.20	±1.20*	±1.15*	±0.57
Cortisol (µg/dL)	G-1	1.59	0.88	3.00	2.30	1.81	1.11	0.79	0.85	1.11	1.38	1.43
		±0.47	±0.00*	±0.00*	±0.29*	±0.37*	±0.43*	±0.24*	±0.07	±0.33*	±13.49*	±0.19*
	G-2	2.42	0.56	1.36	1.46	1.27	0.68	0.56	0.57	0.98±	0.67	0.64
		±0.11	±0.00	±0.58	±0.80	±0.64	±0.12	±0.03	±0.03	0.47	±0.12	±0.10
Glucose (mg/dL)	G-1	131.9	136.07	156.93	161.07	168	170.8	161.07	152.77	148.6±	140.23	144.43
		±1.98	±1.76*	±5.57	±5.53	±1.4*	±4.79*	±1.73	±2.73	3.12	±3.12	±3.67
	G-2	108.33	145.8	150	138.6	143.02	141.63	144.43±	144.37	137.27±	130.53	123.57
		±4.17	±2.86	±4.56	±3.46	±3.48	±1.65	3.85	±1.32	2.45	±2.03	±3.7
Urea (mmol/L)	G-1	28.0	28.9	37.63	40.33	43.62	43.46	40.53	38.10	35.83	32.43	31.23
		±2.20	± 2.56	±2.32	±2.18	±2.12	±2.66	±2.85	±4.23	±4.27	±3.88	±2.24
	G-2	25.2	31.50± 0.00	34.20	39.96	36.86	34.60	34.43	32..43	29.73	30.63	29.40
		±1.66		±0.00	±0.93	±1.44	±2.32	±2.53	±3.11	±2.72	±3.51	±1.77
Creatinine (mg/dl)	G-1	1.00	1.03	1.30	1.40	1.50±	1.53±	1.43	1.33	1.26	1.13	1.13
		±0.00	±0.03	±0.05	±0.10	0.11	0.13	±0.08	±0.08	±0.12	±0.03	±0.03
	G-2	1.06	1.00	1.10	1.43	1.23±	1.20	1.20	1.13	1.06	1.10	1.03
		±0.06	±0.00	±0.00	±0.06	0.03	±0.05	±0.05	±0.06	±0.03	±0.05	±0.03

Means (± SE) with a star symbol * are significantly different at p≤0.05 with the correlated mean at the other treatment in the same column

4. DISCUSSION

The current study was seeking to evaluate the incidence of In this investigation the combination of α2-adrenergic agonist DEX with opioid (Nalbuphine) as a premedication was tested to improve anesthetic gain and preserve cardiopulmonary and hemodynamic stability under a TIVA protocol, including ketamine for induction and propofol for maintenance. The combination of DEX-NAL in one regimen has not been applied before in bucks.

This study indicates that the combination of DEX-NAL as a pre-anesthetic medication significantly improves the sedative, analgesic, behavioral, and clinical effects of TIVA by ketamine for induction and propofol for maintenance. In the present study, DEX-NAL group exhibited a deeper potent, rapid onset with prolonged duration of sedation and improvement in the quality of analgesia than DEX group. These results aligned with earlier studies on equine (Helal et al., 2024), pets (Nishimura et al., 2018), goat (Abouelfetouh et al., 2022), and camel (khalil et al. 2019).

DEX-NAL combinations functioned as multimodal analgesia to control pain by acting on different receptors along the nociceptive system (Kreisler, et al., 2020 and Helal et al., 2024). These results are attributed to the fact that NAL is primarily a kappa agonist/partial mu antagonist analgesic, and it can bind to mu, kappa, and delta receptors, but not to sigma receptors (Chawda et al., 2010). Moreover, NAL appears to be safe for enhancing the neuroleptanalgesia effects with xylazine and possibly other α-2 agonists (Hall et al., 2001). Also, this result suggests that Nalbuphine has an important role as it overcomes the adverse effects of propofol boluses on blood pressure and oxygen saturation.

DEX-NAL group exhibited a rapid onset of smooth induction and prolonged duration of anesthesia and duration of total recovery time, more than DEX group. This result coincides with results reported by Straticò et al. (2021) and attributed to the ability of ketamine to cross the blood-brain barrier and the synergistic effect of opioid and alpha 2 adrenergic agonists synergism.

The current study recommended the following body language indicators to judge the degree of sedation: head deviation, head ground distance, gait scoring, and tongue protrusion. El-Maghraby and Al-Qudah (2005) and Khalil et al (2019) reported that such body language indicators help estimate the degree of muscle relaxation and awareness affected by the sedative effects of the drugs. The degree of ataxia was also recorded through the gait scoring system. DEX-NAL group exhibited a significant change in all body languages comparable to DEX group after premedication. These results coincide with a former study in camel (Khalil et al 2019) and in horse (Dhanjal et al., 2009) reported that the gait score, distance between the head and ground, the degree of tongue protrusion and the degree of salivation were significantly affected after injection of opioids. These results were attributed to the sedative effects after NAL administration (Coetzee et al., 2014).

All bucks in DEX-NAL group revealed smooth recovery; transited from lateral recumbence to sternal recumbence and showed fewer attempts to stand up without any excitement or ataxia, whereas most bucks in DEX group exhibited rapid good to fair recovery with some struggling but stood up unassisted. Similarly, Abouelfetouh et al. (2022) reported that goats administered with nalbuphine-ketamine mixture showed mild ataxia, uncomplicated transition to alertness, and minimal coordinated attempts to stand than those administered with ketamine alone. The calm recovery without agitation associated with nalbuphine administration could be attributed to the fact that NAL primarily acts on c-fiber nociceptors, not motor or sympathetic receptors (Papich 2018).

In the present study, DEX-NAL group body reflexes reached the highest score rapidly (after premedication), which lasted for an adequate period (T75) and decreased gradually to

return to score 0 at T120. However, DEX group reached the highest score later and decreased sharply to return to score 0 at T90. These results supported the adequate degree of muscle relaxation obtained after injection of NAL in the present study.

In our study total mean time of intravenous anesthesia from induction until end of maintenance period is 76.66±2.96 min and this time was considering suitable for most surgical interventions needed general anesthesia in goat including; laparoscopic ovariohysterectomy that took 43 min (Daniel et al., 2019), Ovariectomy that took 50-55 min (Alkhilani 2020), left flank laparotomy that took 6.32 min (Abouelfetouh et al., 2022) and castration that took 16.83 min (Helal et al., 2024).

A balanced multimodal analgesia must possess negligible adverse effects (Verma et al., 2023). In this study, DEX group revealed marked bradycardia after premedication, which was not observed in DEX-NAL group. Similarly, Helal et al. (2024) found the same effect of DEX-NAL combination comparable to DEX alone in donkeys. These findings could be attributed to the ability of NAL (κ agonist) to ameliorate dexmedetomidine-induced bradycardia and hypotension. This could be linked to the activation of κ receptors in several loci in the CNS, which in turn increased the HR (Schindler et al., 2007). Moreover, NAL as κ agonist might effectively influence renal sympathetic supply and increased sodium and potassium reabsorption, enhancing peripheral vascular resistance and restoring reduced BP (Meariman et al., 2022).

Mean systolic BP remained stable within the normal value and showed significantly higher results as compared with those in DEX group, which showed a dramatic decrease after premedication. This result may be attributed to the regulation of baroreflex in arteries via the κ receptor agonism of NAL (Qi and Smith, 2007). These findings were consistent with the results of previous reports asserted that NAL - α2-adrenergic agonist combination showed effective analgesic and sedative outcomes with cardiovascular stability in calves (Coetzee et al., 2014), camels (Khalil et al., 2019), and donkeys (Helal et al., 2024).

In this study, there's a significant decrease in SpO2 in DEX group at all-time points, which wasn't observed in DEX-NAL group, in which the SpO2 remained higher than 94.66 at all-time points of the study and revealed a significantly higher value after induction until the end of the study. This result may be attributed to the regulation of baroreflex in arteries via the κ receptor agonist of NAL (Qi and Smith, 2007) which act to minimize the α2-adrenergic agonist effect that causing intense peripheral vasoconstriction and the reduction of blood flow that leading to greatly reduced oxygen delivery to peripheral tissues (Dzikiti et al., 2014).

In this study, CPK markedly decreased in DEX group at all times of the study. This result could be attributed to DEX acts to decrease the coronary vessel diameter, decrease the heart rate, and decrease the cardiac enzymes (Kundra et al., 2018). On the other hand, the nearly normal values of CPK with a very mild increase in DEX-NAL could be attributed to the activation of κ receptors in several loci in the CNS, which in turn increase heart rate and cardiac enzymes. (Helal et al., 2024). AST and ALT were affected by an increase after premedication till the end of the study in both groups, but more in DEX-NAL group. The increase may be attributed to the fact that NAL is predominantly eliminated and metabolized by the liver, which may have induced hepatocyte stress, causing them to leak AST into the blood (Koichev et al., 1988). Cortisol level showed significantly higher results in DEX group as compared to DEX-NAL group at all times of the study. In previous studies, NAL has been reported to reduce stress-associated behaviors in calves (Coetzee et al., 2014), in camels (Khalil et al., 2019), and in dogs (Torad and Hassan 2018). The result was attributed to the fact that NAL has been reported to enhance postoperative analgesia and decrease surgical stress and pain, which could be pivotal for reducing cortisol release (Kreisler et al., 2020).

The mean glucose value increased in both groups along study time, but recorded a significantly higher result in DEX group than DEX-NAL group. Smith et al., 1996 reported that glucose levels were negatively correlated with cortisol levels. Yuen et al., 1998 attribute the result to that Catecholamines released during stressful procedures lead to increased glucose levels to meet increasing metabolic demands. Also, increasing the glucose level at the following inductions can be attributed to the hyperglycemic effect of ketamine (Khan et al., 2014).

TIVA was achieved by choosing ketamine for induction and propofol for maintenance. Our vision was the standardization of the most suitable anesthesia protocol in goat by choosing the most suitable drugs even for induction and maintenance. Al-Jobory et al. (2007), Clarke et al. (2014), and Naddaf et al. (2015) reported that ketofol combination provided superior induction and muscle relaxation with a longer anesthetic recovery and smoother recovery, which appeared because of the synergistic effect exerted by the mixture. Intermittent bolus of propofol for maintenance yielded a prolonged maintenance period (48.66±5.23 in DEX group and 50.66±2.33 in DEX-NAL. group) with perfect cardiopulmonary status in DEX-NAL and acceptable status in DEX group. Njoku (2015) reported that the intermittent bolus technique has been used as an appropriate choice for anesthesia maintenance using propofol. Rego et al. (1999) and Richardson and Egan (2005) reported that the intermittent bolus technique of remifentanil exhibited characteristics of rapid onset and offset and produced several outcomes such as prolonged maintenance period and overcoming adverse effects related to oxygenation and ventilation.

5. CONCLUSIONS

This study concluded that adding NAL to DEX before TIVA preceded by Ketofol provides a novel anesthetic regimen that improves the quality of anesthesia and recovery with acceptable behavioral, cardiopulmonary, and biochemical outcomes.

CONFLICT OF INTEREST

The authors announce that they have no Conflict of interest.

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