



Assessment of Cardiopulmonary and Electrocardiographic Stability under Three TIVA Protocols in Goats Premedicated with Nalbuphine



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Abstract

THE present study aimed to compare the anaesthetic performance of three total intravenous anaesthesia (TIVA) protocols in Egyptian Baladi goats aged 3–5 months. All animals received nalbuphine (0.5 mg/kg IV) as premedication, followed by induction with ketamine (7 mg/kg) and midazolam (0.7 mg/kg). Maintenance was achieved with propofol alone (P), propofol plus midazolam (PM), or propofol combined with midazolam and ketamine (PMK). Physiological parameters, including heart rate (HR), respiratory rate (RR), oxygen saturation (SpO₂), rectal temperature, and arterial blood pressures (SAP, DAP, MAP), were monitored at 5-minute intervals up to 60 minutes. Electrocardiographic (ECG) variables were assessed at 10, 20, 40, and 60 minutes following nalbuphine administration. No arrhythmias were observed in any group, and minor alterations in ECG waveforms remained within normal limits. All protocols induced reductions in HR, RR, and blood pressures during maintenance, though the PMK group maintained significantly higher HR, RR, and MAP values compared with P and PM. These findings indicate that ketamine minimized the depressant effects of propofol, resulting in more stable hemodynamic and respiratory profiles. Rectal temperature decreased significantly across all groups, with no notable intergroup variation. In conclusion, the PMK protocol offered the most stable anaesthetic profile, combining cardiovascular safety with adequate respiratory function, thereby supporting the role of ketamine as a valuable component of balanced TIVA in goats.

Keywords: Goats, Ketamine, Propofol, Midazolam, ECG.

Introduction

Total intravenous anesthesia (TIVA) and inhalation anesthesia are two of the common types of general anesthesia. TIVA provided better post-operative recovery with fewer post-operative side effects than inhalation anesthesia [1]. Total intravenous anesthesia (TIVA) has become an increasingly utilized technique in veterinary medicine, particularly for small ruminants, due to its feasibility, safety, and ability to maintain a stable anesthetic plane without reliance on inhalant agents. Goats, being sensitive to stress and prone to anesthetic complications, require well-balanced anesthetic protocols that ensure adequate sedation, muscle relaxation, analgesia, and cardiorespiratory stability [2, 3].

Propofol is a phenolic compound unrelated to general anesthetics, non-barbiturates, non-

dissociative, and noncumulative intravenous anesthetic agents [4]. Propofol has good quality anesthesia, has a short duration of action, with rapid recovery. It may be used alone or in combination with other drugs, and has a wide safety range [5].

Ketamine is a dissociative anesthetic drug that has remained the principal component in anesthesia management for small ruminants, due to its affordable cost, analgesia, and wide safety margin [6]; however, it is associated with excitatory signs during recovery. Therefore, it is usually co-administered with other adjuncts, such as benzodiazepines [7], in an effort to improve muscle relaxation and reduce the required dose of ketamine.

The development of drugs with selective opiate receptor activation has resulted in improved analgesia while minimizing respiratory depression and excitatory effects. Nalbuphine is a semi-s [8]. It

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is used to overcome opioid-induced cardiopulmonary depression and sustain κ -mediated analgesia [9]. Nalbuphine is proven to induce comparable analgesia as morphine when given in equal doses [10]. In humans, nalbuphine is regarded as an important element of multimodal anesthesia and used as a pain-relieving medication for moderate and severe conditions, preoperative and postoperative analgesia, and gynecological interventions [11]. Nalbuphine has not been extensively used in veterinary practice; however, some studies of the use of nalbuphine have been reported in goat [9], cats [12], dogs [13], and horses [14]. Therefore, nalbuphine is proposed as an appealing narcotic analgesic with fewer undesirable effects and decreased regulatory limitations than other opioids.

Midazolam is an imidazobenzodiazepine derivative that has been reported as a sedative, muscle relaxant, anticonvulsant [15], and anti-epileptic drug [16] with minimal cardiovascular effects [17]. Premedication with midazolam compared to ketamine alone was found to be associated with smooth induction and excellent muscle relaxation in ponies [18]. Midazolam hydrochloride belongs to the benzodiazepine group of drugs, and it is 4 times more potent than diazepam. In addition, it is water-soluble, which makes it more suitable for intramuscular administration [19].

Monitoring of vital physiological functions such as cardiovascular and respiratory profiles is mandatory in evaluating a drug's suitability as an anaesthetic. It allows one to recognize the extent of physiological stress and to make adjustments in anaesthetic protocol to prevent untoward effects [20].

Therefore, the search for the best sedative-analgesic regimen for long-term surgical interventions (for one hour) in goats is still ongoing. Thus, the present study aimed to identify the most effective total intravenous anesthesia (TIVA) protocol in goats, providing optimal sedation, analgesia, and muscle relaxation, with minimal impact on cardiopulmonary functions.

Material and Methods

This study was in accordance with the guidance of the Mansoura University Animal Care and Use Committee (MU-ACUC), Mansoura, 35516, Egypt. The Approval code was MU-ACUC (VM.MS.23.04.53).

Animals

Eighteen clinically healthy female crossbred Baladi goats ranging from 3-5 months old and weighing 13 ± 4 kg were purchased locally from the Faculty of Agriculture, Mansoura University. Goats were adapted to the facility environment for at least two months before the study. They were housed in three sawdust-bedded rooms in the Mansoura

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They kept on alfalfa, crushed corn, wheat bran, and had free access to water. The animals underwent full pre-anesthetic screening, including complete physical (HR (beat/minute), RR (cycle/ minute), MAP (mm/Hg), Temperature), hematological (Haemoglobin (g/dl), PCV (%), RBCS (106/ μ l), WBCS (103/ μ l), Neutrophil (%), Lymphocyte(%), Eosinophil(%), Monocyte(%), Basophil(%)), and serum biochemical assessments(ALT (unit/l), AST (unit/l), Albumin (g/dl), Glucose (mg/dl), Creatinine (mg/dl), Blood urea (mg/dl)).

Experimental study

The goats were fasted for 12 hours, but water was provided until 2 - 6 hours before induction of anesthesia. The right jugular vein was catheterized using a BIO-FLON IV cannula 22 G (Haryana, India) on disinfected, clipped skin for the administration of the anesthetic drugs.

The animals were randomly allocated into three groups (P: Propofol, PM: Propofol–Midazolam, PKM: Propofol–Ketamine–Midazolam), with six animals in each group, using the sealed opaque envelope method. All animals were premedicated with nalbuphine 2% (Nalufin, Amoun Pharmaceutical Company, Egypt) at a dose of 0.5 mg/kg intravenously (IV). Fifteen minutes later, anesthesia was induced in all animals with a combination of ketamine 5% (Ketamine Hydrochloride, Rotexmedica, Germany) at a dose of 7 mg/kg and midazolam 0.5% (Midathetic, Amoun Pharmaceutical Company, Egypt) at a dose of 0.7 mg/kg IV, administered in the same syringe. Thirteen seconds after induction, and once all reflexes (pedal, corneal, and swallowing) had become sluggish, endotracheal intubation was performed using a silicone tube (internal diameter 6.5 mm, Delta-Tube, Delta Pharma Medical Supplies, Egypt) with the goats positioned in sternal recumbency. A laryngoscope (DeltaScope, Delta Pharma Medical Supplies, Egypt) was used to facilitate the procedure. Immediately after intubation, the animals were placed in left lateral recumbency (Figure 1). Five minutes after induction, anesthesia was maintained for 40 minutes using constant rate infusion (CRI) delivered via an infusion pump (InfuTech VP-50, InfuTech Medical Systems, Egypt). The maintenance regimens were as follows: Group P received propofol at 0.4 mg/kg/min, Group PM received propofol at 0.3 mg/kg/min combined with midazolam at 5 μ g/kg/min, and Group PKM received propofol at 0.2 mg/kg/min combined with ketamine at 0.05 mg/kg/min and midazolam at 5 μ g/kg/min. All drugs were diluted with normal saline to a total volume of 60 ml before administration [21-25].

Ringer's Lactate solution (Lactated Ringer's Injection, Otsuka Pharmaceutical Company, 500 mL

infusion bag) administered at CIR 4 mL/kg/hr. [26]. The endotracheal tube was removed after the goats regained the swallowing reflex. Goats were supplied with 100% oxygen delivered directly to the tube (open insufflation, non-rebreathing) at a fresh gas flow rate of 100 mL/kg/min to maintain high FiO₂ and minimize CO₂ rebreathing throughout TIVA.

Anaesthetic Protocol Assessment

All goats were monitored using a multiparameter monitor (M69S, Guangdong Biolight Meditech Co., Ltd., China). The recorded physiological parameters included heart rate (HR, beats/min), respiratory rate (RR, cycles/min), oxygen saturation (SpO₂, %) measured by pulse oximetry through the tongue, rectal temperature (RT), and blood pressure (systolic, diastolic, and mean arterial pressure, MAP) obtained noninvasively with a cuff (4 cm width) placed over the right brachial artery. These parameters were recorded at baseline (T0), after premedication (T5, T10, T15), five minutes after induction (T20), and during maintenance (T25, T30, T35, T40, and T60).

Electrocardiography (ECG) was performed using a CONTEC system (Contec Medical Systems Co., Ltd., China) following the base-apex method. Recordings were obtained in Lead II with a paper speed of 25 mm/s and sensitivity set at 10 mm = 1 mV. ECGs were recorded at baseline at T0 (Fig. 2A), after premedication at T10 (Fig. 2B), after induction at T20 (Fig. 2C), and at T40 and T60 during maintenance in the PMK group (Fig. 2D & E), the PM group (Fig. 2F & G), and in the P group (Fig. 2H & I).

The onset of anesthesia was defined as the time from administration of the induction agents to the loss of the pedal reflex. Recovery time was defined as the interval from discontinuation of anesthetic infusion to the reappearance of the pedal reflex and included two parameters: (1) sternal recumbency time, the time from drug discontinuation to spontaneous regaining of sternal recumbency, and (2) standing time, the time from drug discontinuation to spontaneous standing.

The quality of induction and recovery was assessed by an experienced anesthetist (ME), who was blinded to the treatment groups, using a modified numerical scoring system as described by [25,27], Table 1. Clinical evaluation of body reflexes during maintenance of anesthesia was performed using a numerical scoring system according to [28] Table 2. Analgesia was evaluated using the pin-prick test, with scores ranging from 0 to 3 based on sensory response, following the method of [29] Table 3. The test was applied starting at the perineal region and progressing cranially toward the head to determine the extent and depth of anesthesia and analgesia. Possible side effects were monitored by continuous observation of the goats during induction,

throughout anesthesia, and during the post-anesthetic recovery period.

Results

Following nalbuphine administration, most physiological parameters (HR, SpO₂, SAP, DAP, MAP) remained statistically comparable to baseline values within each protocol ($p > 0.05$), indicating general cardiovascular stability. However, a significant decrease in respiratory rate ($p < 0.001$) and rectal temperature ($p < 0.001$) was observed across all groups during this phase.

Transition to the induction phase (T15–T20) with ketamine and midazolam was associated with a significant reduction in respiratory rate and arterial blood pressures (SAP, DAP, MAP) across all groups ($p < 0.001$) compared with premedication values, while heart rate, SpO₂, and temperature remained relatively unchanged.

From the onset of the maintenance phase (T25–T60), marked alterations became evident. In the PM and P groups, heart rate, respiratory rate, and arterial blood pressures (SAP, DAP, MAP) showed significant reductions within group compared with induction values ($p < 0.001$). The decline in heart rate was particularly pronounced in the P group at T25 and T30 ($p < 0.001$). Respiratory rate also decreased more markedly in the P group compared with PM and PMK during this phase. In contrast, the PMK group maintained relatively stable values, with most changes remaining non-significant over time. Oxygen saturation was generally stable in PM and P, while PMK showed a mild but significant increase by the end of maintenance ($p < 0.05$). Rectal temperature continued to decrease significantly over time in all protocols ($p < 0.001$), though no significant inter-group differences were detected. The mean $\pm$ SE values of basic physiological parameters are shown in Table 4.

During the premedication phase (T0–T10), within-group analysis showed significant reductions in P, R, and T wave amplitudes as well as in PR and QT intervals compared with baseline values ($p < 0.001$), indicating the initial pharmacological effect of nalbuphine. QRS duration remained relatively stable during this phase.

At induction (T20), the three groups maintained comparable values for all ECG parameters ($p > 0.05$). A consistent reduction in T wave amplitude was observed in all groups ($p < 0.001$), while other parameters (P, R amplitude, PR, QT intervals) demonstrated only mild but statistically significant deviations from baseline.

During the maintenance phase (T40–T60), inter-group differences became more evident. In the PMK group, both P and T wave amplitudes showed significant decreases compared with P and PM ($p < 0.001$), while R wave amplitude increased markedly

at T60 ($p < 0.001$). By contrast, the P and PM groups demonstrated progressive decreases in R wave amplitude over time, most pronounced in the P group. QRS duration remained relatively constant across all groups, with no statistically significant differences at T40 and T60 ($p > 0.05$). PR interval remained stable throughout, with only minor within-group fluctuations that did not translate into significant inter-group variation.

Regarding the QT interval, a significant prolongation was detected in P and PM groups during maintenance (T40–T60, $p < 0.001$), while the PMK group exhibited a progressive shortening, reaching significantly lower values at T60 ($p < 0.001$). The mean $\pm$ SE values of ECG amplitudes and durations (Table 5).

For swallowing time, PM animals exhibited significantly longer values compared with P ($p = 0.005$), while PMK did not differ considerably from PM ($p = 0.097$). In contrast, PMK demonstrated a significantly prolonged swallowing time compared with P ($p < 0.001$). A similar trend was observed for sternal recumbency time, where both PM and PMK groups took significantly longer to regain the sternal position compared with P ($p < 0.001$ for both). No significant difference was detected between PM and PMK ($p = 0.221$). For standing time, both PM and PMK groups required significantly more time to stand compared with P ($p < 0.001$ for both), whereas the difference between PM and PMK remained non-significant ($p = 0.285$, Table 6).

Qualitative assessment revealed that all protocols provided smooth induction, while the PMK protocol offered the best overall performance. It ensured the most profound analgesia (100% score 3), maximal jaw relaxation (100% score 3), and complete abolition of palpebral and pedal reflexes in all animals. In contrast, the PM and, especially, the P protocol were associated with weaker analgesia and incomplete muscle relaxation, although the recovery quality was superior in the P group (Table 7).

Discussion

In the present study, the choice of these drugs is based on their lesser effect on cardiopulmonary function, with the achievement of the optimum sedation, analgesia, and complete muscle relaxation.

Following nalbuphine administration, a non-significant increase in heart rate (HR) and blood pressure was observed. This aligns with previous findings in dogs and humans, suggesting that nalbuphine has minimal impact on the cardiovascular system [30,31]. The slight sympathomimetic effect may be attributed to its κ -receptor activation within the CNS [32], which could transiently enhance sympathetic output, particularly affecting renal sympathetic tone and peripheral vascular resistance [33,34]. While baroreflex regulation, which helps

control blood pressure via arterial pressure sensors, is influenced by the activation of κ -receptors, the overall effect on blood pressure is usually moderate. The baroreflex may be altered slightly by nalbuphine, leading to a gradual, non-significant increase in BP during anesthesia [35] as reported in calves [36]. The elevated heart rate may also be partly attributed to stress-related sympathetic stimulation during handling and instrumentation [37]. The respiratory rate (RR) in this study showed a slight decrease, likely due to nalbuphine's mild central depressant action. However, SpO₂ remained within normal limits, confirming adequate ventilation as reported in [9,38]. The significant reduction in rectal temperature could be attributed to the depressant effect of anesthetic agents on the thermoregulatory center, leading to impaired heat production and increased heat loss as reported by [39]. Despite the known sympathomimetic effects of ketamine. A mild decrease in heart rate and blood pressure was observed following induction. This transient reduction is explained by [40] as it may be attributed to the central depressant effect of midazolam, which reduces sympathetic outflow via its action on the vasomotor center [41], leading to vasodilation and decreased systemic vascular resistance [42]. Moreover, [43] reported that midazolam slightly decreases the MAP below the normal range of 80 to 110 mmHg in awake goat. As documented in earlier studies, this inhibitory influence may temporarily outweigh ketamine's stimulatory effect, particularly when both drugs are administered concurrently [44]. Although some studies have reported a mild increase in heart rate following midazolam administration, this effect appears to be variable and may depend on dose, timing, and species-specific responses. [21, 27, 45, 46].

The reduction in respiratory rate (RR) observed in this study after induction of anesthesia could be primarily attributed to the respiratory depressant effect of midazolam, as reported in pigs [47]. Otherwise, ketamine is known to maintain or slightly stimulate respiration when used alone; its combination with midazolam often results in a clinically relevant decrease in RR [48].

During the maintenance phase, significant differences were noted among the groups. The P group exhibited a significant decrease in HR and RR, coupled with progressive hypotension toward the end of the observation period. These findings may be explained by [49], who found a dose-dependent cardiovascular depressant effect of propofol when used alone, likely due to its vasodilatory and myocardial depressant actions. Furthermore, Respiratory depression agrees with the results found by [50], attributed to a decrease in tidal volume and respiratory rate in many species.

In the PM group, hemodynamic parameters remained relatively stable throughout the anesthetic period, characterized by significant reductions in heart rate (HR) and respiratory rate (RR), along with a significant reduction in mean arterial pressure (MAP). The incorporation of midazolam into the maintenance protocol appeared to mitigate the cardiopulmonary depressant effects of propofol on HR and RR, likely due to its central sedative properties and its ability to reduce overall anesthetic requirements, as previously reported by [51]. According to [52], propofol administration may lead to bradycardia and reductions of 15%–30% in systolic (SBP), diastolic (DBP), and mean arterial pressures, depending on the dose. However, [21] demonstrated that premedication with midazolam significantly reduced the induction dose of propofol by approximately 39.7% in healthy goats. Additionally, [53] reported a synergistic interaction between propofol and midazolam, contributing to enhanced hemodynamic stability in pediatric patients through an increase in HR and RR. Therefore, the use of midazolam in combination with propofol in the PM group not only reduced the required propofol dose but also helped maintain cardiovascular stability, consistent with findings reported in canine models [51]. The PMK group, which included ketamine in addition to propofol and midazolam, showed the most stable cardiovascular profile, maintaining higher HR, RR, and MAP values throughout. This may be attributed to ketamine's sympathomimetic properties, which counteract the cardiovascular depression of propofol. [53] [54].

In this study, electrocardiographic parameters were monitored to evaluate the cardiovascular effects of total intravenous anesthesia (TIVA) protocols in goats. Following nalbuphine administration, A significant reduction in R-wave and P-wave amplitude was observed, accompanied by a slight shortening of both PR and QT intervals, which may seem paradoxical in the context of an increased heart rate. This phenomenon can be explained by the physiological interplay between cardiac cycle duration, autonomic modulation, and the morphology of surface electrocardiographic signals. As heart rate increases, the durations of atrial and ventricular depolarization shorten, resulting in briefer electrical events. This temporal compression may reduce the amplitude of voltages recorded by surface ECG electrodes[55]. Moreover, the left lateral recumbency position commonly used during goat anesthesia may alter the spatial orientation of the heart within the thoracic cavity. This can result in a transient shift in the cardiac electrical axis, reducing alignment between the mean depolarization vector and surface ECG leads, thereby contributing to the observed decrease in P- and R-wave amplitudes [56,59]. The elevated heart rate could further contribute to the shortening of PR and QT intervals [37, 60].

After induction with ketamine and midazolam, a rise in P-wave amplitude was noted, along with a slight increase in R-wave amplitude and QT interval. Ketamine's known sympathomimetic effect likely contributed to this pattern by increasing myocardial excitability and enhancing atrial depolarization. In contrast, midazolam typically has minimal direct cardiovascular effects, though it may exert mild central sympatholytic [44,61]. During the maintenance of anesthesia, the P group (propofol only) demonstrated the longest QT interval (0.258 s) and a mild increase in QRS duration, consistent with propofol's known myocardial depressant and repolarization-prolonging effects. R-wave amplitude was the lowest among the three protocols, reflecting the absence of sympathetic stimulation to offset propofol's depressant effect. [62]. The combination of midazolam with propofol in the PM group likely attenuated the repolarization prolongation seen with propofol alone, while maintaining cardiovascular stability without large fluctuations in wave amplitudes[63]. PMK group exhibited the shortest QT interval (0.216 s), the highest R-wave amplitude (0.44 mV), and the lowest P-wave amplitude (0.061 mV). The shorter QT is plausibly due to ketamine's sympathomimetic effect counteracting propofol-induced repolarization delay, while the higher R amplitude reflects increased ventricular activation under enhanced sympathetic tone[64]. Importantly, all ECG parameters remained within normal physiological limits throughout the procedure, and no arrhythmias or conduction blocks were observed, suggesting that the protocol provides cardiovascular stability during moderate-duration anesthesia in young native Egyptian goats.

Clinical parameters

The timing of anesthetic induction in the present study was guided by pharmacodynamic considerations. Previous research in dogs demonstrated that nalbuphine achieves peak analgesic effect within 10 to 30 minutes following intravenous administration, with maximal efficacy noted at approximately 20 minutes [13]. Accordingly, a 15-minute interval was selected to ensure sufficient onset of action while maintaining procedural efficiency and providing optimal conditions for induction with ketamine and midazolam.

Induction of anesthesia using a ketamine–midazolam combination administered in a single syringe resulted in a rapid and smooth onset, with no signs of excitement observed. However, transient apnea occurred in approximately 30% of goats across all experimental groups, immediately following drug administration, and lasted for 15–30 seconds. This apnea may be attributed to the rapid intravenous

administration of midazolam at relatively high doses, which can induce respiratory depression or features of midazolam infusion syndrome, as previously reported [65]. Additionally, ketamine has been associated with hypoventilation due to its direct or indirect bronchodilator effects, potentially contributing to apnea [66]. The onset of anesthesia was evident within seconds after induction, confirmed by the loss of consciousness, palpebral reflex, and pedal reflex. The anesthetic depth was maintained for approximately 5–8 minutes until the reappearance of the swallowing reflex. The animals assumed lateral recumbency and lowered their heads within 20–40 seconds following induction.

In the present study, total intravenous anesthesia (TIVA) was maintained using a combination of midazolam, propofol, and ketamine (PMK) resulted in a deeper level of sedation, superior analgesia, and more profound muscle relaxation compared to protocols using propofol alone (P) or midazolam–propofol (PM). The enhanced anesthetic depth and analgesia remained consistent throughout the 60-minute maintenance period. These synergistic effects may be attributed to the combined pharmacological actions of the agents used, which enhance both sedation and analgesia beyond the effect of individual drugs. Similar findings were reported by [67], who demonstrated that xylazine combined with methadone, morphine, or tramadol provided superior sedation and analgesia in sheep compared to xylazine alone. The minimum infusion rate (MIR) of propofol adopted in this study (0.45 mg/kg/min), based on the findings of [68], is lower than the MIRs previously reported in non-premedicated dogs [69]. Although this MIR was sufficient to maintain stable anesthesia in 50% of subjects subjected to standardized noxious stimuli, as reported by [69], it was observed in the present study that two goats in the propofol-only group (P) exhibited partial return of reflexes—such as the swallowing reflex—approximately 18–20 minutes post-induction. This early return of reflexes may indicate a relatively lighter anesthetic plane and possible sympathetic stimulation, as evidenced by subtle spontaneous movements of the facial muscles and lips, consistent with previous observations [70]. These findings suggest that while the selected MIR is generally effective, individual variability and the nature of the surgical or nociceptive stimulus may necessitate adjustments to maintain adequate anesthetic depth [71].

Notably, excellent analgesia was achieved in the PMK group, while propofol alone lacks intrinsic analgesic properties. This highlights the importance of co-administration of a potent preanesthetic analgesic such as nalbuphine to enhance the analgesic profile of the protocol [72]. The inclusion of ketamine, a dissociative anesthetic known for its,

of strong analgesic effects and cardiovascular stability, further improving the anesthetic quality. These findings are consistent with those of [73] and [74], who reported that ketamine–propofol infusion protocols offer superior analgesia compared to propofol alone. Additionally, [75] demonstrated that both ketamine and its active metabolite, norketamine, exert analgesic effects through their interaction with mu and kappa opioid receptors. Among the three protocols, salivation was the only prominent adverse effect, most likely induced by the sialagogue properties of agents like nalbuphine and ketamine as reported in [76,77]. While atropine is well-documented for its anti-salivation effects [78], it was not utilized in the present study but will be incorporated into future protocols to further optimize anesthetic management. Recovery was smooth and uneventful in all groups, assessed by the return of swallowing, pedal, and palpebral reflexes. There were statistically significant variations between the protocols, as animals in the P group regained the swallowing reflex, sternal recumbency, and standing significantly earlier compared with those in the PM and PMK groups. Due to the short context-sensitive time of propofol [79], while ketamine is longer acting and slightly more cumulative than propofol, as reported in [80].

The limitation of the present study, animals were positioned in lateral recumbency during anesthesia. Although right lateral recumbency is generally preferred in small ruminants to minimize ruminal pressure on the diaphragm and to reduce the risk of hypoventilation and regurgitation, in some cases, animals were maintained in left lateral recumbency due to practical constraints. This positioning might have influenced certain cardiopulmonary variables; however, no major adverse effects were observed. Therefore, this factor should be considered as a potential limitation when interpreting the results.

Conclusion

Among the evaluated protocols, the PMK regimen demonstrated the most stable anesthetic profile, characterized by the absence of arrhythmias and superior preservation of cardiovascular and respiratory parameters. Moreover, this protocol provided better analgesia and favorable clinical parameters compared to the other regimens. These findings highlight the beneficial role of ketamine in enhancing the safety, physiological stability, and overall quality of TIVA in goats.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical approval number

This study follows the ethics guidelines of Mansoura University Animal Care and Use Committee (MU-ACUC), Mansoura, 35516, Egypt. The Approval code was MU-ACUC (VM.MS.23.04.53).

TABLE 1. Assessment of Induction and Recovery Quality using a standardized scoring system.

induction score	
Smooth induction, rapidly assumed recumbency, no signs of excitation	Good
Slightly prolonged induction, mild excitation, presence of the swallowing reflex	Fair
obvious excitement, jumps, or attempts to stand after recumbency, full presence of swallowing reflex.	Poor
Quality of recovery score	
smooth, easy transition to alertness, resumption of sternal position, ability to stand within a reasonable amount of time, and ability to walk with minimal ataxia	Good
transient excitement or whole-body movement, some struggles, hyper-responsiveness that disappears once the goat stands unassisted, but with moderate ataxia.	Fair
stereotype behaviour, e.g. circling, premature attempts to stand, prolonged struggling.	Poor

TABLE 2. Assessment of Anaesthetic Depth using a clinical scoring system based on jaw relaxation, palpebral reflex, and pedal reflex.

Clinical parameters	0	1	2	3
Jaw relaxation	Not permitting jaw opening	The animal resists opening and closes its jaw rapidly	The animal has less resistance to opening its jaw and wraps it slowly	There is no resistance and the jaw still opens
Palpebral reflex	Rapid plink	Intact but weak (slow response)	Intact but very light (slow and occasionally response)	Abolished
Pedal reflex	Potent withdrawal	Intact but weak (slow response)	Intact but very light (slow and occasionally response)	Abolished completely

TABLE 3. Assessment of Analgesia using the pin-prick test

Score	Indication
0	(strong reaction) was given if there was a strong reaction to the pin prick
1	(weak reaction) was given if there was a mild and simultaneous reaction to the pin prick test.
2	(moderate reaction) was given if there was moderate but not consistent reaction to the pin prick test
3	if there was no reaction to the pin prick test

TABLE 4. The Cardiovascular parameters in eighteen ketamine/midazolam anaesthetized goats under different anaesthetic protocols.

Parameters	Time		Groups		P value
		PM	P	PMK	
HR	T 0 min	101.33 ± 0.88 ^{aA}	101.33 ± 0.88 ^{aA}	101.33 ± 0.88 ^{aA}	1.000
	T 5 min	100.50 ± 0.76 ^{aA}	100.50 ± 0.76 ^{aA}	100.50 ± 0.76 ^{aA}	1.000
	T 10 min	102.67 ± 0.92 ^{aA}	102.67 ± 0.92 ^{aA}	102.67 ± 0.92 ^{aA}	1.000
	T 15 min	103.00 ± 0.89 ^{aA}	103.00 ± 0.89 ^{aA}	103.00 ± 0.89 ^{aA}	1.000
	T 20 min	99.33 ± 0.76 ^{aA}	99.33 ± 0.76 ^{aA}	99.33 ± 0.76 ^{aA}	1.000
	T 25 min	94.83 ± 1.25 ^{bB}	90.17 ± 0.70 ^{cD}	99.83 ± 0.60 ^{aA}	<0.001
	T 30 min	93.33 ± 1.09 ^{bB}	90.67 ± 1.71 ^{cD}	98.67 ± 0.80 ^{aA}	0.002
	T 35 min	95.33 ± 1.11 ^{bA}	95.33 ± 1.11 ^{bA}	98.67 ± 0.56 ^{aA}	0.050
	T 40 min	95.33 ± 1.11 ^{bA}	95.50 ± 1.26 ^{bA}	100.33 ± 0.71 ^{aA}	0.010
	T 60 min	94.00 ± 1.37 ^{bA}	93.17 ± 1.60 ^{bA}	102.33 ± 1.09 ^{aA}	<0.001
P value		<0.001	<0.001	0.064	
RR	T0 min	25.17 ± 0.83 ^{aA}	25.17 ± 0.83 ^{aA}	25.17 ± 0.83 ^{aA}	1.000
	T5 min	21.67 ± 0.56 ^{bA}	21.67 ± 0.56 ^{bA}	21.67 ± 0.56 ^{bA}	1.000
	T10 min	21.17 ± 0.48 ^{bA}	21.17 ± 0.48 ^{bA}	21.17 ± 0.48 ^{bA}	1.000
	T15 min	20.50 ± 0.22 ^{bA}	20.50 ± 0.22 ^{bA}	20.50 ± 0.22 ^{bA}	1.000
	T20 min	13.00 ± 0.58 ^{cA}	13.00 ± 0.58 ^{cA}	13.00 ± 0.58 ^{cA}	1.000
	T25 min	13.00 ± 0.51 ^{cA}	10.50 ± 0.72 ^{dB}	14.50 ± 0.76 ^{bA}	<0.001
	T30 min	14.83 ± 0.60 ^{cA}	12.50 ± 0.99 ^{dB}	16.00 ± 0.73 ^{bA}	<0.001
	T35 min	14.83 ± 0.48 ^{cA}	11.00 ± 0.89 ^{dB}	16.67 ± 0.80 ^{bA}	<0.001
	T40 min	14.67 ± 0.33 ^{cA}	11.50 ± 0.99 ^{dB}	16.33 ± 0.49 ^{bA}	<0.001
	T60 min	14.50 ± 0.43 ^{cA}	11.33 ± 0.76 ^{dB}	14.33 ± 0.56 ^{cA}	<0.001
P value		<0.001	<0.001	<0.001	<0.001
SPO2	T 0 min	96.17 ± 0.40 ^{aA}	96.17 ± 0.40 ^{aA}	96.17 ± 0.40 ^{aA}	1.000
	T 5 min	96.00 ± 0.37 ^{aA}	96.00 ± 0.37 ^{aA}	96.00 ± 0.37 ^{aA}	1.000
	T 10 min	96.17 ± 0.31 ^{aA}	96.17 ± 0.31 ^{aA}	96.17 ± 0.31 ^{aA}	1.000
	T 15 min	95.67 ± 0.42 ^{aA}	95.67 ± 0.42 ^{aA}	95.67 ± 0.42 ^{aA}	1.000
	T 20 min	96.50 ± 0.22 ^{aA}	96.50 ± 0.22 ^{aA}	96.50 ± 0.22 ^{aA}	1.000
	T 25 min	97.33 ± 0.33 ^{aA}	97.33 ± 0.33 ^{aA}	97.50 ± 0.22 ^{aA}	0.428
	T 30 min	97.17 ± 0.40 ^{aA}	97.17 ± 0.40 ^{aA}	97.00 ± 0.37 ^{aA}	0.765
	T 35 min	96.67 ± 0.49 ^{aA}	96.67 ± 0.49 ^{aA}	97.00 ± 0.37 ^{aA}	0.612
	T 40 min	97.33 ± 0.33 ^{aA}	97.33 ± 0.33 ^{aA}	97.17 ± 0.40 ^{aA}	0.765
	T 60 min	96.17 ± 0.40 ^{aA}	96.17 ± 0.40 ^{aA}	97.33 ± 0.33 ^{bA}	0.032
P value		<0.001	<0.001	<0.001	
RT	T 0 min	39.10 ± 0.07 ^{aA}	39.10 ± 0.07 ^{aA}	39.10 ± 0.07 ^{aA}	1.000
	T 5 min	39.07 ± 0.08 ^{bA}	39.07 ± 0.08 ^{bA}	39.07 ± 0.08 ^{bA}	1.000
	T 10 min	39.00 ± 0.07 ^{bA}	39.00 ± 0.07 ^{bA}	39.00 ± 0.07 ^{bA}	1.000
	T 15 min	39.00 ± 0.07 ^{bA}	39.00 ± 0.07 ^{bA}	39.00 ± 0.07 ^{bA}	1.000
	T 20 min	38.53 ± 0.10 ^{bA}	38.67 ± 0.04 ^{bA}	38.75 ± 0.04 ^{bA}	0.090
	T 25 min	38.42 ± 0.09 ^{bA}	38.33 ± 0.09 ^{bA}	38.55 ± 0.04 ^{bA}	0.180
	T 30 min	38.25 ± 0.07 ^{bA}	38.33 ± 0.05 ^{bA}	38.40 ± 0.03 ^{bA}	0.250
	T 35 min	38.20 ± 0.03 ^{bA}	38.22 ± 0.04 ^{bA}	38.27 ± 0.04 ^{bA}	0.400
	T 40 min	38.13 ± 0.05 ^{bA}	38.13 ± 0.05 ^{bA}	38.10 ± 0.04 ^{bA}	0.800
	T 60 min	38.00 ± 0.04 ^{bA}	38.00 ± 0.04 ^{bA}	38.15 ± 0.08 ^{bA}	0.120
P value		<0.001	<0.001	<0.001	
SAP	T 0 min	117.00 ± 0.68 ^{aA}	117.00 ± 0.68 ^{aA}	117.00 ± 0.68 ^{aA}	1.000
	T 5 min	115.33 ± 0.42 ^{aA}	115.33 ± 0.42 ^{aA}	115.33 ± 0.42 ^{aA}	1.000
	T 10 min	115.33 ± 0.33 ^{aA}	115.33 ± 0.33 ^{aA}	115.33 ± 0.33 ^{aA}	1.000
	T 15 min	117.33 ± 0.76 ^{aA}	117.33 ± 0.76 ^{aA}	117.33 ± 0.76 ^{aA}	1.000
	T 20 min	113.50 ± 1.45 ^{bA}	113.50 ± 1.45 ^{bA}	113.50 ± 1.45 ^{bA}	1.000
	T 25 min	104.83 ± 1.01 ^{cc}	106.67 ± 0.62 ^{cB}	110.17 ± 1.01 ^{cA}	<0.001
	T 30 min	103.83 ± 0.87 ^{cc}	105.17 ± 0.70 ^{cB}	108.17 ± 0.79 ^{cA}	<0.001
	T 35 min	101.33 ± 0.42 ^{cB}	99.83 ± 0.65 ^{cc}	107.00 ± 0.68 ^{cA}	<0.001
	T 40 min	100.33 ± 1.18 ^{cB}	98.67 ± 0.88 ^{cc}	107.83 ± 0.48 ^{cA}	<0.001
	T 60 min	99.00 ± 0.52 ^{cB}	92.50 ± 0.92 ^{dc}	105.33 ± 0.92 ^{cA}	<0.001
P value		<0.001	<0.001	<0.001	
DAP	T 0 min	77.00 ± 0.77 ^{aA}	77.00 ± 0.77 ^{aA}	77.00 ± 0.77 ^{aA}	1.000
	T 5 min	74.83 ± 0.48 ^{bA}	74.83 ± 0.48 ^{bA}	74.83 ± 0.48 ^{bA}	1.000
	T 10 min	75.17 ± 0.40 ^{aA}	75.17 ± 0.40 ^{aA}	75.17 ± 0.40 ^{aA}	1.000
	T 15 min	76.83 ± 0.60 ^{aA}	76.83 ± 0.60 ^{aA}	76.83 ± 0.60 ^{aA}	1.000
	T 20 min	75.50 ± 1.15 ^{bA}	75.50 ± 1.15 ^{bA}	75.50 ± 1.15 ^{bA}	1.000
	T 25 min	68.17 ± 0.94 ^{cc}	72.67 ± 0.42 ^{bB}	72.17 ± 0.70 ^{bA}	<0.001
	T 30 min	69.00 ± 0.77 ^{cc}	69.50 ± 1.05 ^{cB}	72.17 ± 0.60 ^{bA}	<0.001
P value		<0.001	<0.001	<0.001	
DAP	T 35 min	65.17 ± 0.54 ^{cc}	63.17 ± 1.01 ^{dc}	71.17 ± 0.40 ^{bA}	<0.001

	T 40 min	65.50 ± 1.18 ^{cc}	59.83 ± 0.60 ^{dc}	71.33 ± 0.21 ^{ba}	<0.001
	T 60 min	63.83 ± 0.54 ^{cb}	57.67 ± 1.17 ^{dc}	70.00 ± 0.52 ^{ba}	<0.001
P value		<0.001	<0.001	<0.001	
MAP	T 0 min	89.67 ± 0.61 ^{aA}	89.67 ± 0.61 ^{aA}	89.67 ± 0.61 ^{aA}	1.000
	T 5 min	87.50 ± 0.43 ^{aA}	87.50 ± 0.43 ^{aA}	87.50 ± 0.43 ^{aA}	1.000
	T 10 min	87.50 ± 0.43 ^{aA}	87.50 ± 0.43 ^{aA}	87.50 ± 0.43 ^{aA}	1.000
	T 15 min	89.83 ± 0.60 ^{aA}	89.83 ± 0.60 ^{aA}	89.83 ± 0.60 ^{aA}	1.000
	T 20 min	85.17 ± 1.15 ^{ba}	85.17 ± 1.15 ^{ba}	85.17 ± 1.15 ^{ba}	1.000
	T 25 min	79.00 ± 0.86 ^{bb}	82.00 ± 0.36 ^{ba}	82.83 ± 0.79 ^{ba}	0.005
	T 30 min	78.17 ± 0.87 ^{bb}	77.17 ± 1.11 ^{bb}	82.17 ± 0.54 ^{ba}	<0.001
	T 35 min	75.50 ± 0.76 ^{bb}	74.17 ± 0.79 ^{bb}	81.17 ± 0.48 ^{ba}	<0.001
	T 40 min	74.50 ± 1.18 ^{bb}	73.00 ± 0.89 ^{bb}	81.33 ± 0.42 ^{ba}	<0.001
	T 60 min	74.17 ± 0.65 ^{bb}	71.33 ± 0.92 ^{bb}	79.83 ± 0.87 ^{ba}	<0.001
P value		<0.001	<0.001	<0.001	

Heart rate (HR), respiratory rate (RR), oxygen saturation (SpO₂), rectal temperature (Temp), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) expressed as **mean ± standard error (SE)**. Statistical significance is denoted as: ^{a,b} Significant difference compared to baseline within the same treatment group ($p < 0.05$). ^{A, B} Significant difference between treatment groups at specific time points ($p < 0.05$). These determinations were made using two-way repeated measures ANOVA with Duncan's post-hoc testing to account for multiple comparisons across the propofol (P), propofol–midazolam (PM), or propofol–midazolam–ketamine (PMK) treatment groups and ten time points (T0, T5, T10, T15, T20, T25, T30, T35, T40, and T60).

TABLE 5. Electrocardiographic (ECG) values in eighteen ketamine/midazolam-anesthetized goats under different anaesthetic protocols at different time points.

Parameter	Time	Groups			P-value
		PM	P	PMK	
P amplitude	T0 min	0.097 ± 0.002 ^{aA}	0.097 ± 0.002 ^{aA}	0.097 ± 0.002 ^{aA}	0.925
	T10 min	0.075 ± 0.006 ^{ba}	0.075 ± 0.006 ^{ba}	0.075 ± 0.006 ^{ba}	1.000
	T20 min	0.082 ± 0.003 ^{aA}	0.082 ± 0.003 ^{aA}	0.082 ± 0.003 ^{aA}	1.000
	T40 min	0.080 ± 0.004 ^{aA}	0.083 ± 0.003 ^{aA}	0.065 ± 0.002 ^{bb}	<0.001
	T60 min	0.085 ± 0.002 ^{aA}	0.081 ± 0.002 ^{aA}	0.061 ± 0.003 ^{bb}	<0.001
P value		<0.001	<0.001	<0.001	
R amplitude	T0 min	0.617 ± 0.011 ^{aA}	0.617 ± 0.011 ^{aA}	0.617 ± 0.011 ^{aA}	1.000
	T10 min	0.317 ± 0.013 ^{bb}	0.317 ± 0.013 ^{bb}	0.317 ± 0.013 ^{bb}	1.000
	T20 min	0.332 ± 0.013 ^{bb}	0.332 ± 0.013 ^{bb}	0.332 ± 0.013 ^{bb}	1.000
	T40 min	0.310 ± 0.007 ^{bb}	0.285 ± 0.006 ^{bc}	0.350 ± 0.018 ^{ac}	<0.001
	T60 min	0.308 ± 0.007 ^{bb}	0.280 ± 0.008 ^{cc}	0.450 ± 0.022 ^{ad}	<0.001
P value		<0.001	0.074	<0.001	
T amplitude	T0 min	0.318 ± 0.009 ^{aA}	0.318 ± 0.009 ^{aA}	0.318 ± 0.009 ^{aA}	1.000
	T10 min	0.300 ± 0.006 ^{bb}	0.300 ± 0.006 ^{bb}	0.300 ± 0.006 ^{bb}	1.000
	T20 min	0.210 ± 0.003 ^{cc}	0.210 ± 0.003 ^{cc}	0.210 ± 0.003 ^{cc}	1.000
	T40 min	0.268 ± 0.011 ^{bd}	0.262 ± 0.006 ^{bd}	0.208 ± 0.004 ^{cd}	<0.001
	T60 min	0.263 ± 0.006 ^{bd}	0.260 ± 0.006 ^{bd}	0.193 ± 0.004 ^{ce}	<0.001
P value		<0.001	<0.001	<0.001	
QRS duration	T0 min	0.069 ± 0.003 ^{aA}	0.069 ± 0.003 ^{aA}	0.069 ± 0.003 ^{aA}	1.000
	T10 min	0.066 ± 0.002 ^{aB}	0.066 ± 0.002 ^{aB}	0.066 ± 0.002 ^{aB}	1.000
	T20 min	0.076 ± 0.002 ^{ac}	0.076 ± 0.002 ^{ac}	0.076 ± 0.002 ^{ac}	1.000
	T40 min	0.060 ± 0.001 ^{ad}	0.064 ± 0.002 ^{ad}	0.066 ± 0.002 ^{aB}	0.100
	T60 min	0.068 ± 0.001 ^{aA}	0.065 ± 0.002 ^{ad}	0.065 ± 0.002 ^{aB}	0.267
P value		<0.001	<0.001	<0.001	
PR interval	T0 min	0.138 ± 0.002 ^{aA}	0.138 ± 0.002 ^{aA}	0.138 ± 0.002 ^{aA}	1.000
	T10 min	0.127 ± 0.002 ^{aB}	0.127 ± 0.002 ^{aB}	0.127 ± 0.002 ^{aB}	1.000
	T20 min	0.127 ± 0.001 ^{aB}	0.126 ± 0.001 ^{aB}	0.126 ± 0.001 ^{aB}	1.000
	T40 min	0.136 ± 0.002 ^{aA}	0.141 ± 0.001 ^{aA}	0.136 ± 0.002 ^{aA}	0.085
	T60 min	0.137 ± 0.002 ^{aA}	0.138 ± 0.003 ^{aA}	0.133 ± 0.002 ^{aB}	0.336
P value		<0.001	<0.001	<0.001	
QT interval	T0 min	0.235 ± 0.002 ^{aA}	0.235 ± 0.002 ^{aA}	0.235 ± 0.002 ^{aA}	1.000
	T10 min	0.213 ± 0.005 ^{bb}	0.213 ± 0.005 ^{bb}	0.213 ± 0.005 ^{bb}	1.000
	T20 min	0.248 ± 0.004 ^{ac}	0.248 ± 0.004 ^{ac}	0.248 ± 0.004 ^{ac}	1.000
	T40 min	0.252 ± 0.003 ^{ad}	0.258 ± 0.004 ^{ad}	0.241 ± 0.001 ^{bd}	0.022
	T60 min	0.253 ± 0.002 ^{ad}	0.258 ± 0.001 ^{ad}	0.218 ± 0.005 ^{be}	<0.001
P value		<0.001	<0.001	<0.001	

Electrocardiographic (ECG) amplitudes and durations were expressed as **mean ± standard error (SE)**. Statistical significance was denoted as: small letters indicate a significant difference compared to baseline within the same treatment group ($p < 0.05$). Capital letters indicate a significant difference between treatment groups at specific time points ($p < 0.05$). These determinations were made using two-way repeated measures ANOVA with Duncan's post-hoc testing to account for multiple comparisons across the propofol (P), propofol–midazolam (PM), or propofol–midazolam–ketamine (PMK) treatment groups and ten time points (T0, T5, T10, T15, T20, T25, T30, T35, T40, and T60).

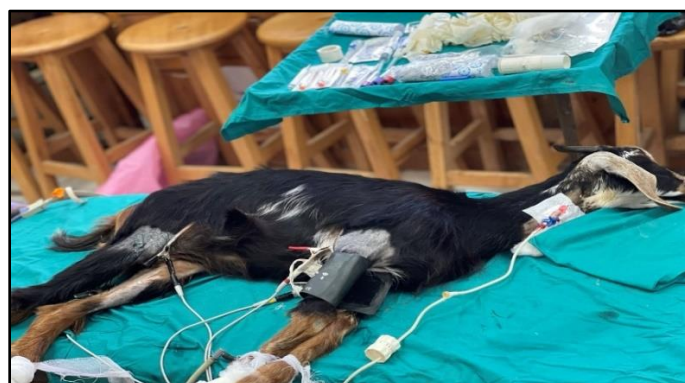
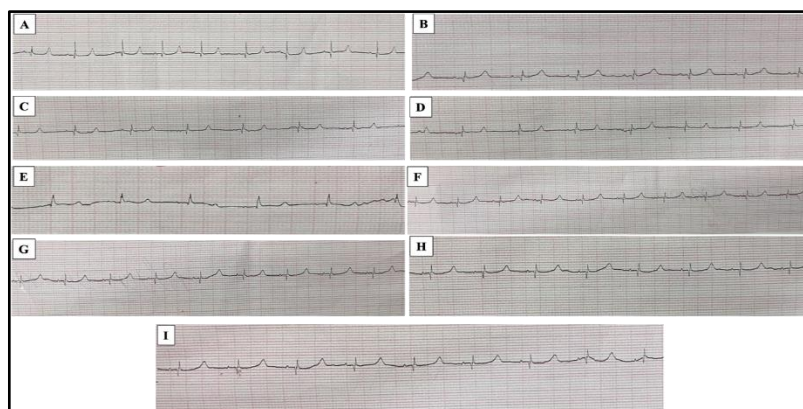
TABLE 6. The recovery period times in eighteen ketamine/midazolam-anesthetized goats under different anaesthetic protocols.

Time	P	PM	PMK
Time to recovery of the swallowing reflex (min)	3.00±0.89 ^a	5.17±1.47 ^b	6.33±0.82 ^b
Time to sternal recumbency (min)	7.17±1.94 ^a	12.00±1.41 ^b	13.50±1.05 ^b
Time to standing (min)	15.83±1.33 ^a	20.38±1.83 ^b	22.33±1.03 ^b

The recovery times (min) were expressed as mean ± standard error (SE). Statistical significance was denoted as: small letters indicate a significant difference ($p < 0.05$) between the propofol (P), propofol–midazolam (PM), or propofol–midazolam–ketamine (PMK) treatment groups.

TABLE 7. The score of induction, recovery, analgesia, jaw relaxation, palpebral, and pedal reflex quality in eighteen ketamine/midazolam-anesthetized goats under the propofol (P), propofol–midazolam (PM), or propofol–midazolam–ketamine (PMK) treatment groups.

Parameter / score	P	PM	PMK
Quality of induction	Good 100% (n=6)	Good 100% (n=6)	Good 100%
Quality of recovery	Good 100% (n=6)	Good 66.7% (n=4) Fair 33.3% (n=2)	Good 66.7% (n=4) Fair 33.3% (n=2)
Analgesia	(2) 50% (n=3) (1) 16.7% (n=1) (3) 33.3% (n=2)	(2) 50% (n=3) (3) 50% (n=3)	(3) 100% (n=6)
Jaw relaxation	(2) 50% (n=3) (3) 50% (n=3)	(3) 66.7% (n=4) (2) 33.3% (n=2)	(3) 100% (n=6)
Palpebral reflex	(2) 50% (n=3) (3) 50% (n=3)	(3) 66.7% (n=4) (2) 33.3% (n=2)	(3) 100% (n=6)
Pedal reflex	(2) 50% (n=3) (3) 50% (n=3)	(3) 66.7% (n=4) (2) 33.3% (n=2)	(3) 100% (n=6)

**Fig. 1. A goat under general anesthesia in left lateral recumbency during the experimental procedure****Fig. 2. Representative ECG traces (25 mm/s and 10mm/mV), recorded from goats subjected to the three anesthetic protocols (PMK, PM, and P) at different time intervals during the experimental period. A: Baseline at T0, B: After nalbuphine at T10, C: After induction at T20, D: The PMK group at T40, E: the PMK at T60, F: The PM group at T40, G: The PM at T60, H: The P group at T40, and I: The P group at T60.**

References

- Soliz, J. M., Ifeanyi, I. C., Katz, M. H., Wilks, J., Cata, J. P., McHugh, T. and Gottumukkala, V. Comparing postoperative complications and inflammatory markers using total intravenous anesthesia versus volatile gas anesthesia for pancreatic cancer surgery. *Anesthesiology and Pain Medicine*, **7**(4), e13879 (2017).
- Dzikiti, T. B. Intravenous anaesthesia in goats: A review. *Journal of the South African Veterinary Association*, **84**(1), 1-8 (2013).
- Tokimitsu, K., Yachida, M., Miki, W., Kuramoto, T., Mochizuki, N., Yoshida, S., ...and Morita, Y. Clinical Consideration in Total Intravenous Anesthesia Using Xylazine and Propofol in Calves. *The Thai Journal of Veterinary Medicine*, **54**(4), 1-5 (2024).
- Celestine Okwudili, U., Chinedu Athanasius, E. and Rita Ijeoma, U. Assessment of common anaesthetic and clinical indices of multimodal therapy of propofol, xylazine, and ketamine in total intravenous anaesthesia in West African dwarf goat. *Journal of Veterinary Medicine*, **2014**(1), 962560 (2014).
- Steffey, E. P., Brosnan, R. J., Galuppo, L. D., Mama, K. R., Imai, A., Maxwell, L. K., ... and Stanley, S. D. Use of propofol-xylazine and the anderson sling suspension system for recovery of horses from desflurane anesthesia. *Veterinary Surgery*, **38**(8), 927-933 (2009).
- Berry, S. H. Injectable anesthetics. Veterinary anesthesia and analgesia: *The fifth edition of Lumb and Jones* 277-296 (2015).
- Maney, J. K., Durham Jr, H. E., Goucher, K. P. and Little, E. L. Induction of anesthesia and recovery in donkeys sedated with xylazine: a comparison of midazolam-alfaxalone and midazolam-ketamine. *Veterinary Anaesthesia and Analgesia*, **45**(4), 539-544 (2018).
- Clarke, K. W., Trim, C. M. and Hall, L. W. Chapter 16, Anaesthesia of the cat. *Veterinary Anaesthesia (11th edn)*. Saunders (2014).
- Abouelfetouh, M. M., Salah, E., Liu, L., Khalil, A. H., Zhang, Q., Ding, M. and Ding, Y. Immediate postoperative analgesia of nalbuphine-ketamine combination compared with ketamine alone in xylazine-sedated goats undergoing left flank laparotomy. *Animals*, **12**(4), 509 (2022).
- Miller, R. R. Evaluation of nalbuphine hydrochloride. *American Journal of Hospital Pharmacy*, **37**(7), 942-949 (1980).
- Amin, O. A. I., Ibrahim, M. A. M. and Salem, D. A. E. Nalbuphine versus midazolam as an adjuvant to intrathecal bupivacaine for postoperative analgesia in patients undergoing cesarean section. *Journal of Pain Research*, 1369-1376 (2020).
- Kreisler, R. E., Cornell, H. N., Smith, V. A., Kelsey, S. E. and Hofmeister, E. H. Use of nalbuphine as a substitute for butorphanol in combination with dexmedetomidine and tiletamine/zolazepam: a randomized non-inferiority trial. *Journal of Feline Medicine and Surgery*, **22**(2), 100-107 (2020).
- Torad, F. A. and Hassan, E. A. Sedative, analgesic, and behavioral effects of nalbuphine-xylazine and nalbuphine-midazolam combinations in dogs. *Journal of Veterinary Behavior*, **28**, 40-45 (2018).
- Harish Kulkarni, H. K., William, B. J., George, R. S. and Kannan, T. A. Analgesic and adjunct actions of nalbuphine hydrochloride in xylazine or xylazine and acepromazine premedicated horses *Indian J. Anim. Res.*, **49** (5), 699-703 (2015).
- Shyken, J. M., Babbar, S., Babbar, S. and Forinash, A. Benzodiazepines in pregnancy. *Clinical Obstetrics and Gynecology*, **62**(1), 156-167 (2019).
- Hamano, S. I., Sugai, K., Miki, M., Tabata, T., Fukuyama, T. and Osawa, M. Efficacy, safety, and pharmacokinetics of intravenous midazolam in Japanese children with status epilepticus. *Journal of the Neurological Sciences*, **396**, 150-158 (2019).
- Kropf, J. and Hughes, J. L. Effects of midazolam on cardiovascular responses and isoflurane requirement during elective ovariohysterectomy in dogs. *Irish Veterinary Journal*, **71**(1), 26 (2018).
- Allison, A., Robinson, R., Jolliffe, C. and Taylor, P. M. Evaluation of the use of midazolam as a co-induction agent with ketamine for anaesthesia in sedated ponies undergoing field castration. *Equine Veterinary Journal*, **50**(3), 321-326 (2018).
- Stegmann, G. F. Observations on the use of midazolam for sedation, and induction of anaesthesia with midazolam in combination with ketamine in the goat. *Journal of the South African Veterinary Association*, **69** (3), 89-92 (1998).
- Yadav, M., Rastogi, S. K., Madan, A. K., Das, A. K., Huozha, R., Manjari, P. and Kumar, S. Electrocardiographic, clinical and haematological evaluation of propofol and xylazine-ketamine anaesthesia in Goat. *Small Ruminant Research*, **230**, 107168 (2024).
- Dzikiti, B. T., Stegmann, F. G., Dzikiti, L. N. and Hellebrekers, L. J. Total intravenous anaesthesia (TIVA) with propofol-fentanyl and propofol-midazolam combinations in spontaneously-breathing goats. *Veterinary Anaesthesia and Analgesia*, **37**(6), 519-525 (2010).
- Larenza, M. P., Bergadano, A., Iff, I., Doherr, M. G. and Schatzmann, U. Comparison of the cardiopulmonary effects of anesthesia maintained by continuous infusion of ketamine and propofol with anesthesia maintained by inhalation of sevoflurane in goats undergoing magnetic resonance imaging. *American Journal of Veterinary Research*, **66**(12), 2135-2141 (2005).
- Asif, M., Khan, M. A. and Akbar, H. Development of novel total intravenous anesthesia protocol using

- constant rate infusion in goats during pain management. *JAPS: Journal of Animal & Plant Sciences*, **32**(2),309-314 (2022).
24. Yakubu, A. S., Ja'afar, S., Sulaiman, F., Abubakar, A. A., Elsa, A. T., Kene, R. O. C. and Adeyanju, J. B. Hematological and cardiopulmonary effects of propofol anesthesia in red Sokoto goat of Nigeria. *Animal Science Reporter*, **13**(2),16-27 (2020).
 25. Abouelfetouh, M. M., Salah, E., Liu, L., Khalil, A. H., Zhang, Q., Ding, M. and Ding, Y. Immediate postoperative analgesia of nalbuphine-ketamine combination compared with ketamine alone in xylazine-sedated goats undergoing left flank laparotomy. *Animals*, **12**(4), 509 (2022).
 26. Dzikiti, T. B. Towards Total Intravenous Anaesthesia in Goats (*Doctoral dissertation*, University of Pretoria) (2010).
 27. Dzikiti, T. B., Zeiler, G. E., Dzikiti, L. N., and Garcia, E. R. The effects of midazolam and butorphanol, administered alone or combined, on the dose and quality of anaesthetic induction with alfaxalone in goats. *Journal of the South African Veterinary Association*, **85**(1), 1-8 (2014).
 28. Ragab, G., Hassan, S. E., Fathi, M. Z. and Hagag, U. Clinicophysiological and hematobiochemical effect of dexmedetomidine or diazepam with ketamine and propofol in total intravenous anesthesia in goats. *Beni-Suef University Journal of Basic and Applied Sciences*, **11**(1), 54 (2022).
 29. Daradka, M. and Ismail, Z. B. Evaluation of the clinical and analgesic effects of subarachnoid ketamine-lidocaine administration in goats undergoing mastectomy. *Veterinary Medicine: Research and Reports*, 35-39 (2014).
 30. Gunion, M. W., Marchionne, A. M. and Anderson, C. T. Use of the mixed agonist–antagonist nalbuphine in opioid based analgesia. *Acute Pain*, **6**(1), 29-39 (2004).
 31. Torad, F. A. and Hassan, E. A. Sedative, analgesic, and behavioral effects of nalbuphine-xylazine and nalbuphine-midazolam combinations in dogs. *Journal of Veterinary Behavior*, **28**, 40-45 (2018).
 32. Schindler, C. W., Graczyk, Z., Gilman, J. P., Negus, S. S., Bergman, J., Mello, N. K. and Goldberg, S. R. Effects of kappa opioid agonists alone and in combination with cocaine on heart rate and blood pressure in conscious squirrel monkeys. *European Journal of Pharmacology*, **576**(1-3), 107-113 (2007).
 33. Grillo, A., Salvi, L., Coruzzi, P., Salvi, P. and Parati, G. Sodium intake and hypertension. *Nutrients*, **11**(9), 1970 (2019).
 34. Meariman, J. K., Sutphen, J. C., Gao, J. and Kapusta, D. R. Nalfurafine, a G-protein–biased KOR (Kappa Opioid Receptor) agonist, enhances the diuretic response and limits electrolyte losses to standard-of-care diuretics. *Hypertension*, **79**(2), 379-390 (2022).
 35. Qi, W. and Smith, F. G. Kappa opioids modulate the arterial baroreflex control of heart rate in conscious young sheep. *Canadian Journal of Physiology and Pharmacology*, **85**(8), 811-817 (2007).
 36. Coetzee, J. F., Lechtenberg, K. F., Stock, M. L. and Kukanich, B. Pharmacokinetics and effect of intravenous nalbuphine in weaned Holstein calves after surgical castration. *Journal of Veterinary Pharmacology and Therapeutics*, **37**(2), 169-177 (2014).
 37. Kitajima, K., Oishi, K., Miwa, M., Anzai, H., Setoguchi, A., Yasunaka, Y. and Hirooka, H. Effects of heat stress on heart rate variability in free-moving sheep and goats assessed with correction for physical activity. *Frontiers in Veterinary Science*, **8**, 658763 (2021).
 38. Gunion, M. W., Marchionne, A. M. and Anderson, C. T. Use of the mixed agonist–antagonist nalbuphine in opioid based analgesia. *Acute pain*, **6**(1), 29-39 (2004).
 39. Díaz, M. and Becker, D. E. Thermoregulation: physiological and clinical considerations during sedation and general anesthesia. *Anesthesia Progress*, **57**(1), 25-33 (2010).
 40. Jangra, S. K., Chawla, S. K., Peshin, P. K., Tayal, R., Singh, J. and Behl, S. M. Cardiopulmonary effects of midazolam in goats. *Indian Journal of Veterinary Surgery*, **29**(1), 20-24 (2008).
 41. Katzung, B. G., Masters, S. B. and Trevor, A. J. (Eds.). *Basic & clinical pharmacology* (2004).
 42. Colussi, G. L., Di Fabio, A., Catena, C., Chiuch, A. and Sechi, L. A. Involvement of endothelium-dependent and-independent mechanisms in midazolam-induced vasodilation. *Hypertension Research*, **34**(8), 929-934 (2011).
 43. Haskins, S., Pascoe, P. J., Ilkiw, J. E., Fudge, J., Hopper, K. and Aldrich, J. Reference cardiopulmonary values in normal dogs. *Comparative Medicine*, **55**(2), 156-161(2005).
 44. Miller, R. D., Eriksson, L. I., Fleisher, L. A., Wiener-Kronish, J. P., Cohen, N. H. and Young, W. L. Miller's anesthesia e-book. *Elsevier Health Sciences* (2014).
 45. Stegmann, G. F. and Bester, L. Sedative-hypnotic effects of midazolam in goats after intravenous and intramuscular administration. *Veterinary Anaesthesia and Analgesia*, **28**(1), 49-55 (2001).
 46. Stegmann, G. F. Observations on the use of midazolam for sedation, and induction of anaesthesia with midazolam in combination with ketamine in the goat. *Journal of the South African Veterinary Association*, **69**(3), 89-92 (1998).
 47. Smith, A. C., Zellner, J. L., Spinale, F. G. and Swindle, M. M. Sedative and cardiovascular effects of midazolam in swine. *Lab. Anim. Sci.*, **41**(2), 157-161 (1991).
 48. Tranquilli, W. J., Thurmon, J. C. and Grimm, K. A. (Eds.). *Lumb and Jones' veterinary anesthesia and analgesia*. John Wiley & Sons (2013).

49. Hopkins, A., Giuffrida, M. and Larenza, M. P. Midazolam, as a co-induction agent, has propofol sparing effects but also decreases systolic blood pressure in healthy dogs. *Veterinary Anaesthesia and Analgesia*, **41**(1), 64-72 (2014).
50. Hristova, T. S., Keating, S. C., McCoy, A. M., Strahl-Heldreth, D. E., Doodnaught, G. M., Sieja, K. M. and Swanson, K. S. Heart rate, arterial pressure and propofol-sparing effects of guaifenesin in dogs. *Veterinary Anaesthesia and Analgesia*, **50**(1), 50-56 (2023).
51. Sánchez, A., Belda, E., Escobar, M., Agut, A., Soler, M. and Laredo, F. G. Effects of altering the sequence of midazolam and propofol during co-induction of anaesthesia. *Veterinary Anaesthesia and Analgesia*, **40**(4), 359-366 (2013).
52. Magella, H. A. D. and Cheibub, Z. B. Propofol: revisão bibliográfica. *Rev. bras. anestesiologia*, 289-93 (1990).
53. Robinson, R. and Borer-Weir, K. The effects of diazepam or midazolam on the dose of propofol required to induce anaesthesia in cats. *Veterinary Anaesthesia and Analgesia*, **42**(5), 493-501 (2015).
54. Covey-Crump, G. L. and Murison, P. J. Fentanyl or midazolam for co-induction of anaesthesia with propofol in dogs. *Veterinary anaesthesia and analgesia*, **35**(6), 463-472 (2008).
55. He, J., Kinouchi, Y., Yamaguchi, H. and Miyamoto, H. Exercise-induced changes in R wave amplitude and heart rate in normal subjects. *Journal of electrocardiology*, **28**(2), 99-106 (1995).
56. Fine, D. M. Skills Laboratory: How to determine and interpret the mean electrical axis. *Veterinary medicine*, **101**(1), 28-36 (2006).
57. Kawicka, M., Lewicki, M., Frydrychowski, P., Michałek, M. and Noszczyk-Nowak, A. Comparative analysis of ECG records depending on body position in domestic swine (*Sus scrofa domestica*). *Porcine Health Management*, **8**(1), 39 (2022).
58. Santarosa, B. P., Lourenço, M. L., Dantas, G. N., Ulian, C. M., Heckler, M. C., Sudano, M. J., ... and Chiacchio, S. B. Electrocardiographic parameters of the American Miniature Horse: influence of age and sex. *Pesquisa Veterinária Brasileira*, **36**(06), 551-558 (2016).
59. Rishniw, M., Porciello, F., Erb, H. N. and Fruganti, G. Effect of body position on the 6-lead ECG of dogs. *Journal of Veterinary Internal Medicine*, **16**(1), 69-73 (2002).
60. Rabkin, S. W. Measurement of the QT interval: Lessons from thirty-two animal species for the correction of the QT interval by heart rate. *Int. J. Clin. Cardiol.*, **5**, 127 (2018).
61. Hidaka, S., Kawamoto, M., Kurita, S. and Yuge, O. Comparison of the effects of propofol and midazolam on the cardiovascular autonomic nervous system during combined spinal and epidural anesthesia. *Journal of Clinical Anesthesia*, **17**(1), 36-43 (2005).
62. Dennis, S. G., Wotton, P. R., Boswood, A. and Flaherty, D. Comparison of the effects of thiopentone and propofol on the electrocardiogram of dogs. *Veterinary Record*, **160**(20), 681-686 (2007).
63. Komatsu, T., Singh, P. K., Kimura, T., Nishiwaki, K., Bando, K. and Shimada, Y. Differential effects of ketamine and midazolam on heart rate variability. *Canadian Journal of Anaesthesia*, **42**(11), 1003-1009 (1995).
64. Khaleghi, M., Sarchahi, A. A., Kazemi Mehrjerdi, H., Rasekh, M. and Saadati, D. Effects of ketamine, propofol and isoflurane on electrocardiographic variables in clinically healthy dogs premedicated with medetomidine and midazolam. *In Veterinary Research Forum*, **15**, 187-194 (2024).
65. Gonzalez Castro, L. N., Mehta, J. H., Brayanov, J. B. and Mullen, G. J. Quantification of respiratory depression during pre-operative administration of midazolam using a non-invasive respiratory volume monitor. *PLoS One*, **12**(2), e0172750 (2017).
66. Stegmann, G. F. Observations on some cardiopulmonary effects of midazolam, xylazine and a midazolam/ketamine combination in the goat. *Journal of the South African Veterinary Association*, **70**(3), 122-126 (1999).
67. de Carvalho, L. L., Nishimura, L. T., Borges, L. P., Cerejo, S. A., Villela, I. O., Auckburally, A. and de Mattos-Junior, E. Sedative and cardiopulmonary effects of xylazine alone or in combination with methadone, morphine or tramadol in sheep. *Veterinary Anaesthesia and Analgesia*, **43**(2), 179-188 (2016).
68. Ferreira, J. P., Ndawana, P. S., Dzikiti, L. N. and Dzikiti, B. T. Determination of the minimum infusion rate of propofol required to prevent purposeful movement of the extremities in response to a standardized noxious stimulus in goats. *Veterinary Anaesthesia and Analgesia*, **43**(5), 519-527 (2016).
69. Mannarino, R., Luna, S. P., Monteiro, E. R., Beier, S. L. and Castro, V. B. Minimum infusion rate and hemodynamic effects of propofol, propofol-lidocaine and propofol-lidocaine-ketamine in dogs. *Veterinary Anaesthesia and Analgesia*, **39**(2), 160-173 (2012).
70. Prassinis, N. N., Galatos, A. D. and Raptopoulos, D. A comparison of propofol, thiopental or ketamine as induction agents in goats. *Veterinary Anaesthesia and Analgesia*, **32**(5), 289-296 (2005).
71. Eger, E. I., Johnson, B. H., Weiskopf, R. B., Holmes, M. A., Yasuda, N., Targ, A. and Rampil, I. J. Minimum alveolar concentration of 1-653 and isoflurane in pigs: definition of a supramaximal stimulus. *Anesthesia & Analgesia*, **67**(12), 1174-1176 (1988).
72. Glowaski, M. M. and Wetmore, L. A. Propofol: application in veterinary sedation and anesthesia. *Clinical Techniques in Small Animal Practice*, **14**(1), 1-9 (1999).

73. Celestine Okwudili, U., Chinedu Athanasius, E., and Rita Ijeoma, U. Assessment of common anaesthetic and clinical indices of multimodal therapy of propofol, xylazine, and ketamine in total intravenous anaesthesia in West African dwarf goat. *Journal of Veterinary Medicine*, **2014**(1), 962560 (2014).
74. Sabertanha, A., Shakhsemampour, B., Ekrami, M. and Allahyari, E. Comparison of infusion of propofol and ketamine-propofol mixture (Ketofol) as anesthetic maintenance agents on blood pressure of patients undergoing orthopedic leg surgeries. *Anesthesiology and Pain Medicine*, **9**(6), e96998 (2019).
75. Annetta, M. G., Iemma, D., Garisto, C., Tafani, C. and Proietti, R. Ketamine: new indications for an old drug. *Current Drug Targets*, **6**(7), 789-794 (2005).
76. Boscan, P., Pypendop, B. H., Solano, A. M. and Ilkiw, J. E. Cardiovascular and respiratory effects of ketamine infusions in isoflurane-anesthetized dogs before and during noxious stimulation. *American Journal Of Veterinary Research*, **66**(12), 2122-2129 (2005).
77. Gomes, V. H., Marques, J. L. R., Borré, L. D. S. J., de Cerqueira Teixeira, J. G. and da Silva, M. F. A. Comparison of the sedative effects of three nalbuphine doses, alone or combined with acepromazine, in dogs. *American Journal of Veterinary Research*, **83**(7) (2022).
78. Maravi, M. S., Dewangan, R. and Tiwari, S. K. Effects of propofol on Clinico-Physiological and Haemato-Biochemical profiles in atropinized goats. *Indian Journal of Small Ruminants* **24**(1), 187-190 (2018).
79. Sahinovic, M. M., Struys, M. M. and Absalom, A. R. Clinical pharmacokinetics and pharmacodynamics of propofol. *Clinical Pharmacokinetics*, **57**(12), 1539-1558 (2018).
80. Hodgkinson, O. and Dawson, L. Practical anaesthesia and analgesia in sheep, goats and calves. *In Practice*, **29**(10), 596-603 (2007).

تقييم الاستقرار القلبي-التنفسي والكهربائي القلبي تحت ثلاثة بروتوكولات للتخدير الكلي الوريدي (TIVA) في الماعز بعد التمهيد بنالبوفين

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الملخص

هدفت الدراسة الحالية إلى مقارنة الأداء التخديري لثلاثة بروتوكولات للتخدير الكلي الوريدي (TIVA) في الماعز البلدي المصري بعمر 3-5 شهور. حيث تلقت جميع الحيوانات النالبوفين (0.5 ملغ/كغ وريدياً) كمهدئ قبل التخدير، تلاه إعطاء الكيتامين (7 ملغ/كغ) مع الميدازولام (0.7 ملغ/كغ) كجرعة استقرارية. وتمت صيانة التخدير إما بالبروبوفول منفرداً (P)، أو بالبروبوفول مع الميدازولام (PM)، أو بالبروبوفول مع الميدازولام والكيتامين (PMK). جرى قياس المؤشرات الفسيولوجية والتي شملت معدل ضربات القلب (HR)، معدل التنفس (RR)، نسبة تشبع الأكسجين (SpO₂)، درجة الحرارة الشرجية، وضغوط الدم الشريانية (SAP, DAP, MAP) على فترات متتالية كل 5 دقائق حتى الدقيقة 60. كما تم تقييم متغيرات التخطيط الكهربائي للقلب (ECG) عند الدقائق 10 و 20 و 40 و 60 بعد إعطاء النالبوفين. لم تُسجل أية اضطرابات نظم قلبية في أي من المجموعات، وكانت التغيرات البسيطة في موجات التخطيط ضمن الحدود الطبيعية. أظهرت جميع البروتوكولات انخفاضاً في HR و RR وضغوط الدم أثناء فترة الصيانة، إلا أن مجموعة PMK حافظت على قيم أعلى معنوياً في HR و RR و MAP مقارنة بمجموعتي P و PM. وتشير هذه النتائج إلى أن الكيتامين قلل من التأثيرات المثبطة للبروبوفول، مما أدى إلى استقرار أفضل في المؤشرات القلبية التنفسية. كما انخفضت درجة الحرارة الشرجية بشكل ملحوظ في جميع المجموعات دون وجود فروق معنوية بينهما وفي الختام، وفر بروتوكول PMK أكثر الملفات التخديرية استقراراً من حيث سلامة الجهاز القلبي الوعائي مع كفاءة وظيفية تنفسية مناسبة، مما يدعم دور الكيتامين كعنصر مهم في بروتوكولات التخدير الكلي الوريدي المتوازن في الماعز.

الكلمات الدالة: ماعز، كيتامين، بروبوفول، ميدازولام، تخطيط القلب الكهربائي.