RESEARCH ARTICLE

Physiological and Haemato-Biochemical Alterations in the Ketamine-Propofol-Isoflurane and Tiletamine-Zolazepam-Isoflurane Anaesthetic Protocols in Cats

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Abstract

The present clinical study involved 12 cats of different age, sex, and breed presented for various surgeries, which were randomly divided into two groups, each group consisting of six cats. Induction of anaesthesia was achieved by administration of ketamine @ 2 mg/kg b.wt. in combination with propofol @ 2 mg/kg b.wt., intravenously in group I and tiletamine @ 5 mg/kg b.wt. in combination with zolazepam @ 5 mg/kg b.wt., intramuscularly in group II. It was maintained by isoflurane with 100% oxygen using a face mask connected with small animal inhalant anaesthesia machine. Significant decrease in rectal temperature, respiration rate and plasma total protein, and non-significant alteration in heart rate, SpO_2, ALT, BUN and creatinine were observed during the maintenance phase in both groups, but within normal physiological range. However, no significant difference was noted between groups at any point of time in any of the parameters evaluated. Overall satisfactory outcome from the anaesthesia was achieved in both groups, yet group I showed slightly better result than group II.

Key words: Cats, Clinico-physiological effects, Haemato-biochemical alterations, Isoflurane, Ketamine-propofol, Tiletamine-zolazepam.

Ind J Vet Sci and Biotech (2026): 10.48165/ijvsbt.22.1.18

Introduction

Cats can be challenging to manage, especially for diagnostic tasks like blood sampling or procedures such as echocardiography. Therefore, sedation or general anaesthesia is often necessary for routine diagnostic or surgical procedures (Moffat, 2008). Ketamine provides acute analgesia with a quick start and brief duration of effect. Due to sympathetic nervous system activation, it usually causes mild increase in blood pressure, heart rate, and breathing. It also causes convulsions, excessive muscular tone, and spontaneous muscle activity (Clarke and Trim, 2013; Reed *et al.,* 2019). Tiletamine is a long-acting, dissociative anaesthetic with pharmacologic properties similar to those of ketamine. However, its potency and duration of action fall between those of phencyclidine and ketamine. Tiletamine also provides greater analgesic effects than ketamine. When used alone, it can induce catalepsy in all species (Kwon *et al.,* 2003). Zolazepam, a benzodiazepine derivative with pharmacological properties similar to diazepam, induces amnesia, has minimal impact on cardio-respiratory function, and offers strong anticonvulsant effects. It is considered relatively safe even at higher doses and is the only benzodiazepine approved by the FDA for use in animals. Combined with tiletamine, zolazepam enhances central nervous system effects and reduces skeletal muscle hyperactivity (Kwon *et al.,* 2003; Lee *et al.,* 2018).

Propofol is a special kind of intravenous anaesthetic agent used for both induction and maintenance in dogs and cats. It is non-barbiturate, non-steroid, hypnotic alkylphenol, and ultrashort acting (Jimenez *et al.*, 2012; De Vries *et al.,* 2013; Abdelhakiem, 2019). When administered together, ketamine and propofol (Ketofol) exhibit an additive effect

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How to cite this article: Badi, R. N., Vadalia, J. J., Sharma, A., Sharma, A. K., & Dodia, V. D. (2026). Physiological and Haemato-Biochemical Alterations in the Ketamine-Propofol-Isoflurane and Tiletamine-Zolazepam-Isoflurane Anaesthetic Protocols in Cats. Ind J Vet Sci and Biotech, 22(1), 91-95.

Source of support: Nil

Conflict of interest: None

Submitted 07/11/2025 **Accepted** 02/12/2025 **Published** 10/01/2026

(Hui *et al.,* 1995), and provides effective and safe sedation and analgesia for painful procedures, streamlining administration and improving patient comfort (Willman and Andoltatto, 2007). Isoflurane has relatively low blood solubility, which contributes to several advantageous properties, including low biodegradability, quick onset of action, and quick recovery. However, like other inhalant anaesthetics, it depresses cardiovascular, pulmonary, and neurological functions in a dose-dependent manner (Steffey and Howland, 1978). The present clinical study was undertaken to evaluate and compare the clinico-physiological and haemato-biochemical effects of the ketamine-propofol-isoflurane and tiletamine-zolazepam-isoflurane anaesthetic protocols in cats.

Materials and Methods

The present clinical study involved 12 cats, which were randomly divided into two groups, each group consisting of six cats regardless of age, sex, breed, cause, or type of surgery. The animals were fasted for 12 h, with water withheld for 6 h before anaesthesia. Each animal underwent a pre-anaesthetic evaluation, which included measurement of rectal temperature (°F), heart rate (beats/min), respiration rate (breaths/min), mucous membrane color and capillary refill time. Induction of anaesthesia was achieved by administration of ketamine @ 2 mg/kg b.wt. in combination with propofol @ 2 mg/kg b.wt., intravenously in group I and tiletamine @ 5 mg/kg b.wt. in combination with zolazepam @ 5 mg/kg b.wt., intramuscularly in group II. Thereafter, the anaesthesia was maintained by isoflurane with 100% oxygen using a face mask connected with small animal inhalant anaesthesia machine. Any complication observed during induction, maintenance, and recovery period were recorded and managed accordingly.

Monitoring of Clinico-Physiological Parameter

Heart rate, respiratory rate, rectal temperature and saturation percentage of oxygen (SpO_2) were recorded at 0 min (prior to administration of any anaesthetic drug), 10 min after administration of anaesthetic combination and thereafter at every 10 min intervals up to 40 min during maintenance anaesthesia using multipara monitor or standard techniques.

Haemato-Biochemical Parameter

Blood samples (1.5 mL) were collected in sterile heparin vacutainers at 0 min (prior to administration of any anaesthetic drug), and 20 and 40 min after administration of anaesthetic combination. Haematological parameters were analyzed using automatic haemato-analyzer (Abacus Vet5; Diatron; Budapest, Hungary). Biochemical parameters, *viz.,* total protein, alanine aminotransferase, blood urea nitrogen and creatinine were analyzed by using an automatic biochemical analyzer (LW C 100 auto-chemistry analyzer; Shenzhen Landwind Medical; Shenzhen, China).

The data was analyzed using GraphPad Prism 10.4.1. The different clinico-physiological and haemato-biochemical parameters between groups were compared by simple t-test and within treatment (across different time period) were compared by one-way ANOVA and Tukey's HSD *post hoc* test.

Results And Discussion

Effect on Clinico-Physiological Parameter

Mean values of rectal temperature decreased highly significantly ($p \leq 0.01$) at 20th and 40th min in group I and at 20th, 30th and 40th min in group II during observation period, but non-significant difference was observed between groups. Mean values of heart rate increased non-significantly at 10th and 20th min, then gradually decreased at 30th and 40th min in group I. Heart rate increased non-significantly at 10th min, then decreased at 20th min, and remained relatively stable at 30th and 40th min in group II. The mean respiration rates exhibited a significant decrease ($p \leq 0.05$) in group I and a highly significant decrease ($p \leq 0.01$) in group II throughout the maintenance anaesthesia following the administration of the anaesthetic combination, but difference between groups was non-significant (Table 1). Similarly, Sayyed Mohd (2019) and Patel *et al*. (2022) reported significant

Table 1: Mean ±SE values of rectal temperature, heart rate, respiration rate andsaturation of peripheral oxygen at different time interval in different groups

Parameter	Group	0 min (Before induction)	Post-induction interval				p-value
			10 Min	20 Min	30 Min	40 Min	
Rectal temperature (°F)	I	$102.47\pm0.45^{a}_{A}$	$100.52\pm0.75^{ab}_{A}$	$99.32\pm1.07^{b}_{A}$	$99.75\pm0.51^{ab}_{A}$	$98.25\pm0.68^{b}_{A}$	0.0057
	II	$101.52\pm0.55^{a}_{A}$	$100.02\pm0.37^{ab}_{A}$	$98.55\pm0.74^{b}_{A}$	$98.40\pm0.90^{b}_{A}$	$98.35\pm0.62^{b}_{A}$	0.0080
Heart rate (beat/min)	I	$149.17\pm10.68^{a}_{A}$	$167.17\pm10.50^{a}_{A}$	$173.50\pm12.62^{a}_{A}$	$158.33\pm7.72^{a}_{A}$	$157.83\pm8.89^{a}_{A}$	0.4520
	II	$140.83\pm3.27^{a}_{A}$	$174.17\pm19.55^{a}_{A}$	$160.17\pm13.33^{a}_{A}$	$160.33\pm11.02^{a}_{A}$	$158.67\pm9.86^{a}_{A}$	0.4834
Respiration rate (breath/min)	I	$41.50\pm5.85^{a}_{A}$	$28.33\pm2.60^{ab}_{A}$	$26.83\pm2.24^{b}_{A}$	$26.67\pm2.55^{b}_{A}$	$25.67\pm2.68^{b}_{A}$	0.0177
	II	$44.83\pm2.10^{a}_{A}$	$30.00\pm2.74^{b}_{A}$	$29.33\pm3.32^{b}_{A}$	$27.33\pm3.70^{b}_{A}$	$27.00\pm3.70^{b}_{A}$	0.0027
Saturation of peripheral oxygen (SpO_2) (%)	I	$94.17\pm1.33^{a}_{A}$	$93.67\pm1.96^{a}_{A}$	$95.67\pm1.28^{a}_{A}$	$98.17\pm0.60^{a}_{A}$	$96.33\pm1.15^{a}_{A}$	0.1584
	II	$94.00\pm1.37^{a}_{A}$	$91.50\pm2.77^{a}_{A}$	$91.33\pm2.51^{a}_{A}$	$96.50\pm1.43^{a}_{A}$	$92.00\pm2.31^{a}_{A}$	0.3884

Means bearing different capital subscripts (A, B) between the groups and small superscripts (a,b) within the group differ significantly ($p \leq 0.05$)

decrease in rectal temperature and respiration rates in cats after administration of combination of dexmedetomidine-ketamine-propofol and tiletamine-zolazepam, respectively, while Sayyed Mohd (2019) and Nejamkin *et al.* (2020) reported significant decrease in heart rate in cats after administration of combination of dexmedetomidine-ketamine-propofol and tiletamine-zolazepam, respectively. Bhowmik (2016) observed a decrease in rectal temperature in cats during isoflurane anaesthesia. This decrease in rectal temperature might be due to depression of the thermoregulatory center, reduction in basal metabolic rate, peripheral vasodilation and inhibition of muscular activity. Initially increased heart rate and decreased respiration rate after administration of ketamine-propofol or tiletamine-zolazepam might be due to sympathetic nervous system stimulation and depression of the respiratory centre. Mean value of saturation of peripheral oxygen altered non-significantly in both group and non-significant difference was observed between groups (Table 1).

Effect on Haematological Parameter

The mean values of haemoglobin, packed cell volume, total erythrocyte count and total leukocyte count showed a non-significant decline (p>0.05) from baseline in both groups, but remained within normal physiological range, and non-significant differences were observed between groups at various time intervals (p>0.05) (Table 2). Sayyed Mohd (2019) reported haemoglobin and RBCs value unaltered, whereas PCV and WBCs value decreased significantly in dexmedetomidine-ketamine-propofol anesthetized cats. Patel *et al.* (2022) found similar results after administration of tiletamine-zolazepam in cats. Zlateva and Marinov (2015) observed decrease in haemoglobin, PCV and RBCs values in acepromazine premedicated and isoflurane maintained cats. Gradual decline in haemoglobin, packed cell volume, and total erythrocyte might be attributed to the sequestration of circulating blood cells in the spleen and lungs or vasodilatory effects of general anaesthesia, causing fluid shifts from tissues to blood vessels to maintain cardiac output. Decline in total leukocyte count might be due to the combined effects of immune modulation, haemodilution, and redistribution of leukocytes in the spleen and other secondary reservoirs.

The mean values of total neutrophils showed a non-significant increase (p>0.05) from baseline in both group, but remained within normal physiological range. However, non-significant (p > 0.05) differences were observed between groups at various time intervals (Table 2). Similarly, Sodagar *et al.* (2021) reported increased neutrophil after administration of tiletamine-zolazepam in cats. Increase in neutrophil count from baseline in both groups can be attributed to the stress response triggered by anaesthesia and surgical procedures, leading to the release of cortisol and other stress hormones. The mean values of lymphocytes, monocytes and eosinophils showed non-significant (p>0.05) alteration in both group and non-significant (p>0.05) difference between two groups. Alternation in differential leucocyte count values might be due to effect of glucocorticoid on blood cells or pooling of circulating blood cells in the spleen.

Effect on Biochemical Parameter

The mean values of total protein exhibited a highly significant decrease (p≤0.01) from baseline value in group I, while in group II it exhibited a non-significant decrease (p>0.05). The mean values of alanine aminotransferase decreased, and BUN and creatinine increased non-significantly (p>0.05) from the baseline value in both groups. Furthermore, between-

Table 2: Mean ±SE values of haematological parameters at different time interval in different groups

Parameters	Group	0 min (Baseline before induction)	Post-induction 20th min	Post-induction 40th min	p-value
Haemoglobin (g/dL)	I	11.35±0.83^{aA}	9.90±0.73^{aA}	9.42±0.71^{aA}	0.2056
	II	11.50±0.90^{aA}	10.45±0.80^{aA}	10.42±1.13^{aA}	0.6654
Packed cell volume (%)	I	36.01±2.57^{aA}	32.85±2.18^{aA}	30.37±2.12^{aA}	0.2514
	II	34.57±1.66^{aA}	32.14±1.99^{aA}	30.06±1.55^{aA}	0.2203
Total erythrocyte count (million/ cu.mm)	I	7.30±0.61 ^{aA}	6.57±0.68 ^{aA}	5.80±0.69 ^{aA}	0.3068
	II	7.32±0.34 ^{aA}	6.50±0.54 ^{aA}	6.14±0.32 ^{aA}	0.1524
Total leukocyte count (thousand/ cu.mm)	I	12.55±1.66^{aA}	11.23±1.96^{aA}	9.99±1.84^{aA}	0.6199
	II	11.41±2.08^{aA}	11.31±2.68^{aA}	9.38±2.11^{aA}	0.7861
Neutrophils (%)	I	48.17±2.69^{aA}	49.17±5.25^{aA}	49.67±6.23^{aA}	0.9766
	II	49.83±3.85^{aA}	50.33±5.09^{aA}	51.33±4.78^{aA}	0.9729
Lymphocytes (%)	I	46.83±3.00^{aA}	46.67±5.30^{aA}	45.67±6.23^{aA}	0.9844
	II	45.00±4.10^{aA}	45.00±4.23aA	44.00±3.88^{aA}	0.9801
Monocytes (%)	I	3.17±0.60 ^{aA}	3.42±0.27 ^{aA}	3.46±0.78 ^{aA}	0.9314
	II	3.08±0.45 ^{aA}	3.17±0.79 ^{aA}	3.50±0.72 ^{aA}	0.8984
Eosinophils (%)	I	1.67±0.33 ^{aA}	1.08±0.27 ^{aA}	0.88±0.34 ^{aA}	0.2192
	II	2.08±0.88 ^{aA}	1.50±0.62 ^{aA}	1.17±0.48 ^{aA}	0.6361

Means bearing different capital superscripts (A, B) between the groups and small superscripts (a,b) within the group differ significantly (p ≤ 0.05)

Table 3: Mean ±SE values of biochemical parameters at different time interval in different groups

Parameters	Group	0 min (Baseline before induction)	Post-induction		p-value
			20th min	40th min	
Total protein (g/dL)	I	7.21±0.39^{aA}	6.07±0.27^{bA}	5.73±0.22^{bA}	0.0088
	II	6.63±0.25^{aA}	6.25±0.19^{aA}	5.52±0.66^{aA}	0.2030
Alanine amino transferase (IU/L)	I	35.10±9.56^{aA}	34.79±10.14^{aA}	23.95±2.45^{aA}	0.5595
	II	32.62±7.97^{aA}	32.08±5.27^{aA}	26.87±6.65^{aA}	0.7958
Blood urea nitrogen (mg/dL)	I	30.76±2.76^{aA}	30.83±3.07^{aA}	30.87±4.91^{aA}	0.9998
	II	30.59±6.32^{aA}	32.23±4.33^{aA}	32.39±3.08^{aA}	0.9572
Creatinine (mg/dL)	I	0.93±0.20^{aA}	0.93±0.15^{aA}	0.98±0.14^{aA}	0.9576
	II	0.60±0.17^{aA}	1.00±0.18^{aA}	0.71±0.14^{aA}	0.2249

Means bearing different capital superscripts (A, B) between the groups and small superscripts (a,b) within the group differ significantly ($p \leq 0.05$)

groups comparison at different time points revealed no statistically significant differences in any of these parameters (Table 3). Kilic (2017) reported decreased mean value of total protein after administration of ketamine-diazepam-propofol anesthesia in cats. Wycislo *et al.* (2014) observed a significant decrease in total protein values in domestic cats given tiletamine-zolazepam. The reduction in total protein levels after anaesthesia administration can be attributed to several factors, including haemodilution caused by inter-compartment fluid shifts, blood loss, protein catabolism, and protein redistribution. Further, Sayyed Mohd (2019) and Patel *et al.* (2022) reported non-significant decrease in ALT in dexmedetomidine-ketamine-propofol and tiletamine-zolazepam anaesthetised cats. This decrease might be attributed to the anesthetics' impact on cardiac output and subsequent reduction in hepatic blood flow, leading to lower liver enzyme production. Sayyed Mohd (2019) also reported non-significant increase in BUN value during surgery in dexmedetomidine-ketamine-propofol anaesthetized cats, while Sodagar *et al.* (2021) and Patel *et al.* (2022) noticed similar increase in blood urea nitrogen and reduction in creatinine after tiletamine-zolazepam administration in cats. This elevation might be attributed to the temporary inhibitory effects of anaesthetics on renal blood flow, as well as alterations in cardiovascular and neuroendocrine activities.

Conclusions

The findings of the present study revealed non-significant differences in all the physiological parameters between ketamine-propofol-isoflurane and tiletamine-zolazepam-isoflurane anaesthetic protocols in cats undergoing various surgical procedures. However, significant decrease in rectal temperature and respiration rate and non-significant alteration in heart rate and SpO_2 were observed in both groups during the maintenance phase. In all the haemato-biochemical parameters non-significant differences were observed between the groups. However, significant decrease in total protein in group I and non-significant alteration in other haemato-biochemical parameters were observed in both groups during the maintenance phase, within normal physiological range. Overall observations showed satisfactory outcomes from the anaesthesia in both groups, yet group I showed slightly better result than group II.

Acknowledgement

Authors are grateful to the authorities of Kamdhenu University and the Principal, College of Veterinary Science & AH, and Head, Veterinary Clinical Complex, KU, Junagadh for the support and facilities provided.

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