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Comparative evaluation of haemodynamic, haematobiochemical and ECG responses to tiletamine-zolazepam and ketamine-dexmedetomidine as induction agents in dogs undergoing soft tissue surgeries

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The selection of appropriate anaesthetic agents is critical for minimizing physiological stress during surgery. This study compared the clinicophysiological, haematobiochemical, and electrocardiographic responses to Tiletamine–Zolazepam (T–Z) and Ketamine–Dexmedetomidine (K–D) combinations in dogs undergoing soft-tissue surgeries. Forty client-owned dogs, classified as ASA II, were randomly allocated into two groups (n = 20). All dogs received intramuscular butorphanol (0.2 mg/kg body weight) and glycopyrrolate (0.01 mg/kg) as premedication. Anaesthesia was induced with T–Z (4 mg/kg body weight) in group I and K–D (ketamine 5 mg/kg + dexmedetomidine 7 µg/kg) in group II, and maintained with isoflurane. Heart rate, respiratory rate, rectal temperature, mean arterial pressure, SpO, , ETCO, , and ECG were recorded at predefined intervals. Blood samples collected at corresponding time points were analysed for haemoglobin, total leucocyte count (TLC), packed cell volume (PCV), AST, ALT, ALP, total protein, blood urea nitrogen, and creatinine. T–Z produced a mild positive chronotropic effect, whereas K–D was associated with bradycardia and more pronounced respiratory depression. Blood pressure increased transiently in group II, while group I showed a slight early decline followed by normalization. ECG alterations were mild, with occasional minor conduction disturbances in both groups. A significant post-induction decrease in Hb and PCV occurred in both groups, persisting through recovery; TLC decreased in group I but remained stable in group II. Serum biochemical values were largely unchanged, except for an increase in creatinine in group I. Intergroup differences were insignificant except for post-induction PCV values. Both protocols were well tolerated; however, T–Z offered a more stable cardiopulmonary profile, supporting its use where minimization of cardiovascular depression is desired. Continuous monitoring remains essential to ensure anaesthetic safety.

Key words: *Clinico-physiological effects, Dogs, Ketamine-Dexmedetomidine, Tiletamine-Zolazepam*

The selection of appropriate anaesthetic induction agents is a critical component of veterinary surgical practice, as it directly influences patient safety and the incidence of cardiopulmonary complications (Hellyer *et al*., 1989). Tiletamine, a dissociative anaesthetic with pharmacodynamic properties similar to ketamine, possesses a longer half-life and superior analgesic effects (Chang and Jang, 1998). However, its use as a sole agent may induce convulsions, necessitating its combination with zolazepam, a benzodiazepine with anticonvulsant properties that mitigates excitatory reactions and enhances muscle relaxation (Noh *et al*., 2012). Although widely used, the tiletamine–zolazepam (T–Z) combination can produce cardiovascular alterations, including tachycardia and transient hypotension (Hellyer *et al*., 1989).

Ketamine–Dexmedetomidine (K–D) offers an alternative induction regimen by pairing the dissociative action of ketamine with the potent sedative, analgesic, and sympatholytic effects of dexmedetomidine. This combination has been reported to maintain cardiovascular stability and reduce inhalant anaesthetic requirements (Lee *et al*., 2018). Nonetheless, K–D may induce bradycardia and decreased cardiac output, reflecting the dose-dependent cardiovascular effects of α, -agonists (Bhatt *et al*., 2024). Studies also indicate that K–D often results in lower heart and respiratory rates compared to other induction protocols.

Electrocardiographic (ECG) monitoring during anaesthesia remains indispensable, as both T–Z and K–D have been associated with mild ECG alterations, including arrhythmias and changes in wave amplitude (Dehariya *et al*., 2024). Despite their frequent clinical use, comparatively few studies have systematically evaluated the combined effects of these protocols on haemodynamic, respiratory, and ECG variables in dogs undergoing soft tissue surgeries (Tiwari *et al*., 2024).

Haematological and biochemical responses to these agents also warrant attention. T–Z administration has been reported to cause hypoxaemia and significant reductions in erythrocyte count, haematocrit, and haemoglobin concentrations within 30 min of induction (Celyan *et al*., 2007). Conversely, ketamine–medetomidine combinations have been associated with transient decreases in haematocrit, haemoglobin,

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erythrocyte count, and lymphocyte levels, accompanied by increases in leucocyte, neutrophil, and creatinine concentrations, while blood urea nitrogen (BUN) and alanine aminotransferase (ALT) tend to remain stable (Umar *et al.,* 2013).

Given these pharmacological and physiological considerations, a direct comparison of T–Z and K–D is valuable for guiding evidence-based anaesthetic selection in small animal practice. The present investigation aims to evaluate and compare the clinico-physiological, haematobiochemical, and electrocardiographic responses to these two induction regimens in dogs undergoing soft tissue surgeries.

Materials and Methods

This study was conducted on client-owned dogs of both sexes presented to the Multi-Specialty Veterinary Hospital, Teaching Veterinary Clinical Complex, Guru Angad Dev Veterinary and Animal Sciences University, for various soft tissue surgeries. All dogs were classified as American Society of Anesthesiologists (ASA) Category II based on their clinical status. A total of 40 dogs were randomly allocated into two groups of 20 animals each.

The surgical cases included ear haematoma (6/40), cystotomy (4/40), skin and mammary tumour excision (19/40), ectopic testicle (3/40), perineal hernia (4/40), benign eyelid growth (1/40), inguinal hernia (2/40), and digit amputation (1/40). For venous access, the cephalic or saphenous area was clipped and aseptically prepared for intravenous (IV) catheter placement, facilitating drug administration, blood sampling, and fluid therapy.

All dogs were premedicated intramuscularly with butorphanol tartrate (0.2 mg/kg body weight) and glycopyrrolate (0.01 mg/kg). After a 10 min interval, anaesthesia was induced with tiletamine–zolazepam (T–Z, 4 mg/kg IV) in group I and with a ketamine–dexmedetomidine combination (ketamine 5 mg/kg + dexmedetomidine 7 μg/kg IV; K–D) in group II. Following induction, endotracheal intubation was performed, and anaesthesia was maintained with isoflurane using a standard small-animal anaesthetic workstation connected to a multi-parameter veterinary monitor (New Gen Medical System).

Heart rate (HR), respiratory rate (RR), and rectal temperature (RT) were recorded at baseline (pre-anaesthesia; 0), immediately post-induction (PI), and at 10 min intervals during maintenance up to 15 min post-recovery (15PR). Mean arterial pressure (MAP) was measured at baseline, PI, and subsequently every 10 min during maintenance. Oxygen saturation (SpO,) and end-tidal carbon dioxide (ETCO,) were recorded from PI onward at 10 min intervals.

Electrocardiographic monitoring was carried out using a BPL Medical Cardiart 6208 View 4-lead ECG unit set at a paper speed of 50 mm/s. ECG recordings were obtained at 0, PI, 15, 30, 60, 90, and 120 min, and at 15PR. The parameters evaluated included P-wave amplitude and duration, PR interval, QRS complex amplitude and duration, and ST-segment duration.

Blood samples were collected at four time points: before pre-anaesthesia (T0), post-induction (T1), during maintenance (T2), and during recovery (T3). For haematology, 1 mL of venous blood was drawn into EDTA tubes and analysed using a Mythic 18 Vet haematology analyser. For serum biochemistry, 2 mL of venous blood was collected in plain vacutainers at each time point. Samples were centrifuged at 2500 rpm for 15 min, and the serum was analysed using a Vitros® 350 chemistry analyser. Parameters assessed included haemoglobin (Hb), total leucocyte count (TLC), packed cell volume (PCV), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein (TP), blood urea nitrogen (BUN), and creatinine.

Within-group comparisons of mean values at different time points relative to baseline were performed using paired t-tests. Between-group comparisons were analysed using independent t-tests. Significance was assessed at 95% ($P < 0.05$) and 99% ($P < 0.01$) confidence levels.

Results and Discussion

Haematological analysis (Tables 1 and 2) revealed a marked reduction in haemoglobin (Hb) and packed cell volume (PCV) in both groups following induction, with values remaining low through recovery. Total leukocyte count (TLC) decreased in group I but remained stable in group II. Serum biochemical parameters showed no major alterations except for a significant increase in creatinine in group I. No significant intergroup differences were observed

Table 1: Mean±SE values of haematobiochemical parameters in two groups at various time intervals.

Parameters	Group	T_0	T_1	T_2	T_3
Hb (g/dL)	**Group I**	13.77±0.57	9.82±0.30**	9.89±0.44**	9.02±0.45**
	Group II	13.26±0.32	10.45±0.32**	10.49±0.37**	9.80±0.39**
TLC (10^3/dL)	**Group I**	13.43±1.15	10.82±1.02**	10.45±1.02**	10.79±0.74**
	Group II	12.91±1.01	12.96±0.66	12.49±0.55	11.69±0.52
PCV (%)	**Group I**	36.63±1.23	26.75±0.71**a	27.22±1.08**	26.76±1.28**
	Group II	34.11±0.99	29.05±0.77**b	29.42±0.80**	29.49±1.10**

Asterisked values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group

Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

Table 2: Mean±SE values of biochemical parameters in two groups at various time intervals.

Parameters	Group	T_0	T_1	T_2	T_3
AST (U/L)	**Group I**	33.80±1.69	36.80±2.33	37.75±2.52	34.25±1.82
	Group II	38.75±3.49	40.20±3.35	38.10±2.72	38.25±2.64
ALT (U/L)	**Group I**	56.25±11.88	47.85±11.25	45.70±12.19	45.95±12.11
	Group II	35.80±5.98	35.85±7.73	31.10±4.55	28.1±3.03
ALP (U/L)	**Group I**	289.65±109.32	197.3±66.05	237.75±83.89	231.15±75.67
	Group II	135.55±38.15	77.40±8.35	92.75±16.99	100.38±17.21
TP (g/dL)	**Group I**	6.78 ±0.21	6.58±0.25	6.72±0.25	6.68±0.17
	Group II	6.56±0.24	6.54±0.26	6.48±0.25	6.59±0.23
BUN (mg/dL)	**Group I**	13.80±1.45	15.55±2.49	15.19±2.37	14.15±1.86
	Group II	16.38±2.25	11.46±2.24	12.50±2.18	12.13±1.50
Creatinine	**Group I**	0.90±0.08	1.10±0.16*	1.15±0.17*	1.07±0.15
(mg/dL)	**Group II**	0.89±0.06	0.97±0.12	0.83±0.10	0.93±0.11

Asterisked values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group

Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

except for PCV post-induction. In group I (Tiletamine–Zolazepam), HR increased highly significantly (P<0.01) immediately after induction and remained elevated at 10 min (P<0.05). Minor fluctuations occurred thereafter until 80 min, followed by a significant decline at 90 min, and a marked rise during recovery. By 15 min post-recovery, HR approached baseline (Table 3). The rise in HR is consistent with the sympathomimetic effects of tiletamine, which increases catecholamine release and stimulates cardiac activity (Hampton *et al*., 2019). Zolazepam provides muscle relaxation but does not counteract this stimulatory influence (Hellyer *et al*., 1989).

In group II (Ketamine–Dexmedetomidine), HR showed a significant reduction (P<0.05) post-induction, with significant decreases observed at 10, 20, 60, 70, 80, and 90 min. Non-significant reductions occurred at 30–50 min, and a highly significant drop persisted during recovery. HR returned near baseline by 15 min post-recovery. This pattern aligns with the pharmacodynamics of dexmedetomidine, an α, -agonist that reduces sympathetic outflow and increases vagal tone, resulting in bradycardia despite ketamine's mild stimulatory action (Ross *et al*., 2019).

Between-group comparison demonstrated consistently higher HR in group I than group II throughout maintenance and recovery, with HR in group II remaining significantly lower than baseline for most intervals.

Mean RR (Table 4) showed a highly significant (P<0.01) decline in both groups following induction. RR remained low during maintenance, except for a non-significant fall at 80 min in group I. During recovery, group I exhibited a non-significant increase in RR at 100–110 min and significant increases (P<0.05) at 120 and 130 min. In group II, RR decreased significantly at 100 min (P<0.01) and at 110 min (P<0.05), with non-significant decreases thereafter. By 15 min post-recovery, RR in both groups approached baseline.

The reduction in RR is attributable to central respiratory depression caused by both protocols. T-Z suppresses respiratory centres through CNS depression (Hellyer *et al*., 1989), while dexmedetomidine reduces respiratory drive via α, -receptor-mediated suppression of sympathetic activity (Pleyers *et al*., 2020). A significant difference in RR between groups was noted post-induction and during early recovery.

Rectal temperature (Table 5) significantly decreased (P<0.01) in both groups from induction through recovery, likely due to reduced metabolic rate, decreased muscle activity, and alterations in thermoregulatory control (Ponder and Clark, 1980). Group II showed non-significant declines at 70–90 min. No significant intergroup differences were detected, and RT returned near baseline in both groups by 15 min post-recovery.

MAP (Table 6) in group I showed a non-significant decrease from baseline following induction up to 50 min, followed by a non-significant rise through 90 min. Conversely, group II exhibited a significant increase (P<0.05) in MAP post-induction and a highly significant elevation (P<0.01) between 10–30 min, with variable non-significant fluctuations thereafter. MAP was consistently higher in group II than group I from induction to 50 min. The transient hypertension in group II is consistent with dexmedetomidine-induced vasoconstriction and baroreceptor-mediated responses (Weerink *et al*., 2017). The slight hypotension in group I aligns with the initial vasodilatory and myocardial depressant effects of T-Z (Hellyer *et al*., 1989).

SpO_2 values (Table 7) decreased significantly (P<0.01) in both groups after induction. In group I, SpO_2 remained comparable to baseline during maintenance, while group II showed a significant drop

Table 3: Mean±SE values of heart rate (beats/min) recorded in two groups at various time intervals.

Group	0	PI	Maintenance (min)							Recovery (min)						PR
			10	20	30	40	50	60	70	80	90	100	110	120	130	15
I	127.70	164.00	155.15	146.60	139.05	138.00	134.07	132.80	120.12	141.5	105.00	165.10	176.55	180.65	180.70	128.30
(n=20)	±9.02	±7.68^{a**}	±6.60^{a*}	±5.78^{a}	±5.50^{a}	±5.64^{a}	±6.56^{a}	±7.26^{a}	±9.06^{a}	±16.90^{a}	±00.00^{a*}	±6.93^{a*}	±7.39^{a**}	±5.94^{a**}	±5.61^{a**}	±8.50
II	115.75 1	97.20	91.30	94.90	100.55	98.10	99.87	94.44	91.66	89.00	88.50	75.89	79.84	80.52	81.31	113.40
(n=20)	±5.2	±4.70^{b*}	±6.69^{b*}	±4.98^{b*}	±5.14^{b}	±4.90^{b}	±3.97^{b}	±3.64^{b*}	±5.10^{b*}	±7.03^{b*}	±6.83^{b*}	±3.01^{b**}	±3.31^{b**}	±5.08^{b**}	±5.13^{b**}	±5.12

Asterisk values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group
Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

Table 4: Mean±SE values of respiratory rate (breath/min) recorded in two groups at various time intervals.

Group	0	PI	Maintenance (min)							Recovery (min)						PR
			10	20	30	40	50	60	70	80	90	100	110	120	130	15
II	37.70	17.65	18.35	18.40	16.25	14.52	16.14	19.50	17.00	27.50	10.00	42.90	47.95	52.25	53.80	34.30
(n=20)	±2.69	±4.36^{a**}	±3.73**	±2.38**	±2.21**	±1.98**	±2.41**	±2.15**	±2.36**	±10.02	±0.00**	±4.04^{a}	±5.33^{a}	±5.66^{a*}	±6.06^{a*}	±2.50
II	35.603	2.65	10.90	17.55	14.20	15.55	15.06	15.11	15.33	13.00	13.25	22.05	25.78	31.15	29.26	35.00
(n=20)	±2.9	±1.22^{b**}	±1.42**	±1.72**	±1.68**	±1.44**	±1.38**	±1.03**	±1.62**	±1.08**	±2.65**	±2.51^{b**}	±2.02^{b*}	±3.71^{b}	±2.58^{b}	±2.23

Asterisk values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group
Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

Table 5: Mean±SE values of rectal temperature (°F) recorded in two groups at various time intervals.

Group	0	PI	Maintenance (min)							Recovery (min)						PR
			10	20	30	40	50	60	70	80	90	100	110	120	130	15
I	102.61	100.80	100.46	100.42	99.79	99.94	99.50	99.19	98.98	98.60	99.10	99.18	99.19	99.25	99.26	102.90
(n=20)	±0.18	±0.33**	±0.46**	±0.35**	±0.60**	±0.36**	±0.41**	±0.57**	±0.51**	±0.52**	±00.00**	±0.35**	±0.34**	±0.33**	±0.29**	±0.22
II	102.5	100.90	100.58	100.30	99.99	99.40	99.20	98.77	99.00	97.92	97.55	99.05	98.87	98.85	98.75	102.21
(n=20)	6±0.15	±0.34**	±0.35**	±0.37**	±0.39**	±0.51**	±0.64**	±1.06**	±1.55	±2.35	±2.35	±0.34**	±0.33**	±0.35**	±0.36**	±0.19

Asterisk values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group
Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

Table 6: Mean±SE values of mean arterial blood pressure (mmHg) recorded in two groups at various time intervals.

Group	0	PI	Maintenance (min)								
			10	20	30	40	50	60	70	80	90
I(n=20)	83.35±2.58	81.25±3.14^{a}	84.35±3.66^{a}	83.80±4.35^{a}	78.65±5.26^{a}	74.00±5.48^{a}	78.64±7.50^{a}	93.30±9.92	96.37±6.04	88.75±7.12	88.23±24.21
II(n=20)	89.55±3.29	111.30±8.86^{b*}	117.15±7.44^{b**}	115.55±5.73^{b**}	113.55±4.70^{b**}	94.95±4.75^{b}	96.56±4.28^{b}	96.55±8.90	96.83±13.58*	81.00±17.36*	88.66±25.62

Asterisk values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group
Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

Table7: Mean±SE values of SpO_2 (%) recorded in two groups at various time intervals.

Group	0	PI	Maintenance (min)								
			10	20	30	40	50	60	70	80	90
I(n=20)	83.35±2.58	81.25±3.14^{a}	84.35±3.66^{a}	83.80±4.35^{a}	78.65±5.26^{a}	74.00±5.48^{a}	78.64±7.50^{a}	93.30±9.92	96.37±6.04	88.75±7.12	88.23±24.21
II(n=20)	89.55±3.29	111.30±8.86^{b*}	117.15±7.44^{b**}	115.55±5.73^{b**}	113.55±4.70^{b**}	94.95±4.75^{b}	96.56±4.28^{b}	96.55±8.90	96.83±13.58*	81.00±17.36*	88.66±25.62

Asterisk values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group
Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

Table 8: Mean±SE values of $EtCO_2$ (%) recorded in two groups at various time intervals..

Group	0	PI	Maintenance (min)								
			10	20	30	40	50	60	70	80	90
I(n=20)	36.80±3.73	40.25±3.84	41.75±3.67	41.00±3.58	43.35±4.04	44.13±4.68	43.60±3.87	44.88±3.51	43.75±3.48	43.70±3.20
II(n=20)	36.75±3.22	35.30±3.03	37.35±2.56	37.15±2.44	35.50±2.41	38.25±2.48	38.50±2.31	41.00±3.16	44.25±3.11	43.50±3.57

Asterisk values differ significantly (*P<0.05; **P<0.01) from the baseline value of the group
Values with different alphabets differ significantly (P<0.05) between the groups at corresponding time interval

at 10 min followed by stabilization. No significant intergroup differences were identified. The early reduction in SpO, likely reflects transient hypoventilation and respiratory depression. T-Z may also cause peripheral vasoconstriction, reducing pulse oximetry accuracy (Jin *et al*., 2016).

ETCO, values (Table 8) showed a non-significant rise in both groups post-induction and remained mildly elevated during maintenance and recovery. Intergroup differences were minimal. Under general anaesthesia, reduced metabolic rate lowers CO, production, mitigating changes even when RR declines (Akkermans *et al*., 2018). Efficient gas exchange in healthy animals helps maintain stable ETCO, (Hendricks and King, 1994).

Group-level ECG parameters remained within normal limits, with no significant differences between protocols. Isolated abnormalities were detected in individual animals. These included a notched P-wave in a Golden Retriever (group II), indicative of possible left atrial enlargement; a missed P-wave in a German Shepherd (group I), suggestive of atrial fibrillation or atrial standstill; a prolonged PR interval in a Dachshund (gGroup II), consistent with first-degree AV block; and a peaked QRS complex in a Labrador Retriever (group I), possibly reflecting left ventricular enlargement. These findings appear incidental rather than drug-related.

Overall, both T-Z and K-D induction protocols were well tolerated and did not produce adverse haematological, biochemical, or electrocardiographic changes. T-Z caused significant increases in HR but exerted comparatively mild effects on respiratory and haemodynamic parameters. K-D provided more consistent blood pressure stability but produced more pronounced bradycardia and respiratory depression. These outcomes reflect the characteristic pharmacodynamic profiles of dissociative anaesthetics and β, -agonists.

To conclude, both T-Z and K-D are effective and safe induction agents for canine soft tissue surgeries. Anaesthetic protocol selection should be guided by the patient's cardiovascular and respiratory status. T-Z may be preferred where avoidance of bradycardia is critical, whereas K-D may be advantageous in patients requiring better blood pressure control. Continuous monitoring remains essential to ensure perioperative safety.

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