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Efficacy of zoletil, midazolam-zoletil and dexmedetomidine-zoletil in dogs premedicated with tramadol

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Abstract
The present study was undertaken to evaluate the efficacy of Zoletil, Midazolam-Zoletil and Dexmedetomidine-Zoletil with tramadol in dogs on clinical and cardio-respiratory changes in eighteen clinical cases of dogs requiring elective surgery. Anaesthesia was induced by Zoletil @ 5 mg/kg body weight in Group Z, Midazolam and Zoletil @ 0.2 mg/kg and 5mg/kg body weight in Group MZ and Dexmedetomidine and Zoletil @ 5 µg/kg and 5 mg/kg body weight in Group DZ intravenously respectively in all the groups. Significant differences were recorded in the time of induction, depth of anaesthesia and anaesthetic duration. Baseline physiological parameters (pulse rate, respiratory rate, SpO_2 and rectal temperature) were studied and changes during maintenance remained within biologically acceptable limits.

Keywords: Dexmedetomidine, dog, midazolam, tramadol, zoletil

1. Introduction
Elective surgical procedures commonly performed in companion animals are castration and ovariohysterectomy; which requires a good anaesthetic. Induction and recovery are two crucial phases of general anaesthesia; as the majority of potentially fatal risks can happen in these two phases. Consequently, anaesthesia must have the quality of a rapid onset and easy recovery (Salve *et al*., 2022) [23]. Zoletil is a non-opioid and non-barbiturate injectable anaesthetics for dogs (Kucharski and Kiełbowicz, 2021) [12]. Tiletamine-zolazepam combination is mainly used as pre-anaesthetics, sedation and general anaesthesia for diagnostic and minor surgical procedures in dogs (Nam *et al*., 2013) [19]. Canines metabolises Zolazepam more quickly than tiletamine, which can lead to momentary tachycardia, athetoid movements with sluggish recovery (Koli *et al*., 2021) [11]. Dexmedetomidine are selective alpha 2 agonist having sedative, anxiolytic, anti-sympathetic and analgesic properties (Liang *et al*., 2021) [15], however, it has the potential to elicit dose-dependent cardiopulmonary depression in a way similar to other alpha 2-adrenoceptor agonists (Nishimura *et al*., 2018) [20]. Midazolam is a water-soluble imidazole benzodiazepine derivative with minimal cardiopulmonary effects, induces hypnosis, sedation and muscle relaxation, but lack of analgesic properties (Ahmad *et al*., 2013) [1]. Considering the above facts, present study was undertaken to study the clinical and cardio respiratory changes, as well as to evaluate the effectiveness of intravenous Zoletil, Midazolam-Zoletil and Dexmedetomidine-Zoletil in dogs premedicated with Tramadol.

2. Materials and Methods
The present clinical study was conducted on eighteen (n=18) canine patients presented for elective surgery. Animal were preoperatively withheld food for 12 hours and water for 6 hours prior to the study.
The animals were randomly divided into 3 group's viz. Group-Z, Group-MZ and Group-DZ comprising of 6 animals in each. The studied dogs had a mean body weight of 12.92±1.41 kgs and age ranged from 9 months to 84 months (7 years) from different breeds. Routine clinical examination was carried out before the anaesthetic trial by evaluating the baseline values of physiological parameters, haematological and serum biochemical evaluations and the surgical site was prepared for aseptic surgery as per the selective elective surgery. All the animals were premedicated with glycopyrrolate @ 0.01 mg/kg body weight and tramadol @ 4 mg/kg body weight through intramuscular route.

Fifteen minutes following premedication, anaesthesia was induced with Zoletil @ 5 mg/kg body weight in Group Z, Midazolam @ 0.2 mg/kg body weight and Zoletil @ 5 mg/kg body weight in Group MZ and Dexmedetomidine @ 5 µg/kg body weight and Zoletil @ 5 mg/kg body weight in Group DZ intravenously respectively. Time and quality of sedation, time for induction (minutes), quality of induction, intra-operative analgesia, depth and duration of anaesthesia (minutes), time and quality of recovery were assessed. Time of sedation was recorded from the administration of premedication to the animal showed the first sign of sedation. Induction time was recorded from the administration of induction agent till the animal loses its reflexes and was expressed in minutes. Recovery time was calculated from the discontinuation of anaesthesia till the animal's ability to walk unassisted and was expressed in minutes. Sedation scoring was carried out as per Amengual *et al.* (2013) [2], quality of induction anaesthetics was evaluated as per Maddern *et al*. (2010) [17], quality and depth of analgesia was evaluated as per Ahmad *et al*. (2013) [1] and recovery quality was evaluated as per the method described by Hc *et al.* (2005) [8]. Rectal temperature (°C), respiration rate (breath/minute), heart rate (beats/minute) and SpO_2 (%) were recorded before premedication (0 min), at 15 min (before induction), 30 minutes and 60 minutes following induction. Recorded data were analysed by statistical package SPSS version 27.0.

3. Results

3.1 Clinical parameters

Sedation time and quality of sedation were absent in all the groups. Induction time was recorded with highly significant difference ($p<0.01$) between the groups and shortest induction time was recorded in Group DZ (1.62±0.24 minutes), followed by Group MZ (8.50±0.6 minutes) and Group Z (3.75±0.25 minutes) (Table-1 and Fig.1). Quality of induction was smooth and uneventful in all the three groups of animals (Table 1). Animals in Groups Z and MZ recorded with intact but very light (slow and occasional response) pedal reflex, while all the animals in Group DZ observed with complete abolish of pedal reflex. Depth of anaesthesia was observed with significant ($p\leq0.05$) difference among the three groups (Table 1). All the animals in Group DZ (2.75±0.25) recorded with complete abolish of palpebral reflex, while Group MZ (1.00±0.00) recorded with intact but weak (slow response) palpebral reflex, and Group Z (0.00±0.00) recorded with intact and strong palpebral reflex.

Duration of anaesthesia recorded with highly significant difference ($p<0.01$) between the groups, where duration of anaesthesia was recorded longest in Group DZ (40.75±1.49 minutes), followed by Group MZ (27.50±1.44 minutes) and Group Z (11.25±1.25 minutes) (Table 1 and Fig.1). Time for recovery recorded with significant difference ($p<0.01$) in Group Z (73.00±11.75 minutes), Group MZ (96.25±23.04 minutes) and Group DZ (167.50±17.85 minutes) (Table 1 and Fig.1) and prolonged recovery time was recorded in Group D. Recovery was smooth in all the animals and the animals can stand in normal position following several attempts while being ataxic when standing or walking (Table 1).

Table 1: Mean±SE values of clinical parameters recorded in Group Z, MZ and DZ

Parameters	Group Z	Group MZ	Group DZ	P value
Time of induction (minutes)	8.50 ± 0.64^{C}	3.75 ± 0.25^{B}	1.62 ± 0.24^{A}	0.000**
Quality of induction	1.00±0.00	1.00±0.00	1.00±0.00	1.000^{NS}
Evaluation of intra-operative analgesia	2.00±0.41	2.50±0.28	3.00±0.00	0.103^{NS}
Depth of anaesthesia	0.00 ± 0.00^{A}	1.00 ± 0.00^{B}	2.75 ± 0.25^{C}	0.005**
Duration of anaesthesia (minutes)	11.25 ± 1.25^{C}	27.50 ± 1.44^{B}	40.75 ± 1.49^{A}	0.000**
Time of recovery (minutes)	73.00 ± 11.75^{A}	96.25 ± 23.04^{C}	167.50 ± 17.85^{B}	0.013*
Quality of recovery (minutes)	3.00±0.00	3.00±0.00	3.00±0.00	1.000^{NS}

:**($p\leq0.05$), *:** ($p\leq0.01$), ^{NS}: Non-significant. Values in the same row with similar superscript do not differ significantly

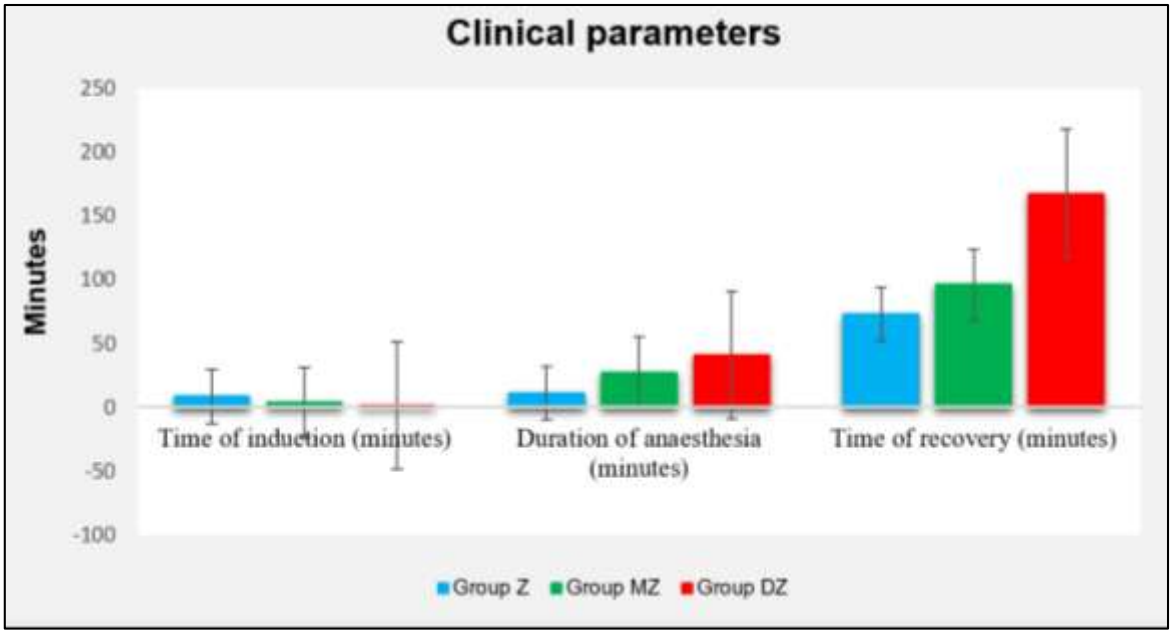

Fig 1: Time of induction, time of anaesthesia and time of recovery in Group Z, Group MZ and Group DZ.

3.2 Physiological parameters

Rectal temperature recorded with significantly decreased ($p \leq 0.05$) from baseline during 30 and 60 minutes of observation in Group Z (37.37±0.13 °C and 37.22±0.39 °C) and MZ (37.57±0.27 °C and 37.72±0.14 °C) and non-significantly ($p \geq 0.05$) decreased in Group DZ at 30 and 60 minutes (37.57±0.20 °C and 37.35±0.34 °C) (Table. 2). Heart rate recorded with non-significantly ($p \geq 0.05$) increased from the baseline recorded at 15 minutes (132.00±10.46, 139.75±16.39 and 122.75±12.05 beats/ minute) and 60 minutes (175.25±26.82, 165.50±6.88 and 121.75±9.33 beats/ minute) in all the groups respectively. Out of which in Group MZ, the heart rate recorded highest at 30 minutes (193.00±25.15 beats/ minute). Respiratory rate recorded with non-significantly ($p \geq 0.05$) decreased in Group Z (30.75±1.49 breath/minute) and MZ (26.00±4.37 breath/minute), while respiratory rate decreased significantly ($p \leq 0.01$) in Group DZ (15.00±2.38 breath/minute) at 30 minutes respectively. There was a non-significantly ($p \geq 0.05$) decreased SpO_2 observed from the baseline (98.75±0.47% and 98.75±0.47%), then 30 min in group Z (98.00±0.41%) and 60 minutes in group MZ (97.75±0.63%) respectively.

Table 2: Mean±SE values of rectal temperature (°C), heart rate (beats/ minute), respiration rate (breath/ minutes) and SpO_2 (%) recorded in Group Z, MZ and DZ

Parameters	Group	0 min	15 min	30 min	60 min	P value
Rectal temperature (°C)	Z	38.49±0.19^{b}	38.29±0.27^{b}	37.37±0.13^{a}	37.22±0.39^{a}	0.011*
	MZ	38.67±0.17^{b}	38.10±0.39^{ab}	37.57±0.27^{a}	37.72±0.14^{a}	0.050*
	DZ	38.37±0.41	38.42±0.39	37.57±0.20	37.35±0.34	0.104^{NS}
	P value	0.755^{NS}	0.814^{NS}	0.743^{NS}	0.515^{NS}	
Heart rate (beats/ minute)	Z	110.5±11.98	132.00±10.46	151.00±33.13	175.25±26.82	0.273^{NS}
	MZ	137.00±11.36	139.75±16.39	193.00±25.15	165.50±6.88	0.106^{NS}
	DZ	117.75±15.52	122.75±12.05	115.75±4.73	121.75±9.33	0.965^{NS}
	P value	0.375^{NS}	0.672^{NS}	0.132^{NS}	0.110^{NS}	
Respiration rate (breath/ minutes)	Z	43.50±8.41	44.00±10.86	30.75±1.49	40.50±3.41	0.544^{NS}
	MZ	47.25±6.02	39.75±5.26	26.00±4.37	41.50±7.54	0.127^{NS}
	DZ	43.75±4.58^{c}	33.25±1.11^{bc}	15.00±2.38^{a}	22.00±5.35^{ab}	0.001**
	P value	0.903^{NS}	0.570^{NS}	0.013*	0.066^{NS}	
SpO_2 (%)	Z	98.00±0.00	98.00±0.00	96.50±0.86	98.25±0.25	0.065^{NS}
	MZ	98.25±0.25	98.00±0.00	98.00±0.00	98.00±0.00	0.426^{NS}
	DZ	98.75±0.47	98.75±0.47	98.00±0.41	97.75±0.63	0.410^{NS}
	P value	0.274^{NS}	0.141^{NS}	0.141^{NS}	0.676^{NS}	

*: ($p \leq 0.05$), **: ($p \leq 0.01$) and ^{NS}: Non-significant. Values in the same row and column with similar a superscript do not differ significantly.

4. Discussion

4.1 Clinical parameters

The present study recorded no statistically significant difference in the quality of induction. Similar findings were also reported by Anjana *et al*. (2021) [3] and Koli *et al*. (2021) [11] with slow intravenous administration of tiletamine-zolazepam combination in dogs. Good quality of induction was recorded in present study in all the groups, which might be due to Zoletil (tiletamine-zolazepam), as pharmacological action of tiletamine hydrochloride is characterized by rapid induction and cataleptic anaesthesia (Wilson *et al.*, 1993) [25]. Induction time was recorded with highly significant difference ($p<0.01$) between the groups and shortest induction time was recorded in Group DZ, followed by Group MZ and Group Z. Similar observation in induction time was also reported by Nam *et al*. (2013) [19] in dogs following tramadol-tiletamine-zolazepam-medetomidine combination, Lu *et al*. (2012) [16] in miniature pigs anaesthetized with combination of tiletamine-zolazepam-xylazine-tramadol intramuscularly and Jee *et al*. (2010) [10] in pigs with midazolam-zoletil. Shortest time of induction recorded in Group MZ and DZ might be due to rapid onset of action by midazolam and dexmedetomidine (Dent *et al*., 2019) [4].

There was no significant difference recorded between the groups. Similar findings in pedal reflex were also reported by Anjana *et al*. (2021) [3], Salve *et al*. (2022) [23] and Manjusha and Khan (2023) [18] following intravenous tiletamine-zolazepam in dogs. Complete abolish of pedal reflex recorded in Group DZ might be due to antinociception induced by Dexmedetomidine (alpha-2 agonists) which released acetylcholine in the spinal cord (Ahmad *et al*., 2013) [1].

Depth of anaesthesia observed with significant ($p \leq 0.05$) difference among the three groups. The findings were in accordance to Anjana *et al*. (2021) [3] and Manjusha and Khan (2023) [18] following intravenous administration of tiletamine-zolazepam in dogs. Depth of anaesthetic score was recorded highest in Group DZ might be due to the synergistic interaction of benzodiazepines with alpha-2 agonists making them an ideal choice for increasing the depth of dexmedetomidine-induced sedation (Ahmad *et al*., 2013 and Nishimura *et al*., 2018) [1, 20]. Presence of pharyngeal, laryngeal, corneal, palpebral, and swallowing reflexes in Group Z and MZ might be due to dissociative anaesthesia (Tiletamine) (Dugassa and Fromsa, 2018, Hampton *et al*., 2019) [5, 7].

Duration of anaesthesia recorded with highly significant difference ($p<0.01$) between the groups, where duration of anaesthesia was recorded longest in Group DZ, followed by Group MZ and Group Z. Similar type of findings was also reported by Koli *et al*. (2021) [11] and Salve *et al*. (2022) [23] following intravenous administration of tiletamine-zolazepam in dogs. Longer duration of anaesthesia recorded in Groups MZ and DZ might be due to the co-induction of midazolam and dexmedetomidine with Zoletil, since midazolam and dexmedetomidine possess sedative effects.

Time for recovery recorded with significant difference ($p<0.01$) in Group Z, Group MZ and Group DZ and prolonged recovery time was recorded in Group D. Prolonged recovery time following Zoletil anaesthesia in dogs was also reported by Koli *et al*. (2021) [11] and Patil *et al*. (2023) [21] with constant rate infusion tiletamine-zolazepam in dogs. Prolonged recovery time in Group DZ might be due to the

dose and depth related sedative effects exerted by dexmedetomidine.

Smooth quality of recovery was recorded in the present study with no significant difference between the groups might be due to the residual sedative effect of dexmedetomidine and midazolam and relatively smaller amount of tiletamine used in the study. Similar type of recovery quality was also reported by Anjana *et al*. (2021) [3] in dogs induced with tiletamine-zolazepam anaesthesia. Intravenous administration of dissociative anaesthesia co-administered with other drugs (e.g., α2-adrenergic receptor agonists) might also have attributed to good quality of recovery (Dugassa and Fromsa, 2018) [5].

4.2 physiological parameters

The present study was in accordance to the findings of Lee *et al*. (2018) [14] and Pereira *et al*. (2019) [22] with Tiletamine-Zolazepam anaesthesia in dogs and Granholm *et al*. (2015) [6] following intravenous administration of dexmedetomidine. Decreased rectal temperature recorded in present study might be due to generalized sedation, decrease in metabolic rate, muscle relaxation and central nervous system depression (Lee *et al.*, 2018) [14]. Tiletamine-Zolazepam combination are known to promotes depressant effect on the temperature of dogs (Pereira *et al*., 2019) [22], thereby reducing the overall physiological activity, including regulation of body temperature. The findings of heart rate in present study were similar also reported by Hampton *et al*. (2019) [7] and Manjusha and Khan (2023) [18] following intravenous Zoletil in dogs. Non-significantly increased heart rate at 15 minutes might be due to the administration of anticholinergic (glycopyrrolate) which routinely causes sinus tachycardia (Tranquilli *et al*., 2007) [24]. Sympathomimetic action of tiletamine might also have contributed to increased heart rate (Pereira *et al*., 2019 and Patil *et al*., 2023) [22, 21]. Midazolam decreased myocardial contractility, systemic vascular resistance and preload which might have attributed to compensatory increase in heart rate at 30 minutes in Group MZ (Hopkins *et al*., 2014) [9]. Similar decrease in respiration rate was also reported by Granholm *et al*. (2015) [6] and Dent *et al*. (2019) [4] in dogs following intravenous dexmedetomidine. A non-significant reduction in respiratory rate recorded might be due to the anaesthetic agents (Zoletil and Zoletil-Midazolam) which leads to depression of respiratory centre located in medulla oblongata (Salve *et al*., 2022) [23]. Further, significantly reduction in respiratory rate in Group DZ might be due to the dose and depth related respiratory depression in dogs (Nishimura *et al*., 2018) [20]. In correspondence to this study, Koli *et al*. (2021) [11] and Salve *et al*. (2022) [23] also reported similar findings in dogs following tiletamine-zolazepam anaesthesia and Kuusela *et al*. (2001) [13] following dexmedetomidine premedication in dogs.

5. Conclusions

Based on the current study it has been concluded that clinical and cardio-respiratory changes remained within the physiological limit following intravenous administration of Zoletil, Midazolam-Zoletil, and Dexmedetomidine-Zoletil in dogs. Dexmedetomidine-Zoletil combination provided longer duration of anaesthesia than Midazolam-Zoletil and Zoletil alone; however, Dexmedetomidine-Zoletil combination prolonged the recovery time. Although Zoletil @ 5 mg/kg intravenous could be used for shorter duration surgeries as it induces smooth onset with a shorter and smoother recovery in dogs.

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