RESEARCH ARTICLE

Clinical Attributes of Tiletamine-Zolazepam Induced Anesthesia with and without Xylazine Premedication in Dogs

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Abstract

Two anesthetic protocols were evaluated in 20 dogs (12 Female and 8 Male) of different breeds presented for surgical interventions to study anesthetic efficacy as well as to assess physiological and haemato-biochemical alterations following tiletamine-zolazepam (TZ) combination as induction agent with and without xylazine premedication, and maintenance on isoflurane. The dogs were randomly allotted to two groups consisting of ten patients in each. Atropine (0.04 mg/kg, IM) was common in both groups, and Group I patients also received xylazine (0.5 mg/kg, IM). Induction was achieved by tiletamine-zolazepam @ 3 mg/kg, IV and maintained on isoflurane. The induction time was significantly shorter in Group I where patients were premedicated with xylazine as compared to Group II. An after-effect of TZ induction was transient post-induction apnoea in 11 patients. Baseline physiological parameters (pulse rate, respiratory rate, SpO_2, and rectal temperature) were determined. The changes in physiological parameters during maintenance remained within biologically acceptable limits. Among haemato-biochemical parameters, a non-significant decrease was observed in Hb, PCV, TLC, TEC, TP, AST, ALT, creatinine, and BUN during anesthesia and after recovery. The anesthetic duration and complete recovery time were longer in Group I compared to Group II. The study confirms induction of balanced anesthesia using atropine, xylazine, tiletamine-zolazepam combinations, and isoflurane maintenance with efficient nociception during surgical procedures.

Keywords: Canine patient, Quality of induction and recovery, Surgical anesthesia, Tiletamine-zolazepam combination, Xylazine premedication.

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Introduction

General anesthesia is a drug-induced cognitive state of mind characterized by controlled, however reversible, depression of central nervous system and nociception. Impairment of sensory, motor and autonomic reflexes in various degrees depends on particular medication and technique used (Tranquilli and Grimm, 2015). The pharmacodynamics of tiletamine, dissociative anesthetic agent, is similar to ketamine, but tiletamine has a longer duration of action and greater analgesic effect than ketamine (Chang and Jang, 1998). Drug alone produces a spectrum of CNS effects ranging from excitement and ataxia at low doses to catalepsy and finally general anesthesia at higher dosage (Kwon *et al*., 2003). As, tiletamine may develop convulsions when used alone, a weak anticonvulsant, zolazepam is concomitantly administered to prevent the adverse drug reaction (Noh *et al*., 2012). Tiletamine, only approved for use in combination with a benzodiazepine derivative (Lin, 1996). Benzodiazepine is known for the development of partial or complete memory loss, muscle relaxation, lesser depression of cardio-respiratory functions, strong anticonvulsant effect, and is quite safe (Kwon *et al.,* 2003). TZ combination is licensed for use in cats, but not for dogs, although frequently used in dogs and various other species. The combination may cause pain following IM injection and transient tachycardia in dogs. It may give rise to slow, involuntary, convoluted, writhing (athetoid) movements, ultimately resulting in rough recoveries as the zolazepam metabolizes faster than the tiletamine in canids. TZ is contraindicated in heart or respiratory diseases, severe hypertension, renal or hepatic dysfunction or life-threatening conditions (Plumb, 2018).

An overview through the available literature revealed that TZ combination was available for wildlife anesthesia in India, whereas dogs' preparation is now available in Indian market. The present study was thus to assess anesthetic efficacy as well as to evaluate physiological and haemato-biochemical alterations following tiletamine and zolazepam induction with and without xylazine premedication followed by isoflurane for maintenance of surgical anesthesia in dogs.

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Materials and Methods

The present clinical study was conducted on twenty (n = 20) canine patients presented for planned surgical procedures and subjected to either anesthetic protocol for minor and major surgical procedures. Pre-anesthetic physical examination in all canine patients included clinical anamnesis, baseline data including pulse rate, respiratory rate, rectal temperature, colour of mucous membrane and CRT.

To assess the fitness of canine patient for GA, preoperative physical status of canine patients was determined as per ASA (American Society of Anesthesiologist) standards. The food and water access was ceased 12 hours before pre-anaesthetic drug administration in all canine patients to reduce risk of Gastroesophageal Reflux (GER) (Grubb *et al.,* 2020). Regardless of age, breed, sex, body weight or surgical procedure, they were randomly divided in two groups consisting of 10 patients in each, Group I (AXTZI) and Group II (ATZI). Out of 20 canine patients, six patients were found to be in ASA category 1 (30.00%) as patients were normal and healthy in condition. Twelve patients who had the mild systemic disease were in ASA category 2 (60.00%). However, the rest of two patients were in ASA category 3 (10.00%) as they had moderate to severe systemic disease according to ASA physical status classification. The male-female ratio in both groups was 4:6.

The canine patients covered under Group I (AXTZI) had a mean age of 8.15 ± 1.26 years, ranging from 1.5 to 15 years. The mean age of canine patients under Group II (ATZI) was 8.05 ± 1.20 years with a range of 1.5 to 12 years. An enormous variation in their body weights ranged from 5.50 to 48.00 kg with a mean body weight of 30.15 ± 3.74 kg in Group I (AXTZI). However, patients of Group II (ATZI) had a mean body weight of 27.50 ± 3.03 kg, ranging from 15.00 to 39.50 kg. Catheterization, antibiotic and analgesics administration, as well as fluid disturbances, were corrected prior to surgical treatment.

Pre-anesthetic Medication

The canine patients covered under Group-I (AXTZI) were premedicated with atropine sulfate @ 0.04 mg/kg, and xylazine HCl @ 0.5 mg/kg, loaded in a single syringe and administered intramuscularly. Canine patients were not disturbed for at least 10 to 15 minutes following administration of xylazine injection. While, the patients covered under Group-II (ATZI) were premedicated with atropine sulfate injection alone IM @ 0.04 mg/kg, b. wt.

Induction of Anesthesia

All patient were induced with a non-incremental injectable anesthetic combination of Tiletamine and Zolazepam (TZ), after 10-15 minutes of pre-anesthetic administration @ 3 mg/kg, b. wt. intravenously. Induction Time (seconds) was measured as time-lapse between administration of TZ to relaxation of jaw tone and ease of tracheal intubation. The quality of anaesthetic induction was estimated based on continuously observed basic reflexes and condition of patient, which was scored according to numerical system stated by Tamura *et al.* (2014).

Maintenance of Anesthesia

Maintenance of anesthesia was done using isoflurane following intubation in both the groups connected with the anesthetic machine with a ventilator (Model 2800C Mallard Medical Inc.).

Evaluation of Clinico-Haematol-Biochemical Parameters

Canine patients were monitored for various physiological parameters. Pulse rate, respiratory rate, SpO_2, and rectal temperature recorded starting with N minutes (before pre-anaesthetic drug administration), 0 minute (time of induction), and then every 10 minutes interval up to 60 minutes.

Before pre-anesthetic administration, during anesthesia and following recovery every time, 5 mL blood was obtained aseptically from the cephalic/saphenous vein from all patients. For hematological estimation (Hb, PCV, TLC, TEC), 2 mL of blood was taken in a sterile K_3EDTA vacutainer, and 3 mL of blood in a sterile clot activator for serum biochemical estimation (TP, AST, ALT, creatinine, and BUN).

Quality of Anaesthetic Recovery

All the canine patients were continuously observed for evaluation of the quality of anaesthetic recovery, which was scored according to the numerical system stated by Tamura *et al.* (2014). Other parameters such as duration of anesthesia, standing time, complete recovery time were recorded. The collected data were analyzed using descriptive statistics and test of significance. The means and standard errors (SEs) for various parameters studied in two protocols were determined. Paired 't' test was used to compare the differences between groups.

Results and Discussion

TZ Induction of anesthesia was quick and smooth in Group I, where a xylazine pre-anesthetic agent was used. However, Group II TZ induction was delayed due to a lack of muscle relaxation. The induction time differed significantly ($p < 0.05$) between the two groups (33.10 ± 2.59 vs. 75.70 ± 18.75 sec). Rapid induction observed in patients of Group I (AXTZI) might be due to analgesic effects of xylazine. When xylazine was combined with TZ resulted in adequate muscle relaxation. Hafez *et al.* (2017), Karasu *et al.* (2018) and Ratnu *et al.* (2021) also observed similar findings.

Nearly all patients of both groups had abolished all reflexes within a minute of induction that was an indirect measure of induction and sedation quality. However, in Group II, pharyngeal reflex or swallowing reflex remained

positive for 1-2 minutes, as the level of induction was light in Group II. The present findings corroborated with the observations of Saha *et al.* (2007) and Hafez *et al.* (2017).

Quality of induction was observed to be very smooth in 80.00 (8/10) and 50.00 (5/10) % patients in Group I and Group II, respectively. At the same time, induction was quite smooth in 20.00 (2/10) and 40.00 (4/10) % patients in Group I and Group II, and moderately smooth induction in 10.00 (1/10) % of patients in Group II (Table 1).

Post-induction apnoea and respiratory depression was the major adverse effect after quick intravenous infusion of TZ combination, which occurred shortly after induction and resolved within minutes. Post-induction apnoea was observed in 50.00 (5/10) and 60.00 (6/10) % of patients in Group I and Group II, respectively. Similar results were reported by Savvas *et al.* (2005), Hampton *et al.* (2019[b]) and Ratnu *et al*. (2021) in dogs.

A statistically significant difference ($p < 0.05$) was observed in mean pulse rates (PR) from N minute to 0 minute in both groups. Group II patients specifically had a double-fold rise in pulse rate as compared to Group I patients. The mean pulse rate of patients of both groups also differed significantly at every 10 minutes interval from time of anesthetic induction until 60 minutes. Gradual declining trend observed in the pulse rates of both groups, was within physiological limit up to the recovery period. However, in Group II patients pulse rates were persistently high during maintenance. Statistically significant differences ($p < 0.05$) were observed in mean pulse rates between groups at each interval (Table 2). Double fold increased pulse rate in Group II might be attributed to tiletamine sympathomimetic activity and blockade of norepinephrine reuptake, resulting in a rise in circulating catecholamine concentrations and stimulation of the sinus node, which elevates pulse rate, a well-documented feature of dissociative drugs (Pereira *et al.,* 2019).

Initially, the respiratory rates (RR) were considerably decreased from N minute to 0 minute in both groups. Group I patients had respiratory rates relatively stable during maintenance of anesthesia. However, in Group II patients, respiratory rates changed frequently during maintenance. Three (3/10) patients of Group II had deep breathing with irregular frequency and extended pauses (apneustic breathing pattern). These results were consistent with the findings of Berry (2015). The SpO_2 values of both groups were relatively high throughout the maintenance and varied from 96.6 to 99%.

The rectal temperature varied slightly during maintenance in both groups. However, patients of Group II had a comparatively lower temperature on prolonging maintenance of anesthesia. The decrease in rectal temperature might be related to generalized sedation, a reduction in metabolic rate, and muscle relaxation. These findings were consistent with observations of Lu *et al.* (2014), Hampton *et al.* (2019[a]) and Ratnu *et al.* (2021) in dogs.

Among haemato-biochemical parameters, a non-significant decrease was observed in hemoglobin, packed cell volume, total leukocyte count, total protein, aspartate aminotransferase, alanine aminotransferase, creatinine, and blood urea nitrogen during surgical anesthesia and after recovery as compared to before anesthesia in patients of both the groups (Table 3A, 3B).

Quality of recovery was observed to be very smooth and quick in 10.00 (1/10) % of patients, *i.e.*, only one patient of Group I was able to recover uneventfully without any excitement, paddling or convulsions. Whereas recovery was quite smooth (little excitement, some head movement, some shivering) in 60.00 (6/10) and 50.00 (5/10) % of patients

Table 1: Quality of anaesthetic induction in Group I and Group II patient

	Tiletamine-zolazepam combination	
Induction Score	*Group I (AXTZI) N=10*	*Group II (ATZI) N=10*
4 (Very smooth)	80.00% (8)	50.00% (5)
3 (Quite smooth)	20.00% (2)	40.00% (4)
2 (Moderately smooth)	0.00	10.00% (1)
1 (Poor)	0.00	0.00
Total	100.00% (10)	100.00% (10)

Figures in parentheses indicate the number of patients.

Table 2: Physiological parameters observed during anesthesia in Canine patients of Group I (AXTZI) and Group II (ATZI)

Time monitored	*Pulse rate*		*Respiratory Rate*		*SpO_2 %*		*Rectal Temperature*	
	AXTZI	*ATZI*	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*
N min.	93.00 ± 6.13^{NS}	97.30 ± 4.72^{NS}	35.20 ± 6.08^{NS}	43.90 ± 5.93^{NS}	97.40 ± 0.83^{NS}	98.10 ± 0.40^{NS}	101.98 ± 0.28^{NS}	101.96 ± 0.26^{NS}
0 min.	130.10 ± 7.18*	179.80 ± 10.67*	24.40 ± 3.43^{NS}	25.90 ± 4.13^{NS}	98.50 ± 0.30^{NS}	98.80 ± 0.24^{NS}	101.31 ± 0.50^{NS}	101.01 ± 0.37^{NS}
10 min.	124.90 ± 8.11*	168.50 ± 11.39*	24.50 ± 2.57^{NS}	26.90 ± 4.19^{NS}	99.00 ± 0.33^{NS}	98.40 ± 0.52^{NS}	101.37 ± 0.33^{NS}	100.91 ± 0.35^{NS}
20 min.	118.20 ± 8.27*	160.60 ± 10.20*	24.90 ± 2.69^{NS}	24.60 ± 4.37^{NS}	98.70 ± 0.44^{NS}	98.10 ± 0.58^{NS}	101.16 ± 0.41^{NS}	100.61 ± 0.35^{NS}
30 min.	113.80 ± 7.68*	155.20 ± 10.23*	24.60 ± 2.63^{NS}	19.40 ± 3.48^{NS}	98.60 ± 0.42^{NS}	97.20 ± 0.69^{NS}	101.06 ± 0.34^{NS}	100.47 ± 0.42^{NS}
40 min.	112.10 ± 7.20*	148.30 ± 9.32*	25.00 ± 3.15^{NS}	20.70 ± 3.14^{NS}	98.20 ± 0.48^{NS}	97.00 ± 0.71^{NS}	100.75 ± 0.36^{NS}	100.27 ± 0.42^{NS}
50 min.	107.70 ± 7.08*	142.20 ± 8.31*	27.90 ± 4.77^{NS}	21.50 ± 3.11^{NS}	98.30 ± 0.53^{NS}	96.60 ± 1.15^{NS}	100.75 ± 0.29^{NS}	100.10 ± 0.50^{NS}
60 min.	103.40 ± 5.31*	137.30 ± 8.08*	26.50 ± 3.90^{NS}	24.40 ± 5.03^{NS}	98.50 ± 0.47^{NS}	97.10 ± 0.90^{NS}	100.64 ± 0.25^{NS}	99.91 ± 0.58^{NS}

N min. = before pre-anaesthetic drug administration; 0 min. = time of anaesthetic induction; *Significant difference ($p < 0.05$), ^{NS} Non-significant ($p > 0.05$).

Table 3A: Haematological parameters at different time intervals in anaesthetic Group I and II

	Hemoglobin		*PCV*		*TLC*		*TEC*	
Period/Parameter	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*
Before anesthesia	11.76 ± 0.85	12.17 ± 0.64	34.2 ± 1.92	35.87 ± 1.25	12.71 ± 0.79	11.64 ± 0.54	5.77 ± 0.23	5.87 ± 0.12
During anesthesia	11.22 ± 0.80	11.81 ± 0.51	32.43 ± 2.28	32.57 ± 0.91	12.19 ± 0.94	11.36 ± 0.56	5.47 ± 0.20	5.53 ± 0.14
After recovery	10.91 ± 0.74	11.46 ± 0.47	31.18 ± 2.02	32.97 ± 0.62	11.95 ± 0.70	11.23 ± 0.58	5.19 ± 0.13	5.23 ± 0.19

Table 3B: Serum biochemical parameters at different time intervals in anesthetic Group I and II

	Total Protein		*AST*		*ALT*		*Creatinine*		*BUN*	
Period/Parameter	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*	*AXTZI*	*ATZI*
Before anesthesia	6.31 ± 0.15	6.01 ± 0.11	32.40 ± 1.46	32.90 ± 1.36	46.20 ± 2.52	48.30 ± 2.04	1.15 ± 0.17	1.27 ± 0.22	22.98 ± 1.69	24.16 ± 1.58
During anesthesia	5.99 ± 0.16	5.88 ± 0.12	30.80 ± 1.61	31.30 ± 1.72	43.7 ± 1.41	46.10 ± 1.90	1.10 ± 0.10	1.20 ± 0.15	22.14 ± 1.40	22.45 ± 1.57
After recovery	6.05 ± 0.15[$]	5.82 ± 0.14	31.70 ± 1.26	30.90 ± 1.78	44.20 ± 1.53	46.80 ± 1.79	1.11 ± 0.09	1.22 ± 0.16	22.48 ± 2.29	22.39 ± 1.45

None of the haemato-biochemical parameters differed significantly between periods.

Table 4: Quality of anesthetic recovery in Group I and Group II canine patients

	Anaesthetic protocol	
Recovery Score	*Group I (AXTZI) N=10*	*Group II ATZI) N=10*
4 (Very smooth)	10.00% (1)	0.00%
3 (Quite smooth)	60.00% (6)	50.00% (5)
2 (Moderately smooth)	30.00% (3)	50.00% (5)
1 (Poor)	0.00%	0.00%
Total	100.00% (10)	100.00% (10)

Figures in parentheses indicate the number of patients.

Table 5: Mean (± SE) values of different anesthetic parameters in Group I and Group II patient

Time Interval	*Group I*	*Group II*	*'t' test*
Duration of anesthesia (min)	78.00 ± 7.93	65.10 ± 6.54	0.22[NS]
Standing time (min)	18.20 ± 2.95	20.80 ± 2.94	0.54[NS]
Complete recovery time (min.)	41.50 ± 6.14	37.60 ± 4.25	0.60[NS]

[NS] Non-significant at p>0.05.

in Group I and Group II, and moderately smooth (moderate excitement, some paddling, vocalization, trembling) recovery was found in 30.00 (3/10) and 50.00 (5/10) % of patients in Group I and Group II, respectively. Patients of Group II had a brief window of emerging delirium appearing as a hyperactive motor activity such as paddling, flailing, crying and howling, excitation, which were observed in the immediate post-anesthetic period (Table 4).

The duration of anesthesia and complete recovery time was longer in Group I compared to Group II (Table 5). Tiletamine has a longer duration of effect in canines than zolazepam. The current study closely confirmed the findings of Pablo and Bailey (1999) and Hampton *et al.* (2019[a]) in dogs.

Conclusions

A combination of atropine sulfate and xylazine provides considerable antisialagogue effect, sedation and analgesia during a pre-anesthetic period as compared to atropine alone in canine patients. Tiletamine-zolazepam combination produces smooth induction of anesthesia when administered by slow intravenous injection and results in least adverse effects. Induction of balanced surgical anesthesia using atropine, xylazine, tiletamine-zolazepam combination, and maintenance with isoflurane provides efficient nociception during surgical procedures.

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