RESEARCH ARTICLE

Clinical Evaluation of Tiletamine-Zolazepam CRI with Isoflurane Anaesthesia in Dog

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Abstract

The study was conducted to evaluate two anaesthetic protocols in 12 clinical cases of dogs presented to Veterinary Clinical Complex, COVAS, Parbhani for elective surgeries. These cases were divided into two equal groups (n=6). In both groups, dogs were pre-medicated with inj. Xylazine @ 1 mg/kg intramuscularly and anaesthesia was induced with inj. Tiletamine- Zolazepam (2 mg/kg) intravenously. Anaesthesia was maintained on constant rate infusion (CRI) of Tiletamine-Zolazepam (@ 2 mg/kg/h) in the dogs of group 1 and on Isoflurane in the dogs of group 2. Anaesthesia was assessed based on the quality of induction and recovery time in both groups. Clinico-physiological and haemato-biochemical parameters were measured in both groups at 5 different intervals. The induction score was identical in both groups with prolonged recovery in group 1. Clinico-physiological and haemato-biochemical values were changed from the base line value and return towards the baseline at recovery in both groups.

Key words: Constant rate infusion (CRI), Dog, Isoflurane, Tiletamine- Zolazepam, Zoletil.

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Introduction

Balanced anaesthetic techniques, which combine modest doses of anaesthetics with additional drugs that control reflex reactions to unpleasant stimuli, may decrease patient morbidity and mortality while simultaneously improving the working conditions for the surgeon. As a multimodal analgesic approach, various drugs can be administered in combination by constant rate infusion (CRI) as part of intra-operative analgesia (Dyson, 2008). It is superior to the intermittent re-dosing technique as it keeps the therapeutic concentration stable in the tissues or plasma, and it also lowers the minimum alveolar concentration (MAC) of patient (Docquier *et al.*, 2003). A newly available drug combination Tiletamine-Zolazepam is gaining popularity in small animal anaesthesia. It is potent combination of dissociative and benzodiazepine group. Tiletamine is always combined with benzodiazepine (Zolazepam) in the same proportion to mask the weakness of each other; it facilitates the rapid onset of action and smooth recovery from the surgical plane of anaesthesia (Nam *et al.*, 2013). Therefore the present study was planned to evaluate the clinical effects of tiletamine-zolazepam with isoflurane anaesthesia and the effect of constant rate infusion of tiletamine zolazepam in dogs.

Materials and Methods

The present research work was conducted on 12 clinical cases of dogs presented to Veterinary Clinical Complex, College of Veterinary and Animal Sciences, Parbhani (India) for elective soft tissue surgeries. All dogs were divided randomly into two equal groups irrespective of age, breed, sex and type of surgical intervention. Dogs in both groups were fasted for at least 8 h and water intake was restricted for at least 4 h prior to the surgery. Dogs in group 1 (n=6) and group 2 (n=6) received inj. Xylazine hydrochloride @ 1 mg/kg body weight by the intramuscular route. Ten min later, induction of anaesthesia was done with inj. Tiletamine-Zolazepam (Zoletil 100). All the patients were intubated after induction of anaesthesia. Maintenance of anaesthesia for the dogs in group 1 was done by the constant rate infusion of Tiletamine-Zolazepam @ 2 mg/kg/h, whereas dogs in group 2 were maintained on Isoflurane anaesthesia. Induction score, time to extubate, time to lift head, time to attend sternal recumbency, time to stand up and time for complete recovery were recorded and compared in both groups at five intervals, *viz.,* before and after Induction, intra-operative, after extubation and

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at complete recovery. The quality of induction was scored as per the scale given by White *et al.* (2001) (Table 1). All the patients in both the groups were screened for heart rate, rectal temperature, respiratory rate, haemoglobin, differential leucocyte count, serum alanine transaminase, serum aspartate transaminase, blood urea nitrogen and serum creatinine using standard procedures at before induction, after induction, intra-operative, after extubating and at complete recovery. The data was analyzed statistically using one-way ANOVA through SPSS Software version 24 and mean differences were considered significant at p<0.05 using DMRT post hoc test.

Table 1: Scoring system for the quality of induction of anaesthesia

Criteria	Description	Score
Good	Trachea easily intubated, easy transition to unconsciousness	1
Fair	Several attempts before successful intubation	2
Poor	Trachea difficult to intubate	3
Very poor	Vocalizing, paddling, impossible to intubate	4

Results and Discussions

Quality of Induction

Induction with Tiletamine-Zolazepam under Xylazine premedication provided a smooth transition to unconsciousness with adequate muscle relaxation and good nociception. The quality of induction was good in both groups, which was judged based on the ease of endotracheal intubation. Similar results have been also reported by Hafez *et al.* (2017), Karasu *et al.* (2018), Ratnu *et al.* (2021) and Koli *et al.* (2021) after using Xylazine and Tiletamine-Zolazepam combination. Action of xylazine along with Tiletamine-Zolazepam might have a synergistic effect on the induction and the quality of anaesthesia.

Recovery Time

Irrespective of the duration of anaesthesia, time to extubate, time to lift head, time to attend sternal recumbency, time to stand up and time to complete recovery was significantly shorter in group 2 as compared to group 1 (Table 2). Early recovery in group 2 might be due to maintenance of dogs on gaseous anaesthesia. Moreover, continuous rate infusion of Tiletamine-Zolezapam prolonged the recovery of the patients from anaesthesia in group 1. While standing up, dogs in group 1 showed marked ataxia in the posterior part of the body. Similar observation was made by Koli *et al.* (2021). However, recovery was smooth and without struggling in both groups under study.

Table 2: Recovery time from anaesthesia in group 1 (maintenance by CRI of Zoletil) and group 2 (maintenance by isoflurane) dogs (Mean ± SE)

Parameters	Groups	
	Group 1	Group 2
Time to extubate	16.33 ± 3.61*	5.33 ± 0.76
Time to lift head	45.16 ± 9.07*	15.00 ± 2.55
Time to attend sternal recumbency	72.16 ± 19.88*	28.00 ± 7.66
Time to stand up	103.83 ± 19.04**	38.00 ± 8.54
Time for complete recovery	150.16 ± 22.58**	57.66 ± 9.13

*Significant difference at P<0.01; **Significant difference at P<0.05.

Clinico-Physiological Parameters

Heart rate (HR) of dogs in both groups showed significant transient tachycardia after induction of anaesthesia, which returned to the initial baseline values after 15 min of the induction and started reducing after 15 min (Table 3). This increase in HR was thought due to sympathomimetic action and blocking of noradrenaline reuptake by dissociative anaesthetics which increases catecholamine levels stimulating the SA node to elevate the heart rate. Similar results were also noted by Hafez *et al.* (2017), Pereira *et al.* (2019), Ratnu *et al.* (2021) and Koli *et al.* (2021).

The rectal temperature (RT) of dogs in both groups showed a significant, but gradual reduction throughout the period of anaesthesia. The RT returned to the normal initial values while recovering from anaesthesia in groups 1 and 2 as shown in Table 3. This gradual fall in rectal temperature was thought due to a lack of command over the

Table 3: Mean and SE values of clinico-physiological parameters in dogs under maintenance of anaesthesia by CRI of Zoletil (Gr 1)) and by isoflurane (Gr 2)

		Intervals					ANOVA
Parameters	Groups	At 0	After Induction	Intra- Operative	After- Extubating	Complete Recovery	Significance (P-Value)
Heart Rate (Beats/min)	1	101.83^{ab} ±5.54	117.33^{b} ±3.98	106.83^{ab} ± 6.64	91.50^{a} ±6.83	98.50^{a} ±4.54	0.039
	2	101.00^{b} ±6.06	118.83^{c} ±2.39	87.33^{ab} ±6.97	78.83^{a} ±5.31	94.00^{ab} ±4.44	0.00001
Rectal Temperature (ºF)	1	102.15^{c} ±0.26	102.08^{c} ±0.23	101.75^{bc} ±0.18	100.48^{a} ±0.36	101.05^{ab} ±0.17	0.0002
	2	101.98^{c} ±0.32	101.90^{c} ±0.26	101.57^{bc} ±0.23	100.52^{a} ±0.32	100.87^{ab} ±0.21	0.002
Respiratory Rate (Breaths/min)	1	37.50^{b} ±1.93	26.67^{a} ±1.61	25.83^{a} ±1.11	26.33^{a} ±0.76	36.00^{b} ±2.08	0.00
	2	34.33^{c} ±1.89	22.17^{a} ±1.11	23.50^{ab} ±0.89	27.17^{b} ±1.17	32.17^{c} ±1.56	0.00

"p" value <0.05 suggests a significant difference at 5% level. Means with different superscripts within the row differ significantly.

thermoregulatory center, decreased BMR, muscle relaxation, and a depressed central nervous system under anaesthesia (Lu *et al*., 2014).

As depicted in Table 3, the respiratory rate (RR) reduced significantly after induction and reached towards the initial values at the complete recovery. Additionally, an apneustic respiratory pattern was observed in a few cases after induction, which could be mediated by the agonist action of dissociative anaesthetic on muscarinic cholinergic receptors (Hatch, 1974). Similarly, Phutthachalee *et al*. (2012) and Pereira *et al*. (2019) found the same result when the patients were induced with the Tiletamine-Zolazepam. Apnea after induction and respiratory depression in dogs were seen by Koli *et al*. (2021) after intravenous induction with Tiletamine-Zolazepam.

Haematological Parameters

Haemoglobin showed non-significant variations at different intervals in dogs of group 1 and group 2, and remained in normal reference range throughout the study (Table 4) as was noted by Jena *et al*. (2014) and Aminkov *et al*. (2018).

In differential leucocyte count (DLC) slight neutrophilia was seen after induction of anaesthesia, which might be due to increased cortisol release in response to handling and surgical stress (Tabuchi *et al*., 1989). Lymphocytes decreased non-significantly after induction, which was affected inversely by the neutrophil count. Monocytes, eosinophils and basophils showed non-significant fluctuation at the different intervals of study.

Biochemical Parameters

Alanine transaminase (ALT) fluctuated non-significantly, whereas aspartate transaminase (AST) decreased non-significantly at different intervals of study in both groups (Table 5). This decreasing trend in serum AST was thought due to the hypoxic condition in anaesthesia, which resulted in hepatic hypo-perfusion (Manasa *et al*., 2021). Blood urea

Table 4: Mean and SE values of haematological parameters in dogs under maintenance of anaesthesia by CRI of Zoletil (Gr 1)) and by isoflurane (Gr 2)

Parameters	Groups	Intervals					ANOVA
		At 0	After Induction	Intra-Operative	After-Extubating	Complete Recovery	Significance (P-Value)
Haemoglobin (gm/dL)	1	10.62 ±0.98	11.00 ±0.71	10.98 ±0.88	10.35 ±0.70	11.05 ±0.75	0.965
	2	12.42 ±1.24	12.30 ±1.10	12.32 ±1.41	12.50 ±1.16	12.63 ±1.25	0.999
Neutrophil (%)	1	54.33 ±10.37	61.67 ±9.57	65.67 ±9.29	64.67 ±9.96	68.00 ± 4.98	0.847
	2	70.00 ±5.77	74.00 ±2.37	69.33 ±4.19	76.33 ±3.63	75.00 ± 4.22	0.700
Lymphocyte (%)	1	34.00 ±0.43	29.67 ±10.10	27.67 ±8.35	26.33 ±8.83	25.67 ±5.04	0.963
	2	24.00 ±5.09	19.00 ±1.44	24.00 ±2.78	16.00 ±3.97	18.00 ±5.09	0.504
Monocyte (%)	1	8.00 ±1.55	4.33 ±0.80	3.67 ±0.96	5.67 ±1.41	4.00 ±1.16	0.102
	2	3.67 ±0.96	3.67 ±0.80	4.00 ±0.89	5.67 ±1.20	5.00 ±1.53	0.630
Eosinophil (%)	1	3.33 ±0.84	3.33 ±1.23	3.00 ±0.86	2.33 ±1.20	2.00 ±0.73	0.826
	2	2.00 ±1.03	2.67 ±1.23	2.00 ±0.89	0.33 ±0.33	1.33 ±0.42	0.396
Basophil (%)	1	0.33 ±0.33	0.67 ±0.67	0.00 ±0.00	1.00 ±1.00	0.33 ±0.33	0.783
	2	0.33 ±0.33	0.33 ±0.33	0.67 ±0.42	1.33 ± 0.67	0.67 ±0.42	0.527

None of the haematological parameters varied significantly between intervals (p>0.05).

Table 5: Mean and SE values of biochemical parameters in dogs under maintenance of anaesthesia by CRI of Zoletil (Gr 1)) and by isoflurane (Gr 2)

Parameters	Groups	Intervals					ANOVA
		At 0	After Induction	Intra-Operative	After-Extubating	Complete Recovery	Significance (P-Value)
Alanine Transaminase (IU/L)	1	13.54 ±2.57	11.39 ±2.93	13.55 ±2.61	12.70 ±5.96	19.03 ±5.97	0.790
	2	32.98 ±13.17	33.31 ±16.61	29.44 ±13.54	26.84 ±14.83	33.21 ±13.81	0.996
Aspartate transaminase (IU/L)	1	24.50 ±2.67	20.30 ±2.71	18.86 ±1.27	17.28 ±2.62	22.71 ±1.81	0.202
	2	41.69 ±9.56	39.99 ±10.73	36.46 ±10.86	36.11 ±9.74	36.28 ±9.31	0.991
Blood Urea Nitrogen (mg/dL)	1	18.22a ±0.82	20.17ab ±0.60	22.00b ±0.86	23.67bc ±0.67	25.83c ±0.48	0.000
	2	18.00 ±0.37	16.83 ±0.95	17.83 ±0.75	18.67 ±0.61	18.52 ±0.48	0.436
Creatinine (mg/dL)	1	1.39 ±0.18	1.43 ±0.19	1.74 ±0.28	1.17 ±0.19	1.30 ±0.08	0.344
	2	1.19 ±1.11	1.25 ±0.14	1.12 ±0.15	1.03 ±0.13	1.28 ±0.08	0.607

nitrogen (BUN) increased significantly after induction in group 1, and group 2 showed non-significant momentary increase in BUN values, which returned towards the baseline value at a complete recovery. Significant increment in the BUN value in group 1 was thought due to the nephrotoxic effect of tiletamine at higher doses (Brammer *et al*., 1991; Doerning *et al*., 1992; Karasu *et al*., 2018). Serum creatinine showed transient non-significant increase in both groups after induction followed by non-significant alterations for the rest of intervals. However, obtained results were within the normal range as noted by Brammer *et al*. (1991) and Doerning *et al*. (1992).

Conclusions

The dogs premedicated with Xylazine (1 mg/kg b.wt), induced with Tiletamine-Zolazepam (2 mg/kg b.wt) and maintained on constant rate infusion of Tiletamine-Zolazepam (2 mg/kg b.wt /hr) provided excellent nociception and adequate muscle relaxation essential for soft tissue surgeries, whereas, delayed recovery was the only concerned in dogs maintained with constant rate infusion of Tiletamine-Zolazepam. However, the recovery was smooth in both groups (maintained on constant rate infusion of Tiletamine-Zolazepam or Isoflurane). Haemto-biochemical and clinico-physiological changes were short lived and had no clinical relevance.

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References

Aminkov, B., Mehandzhiyski, N., Aminkov, K., & Peev, I. (2018). Effects of total intravenous anesthesia on hematology and biochemistry values during health checkup in brown bears (*Ursus arctos*). *Tradition and Modernity in Veterinary Medicine*, *2*(5), 94-99.

Brammer, D.W., Doerning, B.J., Chrisp, C.E., & Rush, H.G. (1991). Anesthetic and nephrotoxic effects of telazol in New Zealand white rabbits. *Laboratory Animal Science, 41*(5), 432-435.

Docquier, M. A., Lavand'homme, P., Ledermann, C., Collet, V. & De Kock, M. (2003). Can determining the Minimum Alveolar anesthetic concentration of volatile anesthetic be used as an objective tool to assess antinociception in animals? *Anesthesia and Analgesia*, 97(4), 1033-1039.

Doerning, B.J., Brammer, D.W., Chrisp, C.E., & Rush, H.G. (1992). Nephrotoxicity of tiletamine in New Zealand white rabbits. *Laboratory Animal Science, 42*(3), 267-269.

Dyson, D. H. (2008). Perioperative pain management in veterinary patients. *Veterinary Clinics of North America: Small Animal Practice*, *38*(6), 1309-1327.

Hafez, S.G., Nouh, S.R., & Elkammar, M.H. (2017). Evaluation of total intra-venous anesthesia using ketamine HCl or telazol in Mongrel dogs. *Alexandria Journal for Veterinary Sciences, 53*(2), 99-106.

Jena, B., Das, J., Nath, I., Sardar, K.K., Sahoo, A., Beura, S.S., & Painuli, A. (2014). Clinical evaluation of total intravenous anaesthesia using xylazine or dexmedetomidine with propofol in surgical management of canine patients. *Veterinary World, **7***(9), 671-680.

Karasu, A., Altuğ, N., Aslan, L., Bakir, B., & Yüksek, N. (2018). Evaluation of the anesthetic effects of xylazine-ketamine, xylazine-tiletamine-zolazepam and tiletamine-zolazepam using clinical and laboratory parameters in rabbits. *Medycyna Weterynaryjna-Veterinary Medicine-Science and Practice,74*(10), 646-652.

Koli, P.H., Parikh, P.V., Mahla, J.K., & Barot, H.M. (2021). Clinical attributes of tiletamine-zolazepam induced anesthesia with and without xylazine premedication in dogs. *Indian Journal of Veterinary Sciences and Biotechnology, 17*(4), 61-65.

Li, L., Dong, J., Lu, D., Jiang, S., Lin, D., & Fan, H. (2012). Effects of tiletamine-zolazepam-xylazine-tramadol combination on biochemical and haematological parameters in cats. *Journal of Veterinary Research, 56*(3), 369-372.

Lu, D.Z., Jiang, S., Yu, S.M., & Fan, H.G. (2014). A comparison of anesthetic and cardiorespiratory effects of tiletamine-zolazepam/xylazine and tiletamine-zolazepam/ xylazine/ tramadol in dogs. *Pakistan Veterinary Journal, 34*(1), 63-67.

Manasa, M.R., Dileepkumar, K.M., Anoop, S., Ramankutty, S., Beena, V., & John Martin, K.D. (2021). Evaluation of haematological and serum biochemical profile of propofol-induced isoflurane anaesthesia in geriatric dogs premedicated with diazepam and butorphanol. *Journal of Veterinary and Animal Sciences, 52*(1), 81-84.

Nam, S.W., Shin, B.J., & Jeong, S.M. (2013). Anesthetic and cardiopulmonary effects of butorphanol-tiletamine-zolazepam-medetomidine and tramadol-tiletamine-zolazepam-medetomidine in dogs. *Journal of Veterinary Clinics, 30*(6), 421-427.

Pereira, S.A., Henrique, F.V., Medeiros, L.K., Silva, J.K., Goes, A.B., Vaz, A.F., & Nóbrega, P.I. (2019). Anesthetic quality and cardiovascular and respiratory effects of continuous intravenous infusion of tiletamine-zolazepam in bitches. *Pesquisa Veterinária Brasileira, 39*(3), 214-220.

Phutthachalee, S., Cherdchutham, W., Laikul, A., Phetudomsinsuk, K., Chanda M., & Phukudom, S. (2012). Comparison of the anesthetic effects of tiletamine HCl–zolazepam–xylazine and ketamine–diazepam–xylazine in older foals under field conditions. *Agriculture and Natural Resources, 46*(2), 190-199.

Ratnu, D.A., Parikh, P.V., & Kelawala, D.N. (2021). Effects of tiletamine-zolazepam and isoflurane for induction and maintenance in xylazine premedicated dogs. *The Indian Journal of Veterinary Sciences and Biotechnology, 17*(4), 86-88.

Tabuchi, Y., Shinka S., & Ishida, H. (1989). The effects of anesthesia and surgery on count and function of neutrophils. *Journal of Anesthesia, 3(*2), 123-131.

White, K.L., Shelton, K., & Taylor, P.M. (2001). Comparison of diazepam–ketamine and thiopentone for induction of anaesthesia in healthy dogs. *Veterinary Anaesthesia and Analgesia, 28*(1), 42-48.