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Evaluation of clinical efficacy of Tiletamine and Zolazepam in combination with Xylazine or Dexmedetomidine in Butorphanol and Atropine premedicated dogs for performing surgical procedures

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ABSTRACT

A study was conducted for the clinical evaluation of Tiletamine-zolazepam when used in combination with inj. atropine, inj. butorphanol and either xylazine or dexmedetomidine in 18 client owned dogs presented for ovariohysterectomy. They were divided into two groups: group 1 (n=9) and in group 2 (n=9). The drug regime for groups included inj. butorphanol @ 0.2 mg/kg and inj. atropine @ 0.04 mg/kg followed by inj. xylazine @ 1.0 mg/kg along with tiletamine-zolazepam @ 3.3 mg/kg in group 1 and dexmedetomidine @ 10 µg/kg along with tiletamine-zolazepam @ 4.5 mg/kg in group 2. Animals in both the groups showed smooth induction with adequate muscle relaxation and analgesia. Significant decrease in rectal temperature was noticed in both the groups, which improved during recovery. ECG parameters did not show significant difference from physiological values in majority of animals. Significant increase in heart rate was noticed after induction in both groups, which came back to normal resting values at the end of the study period. Non-invasive blood pressure showed non-significant increase in both the groups initially and later dropped lower than pre-anesthetic value. SpO_2, $EtCO_2$ and $FiCO_2$ values remained within the normal range throughout the procedure. Significant decrease in respiration rate was noticed in both groups with no incidence of apnea. Haematological parameters reduced non-significantly at the end of the study period when compared with baseline value in both the groups. Biochemical parameters and electrolytes did not vary significantly throughout the study period except for glucose which showed a significant increase throughout the study in both the groups. Recovery period was longer in group 2. Vocalization with ataxia and head bobbing was noticed in some animals of group 1 and 2 which ended after recovery without any adverse consequences. The protocol used in the study provided safe and adequate anaesthesia for different surgical manipulations that can be performed under 60 min in dogs.

Keywords: Atropine, Butorphanol, Dexmedetomidine, Dogs, Tiletamine-Zolazepam, Xylazine

Tiletamine is a stable, non-reactive and slightly water soluble aralkylamine which is a long-acting dissociative anaesthetic agent, having twice the potency and longer duration of action than ketamine (Lin *et al*. 1993). Infusion of tiletamine alone lead to extreme increase in muscle tone, muscular twitches and occasional convulsions. So, it is commercially available in combination with benzodiazepine, i.e. zolazepam as a dry powder in a 1:1 ratio popularly known by the tradename Telazol/Zoletil®. Zolazepam is chosen over the other benzodiazepines as it provides profound muscle relaxation along with better amnesia, anticonvulsant and anxiolytic action. Zolazepam is again least likely to cause CNS depression. Even after having these advantages, zolazepam has proved inefficient to alleviate the muscular rigidity and seizure-like manifestations produced by tiletamine hence it is mostly combined with an α2 agonist or an opioid to make it a balanced anaesthesia. Tiletamine can be a very good choice over ketamine in terms of formulation as its commercial preparation is not available as a sole drug but only along with Zolazepam, eliminating its abuse. A very limited work has been done over its usage as induction and maintenance agent as general anaesthetic in dogs. Thus, this study was carried out to evaluate the clinical efficacy of tiletamine-zolazepam in combination with xylazine or dexmedetomidine when used in dogs premedicated with butorphanol and atropine for performing surgical procedures.

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MATERIALS AND METHODS

Adult dogs (18) presented for ovariohysterectomies were the subjects for the study. Subjects were selected irrespective of the breed, age and body weight. The dogs

were randomly divided into two groups. The food was withheld for 12 h and water for at least 4 h. The protocol for the general anaesthesia involved Inj. Butorphanol tartarate @ 0.2 mg/kg body weight, followed by Inj. Atropine sulphate @ 0.04 mg/kg body weight after 15 min in both the groups. Further, after 15 min of Inj. Atropine, the dogs were injected with Inj. Xylazine hydrochloride @ 1 mg/kg and Tiletamine-zolazepam @ 3.3 mg/kg in group 1 and Inj. Dexmedetomidine @ 10 µg/kg body weight and Inj. Tiletamine-zolazepam @ 4.5 mg/kg body weight in group 2. All the drugs were administered by intramuscular route. Animals in both the groups were given oxygen supplementation via endotracheal tube attached to an anaesthetic machine. Baseline data involving heart rate, respiration rate, rectal temperature, electrocardiogram, non-invasive blood pressure, oxygen saturation of haemoglobin, end tidal carbon dioxide ($EtCO_2$) and fractional inspired carbon dioxide ($FiCO_2$) was collected in each case under both the groups. Reflexes like ocular reflexes, jaw relaxation, pedal reflex and response to intubation were monitored and graded during the induction of anaesthesia to ascertain the depth of anaesthesia. Heart rate, respiration rate, non-invasive blood pressure, oxygen saturation of haemoglobin and electrocardiogram readings were recorded at specified time intervals (in minutes) after induction, viz. T_1, T_5, T_{15}, T_{30}, T_{45} and T_{60}. Recovery parameters included time of return of palpebral reflex, time of extubation, time to head raise, time to sternal recumbency and standing ataxia. Haemato-biochemical analysis was done pre, intra and post operatively. Each dog was assessed and assigned a score for quality of induction and recovery from general anaesthesia.

The data of all the objective parameters derived during the study were subjected to statistical analysis via GraphPad InStat® Software, Version 3.01, 32 bits. Analysis of variance (ANOVA) was done with the help of Student-Newman at 5%, 1% and 0.1% level of significance. Various parameters were tested for the intra-group and inter-group comparison using Student-Newman test.

RESULTS AND DISCUSSION

Both the groups showed excellent quality of induction with mean±SE scores of 4.00±0.00 for group 1 and 2. The score for jaw relaxation which is the indicator of muscle relaxation (Naryal 2020) was 2.5±0.18 and 2.6±0.16 for group 1 and 2, respectively showing that muscle relaxation was adequate throughout the study irrespective of different drugs used. Pedal reflex was abolished in both the groups at T_5 with mean±SE scores of 3.0±0.0 in group 1 and 2.9±0.1 in group 2 indicating adequate analgesia was achieved throughout the study period. Among the dogs in group 1 and 2, palpebral reflex vanished from T_5 to T_{60}. The position of the eyeball in both groups was ventral between T_{15} to T_{60}. On intragroup comparison, scores for jaw relaxation and pedal reflex increased significantly between T_5 to T_{60} when compared to the score after drug administration (T_1) (Table 1). There was no significant difference between two groups at all time intervals. Analgesia by α-2 agonists was provided by the activation of heteroceptor (α-2 receptor located on noradrenergic neuron) located in the dorsal horn of spinal cord (Lemke 2004). Also, zolazepam is a centrally acting muscle relaxant providing excellent quality of muscle relaxation (Pereira *et al*. 2019). α-2 agonists, xylazine and dexmedetomidine in present study had additive action on muscle relaxation. Brikas *et al.* (1987) reported that muscle relaxation effect of α-2 agonists is mainly due to the inhibition of intraneural transmission with in the central nervous system. The animals went to lateral recumbency with excellent muscle relaxation and could be intubated easily in group 1 and 2. Mean±SE time of intubation in two groups was 5.75±0.90 min and 7.70±1.83 min, respectively. Mean±SE scores for intubation were 2.50±0.18 in group 1 and 2.80±0.13 in group 2. Highly significant ($p<0.01$) difference was seen in intubation score between groups 1 and 2, with group 2 having a better score. Cullen and Reynoldson (1997) reported that induction was smooth and undesirable effects were abolished with the usage of premedication.

Tachycardia was noticed post drug administration in both the groups. Significant ($p<0.05$) to extremely significant ($p<0.001$) difference was noticed in heart rate within groups at different time intervals. Statistically significant increase in heart rate was seen in group 1 and 2 from baseline value at T_1 and T_5, which then decreased non-significantly up to $T_{60.}$ Heart rate was more in group 1 than group 2. No significant difference was noticed at all time intervals between the groups 1 and 2. Koli *et al*. (2021) and Pereira *et al*. (2019) reported that heart rate increased significantly after induction up to 10 min and this increase in heart rate after induction was attributed to the sympathomimetic activity of tiletamine and blockade

Table 1. Scoring system for quality of induction (Krimins *et al.* 2012)

Score	Quality	Character
4	Excellent	Rapid smooth induction of anaesthesia; no movement; rapidly assumes lateral recumbency with excellent muscle relaxation; loose jaw tone and easy intubation;
3	Good	Profound sedation; eyes droopy; head down; inactive; assumes sternal or lateral recumbency; Tight jaw tone; unable to be intubated;
2	Average	Moderate sedation; mildly aware of the surrounding environment; sternal recumbency only;
1	Poor	Mild to moderate sedation with reduced activity; does not assume sternal or lateral recumbency.
0	Unsatisfactory	Active; aware of the surrounding environment; minimal sedation.

of nor-epinephrine reuptake causing rise in concentration of circulating catecholamine which stimulated sinus node and elevated the heart rate. Nam *et al.* (2013) documented significant decrease in heart rate within 20 min after administration of butorphanol, tiletamine-zolazepam along with α-2 agonist (medetomidine) and further showed that heart rate remained below baseline for up to 60 min. The decrease in heart rate may be due to property of α-2 agonists which causes depression of sympathetic system coupled with increase in parasympathetic effect resulting in reduction of heart rate (Yaygingul and Belge 2018).

Elongation of P interval was two times more than physiological limit in group 1 with highly significant difference ($p<0.01$) at T_{60} between group 1 and group 2. All of the other ECG parameters were within the normal physiological range. Yaygingul and Belge (2018) reported prolongation of P wave in dogs which received α-2 agonist and attributed this change to the cardio-depressant effect of α-2 agonist drugs. Pre-emptive administration of anticholinergics, i.e. atropine in present study prevented occurrence of bradyarrhythmias as reported by Lemke *et al*. (2001). In group 1, one dog showed Mobitz type II atrioventricular blockade just after drug administration (T_1) which resolved after 5 min (T_5) without requiring any treatment. Yaygingul and Belge (2018) reported occurrence of sinoatrial block, 2° Mobitz Type 1 and 2º Mobitz type II block in ECG of dogs that received α-2 agonists.

Non-invasive blood pressure showed non-significant increase up to 30 min and then decreased lesser than baseline values in both the groups. Lu *et al*. (2014) after studying the effects of tiletamine-zolazepam combined with xylazine and tramadol reported that blood pressure (MAP, SBP and DBP) increased significantly from baseline values at 10 min and then decreased till 45 min. The highest value of MAP was noticed at 45 min which is similar to the findings of this study. They proposed that xylazine is known to cause peak increase in blood pressure for about 5-10 min after administration and then fell below baseline values which explains the fall in blood pressure in group 1 of this study up to 30 min with a rise in blood pressure from 45 min.

Group 1 showed significant decrease in respiration rate from baseline value between T_5 to T_{30} and then showed non-significant increase up to 60 min (T_{60}). In group 2, respiration rate showed significant decrease from baseline value between time interval T_1 to T_{15} and then showed increasing trend up to T_{30}, followed by decrease, up to end of the study, i.e. T_{60}. Intergroup comparison between group 1 and group 2 showed statistically insignificant difference at all the time intervals (T_0-T_{60}). It was reported that respiration rate reduced significantly from baseline value and remained below normal physiological range for the dogs, i.e. 18-36 (Feitosa 2014) during first 20 min after induction. Tiletamine is known to cause transient respiratory depression immediately after administration and give rise to an apneustic respiratory pattern characterised by deep breathing with irregular frequency and prolonged pauses (Pereira *et al.* 2019).

No significant difference was recorded on intragroup and intergroup comparison of $EtCO_2$ and $FiCO_2$ in group 1 and group 2 at various time intervals. The values of $EtCO_2$ and $FiCO_2$ remained within the physiological limit throughout the study period. Intragroup comparison of haemoglobin concentration, packed cell volume and total erythrocyte count in group 1 and group 2 showed a non-significant decrease from pre-operative values. Intragroup comparison of total leukocyte count in both group 1 and group 2 showed a non-significant decrease intraoperatively followed by a non-significant increase post-operatively, but lower than pre-operative values. Platelet count showed decreasing trend intra-operatively followed by an increasing trend post-operatively, but remained below pre-operative values in group 1 and post-operative platelet count in group 2 was more than pre-operative count. Biochemical parameters remained within normal physiological limits throughout the study period except for plasma glucose showed a significant increase intra-operatively and post-operatively from pre-operative values in both groups 1 and 2. Intergroup comparison of plasma glucose between two groups showed significant difference at all three intervals. The lowest values recorded pre-operatively were due to the fact that animals were off-feed for 12 h before anaesthetic study. Bouillon *et al.* (2019) stated that α-2 agonists are known to increase glucose concentration in dogs. This effect is due to the inhibition of insulin release from pancreatic beta cells via α2A-adrenoreceptor subtype. Electrolyte concentration was within the normal range throughout the study period and non-significant changes were recorded after intergroup and intragroup comparison.

Time of return of palpebral reflex was recorded when the animal blinked the eyelids for the first-time during recovery on digital palpation of lateral or medial canthus of the eye. It was found that there was delay in the return of palpebral reflex in group 2. Also, the mean time for

Table 2. Scoring system for quality of recovery (Krimins *et al*. 2012)

Score	Quality	Character
4	Excellent	Dog assumes sternal recumbency with little or minimal struggling; stands and walks with minimal effort; no signs of anaesthetic effects.
3	Good	Some struggling; requires some assistance to stand; able to maintain balance once standing; minimal signs of residual anaesthetic effects.
2	Average	Some struggling; repeated attempts to stand and requires assistance to stand; very unstable while walking and unable to maintain balance; some signs of residual anaesthetic effects.
1	Poor	Prolonged struggling; unable to stand without assistance; hyperkinesia in response to manual assistance.

Table 3. Mean±SE values of various recovery parameters (minutes) in the two groups post-operatively

Parameter	Group 1	Group 2
Time to return of Palpebral reflex	62.50±7.15	67.60±12.23
Time to extubation/swallow reflex	95.25±6.58[a]	151.70±10.78[b]
Time to head raise	93.87±4.91[a]	158.00±11.45[b]
Time to sternal recumbency	117.88±8.37[a]	176.00±10.53[b]
Time of standing ataxia	132.38±9.86[a]	216.80±14.98[b]

[a], mean difference between the groups is significant when inter-group comparison was done (P<0.001).

extubation was longer in group 2 compared to group 1. Krimins *et al*. (2012) reported that dexmedetomidine-butorphanol-tiletamine-zolazepam caused increased respiratory depression and induced analgesia for longer duration with increased intensity. It was also observed that the animals in group 2 took longer time to successfully raise the head when compared to group 1 (Tables 2 and 3). Moreover, the animals in group 2 took longer time to return to sternal recumbency compared to group 1. Animals under group 2 took longer time to stand when compared to animals under other group. Ataxia was present during recovery in both the groups. It was reported that dexmedetomidine is more potent than xylazine but xylazine has a wider safety of margin in terms of dosing (Landry and Maza 2020). Kuusela *et al*. (2000) stated that elimination half-life of xylazine is 30.1 min and dexmedetomidine is 47 min and this might be the reason for longer duration of recovery in group 2 compared to group 1 of present study.

There was a decrease in rectal temperature from the baseline value in both the groups at all time intervals. These findings are in agreement with the findings of Ratnu *et al.* (2021) who opined that the drop in the temperature might be due to generalized sedation, reduction in metabolic rate and muscle relaxation. Lu *et al.* (2014) also reported that the administration of α-2 agonists causes the loss of thermoregulatory control mechanism. One dog of group 2 was moderately hypothermic and rest all of the 17 dogs showed mild hypothermia during recovery. Koli *et al.* (2021) proposed that due to the generalized sedation, reduction in metabolic rate and muscle relaxation, a decrease in body temperature will occur and this explains the occurrence of hypothermia during recovery in present study.

Vomiting and urination was not recorded in any of the cases through the study period. Defecation was seen in two dogs of second group after about 5 min after drug administration. One dog in group 1 exhibited head bobbing and dorsoventral nystagmus that lasted for about 3 min and resolved without any treatment. Koli *et al.* (2021) reported moderate excitement, paddling, trembling and vocalization without convulsions in three dogs and some head movement in 6 dogs which received α-2 agonist along with tiletamine-zolazepam. One dog in group 1 showed lateral nystagmus that lasted for 2 min. Nystagmus noticed in dogs during recovery might be due to longer plasma half-life of tiletamine which is 1-2 h (Cullen and Reynoldson 1997). One dog in group 2 exhibited hypoxia and bradycardia after coming into sternal recumbency during recovery which was then provided with fresh oxygen supplementation by mask till recovery and was also administered with atropine at the dose rate of 0.02 mg/kg body weight by intravenous route. Dyson and James-Davies (1999) reported that random intravenous administration of anticholinergics in anaesthetized dogs increases heart rate and blood pressure. The dog recovered uneventfully and was released after it could walk without assistance and demonstrated all the vital parameters in the range of normal physiological value. Hypoxia during recovery can be attributed to the dose dependent respiratory depression of tiletamine-zolazepam and α-2 agonists (Ratnu *et al.* 2021).

On a conclusionary note tiletamine-zolazepam @3.3 mg/kg combined with butorphanol, atropine and xylazine @1 mg/kg and tiletamine-zolazepam @4.5 mg/kg combined with butorphanol, atropine and dexmedetomidine @10 µg/kg used for conducting ovariohysterectomies in dogs proved to be successful as per the present study. Hypertension was observed in both the groups irrespective of premedication administered and did not warrant requirement of any treatment for increased blood pressure.

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