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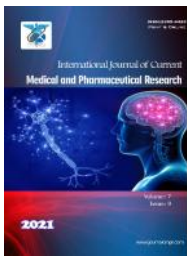

Research Article

CLINICAL STUDIES ON GENERAL ANAESTHESIA USING TILETAMINE-ZOLAZEPAM COMBINATION AS ANAESTHETIC INDUCTION FOR DIAGNOSTIC MRI IN DOGS

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ABSTRACT

An anaesthetic protocol was evaluated in 6 dogs (2 Female, 4 Male) of different breeds presented for different conditions requiring diagnostic MRI. The anaesthetic efficacy as well as physiological and haemato-biochemical alterations following tiletamine-zolazepam (TZ) combination as induction agent with xylazine premedication were assessed to assure an appropriate depth and length of anaesthesia, a regular breathing pattern, and a stable haemodynamic condition without the usage of expensive equipment for anaesthetic maintenance. Patients were premedicated with atropine @ 0.04 mg/kg, and xylazine @ 1 mg/kg, b. wt., intramuscularly. Induction of anaesthesia was achieved by tiletamine-zolazepam @ 8 mg/kg b. wt., intravenously. A quick induction was observed in all the patients, *i.e.* within few minutes. An after-effect of TZ induction was transient post-induction apnoea observed in all patients (nearly 30 seconds). The results suggest that these drug combinations provides up to approximately two hours of anaesthesia with stable physiological parameters and an acceptable level of analgesia while maintaining normal respiration. The changes in SpO_2 and rectal temperature during maintenance remained within biologically acceptable limits. Haemoglobin, PCV, total protein, TLC, TEC, ALT, AST, creatinine, and BUN were all non-significantly different before and after recovery, with the exception of glucose level, which was significantly higher even after recovery. The anaesthetic duration, standing time and complete recovery time were longer. The study confirms induction and maintenance of balanced anaesthesia using atropine, xylazine, tiletamine-zolazepam combinations with efficient nociception during MRI procedures.

INTRODUCTION

Preclinical magnetic resonance imaging (MRI) is now the most versatile imaging modality for determining the anatomical, functional, and physiological characteristics of tissues and organs. Imaging technologies are important in biomedical research because they allow great scope for non-invasive studies of biochemical and biological processes in living animals (Driehuys *et al.*, 2008). Its non-ionizing 3D imaging functionality is truly non-invasive, preventing any ionising radiation exposure to the animals, especially essential during serial imaging, allowing it to exceed modalities such CT, SPECT, and PET.

Use of imaging procedures can affect animal physiology, due to the obligation to anaesthetize the animals for imaging, which in turn includes possible health risks in the imaged animals, a major difference with human MRI. During anaesthesia, there is an inevitable autonomic nervous system depression, which induces cardiovascular-respiratory depression, and hypothermia. Also other procedures connected with imaging such as patient's preparation (e.g., fasting, premedication), blood sampling, and dosage agent administrations can also affect physiology and animal welfare (Tremoleda *et al.*, 2018).

Pre-anaesthetic medications are an essential part for safe anaesthetic maintenance (Vesal *et al*., 2011). Xylazine, α_2 adrenergic agonist develops analgesia, anxiolysis, sedation, sympatholysis and control of hypertension, making it one of the most versatile anaesthetic adjuncts (Jang *et al.*, 2002).

The cyclohexylamine derivative, tiletamine is an injectable anaesthetic (dissociative) agent chemically related to ketamine with cataleptic, analgesic and anaesthetic action, but no hypnotic properties (Clark *et al.* 2013), but tiletamine has a longer duration of action and greater analgesic effect than ketamine (Chang and Jang, 1998). The pharmacodynamic action of tiletamine is antagonist at the N-methyl-D-aspartate (NMDA) receptor, and therefore has good analgesic properties, but has no action at the GABA receptor, hence the lack of the more usual form of hypnosis. As ketamine, tiletamine may be administered by a wide number of different routes. Its plasma half-life in dogs is 1.2 hours and with that of zolazepam up to 4-5 hours (Lin *et al.* 1993).

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Zolazepam is a pyrazolodiazepinone derivative structurally related to the benzodiazepine drugs, used as minor tranquilizer in veterinary medicine. It has nearly four times the potency of diazepam, but it is both water-soluble and un-ionized at physiological pH, meaning that its onset is very fast (DeWald *et al.,* 1977). Benzodiazepine is known for the production of partial or complete memory loss, muscle relaxation, lesser depression of cardio-respiratory functions, strong anticonvulsant effect, and is quite safe even if overdosed (Kwon *et al.,* 2003). In usual practice, dissociative agents are used in combination with sedatives, which reduces or prevent the hallucinatory adverse effects and improve muscle relaxation (Clark *et al.* 2013). However, zolazepam has proved insufficient to remove the unwanted side effects of the dissociative drug; muscle rigidity is common and seizure-like manifestations may be seen, so a specific combination, tiletamine-zolazepam and xylazine (TZX), has been widely used in dogs (Jang *et al.*, 2004).

Intravenous injection of TZ combination at lower dose decreases minute ventilation for one-minute post-injection, while higher dose decreases minute ventilation for at least ninety minutes. TZ combination IV without pre-anaesthetic medication may cause significant variation in breathing patterns (Savvas *et al.,* 2005). TZ contraindicated in acute heart or respiratory diseases, severe hypertension disorder, renal or hepatic dysfunction or other life-threatening conditions (Plumb, 2018).

An overview through the available literature revealed that TZ combination is now available for wildlife as well for dogs' anaesthesia in India. The present study was planned to assess anaesthetic efficacy as well as evaluate physiological and haemato-biochemical alterations following tiletamine and zolazepam induction with xylazine premedication without maintenance agent for MRI diagnostic anaesthesia in dogs.

MATERIALS AND METHODS

The present clinical study was conducted on six (n=6) (4 Male and 2 Female) canine patients presented for planned diagnostic MRI procedures for spinal cord compression, abnormalities in stifle or hip joints. Pre-anaesthetic physical examination in all patients included clinical anamnesis, baseline data including rectal temperature, respiratory rate, pulse rate, colour of mucous membrane and CRT.

Patient Preparation and Stabilization

To assess the fitness of canine patients for GA, physical status was determined as per American Society of Anesthesiologist (ASA) standards. The food and water access was ceased 12 hours before pre-anaesthetic drug administration in all patients to reduce risk of Gastro-Esophageal Reflux (GER) (Grubb *et al.,* 2020).

A 24-gauge IV catheter was placed in the cephalic or lateral saphenous vein for blood sampling, induction agent injection, fluid administration and emergency medication. A ceftriaxone tazobactam @ 15-25 mg/kg, and meloxicam @ 0.2 mg/kg were administered IV. Fluid disturbance was corrected prior to induction by Lactated Ringer solution IV (10 mL/kg/hr). Before undergoing to GA, a lateral radiograph of chest was taken to ensure normal physiology of heart and lung soft-tissues. These study excluded patients under ASA Categories 4 and 5 as well as respiratory compromised (brachycephalic) breed dogs. Patients' ears were plugged with tight cotton ball to prevent hearing impaired issues during MRI procedures.

Pre-anaesthetic Medications

The patients were premedicated with atropine sulphate @ 0.04 mg/kg, and xylazine hydrochloride @ 1.00 mg/kg, loaded in single syringe and administered intramuscularly. Patients were not disturbed for at least 10-15 minutes following xylazine injection.

Induction of Anaesthesia

At first, patients were induced with injectable anaesthetic combination of TZ, after 10-15 minutes of pre-anaesthetic administration. TZ combination @ 8 mg/kg, was injected slow intravenously over a period of 60 seconds. Induction time (seconds) and quality of anaesthetic induction was estimated as stated by Tamura *et al.* (2014). Following induction the shuttle system transported the dog to 3.0 TESLA MRI (Philips Ingenia) or 1.5 TESLA MRI scanner (Philips Achieva A). The strong magnetic field of 3.0 T-MRI was performed separately under the optimal operating conditions for each system (Kang *et al.,* 2017).

Monitoring of Anaesthesia

Canine patients were monitored continuously from the beginning of pre-anaesthetic medications, during anaesthesia throughout the recovery period (Fig. 1). As soon as the patient was sedated, with ensured regular breathing pattern and anaesthesic stage (III), it was transferred on the MRI table. Patients were remotely monitored during MRI procedures to assure an adequate level of anaesthesia as well as to prevent complications if any.

For appropriate maintenance of anaesthesia and recording various parameters in MRI studies, magnet-safe instruments are the indeed requirements. However, these MRI studies were conducted without the use of MRI-specific sophisticated types of equipment (Smith, 2015). Baseline physiological parameters, SpO_2 and rectal temperature, pulse rate, respiratory rate were determined outside the MRI system assembly at various time points, *viz.*, N minute (time before pre-anaesthetic administration), 0 minute (time of anaesthetic induction), 30, 60, 90, 120 minutes and recovery time (R).

Evaluation/ Assessment of Haemato-Biochemical Parameters

Before pre-anaesthetic administration and following recovery period, total 5 mL blood was collected aseptically from the cephalic/saphenous vein from all patients. For haematological estimations (Hb, PCV, TLC, TEC), 2 mL of blood was taken in sterile K_3EDTA vacutainer, and 3 mL of blood was taken in a sterile clot activator for serum biochemical estimations (TP, AST, ALT, creatinine, BUN and glucose).

Quality of Anaesthetic Recovery

All the canine patients were continuously observed for evaluation of quality of anaesthetic recovery, which was scored according to numerical system stated by Tamura *et al.* (2014). Other parameters such as duration of anaesthesia (from administration of TZ intravenously to first voluntary movement/ head raising), standing time (stand up unassisted), complete recovery time (CRT) (resuming regular unaided movement/ normal ambulation) were recorded. Patients

received Lactated Ringers solution (10 mL/kg, IV) at the time of recovery.

Statistical Analysis

SPSS 20.0 software was used for statistical analysis. The physiological parameters were analyzed using one way analysis of variance (ANOVA). A comparison of haemato-biochemical parameters, *i.e.* before anaesthesia and after recovery was made using the paired 't' test. The significance levels of $p<0.05$ indicated that the differences were statistically significant.

RESULTS AND DISCUSSION

Breeds like Golden Retriever, Labrador Retriever and German Shepherd were included in study. The male-female ratio was 4:2. Out of six canine patients, three patients were found to be in ASA category 1. Three patients had mild systemic disease were in ASA category 2. The canine patients covered had a mean age of 5.11±1.16 years with a range of 2.5 to 9 years. A variation in their body weights ranged from 24.00 to 33.00 kg with a mean body weight of 27.66±1.30 kg.

Pre-Anaesthetic Medication and Induction of Anaesthesia

Atropine sulphate administered as pre-anaesthetic prevented hypersalivation, vomition as well as bradycardia, which was satisfactorily achieved, even though two (2/6) patients had vomition as xylazine side effect. Xylazine developed adequate sedation for induction as it favours muscle relaxation as well as allows easy venous catheter placement with only light physical restraint. There were no other major complications observed after the pre-anaesthetic administrations. All patients induced with 8 mg/kg non-incremental TZ combination slow IV. None of the canine patients required an additional dose to maintain anaesthesia. Since the dogs were able to breathe normally, none of them were intubated.

A mean induction time was 32.16±4.38 seconds. Induction with TZ was very quick and smooth in all patients. Almost all reflexes were abolished in nearly all patients within a minute of induction, which provided an indirect assessment of induction and sedation quality. 83.33 (5/6) % patients had decreased salivation and sufficient muscle relaxation (induction score 4, very quick) and the rest 16.167 (1/6) % patient had quite smooth induction (score 3).

A slow intravenous administration of TZ combination developed transient post-induction apnoea. Even with slow intravenous injection all patients had mean transient PIA of 28.16±6.09 seconds. Paddleford and Harvey (1999) observed same results by using xylazine as effective pre-anaesthetic for induction of anaesthesia as it favours muscle relaxation. The positive chronotropic effects of tiletamine/zolazepam probably temporarily and partially counter-balance the bradycardic effect of xylazine (Kim *et al.,* 2007). Jang *et al.* (2002), Kilic and Unsaldi (2005) and Lemke (2007) also observed vomition as xylazine side effect.

Rapid induction observed in all patients might be due to analgesic effects of xylazine. When xylazine was combined with TZ resulted in adequate muscle relaxation. Hafez *et al.* (2017) and Karasu *et al.* (2018) also observed similar findings. The dogs were rapidly anaesthetized after IV injection of TZ and became laterally recumbent within 15 seconds without any signs of excitement (Won *et al.,* 2010). Post-induction apnoea (PIA) and respiratory depression was major adverse effect after quick intravenous infusion of TZ combination, which occurred shortly after induction and resolved within minutes. The similar results were reported by Savvas *et al.* (2005) and Hampton *et al.* (2019[b]) in dogs. Son *et al.* (2015) studied high-resolution fluorodeoxyglucose PET and MRI findings of a pituitary microtumor in a dog under TZ (8 mg/kg) induction IV following medetomidine premedication (20 µg/kg, IM), without any complication during maintenance of anaesthesia.

Monitoring of Anaesthesia

A significant increase ($p<0.05$) was observed within mean pulse rates from N minute (before pre-anaesthetic drug administration) to 0 minute (time of anaesthetic induction). Following 0 minutes, a gradual and significant declining trend was observed in the pulse rates with respect to 30, 60, 90, 120 minutes, and recovery time, which was within physiological limit up to the recovery period. At 120 minutes and recovery time, the pulse rates were however still higher from N minute value (Table 1). Instant increased pulse rate might be attributed to tiletamine's sympathomimetic activity and blockage 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 (Muir *et al.*. 2008; Pereira *et al.*, 2019). The tiletamine is known to maintain or increase cardiac output and vascular resistance and help to balance the depressive effects of other agents (Ko *et al*., 2007; Krimins *et al.,* 2012).

Table 1 Physiological parameters observed during anaesthesia in canine patients

Time monitored	Pulse rate/min	Respiratory rate/min	SpO_2 %	Rectal temperature °F
N minute	85.83±3.21[a]	37.83±2.86[b]	96.50±0.76	101.81±0.24
0 minute	134.67±5.28[d]	27.50±1.56[a]	95.83±0.87	101.71±0.22
30 minutes	120.50±5.34[c]	25.00±0.63[a]	97.83±0.47	101.51±0.22
60 minutes	117.00±5.20[c]	25.00±0.81[a]	97.33±0.42	101.26±0.20
90 minutes	113.33±1.54[c]	24.17±1.42[a]	98.17±0.60	101.06±0.11
120 minutes	103.19±0.81[b]	28.17±1.73[a]	97.00±0.68	101.06±0.16
R minutes	98.33±2.77[b]	38.00±2.58[b]	97.17±1.01	101.38±0.19

N minute = before pre-anaesthetic drug administration; 0 minute = time of anaesthetic induction; R minutes = Recovery Time, Means with different superscripts within column differ significantly ($p>0.05$).

Unlike pulse rate, a statistically significant ($p<0.05$) decrease was observed within mean respiratory rates at different time intervals till 120 minutes of anaesthesia. Initially the respiratory rate was considerably decreased from N minute to 0 minute and then RR was stable at lower level during maintenance of anaesthesia. The mean respiratory rate at recovery time was significantly improved and was at par with N minute value. The SpO_2 values were non-significant and relatively high throughout the maintenance and varied from 95.83 to 98.17%. Rectal temperature varied slightly during maintenance following pre-anaesthetic administration. At the time of recovery period minor increase in RT was observed (Table 1). Respiratory depression during maintenance was consistent with the findings of Hampton *et al.* (2019[b]). The anaesthetic protocols employed did not produce hypoxemia because oxygen saturation percentage of all patients remained within normal threshold limits throughout maintenance. The present findings corroborated well with the results reported by Lee *et al.* (2018) and Pereira *et al.* (2019) in dogs. The decrease in rectal temperature might be related to generalized sedation, a reduction in metabolic rate and muscle relaxation, as were observations of Lu *et al.* (2014) and Hampton *et al.* (2019[a]).

Among haemato-biochemical parameters, there were non-significant differences in values of Hb, PCV, TP, TLC, TEC, ALT, AST, creatinine and blood urea nitrogen, before pre-anaesthetic administration and after recovery, and the values were within physiological limit, except glucose level, which was observed significantly higher at the time of recovery as compared to time before pre-anaesthetic administration (Table 2).

Table 2 Haematological parameters at different time intervals in Anaesthetic protocol

Parameters/Period	Before Anaesthesia	After Recovery	Reference Range	*p* value
Haemoglobin (g/dL)	12.65±0.59	12.43±0.60	11.9-18.9	0.86
PCV (%)	38.31±1.96	37.81±1.74	35-57	0.13
TLC (10^3/µL)	12.06±1.53	11.95±1.50	5.0-14.1	0.37
TEC (10^6/µL)	6.11±0.25	6.08±0.31	4.95-7.87	0.57
TP (g/dL)	6.05±0.30	6.03±0.28	5.4-7.5	0.69
AST/SGOT (IU/L)	32.00±5.44	31.83±4.16	13-37	0.88
ALT/SGPT (IU/L)	36.83±2.00	37.33±1.81	10-109	0.41
Creatinine (mg/dL)	1.05±0.04	1.08±0.06	0.5-1.7	0.17
BUN (mg/dL)	22.33±3.50	24.16±2.13	8-28	0.49
Glucose (mg/dL)*	85.16±3.13	138.50±4.51	76-119	<0.00

*****p<0.05 between periods

The minor decrease in Hb and PCV during the period of anaesthesia or sedation observed might be attributed to the shifting of fluid from extravascular compartment to intravascular compartment in order to maintain normal cardiac output in the patients (Kilic, 2008). Telazol/Zoletil had no significant effect on the clinico-physiological parameters and also hemato-biochemical values of the dogs (Hafez *et al.*, 2017). The values for plasma glucose increased in patients might be due to hyperglycaemic effects of α_2-adrenoceptor agonists, which might be due to the result of α_2-adrenergic receptor inhibition of insulin release by the stimulation of α_2-adrenoreceptors in the pancreatic β cells and to an increased glucose production in the liver (Kilic, 2008). Xylazine can induce increase in plasma glucose secondary to decreased serum levels of insulin. There appears to be similar clinical importance connected with this result in non-diabetic animals (Plumb, 2018).

Recovery Quality

Quality of recovery was observed to be very smooth in 66.66 % of patients, *i.e.*, four out of six patients were able to recover uneventfully without any excitement, paddling or convulsions, whereas recovery was quite smooth with little excitement, some head movement and shivering in 33.33 (2/6) % of patients. Duration of anaesthesia, *i.e.*, induction to first voluntary movement was 122.66±3.08 minutes. The standing time and complete recovery time were longer 66.83±2.41 and 59.66±2.67, respectively.

Recovery was quite delayed in all patients as elimination of tiletamine took longer time in canines. The dogs were kept under constant scrutiny until they had fully recovered (approximately 2.5-3.0 hours). There were no indicators of pain or excitement during the recovery period, which was assessed as calm and peaceful. Despite a lack of coordination, the animal's recovery was marked by quietness, with no signs of pain or agitation, demonstrating the anaesthetic protocol's efficacy. The time between induction to recovery, no vomiting, myoclonic twitching reflexes, or other adverse reactions were detected. Patients' urine output was more after two hours of anaesthetic period.

Tiletamine has a longer duration of effect in canines than zolazepam. This implies that during recovery, patients might have rough recovery due to muscular stiffness, sympathetic activation, and acute delirium, which are side effects of dissociative anaesthetics, as suggested by Landry and Maza (2020). In dogs, with recovery time averaging approximately 4 hrs, the duration of the tiletamine effect is longer than that of zolazepam, so there is a shorter TZ duration of tranquilization (Plumb, 2018).

After surgery, the dogs were monitored periodically until awakened from TZ anaesthesia. They took approximately 8 hrs to fully recover (An *et al.*, 2015). Recovery was considered calm and peaceful, with no signs of pain or excitement. Although a certain lack of coordination was observed, the animal's recovery was characterized by stillness, with no signs of pain or excitement, confirming the effectiveness of the anesthetic . Following xylazine administration polyuria can be seen, probably as a result of decreased production of anti-diuretic hormone (vasopressin) (Plumb, 2018). Lin *et al.* (1993) observed Tiletamine at 4, 8 and 16 mg/kg dose rate to increase urine excretion for 2 hrs in water-loaded rats.

Fig 1 Following anaesthetic induction dog positioned for spinal cord MRI study

CONCLUSIONS

A combination of atropine sulphate and xylazine provides considerable antisialagogue effect, sedation and analgesia during pre-anaesthetic period. Tiletamine-zolazepam combination produces smooth induction when administered by slow intravenous injection and results in least side effects. Induction of balanced anaesthesia using atropine, xylazine, tiletamine-zolazepam combination as well as maintenance provides efficient nociception during MRI studies. This protocol can be used to perform non-surgical operations or transports when long-term anaesthesia is required.

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Conflict of Interest: None.

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