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Effect of Glycopyrrolate-xylazine Supplementation on Zoletil-induced Total Intramuscular Anaesthesia in Dogs

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ABSTRACT

Background: Zoletil has been used at different dose rates with or without preanaesthetics through intramuscular or intravenous routes in canine patients with varying results in other countries. The doses recommended by the manufacturer as well as researchers and the observations on various clinico-physiological and hemodynamic parameters are also highly variable. Keeping these points in mind, the present study was conducted to study anesthetic/sedative effects of intramuscular administration of Zoletil (20 mg/kg) and also to study the effect of glycopyrrolate (0.005 mg/kg)-xylazine (0.5 mg/kg) supplementation on Zoletil (10 mg/kg)-induced total intramuscular anesthesia in dogs.

Methods: Fourteen canine patients were divided into two groups, *viz*., A and B, with seven animals in each group.In group A, Zoletil (tiletamine-zolazepam) at the dose rate of 20 mg/kg body weight was administered intramuscularly as an anaesthetic. In group B, preanesthetic glycopyrrolate at 0.005 mg/kg body weight was administered intramuscularly. After 15 minutes, xylazine at 0.5 mg/kg body weight was administered intramuscularly. After 15 minutes of preanesthetic administration in the B group, anaesthesia was induced intramuscularly with tiletamine-zolazepam @ 10 mg/kg body weight.

Result: Zoletil (Tiletamine-zolazepam, 20 mg/kg IM) (group A) is only recommended for non-surgical/diagnostic (*viz*. Gastro-intestinal endoscopy)/minor surgical procedures in uncooperative dogs. An intramuscular anaesthetic protocol using glycopyrrolate (0.005 mg/kg)-xylazine (0.5 mg/kg) - Zoletil (10 mg/kg IM) (group B) is recommended for major surgical procedures of long duration. Neither the anaesthetic protocol produced any serious deleterious effect on hemato-biochemical and hemodynamic parameters; hence both protocols can be used safely in dogs as per the requirements of the procedure.

Key words: Dogs, Glycopyrrolate, Total intramuscular anaesthesia, Xylazine, Zoletil.

INTRODUCTION

Injectable anesthetic agents as well as inhalation agents are used for general anesthesia. However, intravenous (IV) administration of injectable agents or mask induction with inhalants is usually difficult and/or impossible in fractious, fearful or excited patients. Chamber induction with inhalant anesthetics might be useful in small veterinary patients, but it requires a massive container for large-breed dogs and is still associated with disadvantages, such as airway irritation and stress in patients during the induction phase and the waste gas pollution created. Thus, the agents that can be administered intramuscularly (IM) *viz*. Zoletil, are very useful for sedation or induction of general anesthesia and to perform surgery in order to reduce the stress of handling and the risk of injury to both the animal and the handler (Tamura *et al*., 2015).

Zoletil (Zoletil 50; Virbac, Carros, France) is a combination of equal parts (by weight of free base) of tiletamine hydrochloride, a cyclohexamineanaesthetic and zolazepam hydrochloride, a benzodiazepine tranquilizer. The combination has been widely used for preanesthetic medication, sedation, immobilization and general anaesthesia for diagnostic and minor surgical procedures in dogs, cats, ruminants, pigs and non-domestic animals (Pablo and Bailey, 1999).

An antimuscarinic drug, *e.g*., glycopyrrolate, may be used to control excessive salivation, which is commonly seen in animals receiving the tiletamine-zolazepam combination (Lin, 1996). Glycopyrrolate, a quaternary ammonium compound, does not readily cross the blood-brain barrier and is a more selective peripheral anticholinergic agent. It has been suggested that sinus tachycardia and ventricular arrhythmias are less likely to occur after glycopyrrolate than after atropine sulfate administration (Tranquilli *et al*., 1993). Xylazine, an α-2-adrenoreceptor agonist, produces reliable dose-dependent sedation, analgesia and muscle relaxation in several species, making it one of the most versatile anesthetic adjuncts. It has been combined with tiletamine/zolazepam to increase its anaesthetic and analgesic effects and to reduce the dose of tiletamine/zolazepam required to induce satisfactory anaesthesia (Kim *et al*., 2007).

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Zoletil has been used at different dose rates with or without preanaesthetics through intramuscular or intravenous routes in canine patients with varying results in other countries (Gomez-villamandos *et al*., 2013); however, very few studies have been published in Indian literature. The doses recommended by the manufacturer as well as researchers and the observations on various clinico-physiological and hemodynamic parameters are also highly variable (Ratnu *et al*., 2021). Keeping these points in mind, the present study was conducted to study anesthetic/ sedative effects of intramuscular administration of Zoletil (20 mg/kg) in dogs. And also to study the effect of glycopyrrolate (0.005 mg/kg)-xylazine (0.5 mg/kg) supplementation on Zoletil (10 mg/kg)-induced total intramuscular anesthesia in dogs.

MATERIALS AND METHODS

Animals

Fourteen adult mixed-breed clients owned dogs of either sex presented for the diagnosis and treatment of various surgical procedures were subject of this study. A written and signed consent was obtained from the owners of animals before conducting any surgical procedure. Food was withheld for 12 hours and water for 6 hours prior to the anesthetic trials/surgical procedure. Two anesthetic protocols were used in a randomized order to produce total intramuscular anesthesia in groups A and B, with seven animals in each group. In the animals of group A, Zoletil (50 mg/ml) was administered at a dose rate of 20mg/kg intramuscularly and the time of zoletil administration was considered to be 0 min. In group B, glycopyrrolate (0.005 mg/kg, IM) was followed 15 min later by xylazine (0.5 mg/kg, IM) as preanaesthetics and then zoletil was administered at the dose rate of 10 mg/kg (IM) 15 min after xylazine administration. Time of Zoletil administration was considered 0 min. The evaluation of these two anesthetic protocols were made on the basis of clinical, physiological, hematological and biochemical observations. The quality of anesthesia was assessed by quality of induction, analgesia, body reflexes, muscle relaxation, recovery and complications, if any.

Clinical observations

Quality of sedation

Sedation quality was evaluated on a scoring scale of 0 to 4, *viz*. 0 = Active, aware of the surrounding environment and minimal sedation; 1 = Mild to moderate sedation with reduced activity and animal not assuming sternal or lateral recumbency; 2 = Moderate sedation, mildly aware of the surrounding environment and animal in sternal recumbency; 3 = Profound sedation, eyes droopy, head down, inactive, assuming sternal or lateral recumbency, tight jaw tone and unable to be intubated; 4 = Rapid smooth induction of anaesthesia, no movement, rapidly assumes lateral recumbency with good muscle relaxation and loose jaw tone and easily intubated.

Quality of induction

The quality of intubation was evaluated on a scoring scale of 1 to 3, *viz*. 1 = Difficult intubation, tube could be retained, tight jaw tone accompanied by chewing motion and strong tongue withdrawal; 2 = Easy intubation with a slight coughing or swallowing reflex following intubation but no gagging reflex, relaxed jaw tone, no chewing motion and slight tongue withdrawal; 3 = Rapidly become anesthetized, good muscle relaxation and intubation easily achieved without coughing, gagging, or tongue withdrawal.

Quality of muscular relaxation

The quality of muscular relaxation was evaluated based on the degree of extensor rigidity, resistance of limbs to manipulation and muscle tone on a scoring scale of 1 to 3, *viz*. 1 (poor) = If the animal showed tremors, stiffness, a state of catalepsy, or intense movement; 2 (good) =When moderate maintenance of muscle tone was observed with the occurrence of discrete tremors; 3 (excellent) =Total muscle flaccidity was evident.

Quality of recovery

The quality of recovery from anaesthesia was evaluated on a scale of 1 to 4, *viz*.1 = Prolonged struggling, inability to stand without assistance, hyperkinesis in response to manual assistance and increased rectal temperature associated with increased struggling that results in increased metabolism; 2 = Some struggling, repeated attempts to stand, required assistance to stand, unstable while walking, unable to maintain balance and some signs of residual anaesthetic effects (*e.g*., muscle trembling, salivation, head shaking, vocalization, or defecation); 3 = Some struggling, requiring some assistance to stand, being able to maintain balance once standing and minimal signs of residual anaesthetic effects; 4 = Dog assumed sternal recumbency with little or no struggling, stood and walked with minimal effort and showed no signs of residual anaesthetic effects.

Quality of analgesia

The quality of analgesia was evaluated on a scoring scale 0-3 based on the status of pedal reflexes, *viz*., 0=No pain, excellent analgesia (No response to pedal reflex); 1=Mild pain (Weak response to pedal reflex); 2=Moderate pain (Occasional response to pedal reflex); 3=Severe pain, no analgesia (Strong response to pedal reflex).

Down time

The time (min) elapsed between administration of zoletil to the animals while they were in lateral recumbency was recorded as down time.

Induction time

The time elapsed (min) from the administration of zoletil to the abolition of the pedal reflex and acceptance to endotracheal intubation was recorded as the induction time.

Duration of anaesthesia

The time (min) elapsed from intubation to the first sign of recovery *i.e.*, spontaneous movement of any body parts or tongue flicking/rolling was recorded as the duration of anaesthesia.

Time to extubation/Recovery time

The time (min) elapsed from intubation to extubation was considered the time to extubation or recovery time.

Standing time

The time (min) elapsed from intubation to spontaneously assuming a standing position with weight bearing on all four limbs without assistance was recorded as standing time.

Reflexes

Status of corneal and pedal reflexes was recorded at 0, 15, 20, 30, 40, 50, 60, 70, 80, 90, 105, 120 minutes, or until the end of the observation period. It was graded on a 0 to 3 scale, *viz*., 0 = Absent reflex; 1 = Sluggish reflex; 2 = Moderate reflex; 3 = No change in reflexes.

Eye ball position

Eyeball position was recorded at 0, 15, 20, 30, 40, 50, 60, 70, 80, 90, 105 and 120 minutes, or until the end of the observation period. It was graded on a 0 to 3 scale, *viz*., 0 = Complete ventromedial rotation; 1 = Moderate rotation; 2 =Slight rotation; 3 = No rotation of the eyeball.

Physiological observations

The physiological status of the patients was assessed by recording, heart rate (HR) (beats/min), respiratory rate (RR) (breaths/min), rectal temperature (RT) (°F), mean arterial pressure (MAP) (mm Hg) and arterial hemoglobin oxygen saturation (SPO_2 %).These parameters were recorded by a non-invasive blood pressure monitor before administration of any drug as baseline values and then at 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 105 and 120-minute intervals or till the end of the observation period.

Statistical analysis

The descriptive statistics for various parameters under study across two groups were calculated. The values were represented in the form of Mean±SE for the continuous variables and frequency (percentage) for the categorical variable. Group-wise comparisons of various parameters were done using the independent t-test and chi-square test for independence when appropriate. An independent sample t test was performed to analyze the difference in parameters under study at different time intervals between the two groups. A repeated-measures ANOVA was performed to assess the variation between the time intervals within a group. Pairwise differences at different time intervals within a group was assessed using the LSD (Least Significant Difference) procedure. The results were considered statistically significant at $\alpha = 0.05$. All the statistical analysis was carried out using SPSS 20.0 (IBM Corp. 2011).

RESULTS AND DISCUSSION

Quality parameters

The mean±SE values of sedation quality, induction quality, muscular relaxation quality, recovery quality and analgesic quality scores in the animals of the A and B groups have been shown in Fig 1.

Sedation quality

Excellent sedation was observed in both groups, with mean±SE values of sedation quality of 4±0.0. Sedation quality was assessed by examining the patients' behavioral changes. All animals in both groups showed indications of excellent sedation, including CNS depression, reluctance to move, ataxia, impaired reaction to stimuli and lateral recumbency. Similar findings were recorded by Ratnu *et al.* (2021). Similar to the present study, Krimins *et al*. (2012) reported that Zoletil (TZ) in combination with other premedicant drugs made all dogs deeply sedated, lethargic and unable to walk.

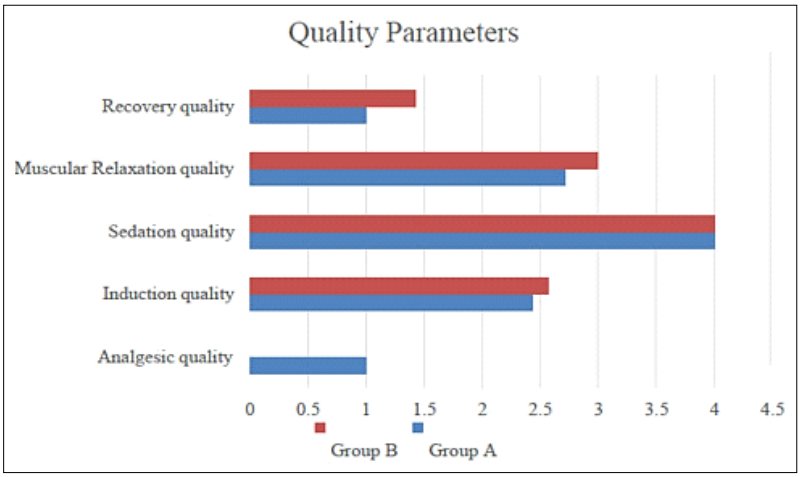

Fig 1: The mean±SE scores of sedation quality, induction quality, muscular relaxation quality, recovery quality and analgesia quality in the animals of the A and B groups.

Induction quality

The mean±SE values of induction quality recorded in the animals of groups A and B were 2.43±0.2 and 2.57±0.2, respectively. No significant difference was noted in the values of induction quality between the two groups, although induction quality was found to be better in group B than group A. In group A, most of the dogs showed coughing or a laryngeal reflex during intubation. Similar observations were also made by Cullen and Reynoldson (1997), who stated that the onset of tiletamine/zolazepam sedation was rapid, but the dogs also exhibited some undesirable effects, like excessive salivation, excitatory muscular activity and coughing, including head and neck rocking, which was not violent.

Recovery quality

The quality of recovery was better in group B than in group A, with mean±SE values of the quality of recovery scores of 1±0 and 1.43±0, in groups A and B, respectively. Recovery quality was found to be poorer in the animals of group A than that of group B. Similar findings have been recorded by Gomez-Villamandos *et al*. (2013), where alpha 2 agonist improved the quality of recovery induced by TZ. Kim *et al*. (2007) observed some undesirable effects like movement of the head and extremities, vocalization, muscle tremors and spasms, paddling of the forelimbs, tongue curling and excitation after intravenous and intramuscular administration of Zoletil (TZ) alone. In the present study also, when TZ was administered alone, some of these undesirable effects were observed, but xylazine at 0.5 mg/kg doses in most dogs in group B moderated these effects.

Analgesia quality

The mean±SE values of the scores of analgesia quality recorded in the animals of groups A and B were 1±0 and 0±0.00, respectively. It was found to be significantly better in group B, followed by group A. Pereira *et al*. (2019) also stated that TZ alone did not provide sufficient analgesia to block the response to the supramaximal noxious stimuli. They suggested that, to obtain satisfactory analgesia, supplementation of analgesic drugs and/or local blockades with the used protocol and/or an increased anesthetic maintenance dose should be considered.

Myorelaxation

In the present study, excellent muscle relaxation, as indicated by no resistance on extension and flexion of the limb, was observed upto a 40 minute observation period in animals of group B. The muscle relaxation and sedation provided by the alpha-2 agonist might have improved Zoletil (TZ)-induced muscle relaxation in terms of duration and quality, as also evidenced by Ko *et al*. (1998). Zoletil alone also produced very good muscle relaxation, which must be due to the central muscle relaxing properties of zolazepam. These observations are in accordance with the findings observed by Duzgun *et al*. (2004).

Duration parameters

Down time

The mean±SE values of the down time (min) recorded in the animals of groups A and B were 2.857±0.472 and 2.571±0.297, respectively (Fig 2). However, no significant ($P<0.05$) difference was observed statistically in the values of down time between A and B groups.

Lee *et al*. (2010) reported that Zoletil (Tiletamine-zolazepam) combinations were well absorbed via the intramuscular route and were associated with rapid induction and lateral recumbency. Zoletil (Tiletamine-zolazepam) in combination with other drugs resulted in a rapid onset of sedation and transition to general anesthesia following a single IM injection.

Induction time

The mean±SE values of the induction time (min) recorded in the animals of group A and B were 4.928± 0.455 and 4.571±0.528, respectively (Fig 2). However, no significant

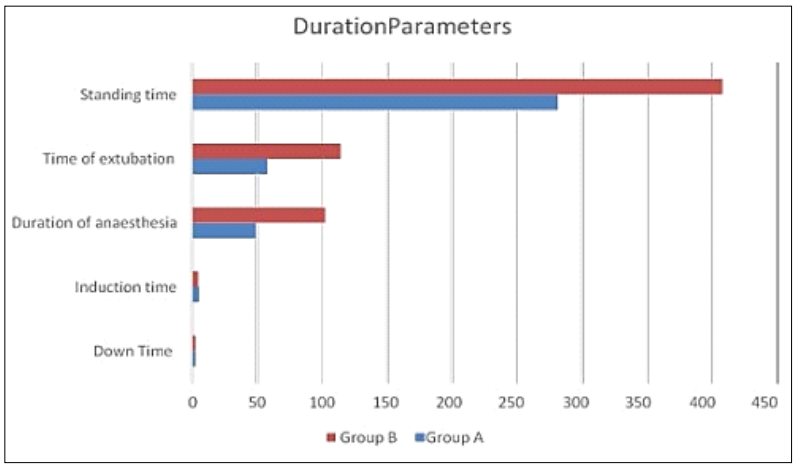

Fig 2: The mean±SE values of down time, induction time, duration of anaesthesia, extubation time and standing time in minutes in the animals of A and B groups.

(P<0.05) difference was observed statistically in the values of induction time between A and B groups. Similarly, Duzgun *et al.* (2004) reported that induction could be achieved within 3-6 min of intramuscular injection of Zoletil alone.

Duration of anaesthesia

The mean±SE values of the duration of anesthesia in the animals of the A and B groups were 49.142±5.165 and 102.428±17.632 min, respectively (Fig 2). It was found to be significantly higher in the animals of group B than that of group A. Lee *et al.* (2010) reported that the combination of TZ with an alpha-2 agonist increased the duration of anesthesia, increased duration of intubation tolerance and lateral recumbency (Ko *et al*., 2007), which is in agreement with the results of the present study.

Time of extubation/recovery time

The mean±SE values of time (min) of extubation in the animals of the A and B groups were 57.857±5.22 and114.428±18.898, respectively (Fig 2). Which was significantly (P<0.05) higher in group B than group A. Hafez *et al*. (2017) reported that dogs treated with tiletamine-zolazepam exhibited a prolonged recovery period in almost all cases due to the longer half-life of tiletamine. The animals of group B took almost double the time to be extubated, when compared to those of group A, this might be due to the combined effects of alpha-2 agonist and TZ when used in combination.

Standing time

The mean±SE values of standing time in the animals of the A and B groups were 281.285±23.625 and 407.714±36.657 min, respectively (Fig 2). Comparison revealed that the time taken by the animals of group B to stand up was significantly (P<0.05) higher than that of group A. Relatively higher standing times in group B might be due to the combined effects of alpha-2 agonist when used with TZ.

Physiological parameters

Heart rates

The heart rate showed a highly significant increase (P<0.05) at 5 min in the animals of both groups, then remained at a non-significantly higher level (P>0.05) up to 30 min, followed by a non-significant (P>0.05) decrease in the end that gradually returned toward baseline (Fig 3). Similar to the results of the present study, Hampton *et al*. (2019) found an increased heart rate after induction of anesthesia. The greatest and most significant change in heart rate was observed after administration of tiletamine-zolazepam (94.9%). The elevation in heart rate observed after induction with dissociative agents was attributed to an increase in sympathetic nervous system outflow and inhibition of norepinephrine reuptake, which caused an increase in circulating catecholamine concentrations and stimulation of the sinus node (Hafez *et al*., 2017). Lower values of heart rate obtained in the animals of group B in the present study might be due to the cardiosuppressive effect of xylazine used in this group.

Respiratory rate

In group A, respiratory rate increased non-significantly (P>0.05) from 20 min to 30 min, followed by non-significant (P>0.05) fluctuation throughout the observation period, while in group B a significant (P<0.05) reduction in respiratory rate was seen at the 10-min time interval, followed by a significant (P<0.05) increase in respiratory rate upto the 105 min interval (Fig 4). A decrease in respiratory rate after TZ administration has also been observed by Krimins *et al*. (2012). Similar to the results of the present study use of an alpha-2 agonist with Zoletil (TZ) resulted in tachypnoea and hypoxemia and caused mild to moderate respiratory depression characterized by an apneustic pattern of ventilation (Lee *et al*., 2010).

Rectal temperature

A non-significant (P>0.05) fall in rectal temperature was recorded in groups A and B after 5 min, which continued up

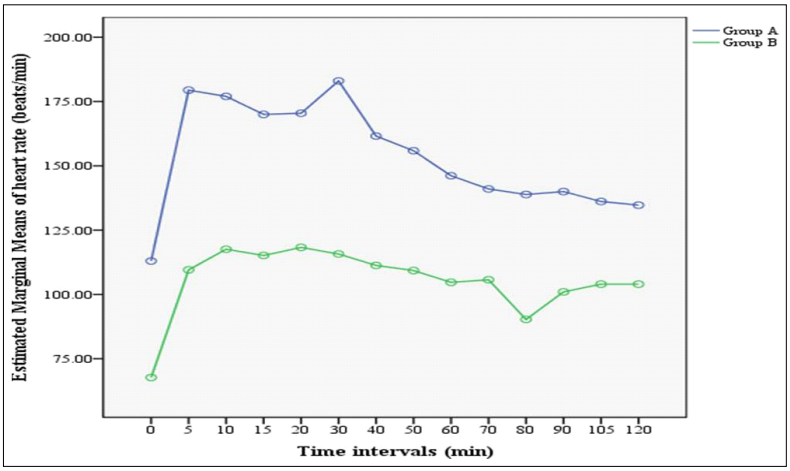

Fig 3: The mean±SE values of the heart rate (beats/min) at different time intervals in the animals of A and B groups.

to 120 min. Similar observations have been recorded previously in dogs following administration of TZ alone or in combination with an alpha-2 agonist due to generalized sedation, decreased metabolic rate, muscle relaxation and CNS depression (Koli *et al*., 2021).

Saturation of peripheral oxygen (SPO_2)

In both groups A and B, the SPO_2 decreased from the base-line values at the 5-min interval, followed by a non-significant increase or decrease ($p>0.05$) at different time intervals followed by a non-significant increase ($P>0.05$) until the end of the observation period. The comparison between the two groups revealed significantly ($P<0.05$) higher SPO_2 values in group A than in Group B initially upto the 40-min time interval, followed by a non-significant difference ($P>0.05$) at the rest of the time intervals. Similar to the present study, Savvas *et al*. (2005) reported that severe hypoxaemia developed within two minutes of TZ administration but started to resolve within 10 minutes. However, no dog became cyanotic during the hypoxaemic period.

Haemodynamic parameters

Mean arterial pressure

In the animals of both groups, the values of MAP fluctuated non-significantly throughout the observation period and remained within the normal physiological limits (Fig 5). When xylazine was combined with TZ, it resulted in an increase in MAP for about 5-10 min and then fell below baseline in dogs (Lu *et al*., 2014), which could partially explain the changes in MAP seen in group B.

Clinical parameters

Status of jaw tone

The jaw tone remained completely abolished from 0 to 40 min in group B and in group A, it was sluggish between the 0 and 40 min time intervals. The comparison between the groups revealed highly significant ($P<0.01$) lower values of the jaw tone scores from 5 to 60 min and significantly lower values from 70 to 105 min in group B than in group A (Fig 6). A higher degree of muscular relaxation in animals of group

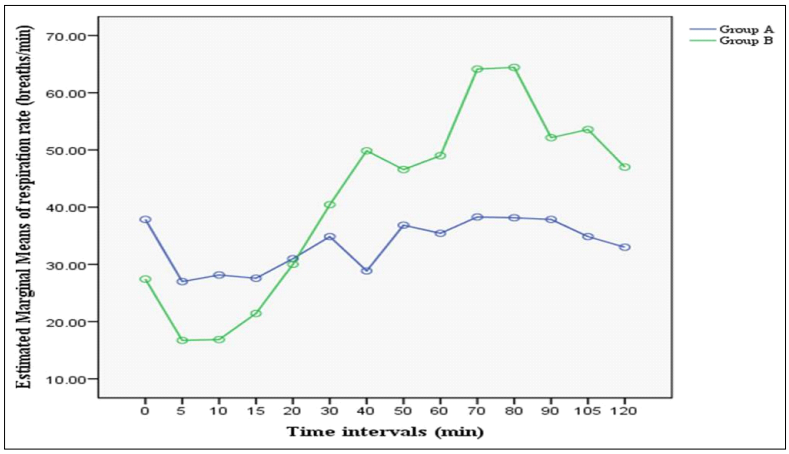

Fig 4: The mean±SE values of the respiratory rate (breaths/min) at different time intervals in the animals of A and B groups.

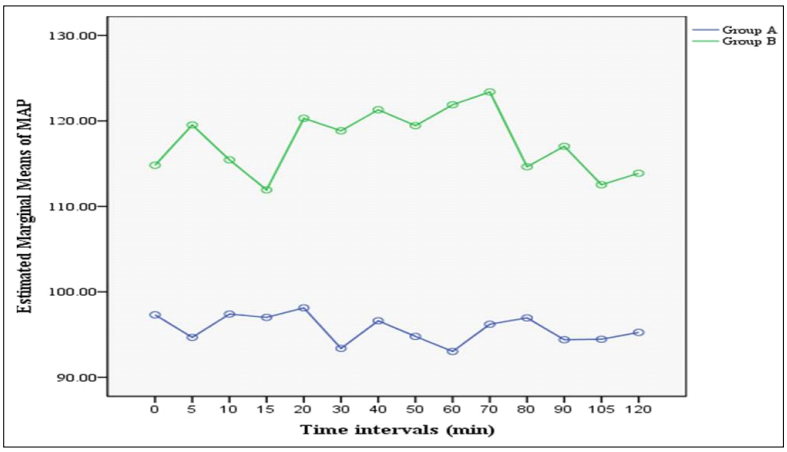

Fig 5: The mean±SE values of the mean arterial pressure (mmHg) at different time intervals in the animals of A and B groups.

B might be due to supplementation with xylazine during Zoletil-induced anaesthesia. At the level of the central nervous system, all alpha-2 agonists, including xylazine, are known to elicit excellent muscle relaxation by inhibiting intraneuronal transmission of impulses (Lemke, 2007). In the animals of group A, jaw tone remained sluggish throughout the observation period even after induction with TZ. It might be due to the cataleptic effects of the drugs on jaw tone.

Pedal reflex

The pedal reflex was completely abolished from 0 to 40 min in the animals of group B, whereas in group A the pedal reflex remained intact on a deep pain stimulus for a period of 0 to 40 min. The comparison between the groups revealed that pedal reflex scores were highly significantly ($P<0.01$) higher in group A than in group B throughout the observation period (Fig 7). Completely abolished pedal reflex in the animals of group B indicates that the surgical plane of anesthesia had been attained with the combined effect of xylazine and TZ. Similar to the observations of the present study, Kwon *et al*. (2003) reported that a deep pedal reflex was shown by all dogs in the control group 10 min after administration of TZ. Similarly, Pablo and Bailey (1999) also stated that the pedal reflex was maintained after administration of TZ alone.

Corneal reflex

When comparison was made, depression of the corneal reflex was found significantly higher in the animals of group B than that of group A (Fig 8). The corneal reflex is present in most instances when Zoletil is administered alone (Hampton *et al*., 2019). In group B, a higher depression of the corneal reflex must be due to the combined effect of xylazine and zoletil used in this group (Sodagar *et al*., 2021).

Eye ball position

In the animals of group A, the eyeball rotated ventromedially to a non significant degree at 5 min, remained so throughout the observation period and finally returned to baseline status gradually at 120 min, while in group B, a significant ($P<0.05$) degree of rotation was observed at 5 min, which continued

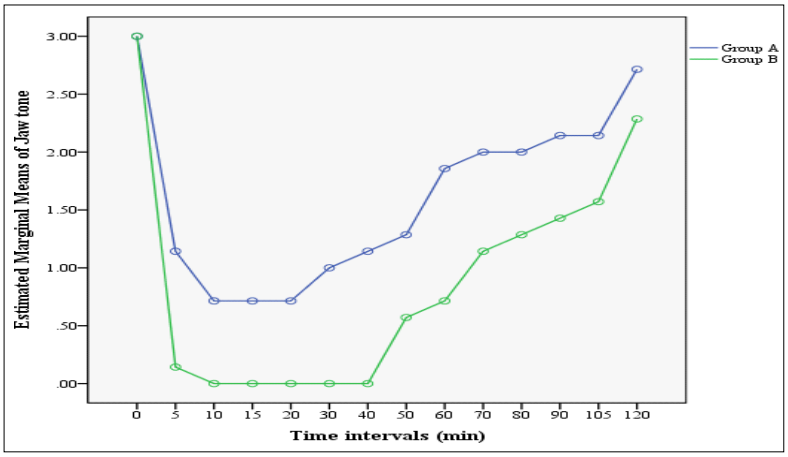

Fig 6: The mean±SE scores of the jaw tone status at different time intervals in the animals of different group.

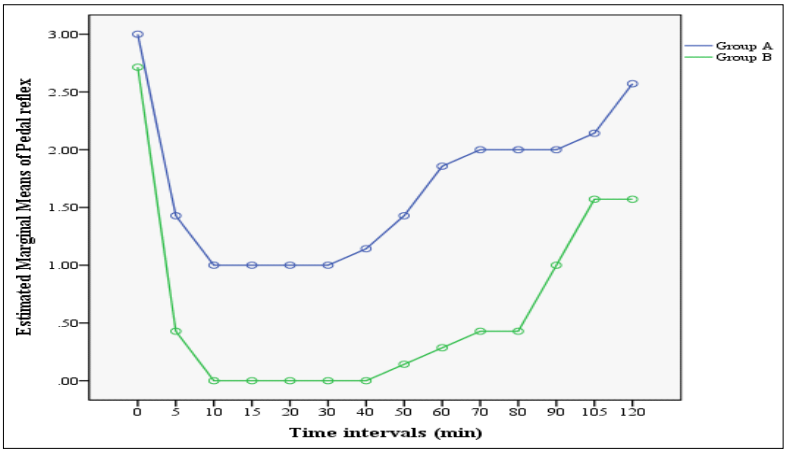

Fig 7: The mean±SE scores of the pedal reflex at different time intervals in the animals of A and B groups.

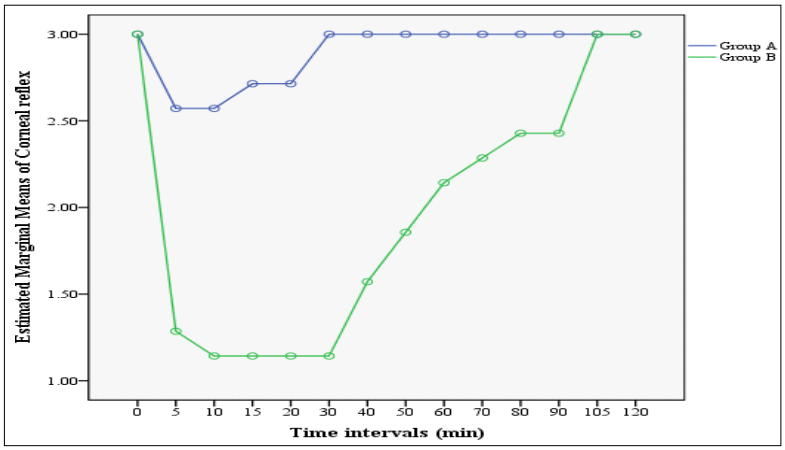

Fig 8: The mean±SE scores of the corneal reflex at different time intervals in the animals of A and B groups.

so up to 50 min, followed by a non-significant (P>0.05) rotation till the end of the observation period. A comparison between A and B groups revealed that the rotation of the eyeball was non-significantly higher in the animals of group B than that of group A. In group B, a higher degree of rotation of the eyeball might be due to the combined effect of zolazepam and xylazine as muscle relaxants.

CONCLUSION

It is concluded from the study that Zoletil (Tiletamine-zolazepam) (20 mg/kg IM) (group A) is only recommended for non-surgical/diagnostic (*viz.*, Gastro-intestinal endoscopy)/minor surgical procedures in uncooperative dogs. An intramuscular anesthetic protocol using glycopyrrolate (0.005 mg/kg)-xylazine (0.5 mg/kg)-Zoletil (tiletamine-zolazepam) (10 mg/kg) (group B) is recommended for major surgical procedures of long duration. Neither the anaesthetic protocol produced any serious deleterious effect on hemato-biochemical and hemodynamic parameters; hence it can be used safely in dogs as per the requirements of the procedure.

Conflict of interest

The authors do not declare any conflict of interest for the research presented in this article.

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