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Comparative evaluation of zoletil and propofol induction in glycopyrrolate-xylazine-butorphanol premedicated dogs under isoflurane maintenance anaesthesia

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The aim of this study was to evaluate two anaesthetic protocols in mixed-breed canine patients. Twelve dogs were randomly allocated into two groups, A and B, with six animals in each group. In group A, glycopyrrolate (0.005 mg/kg body weight, i.m.) was administered first, followed 15 min later by xylazine (0.5 mg/kg, i.m.) and butorphanol (0.2 mg/kg, i.m.). After an additional 15 min, propofol (1%, i.v.) was administered to effect, and anaesthesia was maintained with isoflurane. The time of glycopyrrolate administration was considered as 0 min of the observation period. In group B, the same premedication protocol (glycopyrrolate, xylazine, and butorphanol at identical doses and intervals) was followed. After 15 min, Zoletil® 100 was administered intravenously to effect, and anaesthesia was subsequently maintained with isoflurane.

Overall, the anaesthetic protocol used in group A (glycopyrrolate–xylazine–butorphanol–propofol–isoflurane) was found to be superior to that used in group B (glycopyrrolate–xylazine–butorphanol–Zoletil–isoflurane) with respect to induction quality, recovery quality, analgesic efficacy, and the dose-sparing effect on the maintenance agent. However, the group A protocol was associated with a comparatively prolonged recovery period.

Key words: *Butorphanol, Dog, Glycopyrrolate, Isoflurane, Propfol, Xylazine, Zoletil*

Balanced anaesthesia is a method of giving multiple anaesthetic drugs to animals to achieve the desired level of sedation, analgesia, and muscle relaxation while minimizing the side effects of each drug. Numerous medical and surgical procedures might be facilitated by the creation of a drug or drug combination approach that is safe, efficient, and possibly reversible short-term anesthetic and post-recovery analgesia in dogs.

Glycopyrrolate is associated with a lower likelihood of tachycardia and ventricular arrhythmias compared to atropine sulphate. Xylazine, an α, -adrenoceptor agonist, produces reliable, dose-dependent sedation, analgesia, and muscle relaxation in several species, making it one of the most versatile anaesthetic adjuncts. It has been combined with tiletamine–zolazepam to enhance anaesthetic and analgesic effects while reducing the required dose of tiletamine–zolazepam for satisfactory anaesthesia (Kim *et al*., 2007).

Zoletil® 100 is a combination of tiletamine and zolazepam. Tiletamine provides a greater analgesic effect and higher potency than ketamine (Kwon *et al*., 2003). Zolazepam, a benzodiazepine derivative, induces amnesia, exerts minimal effects on cardiorespiratory function, and demonstrates strong anticonvulsant activity with a wide safety margin at higher doses. When combined with tiletamine, zolazepam enhances the central nervous system effects of tiletamine and minimizes skeletal muscle hyperactivity (Kwon *et al*., 2003; Lee *et al*., 2018). Zoletil has been used at varying dose rates, with or without preanaesthetic medication, via intramuscular or intravenous routes in canine patients, yielding diverse results in different countries (Gomez-Villamandos *et al*., 2013). However, very few studies have been reported in Indian literature. Both the manufacturer-recommended and experimentally used doses, as well as the resulting clinico-physiological and haemodynamic observations, show considerable variation (Ratnu *et al*., 2021).

Considering these factors, the present study was undertaken to evaluate the efficacy of Zoletil and propofol as induction agents in dogs premedicated with glycopyrrolate–xylazine–butorphanol and maintained under isoflurane anaesthesia, using clinical, physiological, haemodynamic, and haematobiochemical parameters as evaluative criteria.

Materials and Methods

Animals

Twelve adult, client-owned mixed-breed dogs presented for various surgical affections were included in the study. Written informed consent was obtained from the owners prior to all diagnostic and surgical procedures. Food and water were withheld for 12 hr and 6 hr, respectively, before anaesthesia. The animals were randomly divided into two groups, A and B, each comprising six dogs (Table 1). Two anaesthetic protocols were evaluated in a randomized design. In both groups, glycopyrrolate (0.005 mg/kg body

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Table 1: Signalment of the animals used in the two groups.

Sl.No.	Sex	Breed	Age(yr)	Weight(kg)	Purpose of anaesthesia	Group
1	Male	German Shepherd	10	43.30	Removal of tumour growth from tail	A
2	Female	German Shepherd	1	17.50	Intramedullary pinning	A
3	Female	Labrador	10	23.70	Mammectomy	A
4	Male	Doberman	1	17.50	Intramedullary pinning	A
5	Male	Non-descript	0.5	15.30	Enucleation of eye ball	A
6	Female	Pitbull	4	20	Intramedullary pinning	A
7	Female	Labrador	9	22	Removal of lipoma	B
8	Female	Rottweiler	8.5	37.50	Mammectomy	B
9	Male	Golden Retriever	5	33	Intramedullary pinning	B
10	Female	Rottweiler	3	24	Surgical correction of cherry eye	B
11	Female	Beagle	0.3	11.20	Surgical correction of cherry eye	B
12	Female	Dachshund	14	8	Surgical correction of cherry eye	B

weight, i.m.) was administered initially as a preanaesthetic. After 15 min, xylazine (0.5 mg/kg, i.m.) and butorphanol (0.2 mg/kg, i.m.) were administered together in the same syringe. Following another 15 min, anaesthesia was induced with Zoletil® 100 (i.v., to effect) in group A, and with propofol (1%, i.v., to effect) in group B. Anaesthesia was maintained with isoflurane in 100% oxygen in both groups. The time of glycopyrrolate administration was designated as 0 min of the observation period.

Clinical observations

Sedation quality was scored on a scale of 0 to 4; where 0 - active, aware of the surrounding environment and minimal sedation, 1 - mild to moderate sedation with reduced activity and animal not assumed 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, assumed sternal or lateral recumbency, tight jaw tone, and unable to be intubated, 4 - rapid smooth induction of anaesthesia, no movement, rapidly assumed lateral recumbency with good muscle relaxation and loose jaw tone and easily intubated.

Quality of induction was scored on a scale of 1 to 3; where 1 - difficult intubation, tube could not be retained, tight jaw tone accompanied by chewing motion, and strong tongue withdrawal, 2 - easy intubation with slight coughing or swallowing reflex following intubation but no gagging reflex, relaxed jaw tone, no chewing motions, and slight tongue withdrawal, 3 - rapidly anaesthetized, good muscle relaxation, and intubation easily achieved without coughing, gagging, or tongue withdrawal.

Muscle relaxation was evaluated based on degree of extensor rigidity, resistance of limbs to manipulation and muscle tone on a score scale of 1 to 3; 1 (poor) - if animal showed tremors, stiffness, state of catalepsy or intense movement, 2 (good) - when moderate maintenance of muscle tone was observed with occurrence of discrete tremors, and 3 (excellent) - total muscle flaccidity was evident.

Recovery from anaesthesia was scored on a scale of 1 to 4 as; 1 - prolonged struggling, unable to stand without assistance, hyperkinesis in response to manual assistance, 2 - some struggling, repeated attempts to stand, requires 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, required some assistance to stand, able to maintain balance once standing, and minimal signs of residual anaesthetic effects, 4 - dog assumed sternal recumbency with little or minimal struggling, stands and walks with minimal effort, and no signs of residual anaesthetic effects. The quality of analgesia was assessed by scoring the pedal reflex. It was done by observing the withdrawal to the digital clamping/pinching reflex of the inter-digital skin of either hind limb. It was scored on scale of 0-3; 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), and 3 - severe pain, no analgesia (strong response to pedal reflex).

Time elapsed (min) from administration of xylazine-butorphanol combination to assuming lateral/sternal recumbency was recorded as down time. Time elapsed (min) from the administration of Zoletil in group A and propofol in group B to the abolition of pedal reflex and acceptance to endotracheal tube was recorded as induction time. Time elapsed (min) from intubation to first spontaneous movement of any body parts or tongue flicking/rolling was recorded as duration of anaesthesia. Time (min) elapsed from intubation to the point when swallowing reflex reappeared and extubation of endotracheal tube done was considered as time to extubation/recovery time. Time elapsed

(min) from extubation to regaining the standing position with weight bearing on all four limbs without assistance was recorded as standing time.

The status of palpebral, corneal, and pedal reflexes was recorded at –30, –15, 0, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, and 120 min, or until the end of the observation period. Reflexes were graded on a 0–3 scale: 0 – absent, 1 – sluggish, 2 – moderate, 3 – normal.

Jaw tone and eyeball position were also recorded at the same time intervals. Jaw tone was graded on a 0–3 scale: 0 – absent, 1 – sluggish, 2 – moderate, 3 – normal. Eyeball position was graded on a 0–3 scale: 0 – complete ventromedial rotation, 1 – moderate rotation, 2 – slight rotation, 3 – no rotation.

Physiological observations

The physiological status of the patients was evaluated by recording heart rate (HR; beats/min), respiratory rate (RR; breaths/min), rectal temperature (RT; °F), mean arterial pressure (MAP; mmHg), arterial haemoglobin oxygen saturation (SpO, ; %), and pulse rate (beats/min). These parameters were measured using a non-invasive blood pressure monitor and pulse oximeter before administration of any drug and immediately after administration of glycopyrrolate at 0 minute (baseline). Subsequent recordings were taken at –30, –15, 0, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, and 120 minutes, or until the end of the observation period.

Haematological and biochemical observations

About 2 mL of venous blood was collected in EDTA-coated tubes at 0, 30, 60, and 120 min. The samples were used for the estimation of haemoglobin concentration (g/dL) using Sahli's haemoglobinometer and packed cell volume (PCV; %) by the haematocrit method. Plasma was separated from the EDTA-treated blood samples by centrifugation, and blood urea nitrogen (mg/dL), creatinine (mg/dL), and glucose (mg/dL) levels were estimated using an automated biochemical analyzer (Mindray BC-30 Vet).

Statistical analysis

Descriptive statistics for all parameters were calculated separately for each group, and the values were expressed as mean±SE. Analysis of variance (ANOVA) was performed to determine significant differences between the groups. Post hoc comparisons were made using Duncan's multiple range test (DMRT) to evaluate pairwise differences. Parameters measured over different time intervals were analyzed using paired t-tests, with mean differences at each interval compared to the corresponding values at 0 min. Visual representation of the data was presented in the form of bar and line diagrams. Results were considered statistically significant at P d" 0.05 and highly significant at P d" 0.01. The same parameters evaluated within each group over time were also analyzed using repeated measures ANOVA.

Results and Discussion

Clinical parameters

In group A, the dose rate of zoletil varied between 2.9 mg/kg and 5.7 mg/kg (Mean±SE, 4.11±0.56) and anaesthesia was maintained with isoflurane at 1% to 2.5% concentration. In group B, propofol dose rate varied from 1.3 mg/kg to 3.5 mg/kg (Mean±SE, 2.23±1.2) and anaesthesia was maintained with isoflurane at 2.0-4.5%. Comparison between A and B groups revealed that the maintenance dose of anaesthesia was higher in group B than group A (Fig. 1).

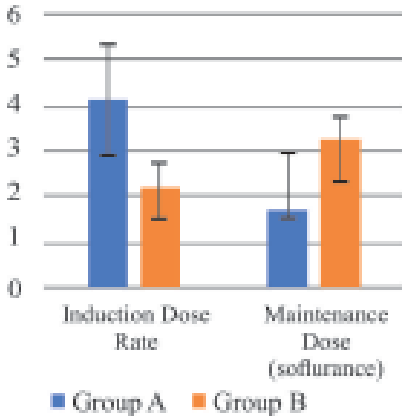

Fig.1: Mean±SE values of the induction and maintenance dose rate of anaesthesia in animals of both groups.

Palpebral reflex was completely abolished from 40 min to 60 min in group A. Jena *et al.* (2014) also reported decrease in the scores of palpebral reflexes after the administration of xylazine and other anaesthetic agents. In group B, the palpebral reflex was completely abolished from 40 min to 80 min. Comparison between the two groups revealed no significant (P>0.05) difference in the status of the palpebral reflex at any time interval of the observation period.

Corneal reflex remained completely abolished from 40 min to 60 min in group A; but in group B, the corneal reflex completely abolished at 40 min and remained so up to 80 min. Similar to the present study, Jena *et al.* (2014) also observed that corneal reflex scores fell non-significantly (P>0.05) from 10 to 60 min in dogs administered with xylazine (0.5 mg/kg, i.v.).

The pedal reflex completely abolished at 40 min and remained so up to 60 min in group A; but in group B, pedal reflex completely abolished at 40 min and remained so up to 80 min. The pedal reflex was completely abolished after induction of anaesthesia in animals of group A indicating that the surgical level of anaesthesia was attained as a combined effect of xylazine and zoletil and resulted in an abolished pain reflex and good quality analgesia. Koli *et al.* (2021) also observed similar results.

The myorelaxation scores remained significantly (P<0.05) higher in animals of group A than in group B

at 0, 5 and 15 min intervals. Myorelaxation scores remained the same in both groups from 40 min to 120 min intervals. Excellent muscles relaxation was indicated by no resistance on extension and flexion of the limb at 20 min interval in animals of group A. The muscle relaxation and sedation provided by alpha-2 agonists might have improved the zoletil (TZ) induced muscle relaxation in terms of duration and quality, as also evidenced by Ko *et al.* (1998).

Excellent muscle relaxation was indicated by no resistance to the opening of jaws from 40 min to 80 min in animals of both groups. At the level of the CNS, all alpha-2 agonists, including xylazine, are known to elicit excellent muscle relaxation by inhibiting intraneuronal transmission of impulses (Lemke, 2007). Similarly, myorelaxation has been found adequate in all the animals after xylazine and tiletamine-zolazepam administration by other researchers (Ratnu *et al.*, 2021; Koli *et al.*, 2021). In group B, a higher degree of rotation of the eyeball was recorded, which might be due to the combined effect of zolazepam and xylazine as muscle relaxants.

Physiological parameters

Comparison between group A and B revealed no significant (P>0.05) difference in the values of heart rate (HR) at any time interval. This indicated dose dependent cardiovascular depression associated with xylazine, propofol and isoflurane. Anticholinergics cause an increase in the HR (Jacobson *et al.*, 1994; Shinde *et al.*, 2018; Saikia *et al.*, 2019). Similar to the present study in the zoletil and propofol groups, a gradual decrease in HR was observed after an initial increase due to the depressant action of propofol on the cardiovascular system (Brussel, 1989; Amengual *et al.*, 2013; Thejasree *et al.*, 2018; Shinde *et al.*, 2018).

The respiratory rate (RR) was significantly higher (P<0.05) in animals of group B than in group A at 20 and 60 min intervals (Fig. 2). In group A, bradypnoea was observed for 2-8 min and also the change in breathing pattern after administration of zoletil. Similar to the present study, a decrease in RR after TZ administration has also been observed by Krimins *et al.* (2012). In group B, bradypnoea was observed only for 20 to 30 min after the administration of propofol. Sahinovic *et al.* (2018) also reported propofol as a potent ventilatory depressant.

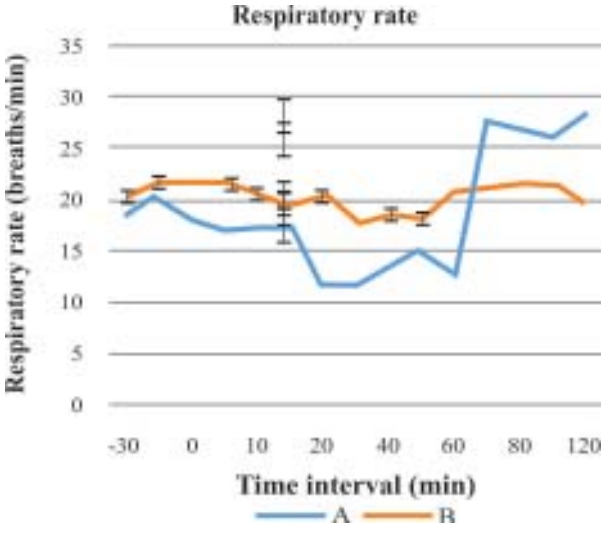

Fig. 2: Mean±SE values of the respiratory rate (breaths/min) at different time intervals in the animals group A and B.

Comparison between groups A and B showed that the rectal temperature (RT) was significantly (P<0.05) higher in group B than in group A between 0 min and 10 min intervals, and significantly higher (P< 0.01) in group B than group A between 15 and 30 min intervals (Fig. 3). In animals of group A, the RT slightly decreased after administration of zoletil. Similar observations have been recorded previously in dogs following administration of TZ alone or in combination with alpha-2 agonists due to generalized sedation, decreased metabolic rate, muscle relaxation and CNS depression (Kwon *et al.*, 2003; Lu *et al.*, 2014; Pereira *et al.*, 2019; Koli *et al.*, 2021).

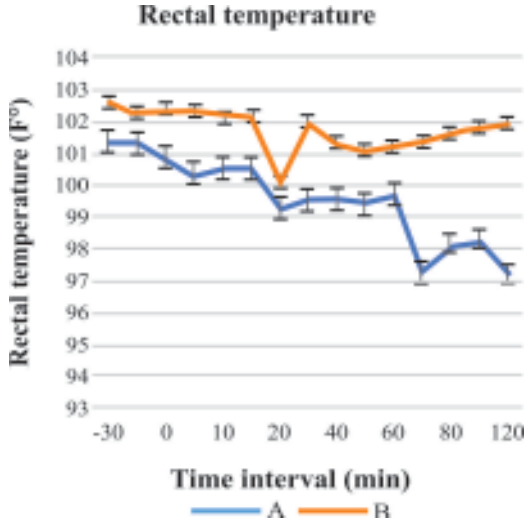

Fig. 3: Mean±SE values of the rectal temperature (F°) at different time intervals in the animals of A and B groups.

Group A pulse rate slightly increased and then decreased after administration of zoletil. Similarly, Kwon *et al.* (2003) correlated the cardiopulmonary and anaesthetic effects of tiletamine-zolazepam (10 mg/kg, i.v.) (TZ), xylazine (1.1 mg/kg, i.m.)-tiletamine-zolazepam (10 mg/kg, i.v.) (XTZ), and medetomidine (30 µg/kg, i.m.)-tiletamine-zolazepam (10 mg/kg, i.v.) (MTZ) in 15 healthy adult mixed breed dogs of either sex.

Haemodynamic parameters

Comparison between the groups A and B revealed no significant (P>0.05) difference in the values of mean arterial pressure (MAP) at any time interval. In group A, MAP decreased non significantly after the administration of zoletil. Similarly, Pereira *et al.* (2019) evaluated the anaesthetic quality and cardiovascular and respiratory effects of continuous intravenous infusion of tiletamine-zolazepam in dogs and found

an increase in HR at 5, 10, 40, and 50 min. Possibly, the increase observed after administration of the zoletil was due to the sympathomimetic action of tiletamine, which increases HR, a characteristic common to dissociative agents.

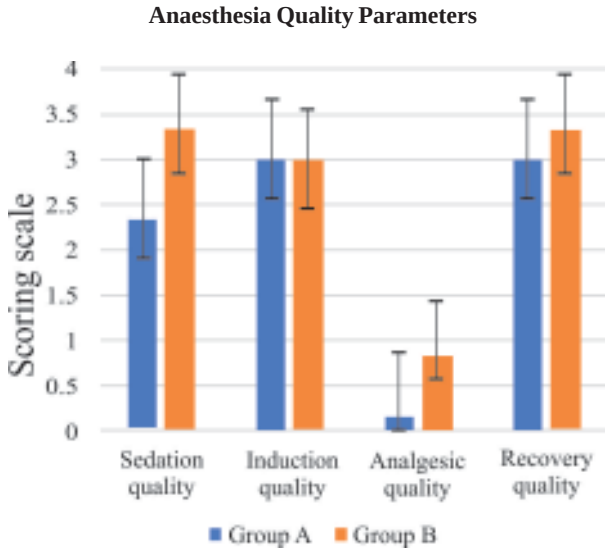

Fig. 4: Mean±SE scores of sedation quality, induction quality, recovery quality, and analgesia quality in the animals of A and B groups.

Animals of A and B groups revealed no significant (P>0.05) difference in SPO2 level at any time interval of the observation period. In both groups, SOP2 showed similar trend after administration of zoletil and propofol**.**

Anaesthesia quality parameters

In group A, moderate sedation was observed (Mean±SE; 2.33±0.49) (Fig. 4). While in animals of group B, slightly better sedation was observed (Mean±SE; 3.33±0.33). Sedation drugs were same in both groups but the results were different, it may be varied due to various factors like age, sex and temperament etc. although comparison between A and B groups revealed no significant (P>0.05) difference in the sedation quality.

Animals in both groups exhibited a rapid and smooth induction (induction score: Mean±SE; 3±0). A comparison between Groups A and B revealed no significant difference (P > 0.05) in induction quality. These findings are consistent with those of Amengual *et al.* (2013), who reported that propofol at similar dosages produced a rapid induction facilitating easy endotracheal intubation in dogs.

In group A, excellent analgesia was observed (Mean±SE: 0.17±0.17), whereas animals in group B exhibited mild pain, reflected by a weak pedal reflex response (Mean±SE: 0.83±0.54). A comparison between the two groups revealed no significant difference in analgesia quality (P > 0.05). The findings of the present study align with those of Ko *et al*. (2007), who reported that the combination of an alpha-2 agonist with TZ enhances both the quality and duration of analgesia. The superior analgesia noted in group A may be attributed to xylazine's central alpha-2 receptor stimulation, which provides more effective analgesia (Hsu, 1985).

In group A, animals demonstrated a Level 4 recovery quality, characterized by assuming sternal recumbency with minimal or no struggling and standing or walking with little effort (Mean±SE: 3±0.26). In contrast, animals in group B exhibited a Level 3 recovery quality, marked by noticeable struggling, the need for some assistance to stand, and the ability to maintain balance once standing (Mean±SE: 3.33±0.21).

Anaesthesia duration parameters

The Mean±SE downtime (min) recorded in Groups A and B was 7±0.52 and 6.67±0.44, respectively. However, no statistically significant difference (P>0.05) was observed between the two groups.

Animals in Group A required a shorter induction time (Mean±SE: 1.42±0.20 min) compared with those in Group B (Mean±SE: 2.25±0.34 min). This difference in induction time between the two groups was statistically significant (P<0.05). These findings are consistent with Anandmay *et al.* (2016), who reported that administering premedicants prior to propofol anesthesia reduces the mean induction time compared to using propofol alone.

The duration of anaesthesia in groups A and B was 90±12.79 min and 70±7.07 min (Mean±SE), respectively. A comparison between the two groups revealed that animals in group A had a significantly longer duration of anaesthesia than those in group B (P<0.05). These findings are supported by Lee *et al*. (2018), who reported that Zoletil (tiletamine–zolazepam) is well absorbed via the intramuscular route and is associated with rapid induction and onset of lateral recumbency.

Animals in group A required significantly more time for extubation/recovery (Mean±SE: 32.33±11.57 min) compared with those in group B (Mean±SE: 11.17±0.95 min) (P<0.05). Tsai *et al.* (2007) reported that the time to first spontaneous movement was 1.87±2.53 min in dogs anaesthetized with isoflurane, compared with 6.14±5.98 min in those receiving propofol-based TIVA. In the present study, recovery was smooth and relatively rapid in both groups, as anaesthesia was maintained with isoflurane. The longer recovery time observed in group A may be attributed to the prolonged effects of Zoletil.

Animals in group A required significantly more time to stand unassisted (Mean±SE: 92.83±18.88 min) compared with those in group B (Mean±SE: 24.83±0.38 min). Tsai *et al*. (2007) similarly reported shorter times to regain a standing position in animals maintained on isoflurane (27.7±17.2 min) following propofol induction (34.5±19.34 min).

Haematobiochemical parameters

Haemoglobin (Hb) values in animals of both groups fluctuated nonsignificantly throughout the observation period. White (1988) reported similar findings in dogs following induction with propofol (10 mg/kg). However, the results of the present study do not align with those of other researchers (Suresha *et al*., 2012; Sharma *et al*., 2014; Zlateva and Marino, 2015), who observed differing trends.

Packed cell volume (PCV) values in animals of both groups fluctuated nonsignificantly throughout the observation period, and no significant differences (P>0.05) were observed between groups A and B at any time interval. In contrast to the present findings, Hauptman *et al*. (2000) reported a decrease in PCV at all-time points following acepromazine administration and during surgery. Similarly, Suresha *et al*. (2012) observed a statistically significant reduction in PCV throughout a 48-hour observation period during diazepam–propofol anaesthesia.

Comparison between the two groups revealed that blood creatinine values at the 0-min interval were significantly higher (P<0.05) in group A than in group B; however, all values remained within the normal physiological range. Similarly, Mohammed *et al*. (2019) reported no significant changes in serum creatinine or blood urea nitrogen levels during propofol anaesthesia in dogs premedicated with xylazine and ketamine. In contrast, Aslam *et al*. (2019) observed increased BUN and creatinine concentrations during xylazine/diazepam–propofol anaesthesia in dogs.

Comparison between groups A and B revealed that BUN values were significantly higher (P<0.05) in group B than in group A at the 0-min and 120-min intervals. Shinde *et al*. (2018), who anaesthetized 12 clinical canine cases with propofol at 4 mg/kg, reported a gradual decrease in BUN levels, while serum creatinine showed minimal alteration.

In group A, blood glucose levels began to rise 30 min after Zoletil administration (Mean±SE: 97.54±8.57) and continued this trend up to 60 min (Mean±SE: 106.32±8.86). Thereafter, glucose levels decreased at the 120-min interval (Mean±SE: 86.46±16.87). In group B, blood glucose also began to increase at the 30-min interval (Mean±SE: 85.86±6.65) and continued to rise up to 120 min (Mean±SE: 106±10.73).

It may be concluded from the present study that the anaesthetic protocol used in group A (glycopyrrolate–xylazine–butorphanol–Zoletil–isoflurane) was superior to that used in group B (glycopyrrolate–xylazine–butorphanol–propofol–isoflurane) with respect to induction quality, recovery quality, analgesia, and dose-sparing effects on the maintenance agent. However, the group A protocol was associated with a prolonged recovery time. Importantly, neither anaesthetic protocol produced any serious adverse effects on cardiopulmonary, haemodynamic, or haematobiochemical parameters.

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