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**RESEARCH ARTICLE**

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# Clinical attributes of etomidate, ketofol and zolefol induced anaesthesia in atropine-xylazine-butorphanol premedicated dogs

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*Three anaesthetic induction protocols were investigated in 18 dogs of different breeds presented for major surgical procedures to study anaesthetic efficacy. All the dogs were premedicated with atropine sulphate (0.04 mg/kg, i.m.), xylazine HCl (1 mg/kg, i.m.) and butorphanol tartrate (0.2 mg/kg, i.m.). Induction was achieved by intravenous administration of etomidate, ketofol (ketamine-propofol) and zolefol (tiletamine-zolazepam-propofol) in groups E, KP and ZP, respectively; and sevoflurane was used as maintenance agent in all three groups. The dose required to induce general anaesthesia and induction time was significantly less/shorter in group E followed by groups KP and ZP. The quality of anaesthetic induction was smooth without any excitation nearly in all dogs of three groups. The recovery after cessation of sevoflurane was significantly faster in group KP as compared to groups ZP and E. The study confirms atropine, xylazine, butorphanol combination with etomidate, ketofol and zolefol as induction agents with sevoflurane maintenance anaesthesia provided efficient nociception during surgical procedures.*

**Keywords:** Atropine-xylazine-butorphanol, Dogs, Etomidate, Ketofol, Sevoflurane, Tiletamine-zolazepam-propofol, Zolefol

The term 'anaesthesia' originates from the Greek word *anaisthaesia*, which means 'loss of sensation' (Tranquilli and Grimm, 2015). In veterinary medicine, general anaesthesia refers to a controlled, reversible state of unconsciousness of central nervous system (CNS) to facilitate surgical or diagnostic procedures in animals. The concept of balanced anaesthesia in veterinary practice includes three primary components: analgesia to alleviate the pain, amnesia to prevent recall, and muscle relaxation to allow easier surgical manipulation (Kumar *et al.*, 2012).

Preanesthetic medications are commonly administered to improve the efficacy and safety of anaesthesia. These drugs help reduce anxiety, provide analgesia, induce sedation, and facilitate muscle relaxation before the induction of anaesthesia. Atropine sulphate and xylazine hydrochloride are routinely used for premedication in veterinary anaesthesia to reduce excessive salivation, prevent respiratory secretions, avoid vagally induced bradycardia and hypotension, and to provide sedation and analgesia (Plumb, 1999; Park *et al.*, 2009).

Etomidate is a short-acting imidazole derivative intravenous anaesthetic particularly useful in cardiovascular and haemodynamically unstable patients (Ruth *et al.*, 2001). At clinical doses, etomidate results in minimal to no change in heart rate, stroke volume, cardiac output, mean arterial blood pressure, central venous pressure or cardiac index (Berry, 2015).

Ketofol, a combination of ketamine and propofol, has gained popularity as an anaesthetic regimen because it enhances safety and efficacy by balancing the cardiovascular effects of the two drugs while reducing the propofol dose required for sedation (Daabis *et al.*, 2009). Similarly, a novel anaesthetic combination such as zolefol (tiletamine + zolazepam + propofol) has shown promise by providing rapid and smooth induction, adequate muscle relaxation, and minimal post-anaesthetic stress (Cruzat *et al.*, 2018). Both ketofol and zolefol are intended to achieve haemodynamic stability, minimise respiratory depression, provide effective analgesia, and facilitate rapid and uncomplicated recovery. Among the inhalational anaesthetics used for maintenance of anaesthesia, sevoflurane is considered one of the safest agents owing to its excellent titratability, minimal cardiovascular depression, and rapid recovery profile (Auer *et al.*, 1978).

Given the limited available research on the use of zolefol in veterinary anaesthesia, the present study aims to compare different induction agents for surgical anaesthesia maintained with sevoflurane.

## Materials and Methods

The present study was conducted on 18 clinical canine cases presented for various surgical procedures between December 2022 and June 2023. Irrespective of age, breed, sex, body weight, or type of surgical intervention, the animals were randomly allocated into three groups comprising six dogs each: group E (etomidate), group KP (ketofol; ketamine–propofol), and group ZP (zolefol; tiletamine–zolazepam –propofol). The study was designed to evaluate and compare the efficacy of these anaesthetic induction protocols in dogs undergoing surgical procedures.

A comprehensive preanaesthetic evaluation was performed in all patients, including detailed history taking, physical examination, haematological assessment, and blood biochemical analysis. The preoperative physical status of each dog was determined according to the American Society of Anesthesiolo-

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gists (ASA) classification system to assess suitability for general anaesthesia. Of the 18 dogs included in the study, 9 (50%) were classified as ASA I, indicating normal healthy patients, while the remaining 9 (50%) were categorized as ASA II, indicating the presence of mild systemic disease. The mean body weight of the animals was 22.33±5.81 kg (range: 7–42 kg), and the mean age was 4.83±1.74 years (range: 1–10 years).

Dogs in all three groups were fasted for 12 hr and deprived of water for 6 hr before anaesthesia to minimize the risk of gastroesophageal reflux (GER) (Grubb *et al*., 2020). All dogs were premedicated with atropine sulphate (0.04 mg/kg body weight, i.m.). Ten minutes later, a combination of xylazine HCl (1 mg/kg) and butorphanol tartrate (0.2 mg/kg), mixed in a single syringe, was administered intramuscularly. After an additional 10 min, anaesthesia was induced according to the respective treatment groups: dogs in group E received etomidate, those in group KP received ketofol (ketamine–propofol, 1:1), and those in group ZP received zolefol (tiletamine–zolazepam–propofol, 1:1). All induction agents were administered intravenously to effect.

In each group, the total dose (mg/kg) required for the induction of anaesthesia, and induction time (time between administration of induction drug to cessation of all reflexes, in seconds) were recorded and documented. Quality of induction was recorded on a score of 1 to 4 as: score 1 – very poor, score 2 – poor, score 3 – fair and score 4 – smooth (Convey-Crump and Murison, 2008). Response to intubation was documented to evaluate the laryngeal reflexes and the feasibility of intubation in the animals using scale developed by Sharma (2012). Sevoflurane was used to maintain anaesthesia throughout the surgical procedure after endotracheal intubation. Concentration of sevoflurane required for maintenance of anaesthesia was also documented.

A 1:1 ketofol mixture was prepared by combining 1 mL of ketamine (50 mg/mL), 4 mL of normal saline, and 5 mL of propofol (10 mg/mL) in a 10 mL syringe. The final solution contained ketamine 5 mg/mL and propofol 5 mg/mL.

To prepare a 1:1 zolefol mixture, 1 mL of zoletil (tiletamine–zolazepam, 50 mg/mL) was drawn into a 10 mL syringe and diluted with 4 mL of normal saline. Subsequently, 5 mL of propofol (10 mg/mL) was added and mixed thoroughly. The resulting 10 mL solution contained 5 mg/mL of zoletil and 5 mg/mL of propofol, yielding a 1:1 zolefol preparation.

The quality of anaesthesia was evaluated using different parameters such as jaw relaxation, palpebral reflex, pedal reflex were recorded at specific time intervals; 0 minute (just after induction), and 10, 20, 30, 45 and 60 minutes after induction (Ahmad *et al*., 2011).

All animals were continuously monitored for assessment of recovery parameters. Recovery time and time to complete recovery were recorded, categorized, and analyzed. The quality of recovery was evaluated using a recovery scoring system ranging from 0 to 4, according to the criteria described by Sharma *et al.* (2016). Additional parameters, including duration of anaesthesia, duration of surgery, time to first head raise, and time to attain sternal recumbency, were also recorded. The collected data were expressed as mean±SE and analyzed between groups using one-way analysis of variance (ANOVA) with the Web Agri Stats Package (WASP).

**Results and Discussion**

The average induction dose rates of anaesthetic agents were observed as 0.93±0.02 mg/kg in the

**Table 1:** Mean±SE values of various anaesthetic parameters in animals of different groups.

| Groups/Anaesthetic parameters | Group E (Etomidate) | Group KP (Ketofol) | Group ZP (Zolefol) |
|---|---|---|---|
| Induction dose required (mg/kg) | $0.93^{C}$±0.02 | $1.50^{A}$±0.05 | $1.15^{B}$±0.03 |
| Induction time (seconds) | $26.67^{C}$±3.33 | $40.83^{B}$±3.96 | $56.66^{A}$±3.07 |
| Quality of induction (1-4) | 3.83±0.17 | 4.00±0.00 | 4.00±0.00 |
| Response to intubation (0-4) | $3.83^{A}$±0.17 | $3.33^{B}$±0.21 | $4.00^{A}$±0.00 |
| Concentration of sevoflurane (%) | 1.74±0.08 | 1.79±0.10 | 1.97±0.08 |
| Duration of anaesthesia (min) | 57.00±10.97 | 53.50±10.85 | 66.17±12.47 |
| Duration of surgery (min) | 48.00±10.94 | 43.84±9.55 | 68.00±15.63 |
| Time take to first head rise (min) | 16.66±1.76 | 14.50±1.52 | 19.33±1.90 |
| Time take to sternal recumbency (min) | 29.00±2.82 | 21.50±2.10 | 26.33±2.78 |
| Recovery time (min) | $9.83^{A}$±1.13 | $6.16^{B}$±0.83 | $10.33^{A}$±1.33 |
| Complete recovery time (min) | $51.50^{A}$±2.21 | $37.50^{B}$±3.81 | $47.5^{AB}$±4.42 |
| Quality of recovery (0-4) | 3.33±0.33 | 3.83±0.17 | 3.83±0.17 |

*Values with superscripts A, B and C differ significantly (P<0.05) between groups.*

**Table 2:** Mean±SE scores of jaw relaxation, pedal reflex and palpebral reflex in animals of different groups at different time intervals.

| Reflexes | | Time (min) | | | | | |
|---|---|---|---|---|---|---|---|
| | **Groups** | **0** | **10** | **20** | **30** | **45** | **60** |
| Jaw relaxation (1-4) | Group E | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 |
| | Group KP | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 3.0±0.0 | 3.0±0.0 | 3.0±0.0 |
| | Group ZP | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 3.0±0.0 | 3.0±0.0 | 3.0±0.0 |
| Pedal reflex (1-4) | Group E | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 |
| | Group KP | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 |
| | Group ZP | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 |
| Palpabral reflex (1-4) | Group E | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 |
| | Group KP | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 |
| | Group ZP | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 | 4.0±0.0 |

etomidate (E) group, 1.50±0.05 mg/kg in the ketofol (KP) group, and 1.15±0.03 mg/kg in the zolefol (ZP) group. Comparison among different groups revealed a significantly ($P<0.05$) lower dose required for the induction of anaesthesia in group E, followed by ZP and KP groups (Table 1). The reduced induction doses observed across all groups may be attributed to the pre-anaesthetic administration of an alpha-2 adrenoreceptor agonist (xylazine) and an opioid analgesic (butorphanol), which likely enhanced the sedative and analgesic effects, thereby reducing the amount of induction agent required. These results align with previous study by Dar *et al*. (2016), who reported that the combination of butorphanol and diazepam reduced the required etomidate dose in dogs from 1.5 mg/kg to 0.97 mg/kg body weight. However, no specific data is currently available for zolefol in combination with atropine-xylazine-butorphanol in dogs.

Transient post-induction apnea and respiratory depression was observed in 2/6 dogs after quick intravenous infusion of zolefol, which resolved after a few minutes. The present finding was well collaborated with Koli *et al.* (2021), who also found post-induction apnoea after fast zoletil administration in dogs. However, no complications were recorded after ketofol and etomidate administration. In contrast to the present study, Gopal (2015) reported transient apnoea after induction with etomidate.

The induction times were 26.67±3.33, 40.83±3.96, and 56.66±3.07 seconds in groups E, KP, and ZP, respectively (Table 1). A significant difference was observed among the groups, with the fastest induction of anaesthesia occurring in group E (etomidate), followed by group KP (ketofol) and group ZP (zolefol). The rapid induction observed in group E may be attributed to the high lipid solubility of etomidate, which facilitates its rapid penetration into the brain (Berry, 2015). The findings of the present study are in agreement with those reported by Hareesh *et al*. (2018), who recorded an induction time of 22.0±0.40 seconds following etomidate administration. However, these results differ from those of Saini (2018), who reported a considerably longer mean induction time of 70.2±4.03 seconds with etomidate.

The quality of induction was smooth and free from excitation in all dogs (6/6) in groups KP and ZP. In group E, induction was smooth in 83.33% (5/6) of the dogs. No significant difference ($P>0.05$) was observed among the groups with respect to the quality of induction. These findings are in agreement with those of Saini (2018), who reported that etomidate provides smooth and good-quality induction. However, Sams *et al*. (2008) and Dar *et al.* (2019) reported difficulties during endotracheal intubation following etomidate induction. Similarly, Taboada and Leece (2014) observed good-quality induction with ketofol in dogs.

The response to intubation was significantly lower in group KP (3.33±0.21) than in group E (3.83±0.17) and group ZP (4.00±0.00). In groups E and ZP, endotracheal intubation was accomplished without coughing in all dogs. In contrast, although four dogs in group KP permitted smooth insertion of the endotracheal tube, two dogs exhibited coughing during intubation. Saini (2018) also reported that the laryngeal reflex remained mildly intact in dogs induced with etomidate. In contrast to the present findings, Taboada and Leece (2014) reported excellent conditions for tracheal intubation in dogs induced with ketofol.

In almost all dogs across the three groups, jaw relaxation, pedal reflex, and palpebral reflex were abolished within one minute of administration of the induction agent (Table 2). This finding served as an indirect indicator of both the induction and sedative quality of the anaesthetic agents. No significant differences were observed among the groups with respect to these parameters. However, dogs in the ketofol and zolefol groups exhibited mild resistance to

jaw opening at 30 min after induction compared with their baseline values. The findings of the present study are in accordance with those reported by Gopal (2015) and Saini (2018), who also observed adequate jaw relaxation and suppression of reflexes following induction of anaesthesia.

The concentrations of sevoflurane required for maintenance of anaesthesia were 1.74±0.08%, 1.79±0.10%, and 1.97±0.08% in groups E, KP, and ZP, respectively. Although the sevoflurane requirement was numerically higher in group ZP, no significant difference (P>0.05) was observed among the groups. The relatively low vaporizer settings required for maintenance of anaesthesia in all groups may be attributed to the analgesic and anaesthetic-sparing effects of butorphanol included in the preanaesthetic regimen. Similar observations were reported by Ko *et al*. (2000) and Inoue *et al*. (2006), who noted reduced inhalant anaesthetic requirements following opioid administration. Furthermore, Kinjavdekar *et al*. (2005) reported that $\alpha_2$-adrenergic agonists exert a pronounced anaesthetic-sparing effect on maintenance anaesthetic agents, thereby reducing the concentration of inhalational anaesthetics required to maintain an adequate depth of anaesthesia.

The mean±SE values for the duration of anaesthesia and duration of surgery are presented in table 1. The shortest duration of anaesthesia (53.50±10.85 min) and surgery (43.84±9.55 min) was observed in group KP, followed by group E (57.00±10.97 min and 48.00±10.94 min, respectively) and group ZP (66.17±12.47 min and 68.00±15.63 min, respectively). Although both parameters were numerically higher in group ZP, no significant difference (P>0.05) was observed among the groups with respect to the total duration of anaesthesia.

The mean±SE values for the time to first head raise and time to attain sternal recumbency were 16.66±1.76 min and 29.00±2.82 min in group E, 14.50±1.52 min and 21.50±2.10 min in group KP, and 19.33±1.90 min and 26.33±2.78 min in group ZP, respectively. Although dogs in group KP showed numerically shorter recovery times, no significant difference (P>0.05) was observed among the groups with respect to either the time to first head raise or the time to attain sternal recumbency. The findings of the present study differ from those of Sams *et al*. (2008) who reported a longer time to sternal recumbency following etomidate induction in dogs premedicated with dexmedetomidine. Similarly, Cullen and Reynoldson (1997) observed prolonged recovery times in dogs receiving zoletil premedication and propofol induction when compared with dogs induced with propofol alone.

The mean±SE recovery time was significantly shorter (P<0.05) in group KP (6.16±0.83 min) compared with group E (9.83±1.13 min) and group ZP (10.33±1.33 min). The rapid recovery observed in group KP may be attributed to the favourable pharmacokinetic profile of ketofol, which facilitates a smoother and faster return to consciousness following discontinuation of anaesthesia. The findings of the present study are in agreement with those reported by Sharma *et al*. (2016) who also observed rapid recovery following ketofol induction in dexmedetomidine-premedicated dogs maintained with isoflurane. Furthermore, Steffey *et al*. (2015) stated that recovery of consciousness is generally expected within 15–20 min after discontinuation of inhalational anaesthetics, irrespective of the induction agent used.

In the present study, the mean±SE values for complete recovery time were 51.50±2.21 min, 37.50±3.81 min, and 47.50±4.42 min in groups E, KP, and ZP, respectively. Comparative analysis among the groups revealed that complete recovery time was significantly shorter (P<0.05) in group KP compared with group E. The findings of the present study are in agreement with those reported by Gopal (2015) who recorded a complete recovery time of 45.00±7.33 min following etomidate anaesthesia in dogs premedicated with xylazine and butorphanol. In contrast, Sams *et al*. (2008) reported a shorter total recovery time (24.20±10.30 min) following midazolam–etomidate anaesthesia. Consistent with the present findings, Cruzat *et al.* (2018) also observed prolonged anaesthesia duration and delayed sternal and standing recovery times in dogs receiving a combination of propofol and zoletil.

The quality of recovery was considered good in all three groups, with no signs of struggling observed. During the recovery period, no abnormal trembling, limb movements, vocalization, urination, or defecation were observed in most dogs. However, two dogs in the etomidate group exhibited hyperactive motor activity, including paddling movements and crying, during the immediate post-anaesthetic recovery period. No significant difference (P>0.05) was observed among the groups regarding recovery quality scores. The present findings are in accordance with those reported by Sastry *et al*. (2021) who observed involuntary limb movements and vocalization following etomidate anaesthesia. In contrast, Hareesh *et al*. (2018) reported rapid and smooth recovery without struggling following propofol and etomidate induction. Similarly, Shinde *et al*. (2018) reported smooth recovery in dogs receiving propofol and ketofol following premedication with xylazine and butorphanol. Furthermore, Love *et al*. (2011) reported that dogs maintained with sevoflurane exhibited significantly better quality of recovery.

Based on the findings of the present study, it can be concluded that the combination of atropine, xylazine, and butorphanol provided effective sedation prior to induction of anaesthesia in all three groups. The etomidate group required a significantly lower induction dose, followed by the ketofol and zolefol groups. Etomidate and ketofol produced faster and smoother induction of anaesthesia compared with

zolefol. Sevoflurane provided satisfactory maintenance of anaesthesia with smooth recovery in all groups. The shortest recovery time was observed in the ketofol group, followed by the etomidate and zolefol groups. Overall, the findings indicate that all three protocols resulted in satisfactory outcomes and provided effective balanced anaesthesia.

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## OBITUARY

**Dr. Indu Vrat Mogha**
**(1 July 1943 - 9 May 2026)**

Dr. Indu Vrat Mogha was born on 1 July 1943 in the village of Tera, District Baghpat, Uttar Pradesh, to Shri Ram Baksh Mogha.

He completed his Bachelor of Veterinary Science (B.V.Sc.) degree in 1969 and obtained his Master of Veterinary Science (M.V.Sc.) degree in 1971. In the same year, he joined government service as a Veterinary Officer in the Department of Pathology. Through his sincerity, dedication, and unwavering commitment to his profession, he rendered exemplary service to the veterinary field and retired honorably in 2003.

Dr. I.V. Mogha was associated with the Division of Surgery, ICAR-Indian Veterinary Research Institute, Izatnagar (Uttar Pradesh), from its inception. He made significant contributions to its growth and development through his dedication, hard work, professional competence, and commitment to excellence. His valuable service to the institution and the veterinary profession will always be remembered with deep respect and gratitude.

Beyond his professional accomplishments, Dr. Mogha was a cheerful, warm-hearted, and fitness-conscious individual who believed in taking everyone along with him. A keen sportsperson, he had a particular fondness for badminton and actively encouraged a healthy, disciplined, and active way of life. He was admired for his honesty, diligence, humility, and compassionate nature. Deeply devoted to his family, society, and the nation, he remained caring and committed to the welfare of others throughout his life.

He is survived by his beloved wife, Mrs. Rajni Mogha; his sons, Mr. Janesh Arya and Mr. Priya Bandhu; and his daughter, Mrs. Priya Mitta. He is also survived by his grandchildren—grandsons Devesh Arya, Yash, and Atharv (Manu), and granddaughters Yukti Arya and Vishwani—as well as his son-in-law, Mr. Devendra.

Dr. Indu Vrat Mogha departed for his heavenly abode on 9 May 2026, leaving behind cherished memories and an enduring legacy of integrity, dedicated service, discipline, compassion, and humanity. His guidance, warmth, kindness, and inspiring presence will be deeply missed by all who had the privilege of knowing and working with him.

May the Almighty grant eternal peace to the departed soul and give the bereaved family the strength and fortitude to bear this irreparable loss. May his noble soul rest in eternal peace.