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Study of anaesthetic parameters in surgical procedures with propofol, Ketofol and Etomidate as induction agents Premidication with glycopyrrolate & isoflurane maintenance in canines

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Abstract
The study has been conducted to 18 nos. canine patients undergoing for elective surgery (castration, spaying etc.) to evaluate the effect of propofol, Ketofol and etomidate on anaesthetic parameters as induction agents with glycopyrrolate premedication and isoflurane maintenance in canines. The cases were divided into three groups randomly *viz*. in group P, KP &E with each group having six animals. Animals of all three groups were premedicated @ 0.01 mg/kg IM with glycopyrrolate, 10 minutes before induction. As induction agent in group P, KP and E, Propofol @ 6mg/kg IV, Ketofol @ 4 mg/kg and etomidate @ 3mg/kg was administered respectively. Maintenance of anaesthesia was carried out by using isoflurane in all the animals in all three groups. All the anaesthetic Parameters (Induction time, quality of induction, intubation score & quality of intubation, quality of analgesia, depth of anaesthesia, myoclonus score and quality of recovery) were studied after induction of anaesthesia.

Keywords: Propofol, Ketofol, etomidate, isoflurane, anaesthetic parameters

1. Introduction
Most often anaesthetic induction in canines were performed with injectable anaesthetics like propofol, ketamine-midazolam, ketamine-propofol (ketofol), and etomidate or less commonly thiopental sodium because administration of intravenous agents leads to rapid loss of consciousness and easy and intubation (Grimm *et al.* 2015) [14]. Propofol (2, 6-diisopropyl phenol) anaesthesia characterize with very rapid onset of action, short duration of action with a complete and rapid excitement-free recovery, with good muscle relaxation, but with poor analgesic properties (Zoran *et al.* 1993, Hall *et al.* 2001) [35, 15]. Propofol is coupled with a speedy induction and recovery that are usually smooth but it also linked with remarkable hyperesthesia and induction of anaesthesia with propofol may be leads to pain on injection, apnea, and mark able drop in arterial blood pressure (BP) and cardiac output. It is the drug of choice in disease states such as intracranial disease because of its capability to decrease intracranial pressure and it's often chosen for patients with hepatopathy and for those where a smooth and speedy recovery is expected (Hofmeister *et al.* 2008, Onkarappa *et al.* 2016) [16, 25]. Intravenous administration of propofol for induction followed by maintenance with inhalant anaesthesia produce safe anaesthesia with antioxidant properties (propofol-nitrous oxide) secondary to its phenol-based chemical structure (Riera *et al.* 2010) [27]. Ketofol induction provides excellent sedative/anaesthetic effect for routine spinal anaesthesia for gynecological, ophthalmological and cardiovascular/cardiothoracic operations in all age patients. The most important plus point of this drug cocktail over single propofol administration is the completely different actions of each drug on hemodynamic profile and respiratory system that increases safety and efficacy and reduces the dose of propofol required and its negative effects (Daabiss *et al.* 2009) [11]. Combination of propofol and ketamine may lessen the negative effects of both anaesthetics as because these two drug acts independently on contrasting extremes – excitation and depression, (Mair *et al.* 2009) [21]. Mixture of ketamine and propofol also known as Ketofol; injected either individually or by mixing in a single-syringe providing the profits of both the drugs, and for reducing the negative effects of both agents (Lee and Lee 2016) [20].

Ketamine and propofol showed extreme opposite action on cardiovascular system from each other, thus balancing each other out when they fused together for anaesthesia (Arora 2007) [4]. Etomidate is an ultra-short acting non-barbiturate IV anaesthetic belongs to group of carboxylate imidazole derivative. Etomidate is distinguished for its better hemodynamic stability, minial respiratory depression, and cerebral protective effects (Robert and Hiller 2006) [28].

2. Materials and Methods

2.1 Outline of research

All animals were brought to the TVCC of C.V.Sc & A.H., Selesih, Aizawl, Mizoram as clinical cases in the Veterinary surgery and radiology department for different surgical procedures like castration, spaying, aural hematoma or other elective surgery were aimlessly divided into group- P, group-KP and group- E in these three groups with six animals in each group. Food and water were withheld for 12 and 6 hours respectively before the anaesthetic trial & surgery in all the animals. Study was conducted in a temperature-controlled environment with the operation theatre temperature maintained at 20 ˚C.

2.2 Drugs used

2.2.1 Glycopyrrolate

Glycopyrrolate (Brand name: Pyrrolate 0.2 mg/ml) was injected intramuscularly to all animals as preanaesthetic @ 0.01 mg/kg body weight**.**

2.2.2 Propofol

Propofol (Brand name: Lipuro-propofol 10mg/ml) was administered intravenously as induction agent in group-P animals @ 6 mg/kg body weight.

2.2.3 Ketofol

Ketofol (ketamine & propofol combination) was administered @ 4mg/kg body weight (each drug 2mg/kg) IV as induction agent in group- KP animals.

2.2.4 Etomidate

Etomidate (Brand name: Lipuro-etomidate 2mg/ml) was administered @ 3mg/kg body weight IV as induction agent in group-E animals.

2.2.5 Isoflurane

Isoflurane (Brand name: Forane) was administered as inhalant anaesthetic to maintain the surgical plane of anaesthesia. Isoflurane was provided @ 20 ml/kg/min at a higher value of 3-5% for initial 5 minutes for stabilization of the patient and then the vaporizer settings were changed accordingly up to 60 mins.

2.3 Anaesthetic protocol

Animals of all three groups i.e., group- P, group-KP and group-E were injected with glycopyrrolate preanaesthetic @ 0.01 mg/kg b/wt. intramuscularly after preanaesthetic evaluation 10 minutes before intravenous administration of induction agents in all animals of all three groups with specific induction agents respectively.

Group-P: Anaesthetic induction was achieved by propofol @ 6 mg/kg b/wt. IV.

Group-KP: Induction by Ketofol @ 4 mg/kg (each drug 2 mg/kg) b/wt. IV.

Group-E: Induction by etomidate @ 3 mg/kg b/wt. IV.

After achieving anaesthetic induction in all animals of three groups, maintenance of surgical anaesthetic plane was performed with inhalant anaesthesia with isoflurane.

2.4 Parameters evaluated

Anaesthetic parameters i.e., Induction time (in seconds), quality of induction, quality of intubation and intubation score, quality of analgesia, depth of anaesthesia, myoclonus score and quality of recovery were assessed. Induction time was assessed by analyzing the duration of time from the administration of induction agent till the animal achieved surgical plane of anaesthesia. Quality of induction, quality of intubation, and myoclonus score were evaluated as per the technique reported by Amenguel *et al*. (2013). Depth of anaesthesia was analyzed as per the procedure described by Ahmad *et al*. (2013) [1]. Quality of analgesia and quality of recovery were evaluated as per the method reported by Jimenez *et al.* (2012) [17].

2.5 Statistical analysis

Statistical analysis was done by using SPSS version 20 where two-way Analysis of variance (ANOVA) was applied for quantitative parameters and the significant values in the ANOVA were further tested through Duncan multiple range test. Results are presented as mean ± SD and differences were considered significant when $p \leq 0.05$.

3. Results and Discussion

3.1 Induction Time (Seconds)

The Mean ± SD values of induction time for the three groups were depicted in the Table 1. The differences in induction time among the three groups were statistically highly significant ($p \leq 0.01$). Induction times in P and KP groups did not differ significantly but both P and KP groups showed significant differences ($p \leq 0.01$) with group E in the values of induction time. The induction time in groups P, KP, and E were recorded as 35.2±2.54, 38.6±3.05 and 48.8±3.10 seconds respectively. The induction time in group-P was recorded as 35.2±2.54 seconds and similarly short induction times were also observed with propofol in canine by (Amengual *et al.* 2013, Robinson and Borer-weir 2013, Chavhan 2014 and Shinde *et al.* 2018) [9, 32] as 20-40 seconds, 20-30 seconds, 31±2.33 seconds, and 22.83 ± 5.92 seconds respectively. In group KP induction time was recorded as 38.6 ± 3.05 seconds and similarly short induction times were also observed with ketofol in canine was recorded by (Bayan and Konwar 2014 and Shinde *et al.* 2018) [32] as 38.17 ± 2.12 seconds and 9.83 ± 2.50 seconds respectively. In group E induction time was recorded as 48.8 ± 3.10 seconds. Rapid induction with etomidate was observed by (Onkarappa *et al.* 2016) [25] in human within 19.2 ± 2.5 seconds. Low induction time is a good quality for induction agents. Significantly low induction time in the group P in compare to KP group and E group by cause of high lipid solubility of propofol and ability to rapidly cross blood-brain barrier. Propofol inflates the sequel of inhibitory neurotransmitter gamma amino butyric acid (GABA) and reduces metabolic activity of brain (Andreoni and Hughes, 2009) [3].

Table 1: Mean ± SD of induction time in groups P, KP, and E

Groups	Time of induction (seconds)
Group-P	35.2 ± 2.54^{A}
Group-KP	38.6 ± 3.05^{A}
Group-E	48.8 ± 3.10^{B}
Significance	**

3.2 Quality of Induction

The quality of induction for all three groups were observed and depicted in Table 2. In animals of group P-83% (5/6) showed smooth induction with no paddling and 17% (1/6) animals recorded with occasional slow paddling movements. Similar finding of smooth induction was observed by (Kulkarni *et al.* 2006 and Muhammad *et al.* 2009) [18, 23]. All the animals 100% (6/6) of group KP recorded with smooth induction with no paddling movements. (Taboada and Leece 2014) [33] Reported better quality of induction with ketofol compared to propofol which is similar with the findings of the present study. In case of group E 67% (4/6) animals recorded with smooth induction without paddling movements and 33% (2/6) animals recorded with occasional slow paddling movements. Similar finding of paddling with etomidate was observed by (Muir and Mason 1989) [24]. In another study higher induction quality score in etomidate group (1.2 ± 0.8) was observed by (Sams *et al.* 2008) [31] which was alike to the current observations. Findings. In group KP Induction quality is better compared to group P and E might be due to combination of propofol and ketamine which ultimately decrease the dose of propofol for induction when compared to propofol alone and combination of propofol and ketamine produce synergistic effect which ultimately provides smooth induction in Ketofol group. Higher incidence of paddling movements with etomidate administration might be due pain on injection also reported by (Muir and Mason 1989) [24] might be of its propylene glycol vehicle or the hyperosmolar nature of commercial products reported by (Grimm *et al.* 2015) [14]. In another study (Dar *et al.* 2016) [12] observed smooth induction with propofol as compared to etomidate which was similar to the present findings.

Table 2: Quality of induction in groups P, KP and E.

Quality of induction	Score	Number of animals in Group P	Number of animals in Group KP	Number of animals in Group E
Smooth transition with no paddling	0	5	6	4
Occasional, slow paddling movements	1	1	0	2
Moderate, sustained paddling movements	2	0	0	0
Marked paddling, struggling or vocalization	3	0	0	0

3.3 Quality of Intubation and Intubation Score

The assessment of intubation quality and intubation score of all three groups were represented in Table 3. During anaesthetic induction in both group P and group KP 83% (5/6) animals showed smooth easy intubation and only 17% (1/6) animals recorded mild coughing. Bufalari *et al.* 1998) [6] observed good-quality of intubation in propofol anaesthesia and (Larisa *et al.* 2008) [19] reported easy and quick endotracheal intubation with aid of laryngoscope in dogs after induction with propofol-thiopental mixture at (1:1) ratio which was almost similar to the present findings of group P. Similarly, Taboada and Leece (2014) [33] and Cima *et al.* (2016) [10] observed better quality of endotracheal intubation in ketofol anaesthesia which was similar to the present findings. In case of group E only 33% (2/6) animals recorded smooth and easy intubation, 50% (3/6) animals recorded with mild coughing and 17% (1/6) animals recorded with swallowing coughing and gagging (failure to intubate). Although Perk *et al.* 2002 [26] evaluated easy intubation with no pharyngeal reflexes in dogs premedicated with atropine-diazepam followed by induction with intravenous administration of etomidate-alfentanil which might be as a result of muscle relaxant property of diazepam and sedative action of alfentanil. In group KP and group P intubation quality were better compared to group E which might be due to better muscle relaxation and narcosis property of propofol and better muscle relaxation and narcosis and better analgesic property of Ketofol which completely abolished the laryngeal reflex. In group E quality of intubation was worse compared to other two groups which might be due to intact laryngeal reflex in intimidate anaesthesia reported by Dar *et al*. (2016) [12].

Table 3: Intubation score in groups P, KP and E.

Quality of analgesia	Intubation Score	Number of animals in Group P	Number of animals in Group KP	Number of animals in Group E
Easy intubation	0	5	5	2
Mild coughing	1	1	1	3
Pronounced coughing	2	0	0	0
Swallowing, coughing and gagging (failure to intubate)	3	0	0	1

3.4 Quality of Analgesia

Quality of analgesia of all the groups were assessed and depicted in Table 4. During anaesthetic trial in both group P and group E 67% (4/6) animals showed no pain while 33% (2/6) animals recorded with mild pain. Animals of group P showed mild pain which might be due to propofol does not produce analgesia by (Grimm *et al.* 2015) [14]. All the animals 100% (6/6) of group KP recorded with no pain during anaesthetic trial which might be due to analgesic effect of ketamine in Ketofol mixture. In group E 67% animals recorded no pain and 33% animals showed mild pain which might be due to etomidate does not produce analgesia by (Grimm *et al.* 2015) [14]. In group KP quality of analgesia was better compared to groups P and E might be due to combination of propofol and ketamine where ketamine provides good analgesia. Higher incidence of pain was observed in group P and group E which might be due to both propofol and etomidate does not produce analgesia so during painful surgical procedures mild pain in some cases were observed in both P and E groups.

Table 4: Quality of analgesia in group P, KP and E

Quality of analgesia	Analgesia score	Number of animals in Group P	Number of animals in Group KP	Number of animals in Group E
No pain	0	4	6	4
Mild pain	1	2	0	2
Moderate pain	2	0	0	0
Severe pain	3	0	0	0

3.5 Depth of Anaesthesia

The anaesthetic depth of three groups were recorded and depicted in Table 5. During anaesthetic protocol in both group P and group E 83% (5/6) of animals showed abolished (no response) palpebral reflex while 17% (1/6) animals recorded with very weak (very slow and occasional response) palpebral reflex. Occasional response of palpebral reflex might be due to pain during painful surgical procedures observed in group P & E as propofol and etomidate does not produce analgesia. In a study mild palpebral reflexes in canines, with premedication of solo pentazocine, or fusion of pentazocine-chloramphenicol followed by anaesthetic induction with propofol in canines reported by (Chandrashekarappa and Ananda 2009) [8] which was similar to the present findings and Similarly, in a study, disappearance of corneal and palpebral reflex in canines were reported with atropine-diazepam premedication followed by induction with intravenous administration of etomidate- alfentanil by Perk *et al.* 2002 [26]. All animals 100% (6/6) of group KP recorded with abolished (no response) palpebral reflex during anaesthetic protocol which might be as a reason of synergetic action of both ketamine and propofol where ketamine provides analgesia which helps to maintain the depth of anaesthesia.

Table 5: Depth of anaesthesia in Group P, KP and E.

Palpebral reflex	Score	Number of animals in Group P	Number of animals in Group KP	Number of animals in Group E
Intact and strong (quick blink)	0	0	0	0
Intact but weak (slow response)	1	0	0	0
Very weak (very slow and occasional response)	2	1	0	1
Abolished (no response)	3	5	6	5

3.6 Myoclonus Score

The myoclonus score of different groups of animals were recorded and depicted in Table 6. During anaesthetic trial in both group P and group KP 100% (6/6) of animals showed no muscle twitching. However (Hofmeister *et al.* 2008 and Forman 2011) [16, 13] observed myoclonus with propofol anaesthesia which was contrary to the present findings. (Grimm *et al.* 2015) [14] Recorded occasional appearance of myoclonus in both dogs and humans, but it was not common. Similarly (Onkarappa *et al.* 2016) [25] recorded no myoclonus with propofol in humans. In a study very low percent of dogs (1.2%) of dogs recorded with myoclonus in propofol anaesthesia recorded by which support the present findings, it might be due to good muscle relaxation quality of propofol. Absence of myoclonus in group KP by the virtue of powerful reciprocal effect of ketamine and ketamine. Ketamine alone might produce muscle twisting but when it is used with good muscle relaxant than it does not show any myoclonus. In case of group E 67% (4/6) animals recorded with no twitching during induction while 33% (2/6) animals recorded with occasional mild twitching. Similar findings were observed by (Muir and Mason 1989, Sams *et al.* 2008 and Rodriguez *et al.* 2012) [24, 31] where canines developed myoclonus after receiving etomidate. The presence of myoclonus response in etomidate induction might be the result of gratification of subcortical structures which usually vanquish the extrapyramidal motor activity recorded by (Grimm *et al.* 2015) [14].

Table 6: Myoclonus score in groups P, KP and E.

Myoclonus	Score	Number of animals in Group P	Number of animals in Group KP	Number of animals in group E
No twitching	0	6	6	4
Occasional, mild muscle twitching	1	0	0	2
Moderate, sustained muscle twitching	2	0	0	0
Severe muscle twitching with opisthotonos and/or extensor muscle rigidity	3	0	0	0

3.7 Quality of Recovery

The quality of recovery of animals in three groups were recorded and depicted in Table 7. During recovery in group P 50% (3/6) of animals showed normal usual transition, normal easy Extubation with some incoordination, and usually persisted silent appearance whereas, 50% (3/6) animals documented with ordinary usual transition, normal Extubation, limited muscle command, frighten, during an early stage of recovery and late phase there was uncoordinated whole body movement with vocalisation. Similar smooth recovery with propofol induction were also observed by (Morgan and Legge 1989, Sams *et al.* 2008 [22, 31], Muhammad *et al.* 2009, Thejasree *et al.* 2017 and Shinde *et al.* 2018) [23, 32]. In case of group KP animals 67% (4/6) recorded with normal routine transition, usual extubation, mild incoordination, and usually remained silent in early stages and in the late period some incoordination was observed. Remaining 33% (2/6) recorded with unremarkable transition, routine Extubation, limited muscle control, and startles, during early phase of recovery and during late phase there was uncoordinated whole-body movement with vocalisation. Similar findings also observed by (Shinde *et al.* 2018) [32] and Thejasree *et al.* 2017) [34] for Ketofol anaesthesia. In group E 83% (5/6) of animals recorded with struggling during transition, difficult Extubation with chewing and coughing elicited, uncoordinated whole body movements, startles, and vocalisation during early phase of recovery and in late phase uncoordinated whole body movements, startles, vocalisation was observed. Remaining 17% (1/6) animals recorded with violent transition, restraint required for Extubation, emergence delirium, thrashing, and hard restrain required during early stage of recovery and in late-stage emergence delirium, thrashing was observed with rough restrain. In group E rough recoveries were observed. Similar findings with etomidate were observed by (Sams *et al.* 2008 and Rodriguez *et al.* 2012) [31, 30] whereas, (Perk *et al.* 2002) [26] reported no anaesthetic complications during recovery might be due to premedication of dogs with premedicated with atropine-diazepam.

Table 7: Quality of recovery in groups- P, KP and E.

Quality of recovery	Score	Number of animals in Group P	Number of animals in Group KP	Number of animals in group E
Early- Extubated, calm transition to alertness, coordinated movement, calm Late- Alert coordinated movement, calm	1	0	0	0
Early- Fairly calm transition, holds head up, no body movement attempted Late-No body movement, holds head up	2	0	0	0
Early- Unremarkable transition, routine extubation, some incoordination, does not startle, generally quiet Late- Some incoordination, generally quiet	3	3	4	0
Early- Unremarkable transition, routine extubation, limited muscle control, startles, may paddle or whine Late- Uncoordinated whole body movements, startles, vocalizes	4	3	2	0
Early- Struggling during transition, difficult extubation with chewing and coughing elicited, uncoordinated whole body movements, startles, vocalizes Late- Uncoordinated whole body movements, startles, vocalizes	5	0	0	5
Early- Violent transition, restrained required for extubation, emergence delirium, thrashing, cannot be restrained easily Late- Emergence delirium, thrashing, cannot be restrained easily	6	0	0	1

4. Conclusion

The current research model was executed for thorough analysis of different anaesthetic parameters with propofol, Ketofol and etomidate as induction agents in glycopyrrolate premedicated dogs maintained under isoflurane anaesthesia during surgery. Time of induction was lowest in group P and highest in group E. Quality of induction was relatively better in groups P and KP compared to group E. Intubation quality and intubation score was relatively better in group P and KP compared to group E. Quality of analgesia was better in group KP compared to groups P and E. Myoclonus was observed in group E but not in group P and KP. Smooth and rapid recovery was observed in group P and KP whereas rough recoveries were observed in group E. Based on the above findings following results conclusion was made- ketofol group showed most suitable results in anaesthetic parameters followed by propofol and etomidate groups.

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