B-4679
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RESEARCH ARTICLE Indian Journal of Animal Research

Anaesthetic Effects of Propofol, Ketamine and their Combination (Ketofol) as Total Intravenous Anaesthesia (TIVA) in Pigs

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10.18805/IJAR.B-4679

ABSTRACT

Background: Endotracheal intubation for inhalation anaesthesia in pigs is not considered a good anaesthetic method as it is technically difficult because of oral anatomy and the presence of excess tissues in the oropharyngeal region. Moreover, the major limitation of inhalation anaesthesia is that it requires the use of a cumbersome and costly anaesthetic machine, including a suitable breathing system and vaporizer and is the exposure of operating-room personnel to the pollution in the ambient air. Therefore, the present study was undertaken to evaluate the effect of propofol, ketamine and their combination 'Ketofol' as a TIVA in pigs.

Methods: The study was conducted in eighteen piglets of either sex. The piglets were randomly divided into three groups with six animals in each group. All the three groups were premedicated with Atropine sulphate @ 0.04mg/kg body weight and Xylazine Hydrochloride @ 1mg/kg body weight I.M. and Medazolam @ 0.5mg/kg body weight I.M. with minimum forcible restraint as pre-anaesthetic. In group-I, propofol @ 5mg/kg body weight, in group-II, ketamine @ 5mg/kg body weight and in group-III, ketofol @ 4mg/kg body weight was administered intravenously for induction after 15 minutes of pre-anaesthetic administration. Surgical anaesthesia was maintained for 90 minutes in all three groups *viz.* group-I, group-II and group-III with propofol @ 2.5mg/kg, ketamine @ 2.5mg/kg and ketofol @ 2mg/kg body weight respectively by intermittent bolus injection (IBI) technique. Clinical and cardiopulmonary profiles were evaluated before administration of the anaesthetic agent (0 minutes) then at 15, 30, 60 and 90 minutes during and after administration of anaesthetic agents to evaluate their anaesthetic effect.

Result: The study revealed that induction time (IT), duration of analgesia (DOA), duration of recumbency (DOR) and recovery time (RT) interval showed better result in the combination of ketamine and propofol group as compared to propofol and ketamine-induced individual group. The temperature and respiration rate was significantly decreased in all the groups at 30 minutes during TIVA whereas heart rate was significantly increased in all the groups at 15 minutes. The combination of ketamine and propofol group showed a consistent diastolic pressure and systolic pressure during the entire period of anaesthesia. The SPO_2 in the ketamine-induced group showed a significant decrease ($P<0.01$) as compared to the propofol and ketofol group. It was concluded that the anaesthetic drug combinations resulted in smooth and uneventful induction with mild cardiopulmonary depressions and rapid recovery.

Key words: Cardiopulmonary, Clinical, Ketamine, Ketofol, Pig, Propofol, TIVA.

INTRODUCTION

Pigs are frequently used for biomedical research or medical training purposes because their cardio-respiratory anatomy and physiology (Hildebrand *et al.,* 2013) and gastrointestinal functions (Kararli, 1995) are very similar to that of humans. Treatment of injuries, fracture, tumour and a host of other internal problems necessitate administration of sedative and/or general anaesthesia. Under these circumstances, maintenance of anaesthesia with injectable anaesthetics might be necessary, as the provision of inhalational anaesthetic drugs is not possible, or even unwanted due to their effects on cardiovascular function (Lundeen *et al.,* 1983). Pigs are not considered as a good subject for inhalation anaesthesia as endotracheal intubation is technically difficult because of oral anatomy and the presence of excess tissues in the oropharyngeal region (Janiszewski *et al*., 2014). Another major disadvantage is the exposure of operating-room personnel to the pollution in the ambient air. Some of the commonly used intravenous anaesthetic drugs causing hypoventilation, respiratory acidosis and potentially hypoxia when used for induction and maintenance of general anaesthesia (Clarke *et al.,* 2014).

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How to cite this article: Saikia, B., Sarma, K., Das, H., Lallianchhunga, M.C., Pal, D. and Sonowal, P.J. (2021). Anaesthetic Effects of Propofol, Ketamine and their Combination (Ketofol) as Total Intravenous Anaesthesia (TIVA) in Pigs. Indian Journal of Animal Research. DOI: 10.18805/IJAR.B-4679.

Submitted: 15-06-2021 **Accepted:** 31-08-2021 **Online:** 16-09-2021

Propofol has long been known to cause hypoventilation or even apnoea in several animal species including dogs and sheep when given intravenously (Lin *et al.,* 1997). Ketamine possibly increases muscle tone and induces spontaneous movement and, occasionally, convulsions (Saikia *et al.,* 2020). The combination of propofol and ketamine has several benefits in the terms of hemodynamic stability, absence of respiratory depression, postoperative analgesia

and recovery (Amornyotin, 2014). To reduce these undesirable effects, a total intravenous anaesthetic (TIVA) protocol containing propofol, ketamine and Ketofol was found to provide stable cardiovascular conditions and excellent antinociception in atropine and xylazine premedicated dogs (Saikia *et al.,* 2019). Therefore, the TIVA may be a good alternative to inhalation anaesthesia to carry out even major long-duration surgical procedure. Maintenance of anaesthesia can be obtained by administering intermittent boluses, continuous rate infusion or by target-controlled infusion. To our knowledge, no comparison has been made among ketamine, propofol and ketofol regarding their anaesthetic effects on clinical and cardiopulmonary in pigs. The primary aim of the current study was to determine the anaesthetic effect of propofol/ketamine/ ketofol as TIVA in pigs.

MATERIALS AND METHODS

The study was carried out on eighteen piglets of either sex between 2-4 month of age those were brought for elective ovariohysterectomy or castration. The piglets were randomly divided into three groups consisting of six animals in each group *viz*. Group-I, II and III. Food was withheld for approximately 12 h before premedication and all pigs were found healthy based on a clinical examination before each experimental session. All the animals were pre-anaesthetised by injecting Atropine Sulphate@ 0.04mg/kg body weight Xylazine Hydrochloride @ 1mg/kg body weight and Medazolam@0.5mg/kg body weight intramuscularly with minimum forcible restraint. Once the signs of sedation became evident, venous access was gained via the ear vein using an IV cannula and the I.V. line were maintained with slow infusion of normal saline solution @15-20 drops/min. Induction and maintenance of anaesthesia were achieved in Group-I, II and III as follows.

The doses of propofol, ketamine and ketofol were chosen based on the results from a previous study.

Monitoring of anaesthesia

In this study, the induction time (IT), duration of analgesia (DAN), duration of anaesthesia (DAN) and recovery time (RCT) were determined. Induction time was determined as the time interval in minutes between the end of drug administration and the time taken for the pig to assume lateral recumbency. The duration of analgesia was determined as the interval in minutes between the disappearance and reappearance of pedal withdrawal reflex. Duration of anaesthesia was determined as the time interval in minutes between the pigs' assumption of lateral recumbency and return to sternal posture. The recovery time is the time interval in minutes between the assumption of sternal posture and when the pigs finally assume standing position without ataxia.

Monitoring of clinical parameters

Rectal temperature was recorded with a clinical thermometer in Fahrenheit (°F) before administration of the pre-anaesthetic agent (0 minutes) thereafter at 15, 30, 60 and 90 minutes of injection of anaesthetic agents. Heart rate (beats/min), respiratory rate (breaths/min) diastolic pressure, systolic pressure and SpO2 were recorded before administration of the pre-anaesthetic agent (0 minutes) thereafter at 15, 30, 60 and 90 minutes of injection of anaesthetic agents using a multiparameter electro cardiogram monitor (PM-9000 Express, Mindary Co., Ltd., Shenzhen, China)

Statistical analysis

Physiological and clinical data were compared among study times and groups using a one-way analysis of variance (ANOVA) for repeated measures. Data were presented as mean ± SE. A p-value of <0.05 was considered significant in all tests.

RESULTS AND DISCUSSION

Monitoring of anaesthesia

The induction time, duration of analgesia (DOA), duration of recumbency (DOR), recovery time (RT) and time interval for incremental maintenance doses of anaesthetics of propofol (Group-I), ketamine (Group-II) and ketofol (Group-III) in pigs have been depicted in Fig 1.

The induction time of Group-II (1.44 ±0.30 min) was significantly (P>0.01) higher than Group-I (0.37 ± 0.02 min) and Group-III (0.48 ± 0.02 min). The induction times in the animals of Group-I and Group-II did not differ significantly. The short induction times were also observed with propofol and ketophol in canine by Bayan and Konwar (2014) and the longer induction time with ketamine anaesthesia was

Group	No. of animals	Pre anaesthetic Dose and route	Anaesthetic for Induction	Anaesthetic dose and route for Maintenance up to 90 minutes
I	6	Atropine@0.04g/kg I/M, Xylazine @ 1 mg/kg, I/M, Midazolam @0.5 mg/kg, I/M,	Propofol,I/V @5mg/kg	Propofol half of induction dose (2.5 mg) I/V(as Intermittent Bolus Injection) each time as required when movement was detected on the application of noxious stimuli for 90 minutes.
II	6		Ketamine I/V @5mg/kg	Ketamine half of induction dose (2.5 mg) I/V (as Intermittent Bolus Injection) each time as required when movement was detected on the application of noxious stimuli for 90 minutes.
III	6		Ketofol I/V @4mg/kg	Ketofol half of induction dose, (2 mg) I/V (as Intermittent Bolus Injection) each time as required when movement was detected on the application of noxious stimuli for 90 minutes.

also observed by Sravanti *et al.* (2016). The rapid onset of induction in Group -I and Group- III might be due to the high lipid solubility of propofol and the ability to rapidly cross the blood-brain barrier. Propofol enhances the effect of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and decreases the brain's metabolic activity.

The duration of analgesia in the animals of Group-I (16.16 ± 0.80min) was significantly ($p<0.01$) shorter than Group- II (20.16±1.22min) and Group- III (20.66 ± 1.14 min) (Fig1) A similar observation of a very short duration of analgesia during propofol anaesthesia in dogs was also reported by Dewangan *et al.* (2010). The need for concurrent administration of analgesics when propofol is used during painful procedures as propofol has minimal analgesic properties (Waelbers *et al.,* 2009). There was no significant difference between the animals of the group- II and group-III. The present findings of group III were closely similar to the findings of Kumar *et al.* (2014). The longer duration of analgesia in the animals of the group- III might be attributed to the cumulative effect of xylazine and ketamine which enhanced the duration of analgesia. Xylazine has good analgesic properties and it was injected as pre-anaesthetic and there is a synergistic effect with ketamine (Kinjavdekar *et al.,* 2005).

In the case of the duration of recumbency, it was the duration of recumbency was significantly ($p<0.01$) longer in group II (116.50±4.57min) as compared to group-I (104.25±1.68min) and group- III (106.83±3.37 min) (Fig 1). The differences between groups I and group- III was non-significant. A shorter recumbency period also reported by Adetunji *et al*. (2002) during propofol anaesthesia premedicated with xylazine and atropine in dogs. The animals of group-III showed a shorter duration of recumbency after ketofol anaesthesia which might be due to the induction and maintenance agent propofol as propofol is rapidly redistributed from the brain to other tissues and is also efficiently eliminated from plasma by hydroxylation by one or more hepatic cytochrome p-450 isoforms which explain its short action and the rapid recovery as compared to ketamine.

The recovery time in group-II (23.67±2.30 minutes) was significantly ($p<0.05$) more than group-I (19.67±1.36 minutes) and group-III (21.17±1.57 minutes). The differences in recovery time between group-I and group- II were non-significant. The shorter recovery time in group-I and group-III in the present investigation was following the earlier reports of Bayan and Konwar (2014) which might be due to the induction and maintenance agent propofol as propofol is rapidly redistributed from the brain to other tissues.

The time interval for incremental maintenance doses of anaesthetics in group III (21 ± 0.77 minutes) and group- II (19.83±1.13) were significantly ($p<0.01$) longer than group I (15.33±1.98). The longer time interval for incremental maintenance doses of ketofol in the animals of group III might be due to the synergistic effect of ketamine and propofol.

The critical analysis reported that the ketofol anaesthesia showed better efficacy on anaesthetic properties than individual use of ketamine and propofol as total intravenous anaesthesia (TIVA) in pigs.

Monitoring of clinical parameters

The effect of anaesthesia on clinical parameters viz. rectal temperature, heart rate (beats/min), respiratory rate (breaths/min) diastolic pressure, systolic pressure and SpO2 are shown in Fig 2.

Rectal temperature decreased insignificantly ($P>0.05$) up to 30th minutes in all the groups (Fig 2) but it remained within the physiological range. Thereafter, the rectal temperature increased insignificantly towards the base value till the end of the observation in all three groups. A decreased in rectal temperature during continuous infusion of propofol in dogs has also been reported by Jena *et al.* (2014). The

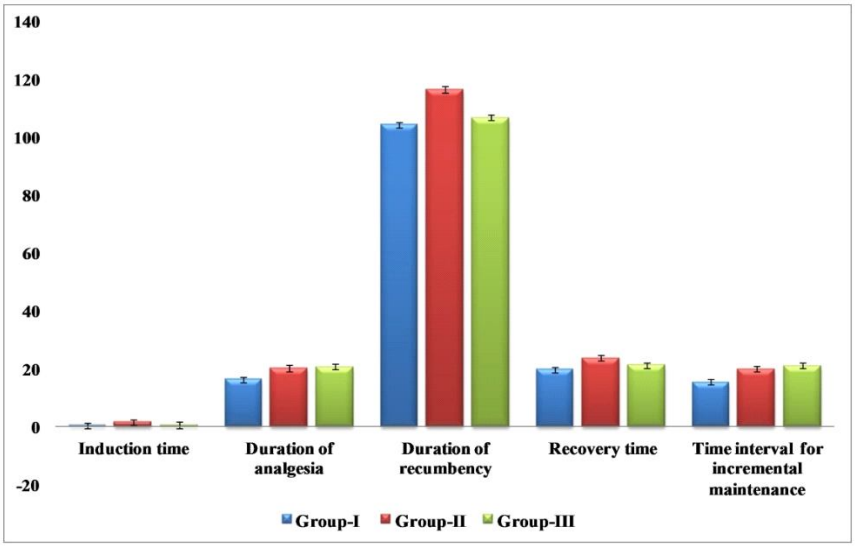

Fig 1: Anaesthetic effects of propofol, ketamine and their combination (ketofol) as total intravenous anaesthesia (TIVA) in pigs.

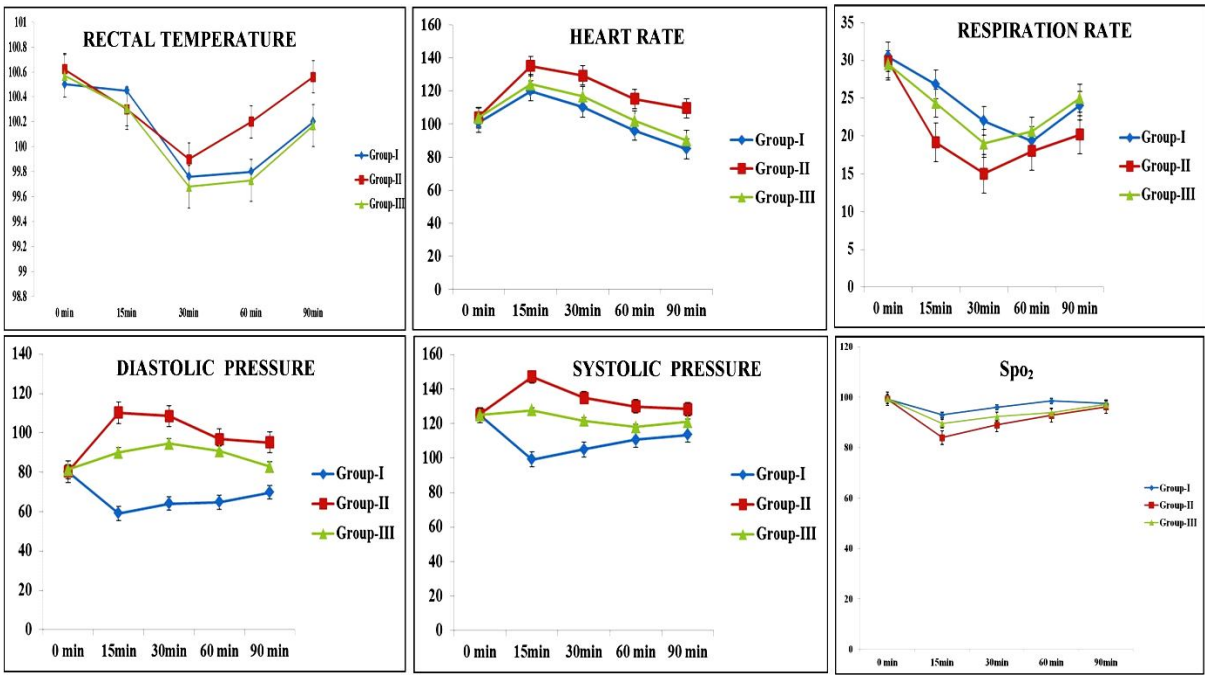

Fig 2: Anaesthetic effects of propofol, ketamine and their combination (ketofol) as total intravenous anaesthesia (TIVA) on clinical parameters in 9gs.

difference in rectal temperature during anaesthesia was insignificant among the three groups up to 30 minutes but a significant difference in rectal temperature was observed among three groups at 60 and 90 minutes (Fig 2) In group-II higher rectal temperature was recorded at 60 and 90 minutes as compared to group-I and group-III. The higher rectal temperature in group II might be due to the presence of sluggish pedal reflex, mild struggling and moderate muscle relaxation towards the end part of observation.

In all the three groups, the heart rates increased significantly (P< 0.01) up to 15 minutes and thereafter it decreased gradually till the end of observation (Fig 2) but remained well within the initial values. There was a significant difference in heart rate among the three groups at different time intervals. A significant increase (P<0.05) in heartbeat was observed in group II from 15 minutes till the end of observation than group I and group III. This might be due to cardiac stimulatory effects of ketamine, which remained increased for some time as also reported by Kumar *et al.* (2014). Similar findings were also reported by Hellebrekers *et al.* (1998) who observed a higher heart rate during TIVA, in a group of dogs receiving ketamine compared to a group of dogs receiving propofol. There was no significant variance in heartbeat at any stage of TIVA between group-I and group III.

There was a significant difference in respiratory rate among the three groups at 15, 30 and 90 minutes during TIVA. A significant decrease (P<0.05) in respiratory rate was observed in the animals of group-II than group-I and group -III. There was no significant variation between group-I and group-III (Fig 2). Ketamine is also a cause of respiratory depression and was observed after bolus administration, often followed by an “apneuistic” breathing pattern, which is characterized by periodic breath-holding on inspiration followed by short periods of hyperventilation (Kastner, 2007).

There was a significant difference (P<0.01) of diastolic pressure and systolic pressure among the three groups till the end of observation. Significantly higher (P<0.01) diastolic and systolic pressure was observed in the group II during TIVA while a significantly lower (P<0.01) diastolic and systolic pressure was recorded in group-I animals for the entire period of TIVA after induction (Fig 2). The diastolic and systolic pressure of group-III animals was more than group-I animals but less than group-II animals till the end of the experiment (Fig 2). Group-III animals showed a consistent diastolic pressure during the entire period of anaesthesia which might be due to the positive synergistic effect of propofol and ketamine when combined together (Larisa *et al.,* 2010).

There was a significant difference (P<0.01) of SPO_2 among the three experimental groups only at 15 and 30 minutes after the end of the experiment no significant difference was recorded among the groups. In group II, a significant decrease (P<0.01) of SPO_2 was observed as compared to group-I and group-III. It might be due to a decrease in respiratory rate which occurred as a result of the cumulative effect of xylazine and ketamine in the early phase of anaesthesia. In addition to this vasoconstriction property of xylazine and ketamine might also lead to low pulse oximeter readings (Watkin *et al*., 1987).

CONCLUSION

The current study shows that pigs anaesthetized with ketofol, an anaesthetic drug combination resulted in the smooth and uneventful induction with mild cardiopulmonary depressions and rapid recovery. Ketofol provides more stable hemodynamic for the induction of anaesthesia in pigs compared to the sole use of propofol and ketamine. Therefore, it helps to maintain oxygen saturation. However, these results need to be confirmed with larger groups in future studies.

ACKNOWLEDGEMENT

The authors are highly thankful to the vice Chancellor, Central Agricultural University, Imphal and Dean, College of Veterinary Sciences and AH, Mizoram for providing the necessary facilities and fund to carry out this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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