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Comparative Evaluation of the Isoflurane-sparing Effects of Premedication with Dexmedetomidine-Butorphanol and Xylazine-Butorphanol in Tiletamine-Zolazepam induced anaethesia in Goats

Sanjaykumar Vithalrao Udharwar[1], John Martin K. D.[2], Sudheesh S. Nair[3], S. Anoop[4], C. Jayakumar [5], Aziz Zarina[6] , Senthilkumar, S[7], and Syam K. Venugopal[8]

[1]Ph. D. Scholar, Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Mannuthy, Thrissur, KVASU, Wayanad, Kerala
[2]Professor and Head, University Veterinary Hospital, Kokkalai, College of Veterinary and Animal Sciences, Mannuthy, Thrissur, KVASU, Wayanad, Kerala
[3] Assistant Professor, Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Pookode, Thrissur, KVASU, Wayanad Kerala
[4]Associate Professor and Head, Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Pookode, Thrissur, KVASU, Wayanad Kerala
[5]Assistant Professor, Department of Animal Reproduction, Gynecology and Obstetrics, College of Veterinary and Animal Sciences, Pookode, Thrissur, KVASU, Wayanad Kerala
[6]Associate Professor and Head, Department of Veterinary Surgery and Radiology, Veterinary College and Research Institute, Salem, TANUVAS, Tamil Nadu
[7]Professor and Head, Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Mannuthy, Thrissur, KVASU, Wayanad, Kerala

Abstract

Isoflurane is frequently used as an inhalant anaesthetic in small ruminants. The drug isoflurane has several adverse side effects, including respiratory depression, hypotension and diminished cardiac output. Additionally, its metabolites pollute the atmosphere. Premedicating goats with an alpha-2 agonist, such as xylazine, is a long-standing practice. Some negative consequences are associated with xylazine and each negative impact is dose-dependent. Additive effects are produced when alpha-2 agonists and opioids are combined so that the dose of the latter can be reduced.

Due to its high price and relatively new introduction dexmedetomidine, although it had advantages over xylazine. In this study, goats were premedicated with xylazine-butorphanol in one group and dexmedetomidine-butorphanol in another group. Anaesthesia was then induced with tiletamine-zolazepam and maintained by isoflurane. It was planned with the hypothesis that a combination of dexmedetomidine along with butorphanol in the partial intravenous anaesthesia protocol might have an isoflurane-sparing effect than xylazine-butorphanol premedication.

Key words: *Anaesthesia, goat*

Introduction

Goats are becoming more significant because they are used as surgical models for a range of biomedical research studies and because they are becoming popular as expensive meat-producing animals. This has led to increased interest in surgeries on goats and a corresponding demand for an effective anaesthetic protocol.

Premedication with alpha-2 agonist medications like xylazine with or without opioids, induction with injectable anaesthetics and inhalant anaesthetic maintenance with isoflurane are frequently used to induce balanced anaesthesia in goats.

The dose for the principal drug, i.e., inhalant anaesthetics, can be reduced in balanced anaesthesia protocols by the sparing action of lesser important drugs such as opioids/sedatives.

Isoflurane alone is insufficient to completely eliminate the autonomic and nociceptive responses to the surgical stimuli, which can result in inadequate analgesia during surgery. (Steffey and Mama, 2007). The

usual adverse effects of isoflurane, such as respiratory depression, hypotension and decreased cardiac output, must be minimised by reducing the amount required to maintain general anaesthesia (Hikasa *et al.*, 2000).

Isoflurane is a chlorofluorocarbon substance that might be harmful to the ozone layer of the earth and might cause global warming. Isoflurane and its metabolic byproducts pollute the atmosphere and damage it (Joubert, 1999). Therefore, any decrease in isoflurane dosage will benefit the patient, surgical team and environment.

Due to their strong analgesic impact, opioid analgesics are said to have an inhalant-sparing effect and minimise the minimum alveolar concentration (MAC) needed to maintain a surgical plane of anaesthesia (Tranquilli *et al.*, 2007). There are reports that including butorphanol in the anaesthetic protocol reduced the isoflurane requirement in goats (Kumar *et al.*, 2013) and cattle (Senthilkumar *et al.*, 2013).

Over the past few years, alpha-2 agonists have gained popularity in balanced anaesthetic approaches, mostly due to their ability to lower the MAC of volatile anaesthetic agents and support postoperative analgesia. According to Poppel *et al.* (2015), a xylazine infusion during isoflurane anaesthesia lowered the quantity of isoflurane in horses by more than 45%. Singh *et al.* (2013) reported greater isoflurane (minimum alveolar concentration) sparing effect of dexmedetomidine in comparison to xylazine and medetomidine in buffaloes.

However, there is a scarcity of literature showing the sparing effect of the combination of alpha-2 agonists and opioids on isoflurane in goats until now. Due to the possibility that premedication with a dexmedetomidine-butorphanol combination could spare the isoflurane, it was decided to compare the isoflurane-sparing effects of this combination to that of xylazine-butorphanol in goats induced with tiletamine-zolazepam and undergoing various surgical procedures.

Materials and Methods

The study was conducted on 12 goats reported with various surgical affections like abdominal hernia, overgrown and pointing horns, fracture of long bones, gangrenous mastitis, etc., at Teaching Veterinary Clinical Complex, Mannuthy and University Veterinary Hospital, Kokkalai, Thrissur of Kerala Veterinary and Animal Sciences University and selected for respective surgeries under general anaesthesia. The clinical status of the animals was assessed by recording heart rate, respiration rate, rectal temperature, electrocardiographic study and by conducting haematological and biochemical examinations.

Experimental design

The animals were randomly divided into groups viz., Group I and II, each group comprising six animals. All the animals fasted for 18 hours, and water was withheld for eight hours before the anaesthesia. The age in months and body weight in kilograms of selected animals were recorded. Detailed physical and clinical examination was performed, and the clinical status of the animals was assessed.

The animals of both groups were premedicated with two different combinations of drugs. Group I (X-B-TZ-Iso) received a combination of xylazine intravenously, at the dose rate of 0.02 mg/kg body weight and butorphanol at the dose rate of 0.05 mg/kg body weight intravenously as premedicants.

Group II (D-B-TZ-Iso) received a combination of dexmedetomidine intravenously, at the dose rate of 2.5 µg/kg body weight and butorphanol at the dose rate of 0.05 mg/kg body weight intravenously as premedicants. In all the animals, induction was done with tiletamine-zolazepam at the dose rate of 2.5mg/ kg body weight IV.

Upon achieving adequate muscle relaxation, the trachea was intubated with a cuffed endotracheal tube of suitable size and was connected to the small animal anaesthesia machine. For maintenance of anaesthesia, isoflurane was administered through an agent-specific vaporiser along with oxygen using a semi-closed rebreathing system. Oxygen 100 per cent along with isoflurane at three per cent was given with a fresh gas flow rate of 3 L/ min for the first three minutes to achieve saturation of the breathing circuit with isoflurane vapours

(Vishnuguruaran *et al.,* 2016). The fresh gas flow rate was then reduced and maintained between 1-2 L/min. The vaporiser setting was altered between zero and three percent during anaesthesia to maintain a uniform surgical plane of anaesthesia, observing the reflexes such as palpebral, swallowing and pedal reflexes and response to surgical stimulation.

Vital parameters like respiration rate, heart rate, SpO_2 and rectal temperature were monitored during the entire anaesthesia using multi-parameter monitor (Skanray True Scan S 400, patient Monitor, Skanray Technologies Ltd.). A single individual evaluated the quality and depth of anaesthesia through a blindfold study.

Scoring was done to assign numerical values starting from 1 to 4 (1-poor, 2-fair, 3-good, 4-excellent) for induction and maintenance quality (Bodh *et al.,* 2015). Qualitative and subjective effects (sedation, analgesia, muscle relaxation) of drugs were judged by observing the physical response of the anaesthetised goats to surgical stimulation during various surgeries. Weaning from the anaesthetic machine was done upon completion of the surgical procedure.

The endotracheal tube was removed on regaining the swallowing reflex. All the animals were administered normal saline in jugular vein throughout the surgery. The animals were monitored till complete recovery. The dial setting of the vaporiser was different in different animals at the end as per the requirement to maintain the surgical plane of anaesthesia. Goats were also observed for any difference in recovery.

Calculation of the amount of liquid isoflurane utilised

The changes in the fresh gas flow rate and vaporiser setting at various times were recorded. The total duration of anaesthesia in minutes was recorded from turning on to off the vaporiser. The data obtained were used for calculating the quantity of isoflurane consumed for the different anaesthetic combinations by following formula (Senthilkumar *et al.,* 2013).

Isoflurane vapour delivered (ml) = vaporiser setting (per cent) x fresh gas flow (litre per minute) x duration (minute) x 10.

The total isoflurane vapour delivered (ml) for the entire duration of anaesthesia was calculated by summing up the isoflurane vapour delivered for each fresh gas flow (FGF) and vaporiser settings employed.

Yadav *et al.* (2021) determined the isoflurane-sparing impact using the same formula used in the anaesthesia study conducted on buffaloes. To bring uniformity to data obtained for various cases in practical but theoretically the same time in various animals, the authors equated the total isoflurane vapour value to 400 kilograms of body weight. (average body of buffaloes) and 40-minute duration. This equation for standard weight and time duration aided in easy statistical comparison. The authors reported a method for calculating the amount of isoflurane vapour required for 400 kilograms and 40 minutes basis (ml) = Total isoflurane vapour delivered (ml) x 400 x 40 / body wt. (kg) x duration of maintenance (minutes).

In the present study, the isoflurane vapour value obtained was equated to 40 kg weight as 40 kg was the average weight of goats and 60 minutes duration,to ring uniformity in data and this set the basis for statistical comparison of percentage reduction in isoflurane utilised in Group I and II. The modified formula was as follows:

Isoflurane vapour delivered for 40 kilograms and 60 minutes basis (ml) = Total isoflurane vapour delivered (ml) x 40 x 60 / body wt. (kg) x duration of maintenance (minutes)

Table 1. Amount of isoflurane utilised (on 40 kg and 60-minute basis in ml) by individual goats of Group I and II during various surgical interventions

Isoflurane liquid utilised (ml)		
Animals	**Group I**	**Group II**
Animal A	13.41	9.79
Animal B	4.64	16.82
Animal C	6.65	4.26
Animal D	2.93	6.04
Animal E	5.13	4.19
Animal F	19.45	6.37
Mean ± S.E.	8.71 ± 2.61	7.92 ± 1.97
t-value (P-value)	0.241^{ns} (0.815)	

ns non-significant (P>0.05)

Table 2. Weight (kg) and duration of anaesthesia (min) of goats of Group I and Group II

Animal	Group I (X-B-TZ-Iso)		Group II (D-B-TZ-Iso)	
	Weight	Duration of anaesthesia	Weight	Duration of anaesthesia
1	16	48	28.2	32
2	40	65	12	68
3	28	42	33.1	32
4	54	44	25.5	29
5	37	76	36	98
6	15.5	24	30.5	32

The effect of ambient temperature and pressure on the calculated volume of liquid isoflurane was neutralized using Avogadro's principle as follows: Isoflurane vapour delivered for 40 kg and 60-minute basis (ml) x 181.4) x ambient temperature /273) x 760/ barometric pressure) The statistical analysis of data was done by one-way analysis of variance (ANOVA) and Demean's multiple range test (Duncan,1955)

Results and Discussion

The current study used a partial intravenous anaesthetic technique to administer anaesthesia. When an inhalational drug such as isoflurane is used as the sole agent, it is often not sufficient to abolish the desired autonomous and nociceptive responses to the surgical stimulus, potentially leading to inadequate peri and post-operative pain (Steffey and Mama, 2007). The use of inhaled anaesthetics along with intravenous medications (analgesics and/or sedatives) is known as partial intravenous anaesthesia (PIVA), which improves cardiopulmonary parameters by reducing the amount of anaesthesia needed by inhaled anaesthetic agents to prevent intraoperative awareness and consequently, lessens their dose-related cardiovascular depressing effects, (Doherty *et al.* (2006).

Since each anaesthetic has distinct pharmacodynamics and pharmacokinetics merits and demerits, it is wise to achieve surgical anaesthesia by combining a number of drugs (balanced anaesthesia), if necessary, to counteract any adverse effects of each agent. Lin (2014) reported that combining analgesic drugs with different pharmacological mechanisms may provide a higher degree of analgesia than each drug administered alone, which may significantly decrease hypnotic agents such as isoflurane.

In the present study, goats were premedicated with dexmedetomidine and xylazine along with butorphanol and anaesthesia was maintained with isoflurane. In veterinary practice, xylazine, an alpha-2 adrenergic receptor agonist, is the most often used sedative and a supplement to general anaesthesia, according to Ponser (2018). This drug produces its effects by binding to alpha-2 adrenergic receptors distributed centrally in the brain or supraspinal (for sedation and some antinociception) and in the dorsal horn of the spinal cord (for antinociception) as well as in the vessel vasculature (for vasoconstriction). Xylazine has a very effective muscle-relaxing action.

Dexmedetomidine is much more specific than xylazine for alpha-2 receptors than α_1 receptors. The pharmacologic effects of dexmedetomidine include depression of the central nervous system (sedation and anxiolysis), analgesia (somatic and visceral) and muscle relaxation (Plumb, 2008).

Butorphanol provides preemptive and postoperative analgesia in goats (Carroll and Hartsfield, 1996). Butorphanol is a partial agonist, antagonist, or k agonist, according to Depenbrock (2017).

Isoflurane is the preferred inhalant for comprising ruminants since it is not arrhythmogenic, relies less on metabolism for removal and has a quicker induction and recovery time (Carroll and Hartsfield, 1996). Isoflurane acts on the spinal cord to restrict movement in response to noxious stimuli. The dorsal horn, which regulates and conveys noxious sensations to other central nervous system locations, is a probable site of action (Jinks *et al.*, 1999).

The amount of isoflurane liquid in ml utilised (on a 40kg and 60-minute basis in ml) by the individual goat is shown in Table 1. It was observed that the volume of isoflurane utilised (mean ± S.E.) in Group I was 8.71 ± 2.61 ml, and in Group II was 7.92 ± 1.97 ml. There was a non-significant ($P>0.05$) difference between the amount of isoflurane utilised between the two groups, i.e., a 9.19% reduction in isoflurane was recorded in Group II, (Table 1). Sharma *et al.* (2014) performed studies on the inhalant-sparing effects in dogs. The authors found that the rapid biotransformation of xylazine, which had an elimination half-life of 30.1 minutes compared to dexmedetomidine, which had a half-life of 47 minutes, was the cause of the sparing effect of halothane in the dexmedetomidine administered group of dogs. When calves were premedicated with opioids such as butorphanol tartrate (0.02 mg/kg body weight) and buprenorphine hydrochloride (0.006 mg/kg body weight), respectively, Senthilkumar *et al.* (2013) obtained 18.7% and 14.63% reduction in MAC of isoflurane. In a study in cows, a continuous rate of lidocaine at a dose rate of 50 ml/kg/min significantly decreased the isoflurane requirement by 16.7% (Vesal *et al.*, 2011). The analgesic effects of butorphanol on the MAC of isoflurane, had been investigated in ruminants (Kumar *et al.*, 2013).

However, the reduction in the quantity of isoflurane in Group II was insignificant compared to goats of Group I, but its combination with opioids and alpha-2 agonists might have potentiated the sparing effect of isoflurane in goats. So, it is concluded that dexmedetomidine-butorphanol did not have a significant isoflurane-sparing effect than xylazine-butorphanol in goats but may be included in the balanced anaesthetic protocol for goats undergoing long-duration surgeries to reduce the quantity of isoflurane required for maintenance.

Conclusion

The inclusion of opioid analgesic (butorphanol) along with alpha-2 agonist (dexmedetomidine) reduced the quantity of isoflurane required for maintenance of anaesthesia in goats undergoing various surgeries induced with tiletamine-zolazepam.

The dexmedetomidine-butorphanol combination has a higher sparing effect (9.19%) on isoflurane than xylazine-butorphanol administration in goats.

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