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Determination of minimum infusion rate of propofol in combination with electroacupuncture in goats

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ABSTRACT

Total intravenous anesthesia (TIVA) is frequently used anesthetic protocol in animals when inhalation anesthesia is not available. To date, it has not yet been known whether electroacupuncture (EA) can affect propofol-based TIVA in goats. Therefore, the present paper aims to determine the minimum infusion rate (MIR) of propofol, in combination with EA, required to preclude purposeful movement of the extremities in response to standardized noxious stimulation in goats. Twelve clinically healthy goats weighing 17.45 ± 2.15 kg were randomly allocated into two groups with six goats each. Propofol alone (P group) and propofol combined with EA (EA-P group). In the EA-P, propofol was given 30 min after EA stimulation. For induction of anesthesia, a bolus of propofol was administered at 4 mg/kg IV, and an infusion dose of 0.4 mg/kg/min was initially set for maintenance. The MIR of propofol in both groups was determined by testing for responses to stimulation (clamping on a digit with Vulsellum forceps) at 10-min intervals after inducing anesthesia until the end period of the experiment. Cardiorespiratory variables and nociceptive threshold were measured throughout anesthesia. The median propofol MIR was significantly lower in the EA-P group than the P group [0.520 (0.467–0.572) and 0.650 (0.600–0.677)], respectively; $p = 0.0013$). In the P group, goats anesthetized with MIR showed a significant increase in heart rate and cardiac index ($p = 0.0010$ and $p < 0.0001$, respectively), and a decrease in respiratory rate ($p = 0.0001$). Additionally, the EA-P showed a significant decrease in hemoglobin oxygen saturation following the initial infusion rate at 2 min ($p = 0.0023$) and 10 min ($p = 0.0007$) as compared to the P group. A significant increase in nociceptive threshold was recorded in the EA-P threshold than that of the P group ($p < 0.005$). EA combined with propofol provides antinociception, decreases the MIR of propofol-based TIVA, and subsequently lessens the negative cardiorespiratory consequences related to propofol anesthesia in goats.

1. Introduction

Electroacupuncture (EA) is the most recent method of manual acupuncture, in which acupuncture needles are placed into specific points on the skin to transmit electrical stimulation. Due to its numerous medical applications, EA has grown in popularity over the last few decades. EA has been shown to successfully improve antinociception in a variety of surgical procedures in humans (Pohodenko-Chudakova, 2005) and domesticated animals (Kim et al. 2004; Sheta et al. 2015), without altering the patients' physiological parameters. Furthermore, EA-based anesthesia has been used successfully in humans to improve antinociception, reduce the amount of anesthetics required, and thus reduce the adverse effects during surgical interventions (Lin et al. 2002). In contrast to other routinely used injectable analgesics, like alpha$_2$ adrenergic agonists, which have unfavourable effects on the lungs, the use of EA in ruminants appears to produce safe antinociception (Abouelfetouh et al. 2021b).

Total intravenous anesthesia (TIVA) is a technique for inducing and

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maintaining anesthesia using an injectable anesthetic (Brown et al. 2018). In veterinary practice, TIVA has been used to produce acceptable depth of anesthesia for surgical procedures in recent years (Brighton, 2013; Herbert et al. 2013). In order to provide adequate antinociception and induce hypnosis during surgical procedures and to lower the dosage of anesthetic required, analgesics have frequently been used in conjunction with anesthetics. In ruminants, to date, the feasibility of EA analgesia in combination with TIVA has not yet been researched.

Propofol is a sedative hypnotic agent that is frequently used for the induction and maintenance of anesthesia in domestic animals (Dzikiti et al. 2010; Cattai et al. 2018). The effects of propofol were directly mediated by activating type A gamma aminobutyric acid ($GABA_A$) receptors, which increased calcium conductance, causing nerve cells to become hyperpolarized and thus blocking the transmission of neuronal impulses (Pascoe, Eugene, 2018). Because propofol is rapidly metabolized and eliminated from the body, it is suitable for TIVA either via continuous infusions or repeated incremental dosages (Mandsager et al. 1995). Propofol, on the other hand, can cause post-induction apnea and cardiorespiratory depression if administered continuously and in a large dose (Galatos, 2011). In addition, propofol alone does not produce analgesia and concurrent administration of analgesics is often necessary to improve the analgesic effects of propofol. (Glowaski and Wetmore, 1999).

To our knowledge, the effect of EA on propofol-based TIVA has not been previously reported in goats. Therefore, the objective of this study was to determine mnimum infusion rate (MIR) of propofol and the associated cardiorespiratory and antinociceptive effects during its combination with EA. Our hypothesis was that EA improves anticonceptive outcome and thus lowers MIR of propofol in goats.

2. Material and methods

2.1. Animals

Yichang White goats aging 10.5 ± 1.8 months and weighing 17.5 ± 2.2 kg were enrolled in this study. For the purposes of this study, all goats were submitted to a comprehensive physical examination and hemato-biochemical profiles including a complete blood count, serum biochemistry and serological determination of Brucella melitensis status. Before the experiment, the animals were acclimatized to the experimental environment for 2 h daily for one week. They were denied access to food for 16–20 h before the beginning of the experiment but gained free access to water. This study was approved by the ethical committee of Huazhong Agricultural University (HZAUGO-2019-007).

2.2. Experimental design

This study used prospective, randomized, and blinded design. A total of twelve goats were randomly assigned to one of two equal sized groups using a computer program (www.randomizer.org) (accessed 29 October 2019): Propofol alone (P) and EA in combination with propofol (EA-P) group. In both P and EA-P groups, the anesthesia was induced and maintained with propofol. Because the induction time of EA is between 25 and 30 min, the goats in the EA-P group received EA 30 min before induction of anesthesia with propofol. The goats were allowed to breathe room air and placed on the right lateral recumbency in preparation for echocardiography. All goats were shaved between the third and sixth intercostal spaces on their right thoraxes on the left flank and placed over the cutout in the table. Cardiorespiratory parameters, nociceptive threshold of the flank, and tone of abdominal musculature were recorded before treatment (s) (baseline), immediately after induction of anesthesia (2 min), and 10 min after induction of anesthesia, and at 10-min intervals thereafter. In addition, biochemical variables were measured at 2 min, time at which propofol infusion last prevented purposeful movement (t-MIR), and 24 h after anesthesia. To determine the MIR required to prevent purposeful movements in response to noxious stimuli, the CRI of propofol was increased or decreased 0.05 mg/kg/min at 10 min after induction, and then at 10-min intervals. The baseline and experimental values were recorded while the goat was in a recumbent position.

2.2.1. Electroacupuncture

The acupuncture seats were aseptically prepared before treatment using betadine antiseptic solution (10 % povidone-iodine). EA stimulation was carried out by an experienced acupuncturist using acupoints set of Bai hui (hundred meetings), San tai (3 platforms), Er gen (ear base), and San yan luo (3 Yang communication). These points have been anatomically referenced for use in veterinary medicine (Klide and Kung, 2002; Shah et al. 2016; Hu et al., 2017). A stainless-steel acupuncture needle with a 0.30 mm diameter and a length of 100 mm was inserted at Bai hui to a depth of around 30 mm perpendicular to the dorsal midline between the spinous processes of the last lumbar and the first sacral vertebrae. At San Tai, the needle was positioned cranioventrally and inserted roughly 40–50 mm deep into the dorsal midline between the spinous processes of the fourth and fifth thoracic vertebrae. The Er gen points were located bilaterally ventrocaudal to the ear base at the depression between the ear base and cranial border of the transverse process of the atlas. In the current research, the left Er gen point was chosen, and the needle was placed in the aforementioned area until it reached the subcutaneous tissue of the left temporal fossa. The needle was inserted at San yan luo in the groove between the common digital extensor and lateral digital extensor muscles of the left forelimb until it reached the subcutaneous tissue of the medial side at a ventromedial angle of about 30 degrees and 5 cm ventral to the lateral tuberosity of the radius. All the inserted needles were connected to specific output ports of a multifunctional electric pulse generator (KWD-808I, Yingdi electronic medical equipment Co., LTD, Changzhou, Jiangsu Province, China). The frequency of EA was set at 60 Hz, and the intensity was held constant at 3.2 V for 30 min (Cheng et al. 2012).

2.2.2. General anesthesia and determination of MIR required to prevent purposeful movements in response to noxious stimuli

Prior to anesthesia, a 22 G 2.5-cm catheter was inserted into each goat's left cephalic vein. A single bolus of propofol at a dose of 4 mg/kg (Reid et al. 1993) was given over a period of 60 s for the induction with an extra dose of 1 mg/kg administered every 15 s, if needed, to facilitate tracheal intubation. A silicon endotracheal tube with a 7.5 internal diameter was inserted with the assistance of a 30-cm lighted laryngoscope blade. The endotracheal tube cuff was immediately inflated to an adequate volume that was considered by judging the size of the endotracheal tube relative to the tracheal diameter. The goats were subsequently placed on the right lateral recumbency and allowed to breathe room air. For maintenance, propofol was initially infused at a dose rate of 0.4 mg/ kg/min [7] using an IV infusion pump (Volumetric infusion pump/controller, IMED Gemini PC-1 v8.13). Before beginning the technique of determining MIR by measuring nociception in response to noxious stimulation, this initial infusion rate was maintained for an equilibration period of 10 min. Nociceptive tests were performed by an investigator who was blinded to the treatment groups. The MIR was determined via digit clamping of the non-dependent thoracic limb, in which Vulsellum forceps was closed on the soft upper part of a single digit of the hoof just below the coronary band for 60 s or until presence of a purposeful movement of the animal. Infusion rates of propofol were adjusted in accordance with nociceptive responses. The positive response was strictly defined as gross movement of the head, trunk, or limbs. Tremors of the stimulated limb was not considered as a positive response. In the presence of a positive response, the propofol infusion rate was increased by 0.05 mg/kg/min. If the response was negative, the rate was instead decreased by 0.05 mg/kg/min and kept constant for another 10 min before delivering the next stimulus. These dosage modifications were carried out until the opposite response occurred (e.g. a positive response when the last dose produced a negative response, or

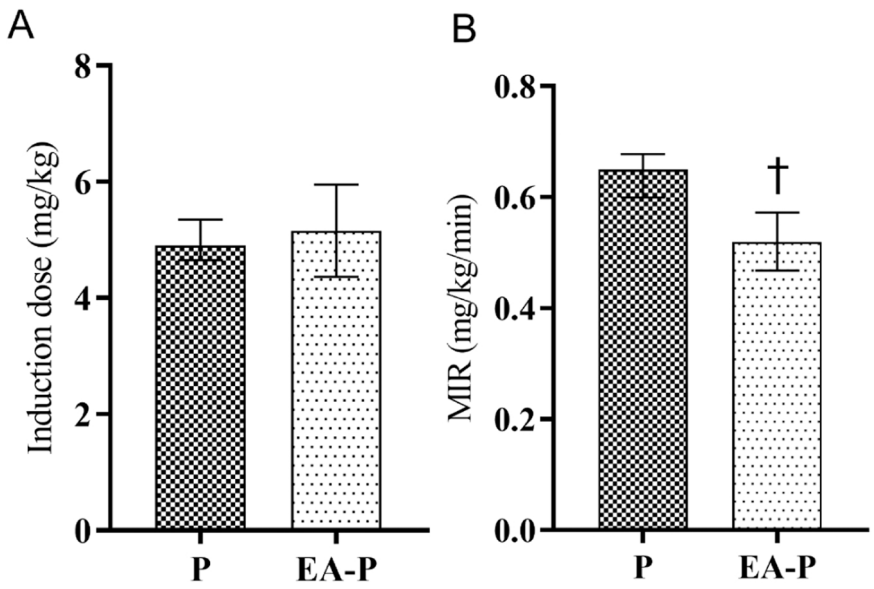

Fig. 1. Median (interquartile range; IQR) of induction dose (mg/kg) (A) and minimum infusion rate (MIR) (mg/kg/min) (B) in propofol (P) group ($n = 6$) and electroacupuncture and propofol (EA-P) group ($n = 6$). † Significant difference compared between both groups ($p < 0.05$).

vice versa). The propofol MIR was determined as the average of the infusion rates that allowed and prevented intentional movement.

2.2.3. Cardiorespiratory parameters and rectal temperature

A multiparameter electrocardiogram monitor (PM-9000 Express, Mindary Co., Ltd., Shenzhen, China) with a rectal temperature probe was used to record heart rate (HR), non-invasive arterial blood pressure [systolic (SAP), diastolic (DAP) and mean (MAP)], respiratory rate (RR), peripheral hemoglobin oxygen saturation (SpO_2), and rectal temperature (RT). SpO_2 was measured by placing the transmittance pulse oximeter probe on the anesthetized goat's tongue. For measuring blood pressures, an appropriately sized cuff (width was about 40 % of the circumference of the limb) wrapped around thigh of the left pelvic limb close to the inguinal groove to measure the pressure of the femoral artery.

Two-dimensional guided M mode echocardiography was used for the cardiac imaging using an ultrasound machine (Siemens, X-300, Seongnam, Korea). The right parasternal long axis view was used to obtain the M mode images. To minimize overestimation, inaccuracies, and inter-observer variability, an experienced echocardiographer was in charge of data collection and measurement of left ventricular (LV) internal dimensions from all M mode images. In this study, the recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging were used as a reference for the echocardiography and linear measurement of the LV internal dimensions during systole (LVIDs), diastole (LVIDd), the interventricular septum dimension (IVSD), and the left ventricular posterior wall dimension (LVPWD) (Lang et al. 2015). An ultrasound integrated software was used to calibrate the LV internal dimensions, which automatically calculate stroke volume (SV) (mL). Cardiac output (CO) (L/min) was calculated by multiplying the ECG-recorded HR by stroke volume (SV); thus, CO = HR * SV. The cardiac index (CI) (L/min/m^2) was measured by dividing the CO by the animal's body surface area (BSA). The equation BSA = 4.688* $W^{(0.8168–0.0154\ *\ logW)}$ was used to estimate BSA, as previously described (Sharkey et al., 2001). (W) refers to the animal's weight.

2.2.4. Nociceptive thresholds and flank muscle tone

A potassium iontophoresis technique was used to determine the nociceptive threshold at the center of the left flank. This technique is applied over the skin and electrically elicit sensory nerve endings and nociception via inducing the gradual influx of potassium ions through the skin. The amount of ions inflowed was directly related to the applied voltage or current (Cui et al. 2017). The flank region was shaved, cleaned with soap and water, and degreased with 75 % ethanol. A modified peripheral nerve stimulator (Direct Current Induction Therapy Apparatus; Shantou Medical Equipment Factory Co., Ltd., Shantou, China) with connected two electrodes was used to convey a pulsed direct current to the skin. The two electrodes were wrapped with gauze tape, soaked in a saturated solution of potassium chloride, and then applied 1–2 cm apart on the skin. The voltage was elevated stepwise to the point at which there were discernable fasciculations of the local skin and muscles and/or the animal's attempts to turn its head towards the flank. At that point, the current was discontinued, and the volt level was recorded. Concerning muscle tone assessment, an examiner who was unaware to the received drugs scored the degree of muscle relaxation during the experiment (Appendix A) (Abouelfetouh et al., 2021a).

2.2.5. Biochemical parameters

Blood samples (3 mL) were collected from the jugular vein using heparin vacuum blood collection tubes (Jiangsu Huida Medical Instruments Co., Ltd, Yancheng city, China). The blood collection time points were 2 min, t-MIR and 24 h after propofol infusion in P and EA-P group. Plasma biochemical indices such as alanine aminotransferase (ALT; IU/L), cardiac troponin I (cTnI; ng/mL), cystatin C (Cys C; ng/mL) and N- terminal pro-brain natriuretic peptide (NT-proBNP; ng/mL) were determined. ALT was measured using automatic dry biochemical analyzer (IDEXX Laboratories, Inc., Westbrook, Maine, US), and the cTnI, Cys C, and NT-proBNP were assayed using analytical Eliza kits purchased from Jiaxing Chaoyunfan Biotech. Co., Ltd, China.

2.3. Statistical analysis

A statistical analysis was performed using Graphpad Prism software version 8.0 (GraphPad Inc, San Diego, CA, USA). Continuous data including cardiorespiratory variables and nociceptive threshold were reported as the mean ± SD, while induction doses, MIRs, and flank muscle tone scores were shown as the median and range. Kolmogorov–Smirnov test was used to assess the normality (Gaussian distribution) of variables. Two-way ANOVA were used to analyze and compare variables within each group and between groups. Unpaired t-tests were used to compare the induction doses and MIRs between groups. p values

Table 1
Cardiorespiratory parameters and rectal temperature measured in goats at baseline and at 2, 10 min, and time at which propofol infusion last prevented purposeful movement (t-MIR) during anesthesia maintenance with propofol alone (P group) or with propofol after electroacupuncture induction (EA-P group).

Parameter	Group	Time points			
		Baseline	**2 min**	**10 min**	**t-MIR**
HR (Beats/min)	P	111.5 ± 10.8	122.5 ± 6.4	142.5 ± 4.3*	144.5 ± 5.3*†
	EA-P	113.6 ± 7.3	111.6 ± 7.5	*$p = 0.0066$	*$p = 0.0038$
				140.6 ± 4.4*	† $p = 0.0010$
				*$p = 0.0020$	128.6 ± 4.4*
					*$p = 0.0373$
CI (L/min/m^2)	P	3.7 ± 0.56	4.7 ± 0.59*†	4.6 ± 0.63*	4.5 ± 0.67† †
	EA-P	3.4 ± 0.99	*$p = 0.0224$ † $p = 0.0002$	*$p = 0.0415$ 3.5 ± 1.1	$p < 0.0001$ 2.6 ± 0.45
			2.9 ± 0.60		
SV (mL)	P	11.4 ± 1.7	12.7 ± 2.2	11 ± 2.3	10.7 ± 1.4
	EA-P	11.6 ± 2.3	10.9 ± 2.4	9.8 ± 3	8 ± 2.3
SAP (mmHg)	P	103.6 ± 4.7	104 ± 6.6	111.5 ± 5	112.3 ± 3.7*
	EA-P	107.1 ± 8.2	112 ± 4.6	119.1 ± 5.4*	*$p = 0.0053$
				*$p = 0.0216$	117.8 ± 3.7
MAP (mmHg)	P	72.3 ± 3.4	68.6 ± 17	75.6 ± 5.6† †	65.3 ± 7.6† † $p = 0002$
	EA-P	83.3 ± 12	91.5 ± 11.2	$p = 0.0006$ 94 ± 4.9	100.3 ± 9.6
DAP (mmHg)	P	52 ± 4.4	49.6 ± 4.8	60 ± 6.5† †	50 ± 5.6† †
	EA-P	53.5 ± 6.8	61.3 ± 10.2	$p = 0.0017$ 77.6 ± 4.6*	$p = 0.0001$ 85.5 ± 9.2*
				*$p = 0.0047$	*$p = 0.0004$
RR (breaths/min)	P	21.8 ± 2	12.5 ± 1.5*†	12.1 ± 1.5*†	15.5 ± 1.6*
	EA-P	22.8 ± 1.5	*$p = 0.0025$ † $p = 0.0096$	*$p < 0.0001$ † $p = 0.0039$	*$p = 0.0001$ 17 ± 2*
			15.8 ± 1.3*	16.6 ± 1.5 *	*$p = 0.0068$
			*$p = 0.0005$	*$p < 0.0001$	
SpO_2 (%)	P	93.6 ± 3.8	75.8 ± 8.8*†	83.1 ± 5.1*†	87.3 ± 9.8
	EA-P	92.8 ± 7.6	*$p = 0.0023$ † $p = 0.0058$	*$p = 0.0007$ † $p = 0.0034$	90.2 ± 6.3
			90.8 ± 4.2	92.6 ± 2.9	
RT (°C)	P	39.2 ± 0.22	39.4 ± 0.22	38.8 ± 0.27*	38.3 ± 0.28*
	EA-P	39.3 ± 0.03	39.2 ± 0.24	*$p = 0.0013$ 38.9 ± 0.28*	*$p = 0.0015$ 38.5 ± 0.18*
				*$p = 0.0127$	*$p = 0.0016$

Heart rate (HR), systolic arterial blood pressure (SAP), mean arterial pressure (MAP), diastolic arterial blood pressure (DAP), respiratory rate (RR), hemoglobin oxygen saturation (SpO2) and rectal temperature (RT).
* Significant difference within each group compared to the baseline ($p < 0.05$). † Significant difference between groups at the same timepoints ($p < 0.05$). Data were expressed as mean ± SD.

< 0.05 were considered statistically significant.

3. Results

3.1. Effect of EA on propofol MIR

The doses of propofol required for induction and maintenance of anesthesia with propofol alone or combined with EA in goats are shown in Fig. 1. There were no significant differences in the propofol dose required for induction of anesthesia between the P and EA-P group. However, additional boluses of propofol over the initial bolus of 4 mg/kg were required in both groups to complete the induction and achieve successful intubation. The median propofol MIR was significantly lower in the EA-P group as compared to the P group ($p = 0.0013$). The time taken to determine propofol MIR was significantly longer in the P group than that of the EA-P group (56 ± 12 and 40 ± 8 min, respectively) ($p = 0.0056$).

Table 2
Plasma biochemical variables measured at 2 min, and time at which propofol infusion last prevented purposeful movement (t-MIR), and 24 h after anesthesia with propofol alone (P group) or with propofol after electroacupuncture induction (EA-P group).

Group	Timepoint	NT-proBNP (ng/mL)	Cys C (ng/mL)	cTnI (ng/mL)	ALT (IU/L)
P	2 min	0.27 ± 0.15	0.22 ± 0.11	0.23 ± 0.05	11.30 ± 1.13
	t-MIR	0.17 ± 0.06	0.17 ± 0.06	0.28 ± 0.04	10.90 ± 0.85
	24 h	0.19 ± 0.05	0.19 ± 0.03	0.22 ± 0.03	12.37 ± 0.72
EA-P	2 min	0.30 ± 0.03	0.23 ± 0.05	0.25 ± 0.07	11.00 ± 1.00
	t-MIR	0.25 ± 0.06	0.18 ± 0.02	0.21 ± 0.04	10.33 ± 0.57
	24 h	0.23 ± 0.03	0.19 ± 0.03	0.23 ± 0.05	12.00 ± 2.00

Cystatin C (Cys C), Cardiac troponin I (cTnI), Alanine aminotransferase (ALT), N-terminal pro-brain natriuretic peptide (NT-proBNP).

3.2. Cardiorespiratory variables of anesthesia maintenance with propofol alone or propofol combined with EA

There were a statistically significant differences within and between the P and EA-P groups (Table 1). Regarding HR and CI, both P and EA-P group showed a significant increase in the HR at ten min following induction of anesthesia and at propofol MIR time ($p < 0.05$), but a significant increase in the CI was observed only in the P group at two and ten min compared to the baseline ($p < 0.05$). Additionally, both groups showed a significant decrease in RR at two, ten min and at propofol MIR time ($p < 0.05$) compared to the baseline. In the P group, all goats became hypoxemic after anesthesia and the mean values of SpO_2 decreased (< 90 %) with a significant difference was reported at two and ten min ($p < 0.05$) compared to the baseline. In the EA-P group, only three goats exhibiting SpO2 values below 90 %, however there were no significant changes observed in the mean SpO_2 values and maintained within the clinically acceptable range (> 90 %). RR decreased significantly in both groups at ten min after anesthesia and at propofol MIR time ($p < 0.05$) compared to the baseline. When comparing the two groups, the EA-P group showed significant decreases in HR and CI at propofol MIR time ($p < 0.05$). In addition, significant increases in the values of MAP, DAP as well as SpO_2 were observed in the EA- P group ($p < 0.05$) compared to the P group.

3.3. Nociceptive thresholds and flank muscle tone

The EA-P showed a significant increase in the nociceptive threshold at two ($p = 0.0066$), ten min ($p = 0.0008$) after induction of anesthesia compared with the P group (Table 3). At the propofol MIR time, the nociceptive threshold in the EA-P group started to decline, but a significant increase was observed ($p = 0.0004$) compared with the P group. Flank muscle tone scores decreased with statistically significant differences were detected at two ($p < 0.0001$), ten min ($p = 0.0076$) in the P group and at two, ten min ($p = 0.0006$) and at the propofol MIR time ($p = 0.0336$) in the EA-P group compared to the baseline. No significant

Table 3
Nociceptive threshold percentage and flank muscle tone measured in goats at baseline and at 2, 10 min, and time at which propofol infusion last prevented purposeful movement (t-MIR) during anesthesia maintenance with propofol alone (P group) or with propofol after electroacupuncture induction (EA-P group).

Parameter	Group	Time points			
	.	**Baseline**	**2 min**	**10 min**	**t-MIR**
Nociceptive threshold[(1)]	P		57.5 ± 17.2†	22.6 ± 6.8†	21.7 ± 9.2†
			† $p = 0.0066$	† $p = 0.0008$	† $p = 0.0004$
	EA-P		100.4 ± 19.1	116 ± 27.6	70.3 ± 15
Flank muscle tone[(2)]	P	2 (3–2)	1 (2–1)*	2 (2–1)*	2 (2–1)
			*$p < 0.0001$	* $p = 0.0076$	
	EA- P	2 (3–2)	1 (2–1)*	1 (2–1)*	2 (2–1)*
			*$p = 0.0006$	*$p = 0.0006$	*$p = 0.0336$

-*Significant difference within each group compared to the baseline ($p < 0.05$).
-†Significant difference between groups at the same time points ($p < 0.05$).
- Data were expressed as mean ± SD [(1)] and median (range) [(2)]

differences were detected in the muscle tone scores between groups (Table 3).

3.4. Biochemical variables

Specific biochemical variables, including ALT, Cys C, cTnI and NT-proBNP, were measured to assess liver, cardiac and kidney functions during anesthesia. There were no significant differences observed in these biochemical indices between the P and EA-P groups (Table 2).

4. Discussion

In this current study, the induction dose of propofol required for induction of anesthesia was similar in both propofol alone and EA and propofol groups. However, the propofol MIR required to prevent purposeful movement in response to noxious stimuli decreased significantly in the EA and propofol group in comparison with the propofol alone [0.520 (0.467–0.572) and 0.650 (0.600–0.677), respectively; $p = 0.0013$], indicating the dose sparing effect of EA on propofol anesthesia in goats. Prior reports had investigated the influence of fentanyl or midazolam on propofol MIR in goats. The CRI of fentanyl (0.02 mg/kg/h) or midazolam (0.3 mg/kg/h) in combination with propofol significantly reduced the propofol MIR as compared to that found with propofol alone (Dzikiti et al. 2010; Ferreira et al. 2016). Their findings are in accordance with that observed in our study. Therefore, the effect of EA is comparable to the propofol sparing effects of fentanyl and midazolam in goats. In addition, the use of EA in conjunction with alfaxalone has been reported to reduce the MIR of alfaxalone in goats (Liu et al. 2021). EA is frequently combined with other analgesics or anesthetics and has long been used as an analgesic in both acute and chronic pain. In goats, EA has been revealed to produce analgesia and reduce the dose of dexmedetomidine and xylazine by 75 % (Liu et al. 2009;Shah et al. 2016). The efficacy of EA combined with general anesthesia has been studied in patients undergoing heart surgery. EA has been shown to lessen the amount of intraoperative anesthetic required, which results in fewer complications and a quicker recovery (Asmussen et al. 2019). Furthermore, epidural anesthesia in combination with EA resulted in a 40–46 % reduction in the amount of lidocaine required to perform abdominal surgery (Qin et al. 1996).

At t-MIR, goats anesthetized with EA and propofol showed a significantly decreased HR and CI compared to those anesthetized with propofol alone. This finding is in accordance with the effect of EA on alfaxalone anesthesia in goats (Liu et al. 2021). The decrease in HR may be attributable to the augmenting effect of EA on vagal tone as well as the suppressing upshot on sympathetic outflow (Nishijo et al. 1997). Furthermore, EA has been reported to induce the release of dynorphin, an endogenous neuropeptide that interacts with presynaptic kappa opioid receptors, inhibiting the release of noradrenaline from sympathetic neurons in the sinus node (Starke et al. 1985;Han and Wang, 1992). Propofol has been reported to lower arterial blood pressure in a dose-dependent manner (Goodchild and Serrao, 1989) as a result of peripheral vasodilation (Wan et al. 2018) and decreased cardiac output (Ren et al. 2018). In this current study, DAP and MAP were significantly lower in goats received propofol alone than those received EA and propofol, which can be explained by the vasopressor effect of EA in response to hypotension (Syuu et al. 2003; Kang and Xia, 2010). The decrease in rectal temperature (RT) during anesthesia may be attributable to a depression in the thermoregulatory centers and a decrease in the skeletal muscle tone and metabolic activity (Ponder and Clark, 1980). RR was significantly reduced during anesthesia with propofol alone compared to EA and propofol. This finding might be due to the significant decrease of the propofol MIR when combined with EA. In addition, EA application has been reported to correct the respiratory depression associated with anesthesia in goats (Shah et al. 2016; Liu et al., 2021). The values of SpO_2 were significantly decreased during anesthesia with propofol alone compared with those of EA and propofol, which may be caused by the respiratory depression as a result of higher doses of propofol required to maintain anesthesia in the propofol group (Read, 2003). In this study, a new anesthetic combination was used, so, we decided to not provide supplemental oxygen to the goats to evaluate the potential effect of this combination on peripheral oxygen saturation (Rodrigo-Mocholí et al., 2016).

In the current study, goats anesthetized with EA and propofol had a significantly higher pain threshold than those anesthetized with propofol alone. The antinociception induced by EA is primarily influenced by two factors: the proper selection of acupuncture points and frequencies. EA frequencies of 30–100 Hz and intensities of 1–3.25 V have been shown to provide effective antinociception for ruminant abdominal surgical procedures (Cantwell, 2010). In this current study, the use of EA of a frequency of 60 Hz has been validated to provide effective antinociception in goats (Cheng et al. 2012). The degree of antinociception induced by EA was measured using potassium iontophoresis technique. This technique provides a tool for determining changes in the nociceptive threshold using a reliable experimental pain stimulus that can be presented rapidly and repeatedly with minimal loss in consistency of a subject's reported pain level (Humphries et al. 1996). Our findings indicate that EA combined with propofol anesthesia has a greater antinociceptive effect than propofol anesthesia alone. Endogenous opioids such as enkephalin, SS-endorphin, and dynorphin are primarily involved in the EA-induced antinociception (Cheng et al. 2012; Zhang et al., 2014).

The small sample size was a limitation of the current study. In

addition, the use of an invasive blood pressure method and blood gas analysis would be better to assess the cardiopulmonary status during anesthesia. The electrical stimulation used to measure the nociceptive threshold could stimulate all nerve terminals, not just those related to pain sensation and could be a confounding factor in assessing pain threshold. Another limitation of this current study was the lack of comparison with sham EA group. Nevertheless, the result of this study provided valuable information on the enhanced antinociception of EA during propofol anesthesia in goats.

5. Conclusion

This research focused on evaluating the effect of EA on propofol-based intravenous anesthesia in goats. EA could provide better antinociception and muscle relaxation as well as improve the anesthetic effect of propofol in goats, with no adverse effect on the liver, kidney, and heart function.

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CRediT authorship contribution statement

Conceptualization and experimental design, Y.D., Y.S. and M.D.; methodology, L.L., M.M.A., R.S., E.S. and S.N.; data curation, L.L. and M. M.A.; software, L.L. and M.M.A.; formal analysis, L.L. M.M.A. and E.S.; investigation, L.L., M.M.A., R.S., E.S. and S.N.; resources, Y.D., Y.S. and M.D.; writing—original draft, M.M.A.; writing—review and editing, Y. D., Y.S., M.D., L.L., M.M.A., R.S., E.S., and S.N.; supervision; Y.D., Y.S. and M.D. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Flank muscle tone scoring system

Score	Description
0	Complete relaxation to palpation with minimal or no tone palpable.
1	Detectable relaxation to palpation with less tone palpable.
2	Normal resting tone: flank has some elasticity to palpation.
3	Mild resistance and tone with gentle pressure on the skin and muscle.
4	Strong resistance and tone with strong pressure on the skin.
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