Journal of Animal & Plant Sciences, 33(6): 2023, Page: 1439-1445
ISSN (print): 1018-7081; ISSN (online): 2309-8694
https://doi.org/10.36899/JAPS.2023.6.0683

ANALGESIC AND PHYSIOLOGIC EFFECTS OF ELECTROACUPUNCTURE AND MEDETOMIDINE IN DOMESTIC GOATS

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ABSTRACT

To evaluate the analgesic and physiological effects of electroacupuncture (EA) and medetomindine in domestic goats. Thirty healthy goats (aged 1-2 years and body weight 22±3.17 kg) were divided into five groups (6 goats/group). Group 1 animals were considered as a control; groups 2 and 3 animals were given 5µg kg^{-1} and 20µg kg^{-1} medetomidine IM respectively; group 4 animals were stimulated with EA for 30 mins and group 5 animals were given EA in combination with 5µg kg^{-1} medetomidine IM. The pain threshold in groups 2 and 3 animals were increased significantly ($p< 0.05$) at 15 to 60 mins compared to group 1. Group 5 animals showed increase ($p< 0.05$) in the pain threshold at 15 to 60 mins compared to animals in group 2 and group 4. Goats in groups 2 and 3 showed decrease ($p< 0.05$) in heart rate, respiratory rate, mean arterial pressure and rectal temperature, whereas animals in group 5 showed less effect on these physiological parameters. Furthermore, goats in group 5 did not have any effect on blood cell count, serum chemistry, or liver health status. The combination of EA plus 5 µg kg^{-1} medetomidine produced adequate antinociception with minimal physiological alteration suggesting that, an effective strategy for clinical observation and minor surgical procedures in domestic goats.

Keywords: Analgesic, electroacupuncture, goats, medetomidine, physiologic effect.

Published first online August 20, 2023 Published final December 13, 2023

INTRODUCTION

Alpha$_2$-agonists are commonly used as pre-anesthetics, sedatives, or combined with opioids or other anesthetic drugs to reduce the required anesthetic doses. Medetomidine has a lipophilic effect, rapidly eliminated, highly effective and less expensive than other α_2-agonists drugs (Miksa *et al*., 2005). According to the ~~a~~ clinical report, analgesia and sedation produced by α_2-agonists were related to the type of α_2-adrenoreceptors, density and site in the treated animal, as well as the drug affinity for the α_2 and α_1-receptors (Shah *et al.,* 2014, 2021). All α_2-agonists available may activate α_1-adrenoreceptors in treated animals. Arousal, restlessness, increased vigilance and locomotor activity are all caused by the activation of α_1-adrenoreceptors. When a high doses of α_2-agonists *i.e.,* xylazine (*e.g.,* 4 to 8 mg kg^{-1} of body weight) were administered, these effects may be obviously observed (Ambrisko and Hikasa, 2002; Shah *et al.,* 2014).

Studies have shown, that stimulating α_1-adrenoreceptors in the CNS provokes binding to α_2-agonist. According to the clinical report, a selective drug for the α_2-adrenoreceptor is more potent in lowering the required drug dose to achieve a similar effect (Sinclair, 2003; Shah *et al.,* 2013). It has been reported that medetomidine has a high (1620:1) selectivity binding ratio,compared to detomidine (260:1), clonidine (220:1) and xylazine (160:1; Alex, 2010). Medetomidine inhibits catecholamine and induces sedation in small animals by acting on presynaptic α_2-adrenoceptors in CNS (Sinclair, 2003). Different doses of medetomidine causes bradycardia, bloating and ruminal atony in goats (Carroll *et al*., 2005).

Acupuncture is an ancient traditional Chinese technique used since the Ming Dynasty (1368-1644 A.D) to relieve pain, cure disease and improve overall health. Dr. Yang Jizhou provided a detail description of acupuncture points and their manipulation methods (Ifrim Chen *et al*., 2019). Electroacupuncture (EA) a is modified method of conventional acupuncture, involves electrical stimulation administered via inserted metal needles into the body's underlying the skin tissues at precise points; however, EA does not provide adequate pain relief alone during or after major surgical procedures. Therefore, using EA in conjunction with analgesic drugs may become a popular method of pain relief. EA combined with analgesic drugs (EA-assisted analgesia or EA-drug balanced analgesia) has been used to control pain for various surgical procedures (Dong and Wang, 2006; Han, 2008; Parmen, 2014). The benefit of this combination required less dosages of the anesthetics, which ultimately reduces the adverse effects of drugs (Qin *et al.,* 1996; Tang *et al*., 1997; Shah *et al*., 2020; 2021).

It is preferable to use EA in combination with specific drugs that may regulate several body functions along with analgesia effects (Dong and Wang, 2006). It has been reported, that EA, in combination with some anesthetic drugs, may release endogenous opioid peptides in the CNS (Shankar *et al*., 1996; Wu *et al*., 2010). Because endogenously produced analgesic substances which allow the anesthetist to reduce the required dose of anesthetic by 50% (Qu *et al*., 1996), which may minimize drug adverse effects. Therefore, in this study we investigated, the benefits and drawbacks along with analgesic and physiologic effects of EA plus medetomidine in goats.

MATERIALS AND METHODS

Experimental design: Thirty female domestic hybrid goats (non-pregnant) and physically in healthy condition, with aged 1-2 years and body weight 22 ± 3.17 kg were randomly selected and distributed into five groups (6 goats/group). All animals were fed green fodder twice a day and offered water *adlibitum.* Deworming was performed and an adaptation period for 10 days were given before starting of the actual experiment. The departmental ethical committee approved the experimental protocol (College of Veterinary Sciences, The University of Agriculture, Peshawar (No. 4306/LM). Group 1 animals (control group) were administered with normal saline solution (0.9% NaCl) at dose rate 0.3ml intramuscularly (IM) into the neck region. Groups 2 and 3 animals were treated with 5 and 20 µg kg^{-1} IM medetomidine (Domitor, Orion Corporation, Espoo, Finland) respectively. Goats in group 4 (EA group) were treated with needle stimulation for 30 mins and the final group 5 animals were treated with EA plus medetomidine at dose of 5 µgkg^{-1}. Medetomidine 5 and 20 µgkg^{-1}dosage were selected after conducting pilot trial on few goats before the start of the actual experiments. In these trials, after increasing the doses of medetomidine, the depth of analgesia was remained the same, while sedation increased in animal. Therefore, medetomidine dosage (*i.e.,* low dose 5 µgkg^{-1} and high 20 µgkg^{-1}) were finally selected. After experiment, *i.e.,* 1-hour post injection drug treated animals were injected with atipamezole hydrochloride (Antisedan, Orion Pharma, Orion Corporation, Espoo, Finland) intravenously to reverse the drug's effects.

Electroacupuncture: EA points were selected, saved and then disinfectant with 75% ethanol and finally scrub with povidone-iodine solution (Shah *et al*., 2021; 2016). Sterilized EA needles with length 75 mm were connected to 1st output port of a pulse generator (Hua Yi, Shanghai, China) and were inserted into the San tai (between the spinous processes of 4th and 5th thoracic vertebrae) and Bai hui (between the last lumbar and the 1stsacral vertebrae) points, and similarly needles connected to the 2nd output port of the same pulse generator, then inserted into the Sanyanluo (5 cm ventral to the lateral tuberosity of the radius in the groove between the common digital extensor and lateral digital extensor muscles of the right forelimb) and Erh gen (ventrocaudal to the ear base at the depression between the ear base and cranial border of the transverse process of the atlas) points. The anatomic locations and details of these EA points have been already previously described (Shah *et al*., 2021; Figure-1). A constant frequency of 60 Hz and current 3-volt was maintained for 30 mins (Shah *et al*., 2016).

Physiological variables: The pain threshold level was measured at the middle of left flank region at 0, 15, 30, 45, 60 mins and 24 hours after treatment. Potassium iontophoresis was used to induce pain by gradually increasing in the amount of potassium ions passing through the skin. Two electrodes soaked in 10% potassium chloride solution were placed 1 to 2 cm apart on flank. A galvanofaradism apparatus (Galvanofaradism, Shantou, China) delivered electric current to the electrodes, which forced potassium ions into the subcutaneous tissues. Voltage was continuously increased and the pain threshold was recorded, when an obvious local skin contraction and head-turning toward the flank region was observed (Cui *et al*., 2017; Shah *et al*., 2021).

The mean arterial pressure (MAP) was measured at 0, 5, 10, 15, 20, 30, 45, 60 mins, and 24 hours using a digital sphygmomanometer (U-Check Technology, Frankfurt, Germany) placed on the radial artery above the elbow joint on the left thoracic limb. Sphygmomanometer monitor's diastolic and systolic MAP (mm Hg) were recorded according to the formula used by Shah *et al*. (2016).

Physiological variables, such as heart rate (HR), respiratory rate (RR) and rectal temperature (RT) were measured at 0, 5, 10, 15, 20, 30, 45, 60 mins and then 24 hours by using a 5-lead ECG monitor (Mindray, PM9000, Guangzhou, China), according to the manufacturer's guidelines.

Biochemical and hematological variables: Blood samples (10 mL) were collected aseptically at 0, 30, 60 mins and 24 hours after treatment. The biochemical variables such as creatinine, aspartate aminotransferase, serum glucose, alanine aminotransferase and blood urea nitrogen levels were measured using a chemistry analyzer (AMP, Piccos, GmbH, Austria).

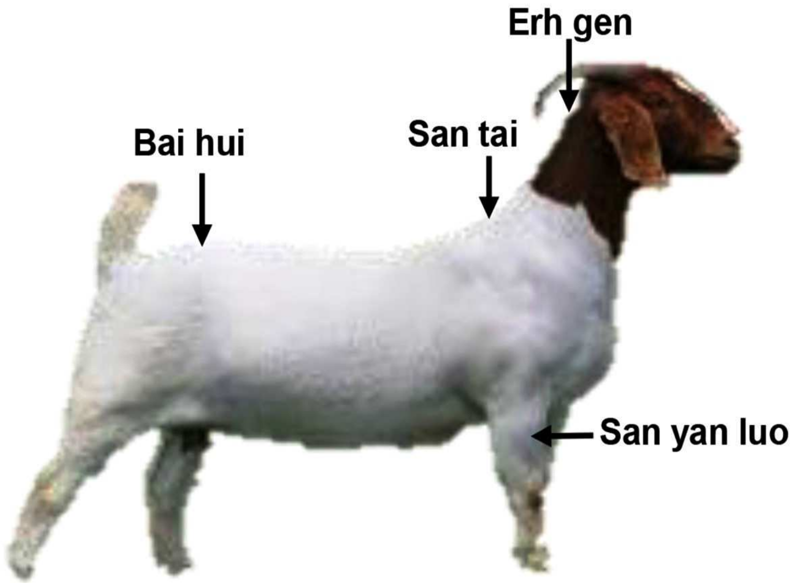

Figure-1 Anatomical illustration of acupoints used for electroacupuncture stimulation in the goats, (1.**Erh gen** [ventrocaudal to the ear base at the depression between the ear base and cranial border of the transverse process of the atlas]; 2. **San tai** [between the spinous processes of the 4th and 5th thoracic vertebrae]; 3. **Bai hui** [last lumbar and the 1st sacral vertebrae] and 4. **Sanyanluo** [5 cm ventral to lateral tuberosity of the radius in the groove between the common digital extensor and lateral digital extensor muscles of the right forelimb]).

Hematological parameters including white blood cell count (lymphocyte, eosinophil, lymphocytes, monocytes, and neutrophils), red blood cell count, hemoglobin level, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin were determined by using blood analyzer (PocH, 100 iV, Sysmex, Japan).

Statistical analysis: The sample size for nociceptive thresholds were determined using the PASS program (NCSS, Kaysville, USA) with the default parameters, *i.e.,* alpha of 0.05 and power of 80%. SPSS Version 16.0 was used to perform repeated measure analysis of variance. Significant differences ($p<0.05$) considered for nociceptive thresholds and the normal distribution of physiologic, biochemical and hematologic variables were determined as previously described by Shah *et al*. (2021).

RESULTS

We found that animals in groups 2 and 3 showed a higher ($p<0.05$) level in the pain threshold values at 15 to 60 mins compared to group 1. Notably, we ~~have~~ also observed an increase ($p<0.05$) in the pain threshold level in group 4 animals at 30 to 60 mins compared to group 1. A maximum increase in the pain threshold level was observed in group 4 at 45 mins. We observed that animals in group 5 showed a high level ($p< 0.05$) in the pain threshold values, when compared to group 1, group 2 and group 4 animals at 15 to 60 mins respectively (**Table 1**).

We also found that drug administered to group 2 animals showed a decrease ($p<0.05$) in the HR values at 10 to 45 mins, whereas treatment to group 3 animals caused a greater reduction ($p<0.05$) in the HR at 5 to 60 mins when compared to animals in group 1. In contrast, no significant ($p>0.05$) changes were observed in HR in group 4 animals. Animals in group 5 showed less effect on HR values; however, still decrease ($p<0.05$) was observed in HR at 15 to 45 mins compared to group 1. We further observed, that treatment to group 2 and group 3 animals showed a decrease ($p<0.05$) in MAP values from 15 to 60 mins, but there was no difference ($p>0.05$) in MAP values in group 4 animals when compared to group 1 animals. Similarly, animals in group 5 animals did not show any changes ($p>0.05$) in MAP values except at 30 to 45 mins (**Table 2**). Moreover, we also calculated the RR values at various time points after EA and drugs administration. We finally learned that animals in group 2 showed a decrease ($p<0.05$) in RR values at 20 to 45 mins. Furthermore, animals in group 3 showed a decrease ($p<0.05$) in RR value from 5 to 60 mins. The RR value on the other hand was unaffected in group 4. Animals in group 5 showed only decrease ($p<0.05$) in the RR value at 30 min, when compared to group 1 goats. The RT values did not decrease ($p>0.05$) in group 2, however animals in group 3 showed a decrease ($p> 0.05$) in RT values from 5 to 60 mins. In contrast, neither animal in group 4 and in group 5 showed any changes (p>0.05) in RT values when compared to group 1 animals (**Table 2**).

Table 1. Effects of EA and medetomidine administration on pain threshold % changes in domestic goats.

Group	Time (minutes)				
	15	30	45	60	24hours
Group 1	11±0.38^{c}	6±0.190^{c}	11±0.38^{d}	6±0.19^{c}	17±0.57
Group 2	30±2.71^{b}	80±1.90^{b}	111±0.96^{b}	57±1.07^{b}	19±0.57
Group 3	45±2.7^{b}	118±20^{a}	145±0.96^{a}	109±1.07^{a}	19±0.57
Group 4	15±0.57^{c}	65±1.34^{b}	70±1.54^{c}	45±2.10^{b}	17±0.38
Group 5	59±1.52^{a}	131±0.80^{a}	162±1.5^{a}	126±1.5^{a}	19±0.57

Values are presented as mean ± standard deviation.
Values within each column shown with different superscript letters (a-d) indicate significant difference (P < 0.05) among groups at that time point.

Table 2. Effects of EA and medetomidine administration on heart rate (beats/minute), mean arterial blood pressure (mmHg), respiratory rate (breaths/min) and rectal temperature (°C) in domestic goats.

Group	Time (minutes)								
	0	5	10	15	20	30	45	60	24 hours
Heart rate (beats minute^{-1})									
Group 1	91±4.16	92±2.0^{a}	89±2.08^{a}	85±2.80^{a}	84±1.58^{a}	91±2.2^{a}	91±5.68^{a}	91±5.0^{a}	91±00.0
Group 2	100±00	85±1.9^{a}	68±1.85^{b}	66±1.74^{b}	61±1.60^{b}	63±1.6^{b}	66±1.0^{b}	84±2.3^{a}	99±1.15
Group 3	88±2.7	63±1.1^{b}	60±0.50^{b}	59±2.30^{b}	58±2.88^{b}	56±20^{b}	56±1.20^{b}	59±1.51^{b}	87±0.20
Group 4	91±1.0	91±3.7^{a}	91±2.20^{a}	88±2.20^{a}	92±4.04^{a}	93±4.4^{a}	92±2.50^{a}	92±3.3^{a}	90±0.90
Group 5	89±2.6	86±2.3^{a}	82±1.50^{a}	63±4.61^{b}	60±2.90^{b}	62±4.0^{b}	63±2.6^{b}	71±2.3^{a}	89±1.61
Mean arterial blood pressure (mmHg)									
Group 1	121±1.2	124±2.3	116±2.4	121±1.02^{a}	118±1.7^{a}	113±1.6^{a}	112±1^{a}	115±1.5^{a}	121±1.77
Group 2	127±0.9	126±1.0	113±2.13	52±00.00^{b}	66±1.50^{b}	81±00.0^{b}	88±1.1^{b}	93±2.60^{b}	128±0.09
Group 3	116±1.1	117±2.7	107±2.42	68±01.35^{b}	76±5.10^{b}	82±3.20^{b}	96±2.6^{b}	96±1.10^{b}	115±1.7
Group 4	137±1.1	135±1.0	137±1.4	136±01.7^{a}	130±1.9^{a}	137±1.0 ^{a}	135±1.4^{a}	136±1.1^{a}	136±1.15
Group 5	124±2.8	114±1.1	112±2.2	105±2.90^{a}	107±3.5^{a}	94±2.50^{b}	91±2.5^{b}	113±2.4^{a}	124±0.3
Respiratory rate (breaths minute^{-1})									
Group 1	22±0.57	22±0.5^{a}	22±0.57^{a}	22±0.5^{a}	22±1.0 ^{a}	22±0.5 ^{a}	22±0.5^{a}	22±0.50^{a}	22±0.5
Group 2	22±2.48	20±2.19^{a}	17±2.07^{a}	17±2.0^{a}	13±3.0^{b}	13±0.7^{b}	12±1.07^{b}	18±2.3^{a}	22±1.0
Group 3	22±0.00	15±0.7^{b}	14±00.0^{b}	13±1.4^{b}	12±1.4^{b}	12±0.0^{b}	14±0.7^{b}	14±0.0^{b}	22±0.0
Group 4	22±1.21	20±30^{a}	21±1.05^{a}	21±1.8^{a}	21±3.0^{a}	20±2.0^{a}	20±2.17^{a}	20±2.30^{a}	21±1.2
Group 5	20±3.0	23±0.7^{a}	20±30^{a}	19±1.4^{a}	18±3.0^{a}	15±1.07^{b}	18±2.0^{a}	23±1.41^{a}	21±1.0
Rectal temperature (°C)									
Group 1	38.0	38.38^{a}	38.33^{a}	38.38^{a}	38.38^{a}	38.11^{a}	38.22^{a}	38.33^{a}	38.0
Group 2	39.0	39.25^{a}	39.00^{a}	39.00^{a}	38.87^{a}	38.88^{a}	38.51^{a}	38.33^{a}	39.0
Group 3	39.0	38.01^{b}	37.46^{b}	38.00^{b}	38.00^{b}	37.61^{b}	37.31^{b}	37.36^{b}	39.0
Group 4	39.0	39.60^{a}	39.00^{a}	39.60^{a}	39.00^{a}	38.60^{a}	39.00^{a}	39.00^{a}	39.0
Group 5	39.0	38.70^{a}	38.40^{a}	38.20^{a}	38.00^{a}	38.00^{a}	37.40^{a}	37.40^{a}	39.0

Values are presented as mean ± standard deviation.
Values within each column shown with different superscript letters (a,b) indicate significant difference (P < 0.05) among groups at that time point.

DISCUSSION

Electroacupuncture is a Traditional Chinese Medicine technique that has been used to treat disease over 2000 years. EA has been successfully used for pain management in humans and animals in many countries (Parmen, 2014). EA frequency and selection of acupoints are important factors influencing EA analgesia. In cattle, EA stimulated with frequency 30-100 Hz has been used for pain control (Wang and Jin, 1989). However, EA with frequency 36 Hz to stimulates acupoints San yanluo, Bai hui, Erh gen, and San tai resulted better analgesia in goats (Liu *et al*., 2009). Different EA frequency stimulated, the release of different opioids peptides (enkephalin and β-endorphin) in the central nervous system (CNS) ~~brains~~ (Han, 2003, 2008). That is EA with frequency 2Hz stimulated to release enkephalin and β-endorphin, whereas frequency of EA with 100 Hz stimulated the release of dynorphin in the CNS (Han, 2003). EA at frequency 60 Hz releases β-endorphin, encephalin and dynorphin simultaneously in the CNS of goat (Cheng *et al*., 2012). This was the philosophy behind, why we selected to use frequency 60 Hz for EA stimulation in the current experiment.

Animal pain thresholds have been measured through various techniques, particularly pinprick scoring

(DeRossi *et al*., 2003; Shah *et al*., 2013; 2014). However, the practical and authentic method for determining the pain thresholds in restrained animals is potassium iontophoresis (Humphries *et al*., 1994, Shah *et al.,* 2016). This method has been used to assess the analgesic score in humans (Ulett *et al*., 1998), in goats (Liu *et al.,* 2009; Shah *et al*., 2021) and sheep (Eisenach *et al*., 1996). In our study, the pain threshold induced by EA increased and reached to a maximum level at 45 mins. These findings were consistent with our previous findings (Shah *et al*., 2016; 2020).

We compared different treatments and found that goats in group 5 resulted in excellent synergistic effects. This synergistic interaction between EA and medetomidine on the other hand could be caused by the co-activation of α_2-adrenergic or opioidergic-noradrenergic receptors (Herradon *et al*., 2008; Kabalak *et al*., 2013). Previous research has also shown that combining EA with anesthetic drugs reduces the required dose of the anesthetics (Liu *et al.,* 2009; Cui *et al*., 2017).

We discovered that medetomidine treatment caused a significant decrease in MAP, HR and RR values, which are in agreement with the previous studies (Kinjavdekar *et al*., 2000; Shah *et al*., 2014). However, in our study EA plus medetomidine administration did not significantly effects the MAP and HR values. Therefore, EA stimulation in combination with anesthetic drug could be is a better choice for controlling hypotension and bradycardia in goats during anesthesia. Previous study reported, that EA stimulation help in relieving hypotension and calcium/magnesium ions concentration in rabbit (Jie *et al*., 1999). It is further conformed, that EA stimulation significantly increased MAP and calcium levels in rabbits, implying that intracellular free calcium/magnesium concentrations may play an important role in regulating MAP parameter (Jie *et al*., 1999).

Bronchoconstriction and pulmonary edema are species-specific side effects of all α_2-agonist (Groeben *et al*., 2004). Unlike medetomidine, dexmedetomidine causes bradypnea in goats (Kästner *et al*., 2007, Shah *et al.,* 2016). In the present study, EA plus medetomidine had less effect on respiratory function than either 5 or 20 µg kg^{-1}drug treatments alone. Previous research found that all α_2-agonists reduce RT in various animal species (Kumar *et al*., 2014; MacDonald *et al*., 1988; Shah *et al*., 2016). In the line with previous research, we found that only 20 µg kg^{-1} medetomidine administration reduced in the rectal temperature in goats; however, this decrease in RT values may be associated with a decrease in body metabolism system, muscular flaccidity and hypothalamic depression (Ahmad *et al*., 2011).

Conclusion: The combination of EA and 5 µg kg^{-1} medetomidine administration produced adequate antinociception in domestic goats with minimal physiological alteration suggesting that this combination might be an effective strategy for goat clinical observation as well for minor surgical procedures.

Acknowledgments: We appreciated Pakistan Science Foundation (PSF/NSLP; KP-UAP No. 691) and Higher Education & Commission Islamabad-Pakistan (Nos. 21-1333/SRGP/R & D/HEC/2016) for financial support to conduct this study.

Conflict of interest: The authors declare no conflict of interest.

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