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Evaluation of acepromazine and butorphanol as preanaesthetics agent in tiletamine-zolazepam induced anaesthesia in dogs undergoing ovariohysterectomy: a perspective study on clinical, physiological, haemodynamic and haematobiochemical parameters

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This study aimed to evaluate the preanaesthetic efficacy of a combination of acepromazine and butorphanol in dogs induced with tiletamine-zolazepam and maintained under isoflurane anaesthesia for elective ovariohysterectomy. A prospective clinical trial was conducted on 12 healthy adult female dogs of various breeds and ages, randomly divided into two groups (n=6). All dogs received atropine sulphate (0.045 mg/kg body wt., i.m.) as premedication. After 5 min, group I animals received acepromazine (ACP) alone (0.03 mg/kg body wt., i.m.), while group II received a combination of ACP (0.03 mg/kg body wt.) and butorphanol (BUT) (0.2 mg/kg body wt.). Anaesthesia was induced by intravenous administration of tiletamine-zolazepam (TZ) until the desired effect was achieved, followed by maintenance with isoflurane (ISO) at a vaporizer setting of 1-2%. The anaesthetic combinations were compared based on clinical, physiological, haemodynamic, haematological, and biochemical parameters. ACP administered intramuscularly before TZ produced only mild sedation, poor muscle relaxation, and inadequate analgesia. The combination of ACP and BUT produced better sedation, analgesia, and muscle relaxation. Further, analgesia was more consistent when BUT was combined with ACP.

***Key words**: Acepromazine, Butorphanol, Dogs, Isoflurane, Tiletamine-Zolazepam.*

Adequate sedation, analgesia, and muscle relaxation are essential components of general anaesthesia in animals. Preanaesthetics play an important role in reducing pain and perioperative stress response in patients. Atropine is the most commonly used anticholinergic drug, which inhibits salivation, bronchial secretion and effectively counters the bradycardia and hypotension associated with laryngeal stimulation or vagovagal reflexes due to traction or pressure on viscera (Vesal *et al*., 2011). Butorphanol (BUT) is a potent opioid analgesic for treating acute nociceptive pain like injury, perioperative pain, postoperative pain, visceral and chronic pain (Ahsan *et al*., 2020). Combining an opioid with α_2 agonist or phenothiazine tranquilizer enhances sedation and analgesia and inhibits the side effects caused by opioid like central nervous system excitation and decreased gastrointestinal tract motility (Gomes *et al*., 2018; Carregaro *et al*., 2020). Acepromazine (ACP) is the most potent neuroleptic agent with comparatively low toxicity (Vesal *et al*., 2011). ACP offers very good muscle relaxation but has no analgesic effect (Grimm *et al*., 2015). ACP when given 15 min prior to any opioid will reduce the occurrence of vomiting (Grimm *et al*., 2015). Tiletamine-zolazepam (TZ) combination produces anaesthesia at high doses and sedation at low doses in dogs and cats, and can be given intravenously or intramuscularly. Isoflurane (ISO) produces least effect on cardiovascular system and produces minimum myocardial depression, no alteration on tissue perfusion, cardiac output and cardiac rhythm (Manjusha *et al*., 2023a). The advantages of ISO over other inhalant anaesthetics are low biodegradability, low blood solubility and absence of catecholamine induced heart arrhythmias (Hellebrekers, 1986).

Despite the extensive research and development of numerous anaesthetic drugs, a quest for devising an ideal anaesthetic combination utilizing the suitable drugs is still on. The objective of the present study was to evaluate acepromazine and butorphanol as preanaesthetic agents in tiletamine-zolazepam induced anaesthesia in dogs undergoing ovariohysterectomy.

Materials and Methods

A total of 12 clinically healthy female dogs, with an average (Mean±SE) body weight of 18.6±1.12 kg, were selected for the study irrespective of their breed and age. Prior to surgery, food and water were withheld for 12 hr and 2 hr, respectively. The animals were randomly assigned to two groups, each comprising six dogs. Initially, all dogs received an intramuscular (i.m.) injection of atropine (0.045 mg/kg body wt.). In the first group (ACP), acepromazine (0.03 mg/kg body wt., i.m.) was administered, while

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in the second group (ACP-BUT), butorphanol (0.2 mg/kg body wt., i.m.) was administered in addition to acepromazine. Anaesthesia was induced by tiletamine-zolazepam (TZ) until the pedal reflex was abolished and muscle relaxation was sufficient for endotracheal intubation. Anaesthesia was maintained with isoflurane (1–2%) in oxygen, delivered through a precision vaporizer.

Sedation and clinical reflexes were evaluated using a numeric descriptive scale (NDS) as per Rafee *et al*. (2015) (Table 1). Heart rate (HR), respiratory rate (RR) and rectal temperature RT) were recorded. Blood pressure, including systolic (SAP), diastolic (DAP), and mean arterial pressure (MAP), was monitored non-invasively using an oscillometric blood pressure device. Physiological parameters were recorded at baseline (BL), at 5 min post-atropine administration (TA), 20 min post-premedication (TP - DEX/ACP-BUT), and at 10 min intervals following tiletamine-zolazepam administration-TZ10, TZ20, TZ30, TZ45, TZ60, TZ75, TZ90, and TZ105. Haematological and biochemical assessments were performed at TZ0, TZ30, TZ60, TZ90, and TZ105.

Table 1: Definition of numerical descriptive scores (NDS) pertaining to various clinical parameters (Rafee *et al*., 2015).

Parameters	**Scores**				
	0	**1**	**2**	**3**	**4**
Palpebral (0-3)	Strong and intact with sudden blink	Intact with weak blink Intact and	Very weak	Reflex absent	-
Pedal (0-3)	Intact and strong withdrawal reflex	weak reflex	Intact and very light reflex; slow response	Reflex absent	-
Jaw relaxation(0-3)	Not willing to the open the mouth	Resistance to open the mouth and closed quickly	Less resistance to open the mouth and closed slowly	No resistance and mouth remains open	-
Salivation (0-3)	Salivation absent	Mild	Moderate	Excessive salivation	-
Sedation score (0-3)	Nil	Mild	Moderate	Severe	-
Induction score (0-2)	Poor (restlessness, excitement, and unable to perform endotracheal tube)	Fair (mild restlessness and excitation)	Good (no excitation, smooth induction and endotracheal intubation)	-	-
Intubation score (0-4)	Poor	Allowing entry but chewing	Allowing deeper entry but coughing	Difficult intubation with slight coughing	Easy intubation without coughing
Recovery score(0-2)	Poor (restlessness)	Fair (relatively smooth with some restlessness)	Good (smooth)	-	-

Statistical analysis of the data was done using SPSS software (Version 20.0; SPSS Inc., IL, USA).

Results and Discussion

The pedal and palpebral reflexes were intact in both groups up to anaesthetic induction with TZ. After induction, both reflexes were completely abolished, which was maintained up to 75 min under ISO with oxygen (Table 2). The ACP-BUT produced neuroleptanalgesia characterized by enhanced sedation and analgesia. The pedal reflex was regained earlier in dogs premedicated with ACP with or without BUT. It could be due to the lack of analgesic properties of ACP (Vesal *et al*., 2011). In both groups, the jaw relaxation scores increased significantly ($P<0.05$) from the baseline value after induction up to 75 min during maintenance with ISO. Muscle relaxation was inadequate after administration of ACP with or without BUT. Similar findings were reported by Pereira *et al*. (2019). Salivation was absent throughout the observation period in both groups.

Mild sedation was noticed after administration of ACP, and moderate sedation was noticed with ACP-BUT. Moderate sedation after the administration of ACP-BUT was reported in dogs (Monteiro *et al*., 2009). In this study, animals of both groups had smooth induction, intubation, and recovery. The recovery time was lesser with ACP, while the sternal recumbency and complete recovery time were higher with ACP-BUT. Recovery from anaesthesia was smooth when ACP or DEX was used as preanaesthetics in dogs (Herbert *et al*. 2013). There

Table 2: The Median (range: maximum and minimum) scores of palpebral reflex, pedal reflex, jaw reflex, salivation. Mean ± standard error values of HR, RR, RT, SBP, DBP, MAP and SpO_2 (%) recorded at 0 (Baseline – BL), five min after administration of atropine (TA), twenty minutes after administration of premedications (TP-ACP-BUT) and 10 (TZ10), 20 (TZ20), 30 (TZ30), 45 (TZ45), 60 (TZ60), 75 (TZ75), 90 (TZ90) and 105 (TZ105) minutes after the administration of the tiletamine-zolazepam (TZ) in both groups.

Variables	Treatment	Time points (minutes)										
		BL	TA	TP	TZ10	TZ20	TZ30	TZ45	TZ60	TZ75	TZ90	TZ105
Palpebral (score 0-3)	ACP	0(0-0)	0(0-0)	0(0-0)	3(3-0) *	3(3-3) *	3(3-3) *	3(3-1) *	3(3-0) *	1(3-0)	0(3-0)	0(3-0)
	ACP-BUT	0(0-0)	0(0-0)	0(1-0)	3(3-0)	3(3-0) *	3(3-0) *	3(3-0)	1(3-0)	0(3-0)	0(3-0)	0(3-0)
Pedal (score 0-3)	ACP	0(0-0)	0(0-0)	0(0-0)	3(3-3)*	3(3-3)*	3(3-3)*	3(3-1)*	3(3-1)*	2(3-0)	0(3-0)	0(3-0)
	ACP-BUT	0(0-0)	0(0-0)	0(1-0)	3(3-3)*	3(3-3)*	3(3-3)*	3(3-0)*	3(3-0)	0(2-0)	0(0-0)	0(0-0)
Jaw relaxation (score 0-3)	ACP	0(0-0)	0(0-0)	0(0-0)	3(3-0)*	3(3-0)*	3(3-0)*	3(3-0)*	3(3-0)	3(3-0)	0(0-0)	0(0-0)
	ACP-BUT	0(0-0)	0(0-0)	0(2-0)	3(3-2)*	3(3-3)*	3(3-3)*	3(3-1)*	3(3-0)	1(3-0)	0(3-0)	0(1-0)
Salivation (score 0-3)	ACP	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)
	ACP-BUT	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)
Heart rate (beats/min)	ACP ±8.8	123.2 ±4.04	143 ±2.25	121.4 ±8.92*	153 ±10.53	119 ±8.76	110 ±16.66	121.2 ±17.3	128 ±16	134 ±14.09	147.21 ±13	47.6
	ACP-BUT	124.4 ±5.71	145.4 ±1.94	130.4 ±3.98	170.6 ±5.31**	126 ±9.59	123.8 ±3.69	122.8 ±11.53	136.2 ±9.96	164 ±7.8	176.6 ±5.02**	179.2 ±6.71**
RR (breaths /min)	ACP	25.2 ±4.32	20.4 ±2.4	32.8 ±8.64	23.6 ±7.11	25.8 ±2.62	33.8 ±3.64	34.4 ±6.01	41.2 ±2.65*	38.4 ±4.96*	42.8 ±1.96**	21.6 ±2.64
	ACP-BUT	33.2 ±13.72	30.6 ±8.44	23.6 ±5.67	19.6 ±2.71	23.6 ±2.04	23.2 ±2.33	24 ±3.85	36.4 ±9.04	34 ±7.32	37.8 ±6.53	23.6 ±1.96
RT (!)	ACP	38.72 ±0.16	38.556 ±0.19	38.376 ±0.09	37.09 ±0.14**	36.612 ±0.31**	35.866 ±0.37**	35.644 ±0.39**	35.404 ±0.46**	35.114 ±0.34**	34.912 ±0.25**	35.61 ±0.73*
	ACP-BUT	39.04 ±0.09	38.82 ±0.11	38.49 ±0.14**	37.53 ±0.19*	36.8 ±0.2**	36.56 ±0.231**	36.17 ±0.23**	35.68 ±0.24**	35.24 ±0.23**	35.31 ±0.26**	35.15 ±0.25**
SAP (mmHg)	ACP	147.8 ±8.91	156.6 ±8.98	138.8 ±3.07	111.4 ±5.71*	106.2 ±9.42	101.6 ±7.67*	96.6 ±6.49*	103.2 ±16.21	101 ±10.12	111 ±11.35	80.4 ±13.06
	ACP-BUT	152.8 ±11.06	157.4 ±8.77	141.8 ±8.9	107.8 ±4.91**	111.4 ±8.18*	118.8 ±6.14	100.2 ±4.62*	108.4 ±7.1*	110.8 ±5.7*	132* ±15.89	87 ±15.57*
DAP (mmHg)	ACP	109.2 ±11.05	83.4 ±12.16	67.8 ±13.09	63 ±9.78	56.8 ±12.11	47.2 ±10.07*	46.8 ±8.49	47.8 ±7.53*	47.8 ±7.17*	59 ±8.12*	80.4 ±13.06*
	ACP-BUT	88.8 ±12.08	96.6 ±12.06	68 ±11.3*	56.8 ±5.62*	63.8 ±7.19	66.8 ±7.93*	49 ±7.23*	59.4 ±8.85*	66.2 ±8.1*	70.2 ±9.36*	87 ±15.57*
MAP (mmHg)	ACP	121 ±10.76	132 ±7.92	100.2 ±9.85	81.4 ±10.23	70.6 ±11.31	65 ±9.05*	63.4 ±7.39*	70.8 ±14.41*	63.8 ±7.67*	77.2 ±8.78*	93.2 ±11.63
	ACP-BUT	109 ±16.03	114 ±9.98	84.8 ±12.73	74.8 ±6.58	82.8 ±7.35*	85.4 ±8.23*	68.6 ±6.62*	75 ±8.43*	76.8 ±8.84*	84.4 ±8.11	99.6 ±13.43
SpO_2 (%)	ACP	99.6 ±0.68	98.4 ±1.17	98.6 ±2.01	98.4 ±5.65	99.4 ±5.49	98.6 ±2.94	98.6 ±5.02	99.2 ±2.4	99.8 ±3.12	99.2 ±3.44	99.6 ±4.57
	ACP-BUT	99.2 ±0.58	99.2 ±0.86	99.2 ±1.07	99.6 ±3.53	98.4 ±4.89	98.6 ±2.38	99.6 ±2.25	99 ±2.77	98 ±3.2	98 ±3.03	99 ±5.78

were no significant changes in the duration of surgery and anaesthesia between the groups, even though the duration of anaesthesia was relatively longer in ACP-BUT. There was no significant difference pertaining to the induction dose of TZ between the groups, although the dosage of TZ required for induction was

Table 3: The Median (Range: maximum and minimum) scores of sedation, induction, intubation and recovery score; mean±SE of weak time , recovery time, sternal recumbency time, complete recovery time, duration of surgery, duration of anaesthesia, induction dose of TZ & total amount of isoflurane (mL/kg/min) († indicates level of significance between groups).

Variable	Treatment	Score/ Value
Sedation score	ACP	1 (1-1)
(score 0-3)	ACP-BUT	2 (2-2)
Induction score	ACP	2 (2-2)
(score 0-2)	ACP-BUT	2 (2-2)
Intubation score	ACP	4 (4-4)
(score 0-4)	ACP-BUT	4 (4-4)
Recovery score)	ACP	2 (2-2)
(score 0-2	ACP-BUT	2 (2-2)
Weak time (min)	ACP	9.8±0.58
	ACP-BUT	9.6±0.81
Recovery time (min)	ACP	29.2±5.25
	ACP-BUT	20±3.48†
Sternal recumbency	ACP	85.4±19.83
time (SRT) (min)	ACP-BUT	138.2±10.28
Complete recovery	ACP	157±41.08
time (CRT) (min)	ACP-BUT	194.6±41.54
Duration of surgery	ACP	45±10.22
(min)	ACP-BUT	41±5.26
Duration of	ACP	78.6±8.77
anaesthesia (min)	ACP-BUT	79.4±8.3
Induction dose of	ACP	4.53±0.49
TZ (mg/ kg)	ACP-BUT	4.49±0.5
Total amount of	ACP	5.44±3.94
isoflurane (mL/kg/min)	ACP-BUT	4.64±2.69†

lesser in the ACP-BUT group (Table 3). The dosage of TZ required for induction with ACP alone was higher (4.53±0.49 mg/kg body wt.) than ACP-BUT (4.49±0.49 mg/kg body wt.). The induction dose of TZ was lower when ACP was used alone or combined with BUT, than reported doses of TZ alone (Nam *et al*., 2013). The amount of ISO required for maintenance was significantly (P>0.05) higher in ACP group (5.44±3.94 mL/kg/min) as compared to ACP-BUT (4.64±3.94 mL/kg/min) (Table 3). It was recorded that the addition of preanaesthetics influenced the induction dose of TZ and, thereby, the maintenance requirement of isoflurane (Manjusha *et al*., 2023b).

There were no significant changes in HR after administering preanaesthetics in both groups. The HR increased significantly (P<0.05) after anaesthetic induction up to 45 min and thereafter, increased towards the recovery period during maintenance with ISO, but there was no significant difference between the groups (Table 2). ACP did not cause any significant change in HR, and bradycardia was not evident at any time interval during the observation period. The hypotensive effect of ACP, together with mild sympathetic weakening, elevated HR in dogs (Vaisanen *et al*., 2002). In this study the RR decreased from the BL after induction in both groups up to 30 min, and thereafter it gradually increased towards the recovery with a significant increase (P<0.05) in the ACP group. Monterio *et al*. (2009) and Gomes *et al*. (2017) reported that the combination of ACP-BUT produced a minimum depression in cardiorespiratory parameters. The RT decreased significantly (P<0.01) after administration of ACP and ACP-BUT, and decreased further after induction with TZ and remained subnormal throughout the observation period (Table 2). ACP causes hypothermia by inducing heat loss from peripheral vasodilation and interrupting thermoregulatory mechanisms (Gross, 2001; Hall, 2001).

The haematological parameters decreased in both groups without any significant changes. However, creatinine values slightly increased after administration of ACP with or without BUT. It could be due to the temporary effect of the drug on urinary rate and GFR (Godinez *et al*. 2019). The SAP, DAP, and MAP decreased after the administration of ACP and BUT, which further decreased significantly (P<0.05) after the administration of TZ and during maintenance with ISO (Table 2). There were no significant changes in SpO_2 within the groups and between the groups at various time intervals during the observation period. The SpO_2 values did not differ from the baseline values under TZ-ISO anaesthesia in dogs (Hampton *et al*., 2019). Similar findings were recorded in the present study.

To conclude, butorphanol improved the quality of sedation induced by ACP and the anaesthesia induced by TZ.

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