Research Article
Electrocardiographic Parameters in Healthy Dogs Anesthetized with Ketamine-propofol Combination and four Different Premedications

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Abstract: Evaluating electrocardiographic parameters in healthy dogs anesthetized with ketamine-propofol combination (ketofol) and medetomidine, acepromazine and acepromazine-morphine as preanesthetic agents. Six healthy adult mix dogs (3 male, 3 female) weighing 17.8±4.8 were include the study. Normal saline, medetomidine 20 µg/kg, acepromazine 0.05 mg/kg or acepromazine 0.05 mg/kg plus morphine 0.5 mg/kg were administered intramuscularly as premedication. Thirty minutes after premedication, rapid bolus intravenous injections of 0.4 mL/kg, 1:1 single syringe ketamine-propofol combination, was administrated for induction. Anesthesia was maintained with isoflurane for 1 h. Electrocardiographic examinations were made before premedication and others at 0, 5, 10, 15, 30 and 60 min after induction. Heart rate, electrical axis of the heart, duration of P, QRS and T waves, length of PR-QT and ST segments, active potential of P, R and T waves studied for any possibility of changes. Evaluation of heart rate in this study showed a significant increase in saline and a significant decrease in medetomidine groups. There were some significant differences in P wave duration and QRS complexes but irregular figure or deviated cardiac axis were not seen in recorded ECGs. The study results revealed prolonged atrial depolarization in all study groups especially in medetomidine and acepromazine-morphine groups. The other parameters were not shown any discussable significant differences.

Keywords: Dog, ECG, ketofol

INTRODUCTION

The use of ketamine-propofol combination (ketofol) has been documented in a number of human clinical settings, including gynecologic, ophthamologic and cardiovascular procedures in children and adults, in separate syringes, as well as mixed in the same syringe. (Andolfatto and Willman, 2011) In human medicine, total intravenous anesthesia with ketamine and Propofol, results stable anesthesia. Propofol has desirable pharmacokinetic properties, such as rapid clearance from the body. (Seliskar *et al.*, 2007) It is widely used; however, it is associated with a narrow margin of safety. Ketamine has many advantages including cardiac stability, preservation of the respiratory drive and analgesic properties. On the other hand, it has significant disadvantages such as psychomimetic effects and a long recovery period (Aouad *et al.*, 2008) Clinical experiences suggest that the use of ketamine-propofol combination has some advantages such as limited incidence of propofol induced respiratory depression, provision of analgesia from the ketamine (Tobias, 2004), decrease the cardiorespiratory side effects (Mair *et al.*, 2009) over using ketamine or propofol alone. As we know, ECG recording is a usual monitoring in operation rooms. Despite recent clinical trials on ketamine- propofol combination in dogs, there is not any reliable document on electrocardiographic evaluation in use of this combination in different anesthetic regimes in veterinary anesthesia. The aim of the present study was to evaluate electrocardiographic parameters in ketamine-propofol induced anesthesia in dog with four different preanesthetic regimes: saline, medetomidine, acepromazine and acepromazine-morphine.

MATERIALS AND METHODS

This project was approved by the local Committee of the Institutional Animal Care and use of Veterinary hospital in Shahid Chamran University of Ahvaz. Six adult mix dogs (3 male and 3 female) weighing 17.8±4.8 (mean±SD) all free from clinical evidence of disease, were enrolled in the study. To check the probability of pregnancy, each female dog experienced an ultrasonographic examination.

Animals were not feed for 12 h before beginning the study. Each pre-anesthetic regime was administered to all six dogs and there was 10 days between each regime study. Normal saline, medetomidine 20 µg/kg,

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acepromazine 0.05 mg/kg and acepromazine 0.05 mg/kg plus morphine sulphate 0.5 mg/kg (all 2 mL in volume) (Muir, 2007) were administered in *Semi membranous/Semi tendineus* muscles. Then an intravenous catheter, Gauge 20 was fixed in left cephalic vein. Thirty minutes later, intravenous rapid bolus injection of 0.4 mL/kg single syringe combination of ketamine HCl (1% dilution) and propofol 1% (1:1 ratio), were administrated for induction of anesthesia (2 mg/kg of each drug). Lerche *et al.* (2000) and Andolfatto and Willman (2011) Following endotracheal intubation, anesthesia was maintained with isoflurane, for 1 h. During the procedure, fluid therapy was done using Lactated ringer's solution, at the rate of 1 mL/kg/hr.

Electrocardiographic examinations were made before premedication (-30) and at 0, 5, 10, 15, 30 and 60 min after induction of anesthesia. The tracing were carried out using a device direct-writing hot-stylus single channel ECG recorder. Animals were held in right lateral recumbency, the electrodes were attached over the elbow and stifle joints with alligator clips after applying ECG gel. A six lead recording, consisting of the three standard bipolar leads (I, II and III) and three unipolar augmented leads (aVR, aVL and aVF), at 1 cm = 1 mV, with the speed of 50 mm/sec (1 mm = 0.02 sec) was made on each animal. Evaluation was normally done using lead II, but if necessary, leads I and III employed (Tilley, 1992a). Following parameters were determined for each animal in each recording time: heart rate, electrical axis of the heart, duration of P, QRS and T waves, length of PR, QT and ST segments, active potential (amplitude) of P, R and T waves.

A one-way Analysis of Variance (ANOVA) was used to evaluate significant differences between anesthetic regimes in electrocardiographic parameters during anesthesia (Statistical analysis was performed between groups). When differences were determined to exist, data was further analyzed using the LSD test. A value of $p<0.05$ was considered significant. All statistical evaluations were done with SPSS 16, IBM software, USA.

RESULTS AND DISCUSSION

The results obtained from the different electrocardiographic parameters are summarized in Table 1. Also changes in heart rate are shown in Fig. 1.

Table 1: Results obtained from the different electrocardiographic parameters

Factor	Time (Min)	-30	0	5	10	15	30	60
P wave	Sal	0.04*	0.04*	0.04*	0.04*	0.04*	0.04*	0.04*
duration	Med	0.05±0.01	0.05±0.01	0.04±0.01	0.04	0.04±0.01	0.04±0.01	0.05±0.01
(sec)	Ace	0.05±0.01	0.05±0.01	0.05±0.01	0.05±0.01	0.05	0.05±0.01	0.05±0.01
	Ace+M	0.05±0.01	0.05±0.01	0.04±0.01	0.05±0.01	0.05±0.01	0.05±0.01	0.05±0.01
QRS	Sal	0.05±0.01	0.05±0.01*	0.05±0.01*	0.05±0.01	0.06±0.01	0.06±0.01	0.06±0.01
complex	Med	0.06±0.01	0.06	0.06±0.01	0.06	0.06	0.06	0.06
duration	Ace	0.05	0.06±0.01	0.06±0.01	0.06±0.01	0.06±0.01	0.06±0.01	0.06±0.01
(sec)	Ace+M	0.06	0.07±0.01	0.06±0.01	0.06±0.01	0.07±0.01	0.07±0.01	0.06±0.01
T wave	Sal	0.05±0.02	0.05±0.01	0.05±0.01	0.05±0.01	0.04±0.01	0.05±0.02	0.05±0.02
duration	Med	0.04±0.01	0.05±0.02	0.05±0.01	0.05±0.01	0.05±0.01	0.06±0.01	0.05±0.01
(sec)	Ace	0.05±0.01	0.06±0.01	0.05±0.01	0.05±0.01	0.05±0.01	0.05±0.01	0.05±0.02
	Ace+M	0.05±0.01	0.06±0.02	0.05±0.01	0.06±0.01	0.07±0.01*	0.06±0.01	0.06±0.02
PR segment	Sal	0.11±0.01	0.11±0.01*	0.11±0.02	0.11±0.01	0.12±0.01*	0.11±0.01*	0.1±0.01*
duration	Med	0.11±0.01*	0.15±0.04	0.15±0.02*	0.14±0.02*	0.15±0.02	0.15±0.02	0.16±0.02
(sec)	Ace	0.12±0.01	0.12±0.01	0.11±0.01	0.11±0.01	0.12±0.01	0.13±0.02	0.13±0.02
	Ace+M	0.13±0.01	0.12±0.01	0.13±0.01	0.14±0.01	0.14±0.02	0.14±0.01	0.13±0.02
QT segment	Sal	0.19±0.01	0.19±0.01*	0.19±0.04*	0.22±0.02	0.21±0.03	0.23±0.02	0.23±0.02
duration	Med	0.2±0.02	0.22±0.02	0.22±0.03	0.23±0.03	0.24±0.02	0.25±0.02	0.25±0.03
(sec)	Ace	0.2±0.02	0.21±0.01$^+$	0.22±0.02	0.22±0.01	0.23±0.01	0.24±0.03	0.25±0.02
	Ace+M	0.21±0.03	0.23±0.01$^+$	0.23±0.01	0.24±0.01	0.24±0.01	0.24±0.01	0.24±0.01
ST segment	Sal	0.09±0.02	0.09±0.02	0.1±0.03	0.11±0.03	0.11±0.02	0.12±0.01	0.12±0.01
duration	Med	0.09±0.02	0.1±0.02	0.1±0.03	0.12±0.02	0.13±0.02	0.13±0.03	0.14±0.03
(sec)	Ace	0.08±0.02	0.08±0.01	0.09±0.02	0.11±0.01	0.11±0.02	0.12±0.03	0.13±0.02
	Ace+M	0.09±0.03	0.1±0.02	0.11±0.02	0.11±0.02	0.1±0.02	0.11±0.02	0.11±0.02
P wave	Sal	0.23±0.08	0.25±0.05*	0.21±0.07	0.21±0.07	0.25±0.05*	0.2±0.08	0.2±0.08
amplitude	Med	0.16±0.08	0.16±0.05	0.18±0.04	0.18±0.04	0.15±0.05	0.15±0.05	0.13±0.05
(mv)	Ace	0.23±0.08	0.23±0.08	0.21±0.04	0.21±0.09	0.21±0.09	0.16±0.05	0.16±0.05
	Ace+M	0.18±0.07	0.16±0.08	0.15±0.08	0.13±0.05	0.13±0.05	0.13±0.05	0.13±0.05
R wave	Sal	0.86±0.26	0.9±0.4	0.86±0.4	0.85±0.41	0.83±0.4	0.8±0.41	0.85±0.42
amplitude	Med	0.093±.0.3	1.2±0.36	1.18±0.37	1.18±0.33	1.2±0.32	1.13±0.37	1.1±0.42
(mv)	Ace	0.83±0.3	0.83±0.25	0.86±0.3	0.81±0.31	0.81±0.31	0.9±0.32	0.91±0.3
	Ace+M	0.9±0.42	0.86±0.39	0.85±0.37	0.85±0.36	0.85±0.36	0.88±0.39	0.93±0.43
T wave	Sal	0.28±0.11	0.26±0.12	0.26±0.12	0.26±0.1	0.23±0.13	0.25±0.13	0.21±0.13
amplitude	Med	0.21±0.09	0.23±0.1	0.25±0.12	0.18±0.04	0.16±0.05	0.26±0.13	0.23±0.13
(mv)	Ace	0.23±0.13	0.23±0.05	0.2±0.06	0.18±0.09	0.2±0.1	0.23±0.12	0.21±.09
	Ace+M	0.2±0.1	0.18±0.13	0.2±0.06	0.21±0.11	0.26±0.1	0.23±0.13	0.2±0.1

Electrocardiographic parameters in six dogs anesthetized with ketamine-propofol combination following 4 different pre-anesthetic regimes (saline (Sal); medetomidine (Med); acepromazine (Ace) and acepromazine+morphine (Ace+M)); Data expressed as mean±standard deviation. In columns, Starred data (*) had significant differences with gray ones; Also, data that shown with (+) have significant differences with each other; ($p<0.05$, CI = 95%); Statistical analysis was performed between groups
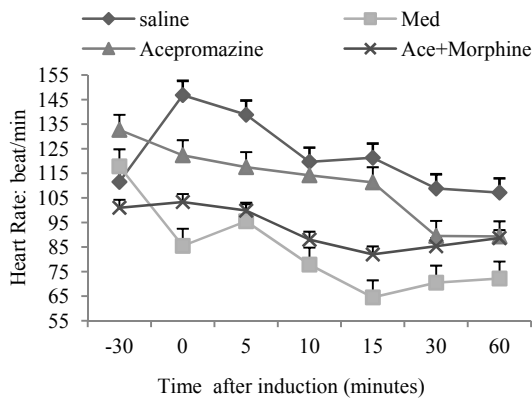
Fig. 1: Heart rate changes in four pre-anesthetic regimes including normal saline, medetomidine (Med), acepromazine (Ace) and acepromazine-morphine in dogs anesthetized with ketamine-propofol combination

During anesthesia, neither malignant arrhythmias nor abnormal electrocardiographic figures were observed and there was not any irregular cardiac (mean electrical) axis in graphs. Significant increase in heart rate in normal saline group and significant decrease in medetomidine group were observed at the time of induction (time: 0). Significant differences in heart rate between saline and acepromazine+morphine limited time of induction and 15 min after induction of anesthesia and between medetomidine and acepromazine limited to time of induction and 10 and 15 min(s) after it. Also, significant differences in heart rate between saline and medetomidine, continued from induction until the end of study.

According to Table 1, in P wave values, there was a significant difference between saline and acepromazine from the baseline untill the end of the study. Other differences were between saline and medetomidine in 1st recording and between saline and acepromazine+morphine in time of induction and 15, 30 and 60 min after induction. Other important changes were in QRS complexes and listed as: Significant differences between saline with acepromazine and acepromazine- morphine combination in time of induction and saline with medetomidine, acepromazine and acepromazine- morphine combination in 5 min after induction.

The anesthetic drugs used in this study did not change the duration of the T-wave, ST segment and the amplitude of the T and R waves, indicating that these drugs had no influence on the ventricular depolarization time as well as ventricular repolarization and ventriclar enlargement (Tilley, 1999b).

There was not any malignant arrhythmia in study groups. Propofol and isoflurane do not cause any malignant arrhythmia (Buhl *et al.*, 2005). In beagles treated with dexmedetomidine alone or combined with propofol or propofol/isoflurane, ventricular arrhythmias were not detected more frequently than those reported in healthy non-anaesthetised dogs (Kuusela *et al.*, 2002).

Evaluation of heart rate in this study showed a significant increase in normal saline and a significant decrease in medetomidine groups. Several studies showed that medetomidine caused a significant decrease in heart rate in dogs (Dodam *et al.*, 2004; Cullen, 1996; Sinclair, 2003; Ko *et al.*, 1996). Medetomidine is a potent a_2-adrenoreceptor agonist in laboratory animals, dogs and cats. Unfortunately, the negative cardiovascular effects of earlier α_2-agonists (xylazine), including bradycardia and associated arrhythmias, hypertension or hypotension and reduced cardiac output, are still observed with medetomidine. It is a potent $\alpha2$-adrenoceptor agonist and stimulates receptors centrally to produce dose-dependent sedation and analgesia and receptors centrally and peripherally to cause marked bradycardia and decrease the cardiac output (Ko *et al.*, 1996). Some of regular cardiac arrhythmias that may produce by pre-anesthetics and anesthetics are: sinus tachycardia due to use of acepromazine, sinus baradycardia due to use of medetomidine and morphine, premature ventricular depolarization due to use of ketamine, ventricular tachycardia after administration of propofol and bradyrrhythmia due to use of isoflurane (Muir, 2007). Two anaesthetic protocols (isoflurane and propofol) did not induce an increased incidence of severe arrhythmias in healthy dogs that undergone orthopedic surgery. In dogs were premedicated with medetomidine or acepromazine and anesthetized with propofol and isoflurane for ovariohysterectomy, minimum heart rate during the 24-h recording period was significantly lower among dogs given medetomidine than among dogs given acepromazine (Vaisanen *et al.*, 2005). Dennis *et al.* (2007) compared the effects of thiopentone and propofol on the electrocardiogram of dogs and found that propofol may be more suitable than thiopentone for dogs with a susceptibility to ventricular arrhythmias or a long QT interval. Bradycardia is a regular phenomenon after isoflurane administration (Muir, 2007). After administration of ketamine-propofol combination, heart rate increased in medetomidine group, however in comparison with other groups, heart rate still low. Except the changes in heart rate after induction in medetomidine group, propofol-ketamine combination produces reliable cardiac stability.

Any irregular or deviated cardiac (mean electrical) axis did not found in all recorded ECGs. Mean electrical axis is used in the clinic to analyze the position of the heart in the thoracic cavity and to diagnose any volume changes of the cardiac enlargement. In this respect, we know that the deviation of the cardiac electric axis to the right indicates

hypertrophy or ventricular right dilatations and the deviation of the cardiac electrical axis to the left indicates dilatation or ventricular left hypertrophy (Tilley, 1992b). Therefore none of the anesthetic drugs could not change mean electrical axis in this study.

Premedication with acepromazine as well as a acepromazine-morphine caused a significant increase in P wave duration. Also acepromazine plus morphine and medetomidine caused significant decrease in P wave amplitude. It's found that echocardiograms following medetomidine administration in dogs with mitral regurgitation showed an increase of the left atrial to aortic root ratio at 30 min after drug administration (Lombard *et al*., 1989). Medetomidine and morphine have little impact on the echocardiographic and electrocardiographic variables in healthy dogs (Saponaro *et al*., 2013).

Acepromazine and acepromazine- morphine combination significantly increased QRS size in time of induction and 5 min after induction. Also medetomidine increased it only in 5 min after induction. Echocardiograms after use of medetomidine in dogs with mitral regurgitation showed that the left ventricular enlargement ratio at 30 min after drug administration (Lombard *et al*., 1989). The acepromazine plus xylazine did not change the duration of the QRS complex in dogs (Sarchahi *et al*., 2009). But Kumazawa *et al*. (1976) reported QRS widening in dogs receiving morphine and halothane. Morphine is generally regarded as having a centrally mediated depressant effect upon the cardiovascular system. Morphine produces a biphasic response; heart rate and mean arterial pressure initially increase followed by a reduction to below baseline levels. According to Weber *et al*., this finding may be related to a prolongation of intraventricular and His bundle conduction times (Weber *et al*., 1995).

Premedication with medetomidine caused a significant increase in T-wave duration only in 15 min after induction. Decreased T wave amplitude and increased duration of T wave has been reported following medetomidine-butorphanol administration in halothane anesthetized buffalos (Malik *et al*., 2011). Changes in T-wave morphology has been reported following medetomidine administration in dogs (Dyson and Pettifer, 1997).

In PR interval, significant differences were found between saline and medetomidine groups in all recording times after induction of anesthesia. The other significant differences were found between saline and acepromazine-morphine in 15 and 60 and between saline and acepromazine in 60 min after induction. It has been reported that the combination of medetomidine plus butorphanol might causes a significant (p<0.05) increase in PR interval 15 min after halothane anesthesia in water buffalos (Malik *et al*., 2011). Carareto *et al*. (2008) evaluated the effects of

propofol and sufentanil on the electrocardiographic parameters of healthy dogs. In their study, first degree atrioventricular block (the prolongation of PR interval greater than 130 milliseconds) occurred in the studied dogs (Carareto *et al*., 2008). The delay in the impulse conduction through the atrioventricular node was likely caused by the dose-dependent vagotonic effect of morphine and medetomidine (Bovill, 1993). These drugs can delay ventricular depolarization due to a prolonged Purkinje fiber potential, thereby resulting in a longer PR interval. Weber *et al*. observed that such opioid produces effects similar to unspecific calcium antagonists, leading to a significant prolongation in atrioventricular electrical conduction (Weber *et al*., 1995).

The results obtained from ECGs shown significant effect of medetomidine and acepromazine-morphine on QT interval in 5 min after induction. The QT interval is the summation of ventricular depolarization and re-polarization and represents ventricular systole. The normal width range of QT interval is 0.15 to 0.25 sec at normal heart rate; varies in heart rate (faster rates have shorter QT intervals and vice versa) (Tilley, 1992c). Therefore slight and temporary increase in QT interval was the effect of anesthetic drugs on the heart rate. Also in this study, despite observed significant differences, all recorded data were within normal range for this parameter.

So, the study results reveal that selected anesthetic regime have distinct effects on quality of anesthesia and shape of ECGs parameters. There was not any malignant arrhythmia in all study groups. Progressive bradycardia was the distinct phenomena in all study groups. Prolonged atria depolarization was found in all study groups especially in medetomidine and acepromazine-morphine. Changes of other ECG parameters were in normal range, reported for dogs in veterinary.

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