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Cardiopulmonary effects of dexmedetomidine, midazolam and butorphanol as preanaesthetics to ketamine hydrochloride anaesthesia in dogs

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ABSTRACT

Aim: The study was carried out to evaluate cardiopulmonary effects of dexmedetomidine, midazolam and butorphanol as preanaesthetics to ketamine hydrochloride anaesthesia in dogs..

Method and Materials: The study was conducted on 32 clinical cases of canine patients divided into four groups, where eight animals were in each group. Dogs were premedicated with dexmedetomidine alone @ 10 µg/kg in DK group, dexmedetomidine @ 10 µg/kg and midazolam @ 0.2 mg/kg in DMK group, dexmedetomidine @10 µg/kg, butorphanol @ 0.2 mg/kg in DBK group and dexmedetomidine @10 µg/kg, midazolam @ 0.2 mg/kg and butorphanol @ 0.2 mg/kg IM in DBMK group. Induction and maintenance of anaesthesia were achieved with ketamine hydrochloride. HR, RR, RT, blood pressure and SpO_2 were recorded at 0, P-10, I-5, 10, 20, 30, 40, 50, 60 and 90 minutes.

Results: Significant ($P<0.05$) alteration in heart rate, respiratory rate and rectal temperature was noticed in all groups after induction of anaesthesia. SBP, DBP and MAP showed the biphasic variation and were significantly changed. SpO_2 remained irregular and within physiological limits.

Conclusion: Dexmedetomidine (10µg/kg) with butorphanol 0.2 mg/kg and midazolam 0.2 mg/kg as preanaesthetic with ketamine hydrochloride induces effective surgical anaesthesia in healthy dogs.

Keywords: Butorphanol, dexmedetomidine, ketamine hydrochloride, midazolam, preanaesthetics, veterinary anaesthesia.

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Introduction

Ketamine as an injectable dissociative anaesthetic is commonly used in combination with α_2-agonists for achieving balanced anaesthesia in small animal (El-Sherif, 2018). Ketamine has negative ionotropic effect on heart and cardiovascular stimulant after intravenous administration, minimal effect on the respiratory system (Berry, 2015) and direct depressive action at thermoregulatory centre (Wright, 1982).

Alpha-2 agonists viz; Xylazine, romifidine, detomidine, medetomidine and dexmedetomidine are commonly used in veterinary practice. Dexmedetomidine is a potent α-2 agonist and more likely to be associated with respiratory depression, bradycardia, hypothermia, biphasic changes in blood pressure (Hall, 2014). Combinations of benzodiazepines and opioids with α_2-agonists show synergism (Tranquilli et al, 1990 and Boehm et al, 2010).

Midazolam is used for general anaesthesia and conscious sedation and act by potentiating the inhibitory action of GABA at benzodiazepine receptors in different body tissues. Respiratory depression, hypoxemia and hypotension could be seen with midazolam (Nordt and Clark, 1997). Midazolam has minimal effects on haemodynamic parameters (Reves et al, 1978).

Butorphanol tartrate is a synthetic opioid, possessing an agonist and antagonist properties. Panting and respiratory depression has been reported with butorphanol (Dyson, 1990). It can cause decrease in heart rate, arterial blood pressure and intestinal motility (Schnellbacher, 2010). Opioid may augment bradycardia and the respiratory depressant action of medetomidine when used in combination (Ko et al, 2000 and Chen et al, 2012).

Although, there are many literatures available regarding combination of dexmedetomidine with opioids, benzodiazepines (Diao et al, 2017) and

ketamine and its effect on primary vital signs (Silva et al, 2010). The purpose of the study was to evaluate cardiopulmonary effects of dexmedetomidine, midazolam and butorphanol as preanaesthetics to ketamine hydrochloride anaesthesia in dogs.

Materials and Methods

Thirty two dogs were included in the study and randomly divided into 4 groups viz., DK, DMK, DBK and DBMK, where 8 dogs were in each group. Preanaesthetic evaluation of dogs was performed on the day before surgery by history, physical and clinical examination. Thereafter, all animals were kept off-feed and off-water for 12 and 6 hours prior to procedures, respectively. Baseline data values of selected parameters viz., clinico-physiological, haemodynamics, and haematobiochemical were recorded. Prior to the general anaesthesia, preanaesthetics were loaded in separate syringes and injected subsequently. All the dogs of the DK group were preanaesthetized with dexmedetomidine (Dextomid 100 µg/ml) alone @ 10 µg/kg BW intramuscular. Animals of DMK group were preanaesthetized with dexmedetomidine @ 10 µg/kg BW and midazolam (Mezolam 1 mg/ml) @ 0.2 mg/kg BW intramuscular. The dogs of DBK group were preanaesthetized with dexmedetomidine @ 10 µg/kg BW and butorphanol (Butodol-2 2 mg/ml) @ 0.2 mg/kg BW intramuscular. All the dogs of DBMK group were preanaesthetized with dexmedetomidine @ 10 µg/kg BW, midazolam @ 0.2 mg/kg BW and butorphanol @ 0.2 mg/kg BW intramuscular. Ketamine (Aneket 50 mg/ml) was used for induction and maintenance of anaesthesia.

Clinico-physiological and haemodynamics parameters were recorded at baseline, 10 minutes after preanaesthetic administration (P-10) and 5 (I-5), 10, 20, 30, 40, 50, 60, 90 minutes after induction. Heart rate (beats/minute), Respiratory rate (breaths/minute) and Rectal temperature (°F) were recorded by the Multiparameter monitor except for initial two observation which were measured with a stethoscope, by seeing thoracic excursion and digital thermometer, respectively. Baseline and P-10 values of SpO_2 (%) were recorded by placing a sensory probe of Multiparameter monitor at ear pinna and the remaining values were with the tongue. Noninvasive Blood Pressure (mm Hg) Values were recorded with the Multiparameter monitor after placing appropriate sized blood pressure cuff on the forelimb, distal to the elbow and proximal to the carpus. Mean arterial pressure was determined by putting values of SAP and DAP in the equation: MAP =DAP + 1/3 (SAP-DAP)

Results and discussion

Clinical efficacy of dexmedetomidine, midazolam and butorphanol as preanaesthetics with ketamine anaesthesia in dogs resulted as follows:

Heart Rate

Decrease in heart rate was noticed in all groups after the induction of anaesthesia when compared with baseline values (Table 1). Heart rate values were decreased initially up to 40 minutes in group DK and DMK, thereafter increased towards the baseline values. In DBMK group drop in heart rate was noticed up to 30 minutes and 50 minutes in DBK. Significant changes were observed for 5 minutes after induction (I-5) to 90 minutes. In group DBMK, heart rate values were significantly differed from baseline value at P-10 minutes and from 10-90 minutes after induction of anaesthesia. When comparison made between the groups, DBK group showed significantly higher heart rate at P-10 minutes than DBMK. Similar to the present study, Gross et al (1990); Kojima et al (2002); Kuo and Keegan (2004); Granholm et al (2007) also observed bradycardia in dogs premedicated with α_2-agonists alone or in combination with butorphanol and midazolam. However, Ko et al (1996) reported alteration cardiorespiratory effects of medetomidine and a medetomidine-butorphanol combination in dogs and Selmi et al (2003) observed significant decrease in HR in cats given a combination of dexmedetomidine (10 µg/kg) and butorphanol (0.2 mg/kg) I/M. Micieli et al (2017) and Congdon et al (2011) reported 55-56% drop in heart rate from baseline values after I/M dexmedetomidine. However, in the present study, heart rate was noticed up to 44% decreased in DK group. In DBK group, drop in heart was up to 50 and it was higher than other groups. Similarly, Braz et al (2010) reported alteration in cardiovascular response during infra-renal aortic cross-clamping in dexmedetomidine anesthetized dogs. However, some authors advocated that intensity of cardiovascular manifestations was dependent on the dose of dexmedetomidine (Ebert et al, 2000), route of administration, the combination of drugs, surgical procedure (Braz et al, 2008), distribution of α_2-adrenoreceptors and according to the animal species (Calzada and Artinano (2001).

Respiration Rate

Respiratory rate was decreased up to 30 minutes in DK, DBK and DMK groups, decreased up to 40 minutes in DBMK group and afterwards increased till the end of the observation periods (Table 2). Significant changes in respiration rate were noticed after induction of anaesthesia in comparison to baseline value. DBK group showed significant decrease in respiration rate than other groups at 10 minutes after induction. DMK and DBMK groups had higher respiration rate than DBK group at 20 minutes after induction. Group DBK exhibited significantly lower respiration rate than DBMK at 30 minutes interval. Rafee et al, (2015) also observed significant changes in respiratory rate with dexmedetomidine and butorphanol premedicated dogs. However, Nishimura et al (2018) reported a significant decrease in RR with dexmedetomidine and butorphanol combination. Contrary, Sahoo et al (2018) reported non-significant changes in respiration rate after administration of dexmedetomidine-butorphanol-midazolam-ketamine anaesthesia in dogs.

Rectal Temperature (°F)

The values of rectal temperature were gradually decreased up to 60 minutes in all groups except DK, thereafter increased up to 90 minutes (Table 3). The group DK showed a continuous decreased temperature up to 90 minutes. After induction of anaesthesia, rectal temperature was significantly differed at 50, 60, 90 minutes in DK group, at 40, 50, 60, 90 minutes in DBMK group and at 20, 30, 40, 50, 60, 90 minutes in DBK group when compared to baseline values within the groups. Temperature changes in the DMK group were non-significant. DK group revealed significantly lower rectal temperature than DBMK and DMK at 90 minutes. Itamoto et al (2000) also reported significant decrease in rectal temperature after medetomidine-midazolam and butorphanol anaesthesia in dogs. Pypendop and Verstegen (1998) and Lemke (2004) reported hypothermia due to Alpha-2 adrenoreceptor agonist. Contrary, Arunkumar et al (2017) and Sahoo et al (2018) observed a non-significant decrease in rectal temperature in dogs.

Table 1: Mean ± S.E. The values of the Heart rate at different time interval in dogs of different groups

Group	Period of observation (Minute)									
	0	p-10	i-5	10	20	30	40	50	60	90
DK	95±4.22	84.±3.51^{ac}	83±4.64*	67.5±3.77*	59.5±3.95*	57±3.46*	53±2.66*	55±2.37*	58±2.44*	63.5±2.57*
DBK	100±5.25	96±4.85^{a}	80.5±5.97*	76±6*	63.5±5.01*	58±4.45*	52.5±2.72*	50.5±1.80*	52.5±2.01*	60.5±1.73*
DMK	79±3.69	74±2.96^{bc}	62±2.91*	55.5±3.07*	51±2.53*	47.5±1.70*	45±1.54*	50±1.62*	54.5±1.45*	67±2.16*
DBMK	82±5.49	71±3.5^{bc*}	72±4.45	64±3.95*	55.5±2.84*	45±2.75*	51.5±2.23*	52.5±2.55*	53.5±1.89*	57±2.15*

*Significantly different from base value (P<0.05)

Values with different superscripts differ significantly (P<0.05) between the groups

Table 2: Mean ± S.E. The values of the Respiration rate at different time interval in dogs of different groups

Group	Period of observation (Minute)									
	0min	p-10	i-5	10	20	30	40	50	60	90
DK	29±1.29	25.62±0.82	22.37±0.70*	19.75±1.06^{a*}	17.75±1.20^{ab*}	16.12±1.39^{ab*}	16±1.26*	16.87±1.56*	18±1.61*	19.5±2.11*
DBK	25.75±0.67	22.87±0.47	16.5±0.53*	13.75±0.64^{b*}	13.37±1.12^{a*}	13.12±0.95^{a*}	14.12±1.10*	14.87±1.02*	17±1.19*	19.25±0.95*
DMK	29±1.28	25.62±1.4	22.12±1.04*	19.75±0.88^{a*}	18.5±1.22^{bc*}	16.87±1.21^{ab*}	17.37±1.36*	18.87±1.15*	20.25±0.9*	23.25±0.75*
DBMK	28.87±1.66	25.37±1.42	22.62±1.20*	20.62±0.99^{a*}	18.75±1.03^{bc*}	17.62±0.98^{b*}	16.8±0.98*	18.5±0.82*	19.5±0.86*	22.5±0.94*

*Significantly different from base value (P<0.05)

Values with different superscripts differ significantly (P<0.05) between the groups

Table 3: Mean ± S.E. The values of the Rectal temperature at different time interval in dogs of different groups

Group	**Period of observation (Minute)**									
	0	p-10	i-5	10	20	30	40	50	60	90
DK	101.31±0.25	101.35±0.29	100.45±0.34	100.27±0.40	99.95±0.41	99.42±0.52	99.22±0.54	98.91±0.58*	98.62±0.53*	98.37±0.61^{a*}
DBK	101.36±0.17	101.35±0.18	100.96±0.18	100.85±0.18	100.41±0.23*	100.12±0.19*	99.97±0.18*	99.68±0.15*	99.5±0.14*	99.67±0.16^{ab*}
DMK	101.62±0.25	101.57±0.32	101.2±0.40	101.18±0.45	101.05±0.48	100.78±0.46	100.5±0.48	100.15±0.39	100.07±0.38	100.37±0.34^{b}
DBMK	101.73±0.23	101.52±0.24	101.4±0.26	101.27±0.29	100.92±0.29	100.58±0.27	100.15±0.26*	99.98±0.28*	99.77±0.26*	100.01±0.17^{b*}

*Significantly different from base value (P<0.05)

Values with different superscripts differ significantly (P<0.05) between the groups

Systolic Blood Pressure (mm Hg)

The Mean±SE values of systolic blood pressure (SBP) were increased up to 20 minutes in DK, DMK and DBMK, and up to 30 minutes in DBK group (Table 4). In the DK group, significant change was observed only at 10 minutes after induction in comparison to the baseline value. In the DBK group, significant changes were observed from I-5 to 50 minutes. In the DMK group, significant changes in SBP were observed from I-5 to 20 minutes. In DBMK group significant changes in SBP was noticed from 10 minutes to 30 minutes. SBP in the DK group was significantly higher than the other groups at 10 minutes after induction. SBP in DBK group was significantly higher than DMK and DBMK at 30 minutes. SBP in DBK group was significantly higher than DK, DMK and DBMK at 40 minutes and remained significantly higher than DMK at 50 minutes. Similar biphasic changes in blood pressure were observed by Kallio et al (1989); Ko et al (2011) and Ahmad et al (2018). However, Rafee et al (2015) and Sahoo et al (2018) observed contrasting non-significant changes in SBP in dogs anaesthetized with the dexmedetomidine, butorphanol, midazolam and ketamine anaesthesia.

Diastolic Blood Pressure (mm Hg)

The Mean±SE value of diastolic blood pressure in all the groups was higher in comparison to baseline values (Table 5). DBP values were increased up to 30 minutes in DBK and DBMK, 20 minutes in DMK and 10 minutes in DK group, thereafter decrease towards baseline values up to 90 minutes. After induction DBP values at 5-50 minutes in DBK, 5-30 minutes in DMK, 10-40 minutes in DBMK and at 10 minutes in DK group were significantly higher in comparison to baseline values within the groups. DBP values for DK group was significantly lower than DMK and DBMK at P-10.Significantly high DBP values were observed in the DBK group than DK and DMK at 30, 40, 50, 60 minutes. DBK and DBMK groups had significantly high DBP values at 60, 90 minutes in comparison DK. Sahoo et al (2018) also observed significant increase in DBP between 15-30 minutes and thereafter gradually decrease after administration of dexmedetomidine-butorphanol-midazolam and ketamine anaesthesia in dogs. Contrary, Selmi et al (2003) observed significant decrease in DAP with combination of dexmedetomidine (10 µg/kg) and butorphanol (0.2 mg/kg) I/M.

Mean Arterial Blood Pressure (mm Hg)

Mean arterial blood pressure (MAP) was increased up to 10 minutes after induction in DK group, up to 30 minutes in DBK and DBMK group, up to 20 minutes in DMK group, thereafter decreased towards baseline values (Table 6). The values of MAP after induction were significantly higher in DK group at 10 minutes, in DBK and DBMK group 10-40 minutes and in DMK group at 5-30 minutes in comparison to baseline value within the groups. DBK group showed significantly higher MAP values at 20-90 minutes than DK. DBK group showed significantly higher MAP values at 30-60 minutes than DMK. DK group showed significantly lower MAP values than DMK at P-10 and DBMK at P-10 and 90 minutes. Ahmad et al (2013) observed an initial increase in MAP and thereafter gradually decreased while Nishimura et al (2018) reported a significant decrease in MAP with dexmedetomidine alone or in combination with butorphanol. Pypendop and Vestergen (1998) observed a significant initial increase in MAP afterwards decrease compared to baseline values. However, MAP values were noticed with initial increase up to 30 minutes in DK group thereafter decreased gradually in present study. Contrary, Feng et al (2015) noticed significant decrease in MAP with combination of dexmedetomidine (25 µg/kg), midazolam (0.45 mg/kg), butorphanol (0.25 mg/kg) and atropine (0.035 mg/kg) in dogs.

SpO_2(%)

After premedication and induction of anaesthesia, the Mean±SE values of SpO_2 in all the groups were remained between 89-94%. No symmetrical pattern of SpO_2 changes was observed. The values were non-significantly differed in comparison to baseline values within the groups, except DBK, where last observation was significantly differed from the baseline value (Table 7). Changes in SpO_2 values were non-significant between the groups. Hunt et al (2012) also reported clinically acceptable limits of SpO_2 in dogs and cats premedicated with buprenorphine-dexmedetomidine prior to elective surgery. However, Biermann et al (2012) reported non-significant alteration at different intervals compared to base value in dexmedetomidine premedicated dogs. Jena et al (2014) reported that SpO_2 remained slightly increased non-significantly at different intervals in dexmedetomidine premedicated dogs, while last observation of the present study was significantly different from baseline value in DBK group.

Table 4: Mean ± S.E. The values of the Systolic blood pressure of dogs of different groups at different interval

Group	Period of observation (Minute)									
	0min	p-10	i-5	10	20	30	40	50	60	90
DK	135±4.19	122.37 ±10.58	147.75±3.75	171.12±2.21^{a*}	157.12±5.23	152.25±6.10^{ab}	140.87±5.73^{a}	136.62±6.69^{ab}	124±8.90	105.25 ±6.90
DBK	125.25 ±2.51	129.37 ±2.17	141.12±1.95*	150.5±3.54^{b*}	162.25±4.38*	168.25±4.62^{a*}	159.12±4.52^{b*}	146.62±3.87^{a*}	135.37±3.24	121.12 ±1.65
DMK	127.87 ±2.15	133.25 ±2.06	141.12±1.95*	146±2.15^{b**}	153.25±3.50*	138.87±3.90^{b}	129.37±2.87^{a}	123.12±2.70^{b}	116.5±2.84	113.87 ±2.25
DBMK	133.62 ±2.59	137.62 ±2.52	141±2.18	146.25±2.34^{b*}	150.5±2.41*	147.12±2.23^{b*}	139.37±1.56^{a}	131.12±1.74^{ab}	123.5±1.63	119.5 ±2.07

*Significantly different from base value (P<0.05)
Values with different superscripts differ significantly (P<0.05) between the groups

Table 5: Mean ± S.E. The values of the Diastolic blood pressure of dogs of different groups at different interval

Group	Period of observation (Minute)									
	0min	p-10	i-5	10	20	30	40	50	60	90
DK	88.75 ±2.65	76.75 ±7.27^{a}	95.62±2.29	111.62±5.25*	99.37±4.39	101.87±5.80^{a}	91.62±5.26^{a}	84.62±5.85^{a}	74.75±5.87^{a}	72.62±4.45^{a}
DBK	85.62 ±1.89	90.12 ±2.16^{ab}	101.12±3.31*	108.25±3.25*	115.75±3.50*	118.37±3.72^{b*}	110.5±2.90^{b*}	102.87±2.09^{b*}	98.25±1.95^{b}	87.87±1.98^{b}
DMK	87.25 ±1.98	93.87 ±2.28^{b}	100.25±3.00*	104.87±2.94*	113.87±3.02*	102.37±3.05^{a*}	95.12±2.81^{a}	88.62±2.49^{a}	80.12±2.15^{ab}	78±0.94^{ab}
DBMK	89.25 ±2.54	93.12 ±2.55^{b}	98.12±3.06	101.12±2.92*	107.12±2.51*	110.62±2.27^{ab*}	104.62±1.86^{ab*}	97.87±1.73^{ab}	90.87±1.63^{b}	83.12±1.58^{b}

*Significantly different from base value (P<0.05)
Values with different superscripts differ significantly (P<0.05) between the groups

Table 6: Mean ± S.E. The values of the mean arterial blood pressure (mm Hg) of dogs of different groups at different interval

Group	Period of observation (Minute)									
	0min	P-10	I-5	10	20	30	40	50	60	90
DK	103.83 ±2.90	91.88 ±7.41^{a}	112.91 ±1.91	131.35 ±3.59*	118.6±4.09^{a}	118.62±5.57^{a}	107.92±5.40^{a}	101.95±5.79^{a}	91.13±6.4^{a}	83.35±4.8^{a}
DBK	98.8 ±2.04	103.17 ±2.04^{ab}	114.41 ±2.37	122.3 ±2.19*	131.21±2.70^{b*}	134.98±2.49^{b*}	126.68±2.00^{b*}	117.43±1.47^{b}	110.61±1.06^{b}	98.92±1.42^{b}
DMK	100.9 ±2.01	106.98 ±2.15^{b}	113.83 ±2.59*	118.55 ±2.49*	126.97±2.78^{ab*}	114.51±3.17^{a*}	106.5±2.77^{a}	100.11±2.49^{a}	92.22±2.25^{a}	90.16±1.22^{ab}
DBMK	104.01 ±2.55	107.91 ±2.54^{b}	112.4 ±2.74	116.07 ±2.48**	121.53±2.07^{ab*}	122.76±1.87^{ab*}	116.17±1.63ab*	108.93±1.64^{ab}	101.71±1.52^{ab}	95.22±1.69^{b}

*Significantly different from base value (P<0.05)
Values with different superscripts differ significantly (P<0.05) between the groups

Table 7: Mean ± S.E. The values of the SpO_2 (%) of dogs of different groups at different interval

Group	Period of observation (Minute)									
	0	P-10	I-5	10	20	30	40	50	60	90
DK	93.37±1.22	88.75±1.06	91.25±1.33	92.25±0.70	92.75±1.34	93.25±1.27	90.87±1.46	92.37±1.22	92.25±1.31	93.62±0.92
DBK	89.87±0.97	90.87±1.21	92.37±0.59	94±0.94	90±0.80	92.62±1.26	92.37±0.86	93.5±0.65	93.75±0.70	94.37±0.84*
DMK	89.25±0.64	89.87±1.09	91.87±0.85	91.75±1.14	91.5±1.13	91±1.42	91.87±0.95	92.87±0.93	93.12±0.66	93.75±0.75
DBMK	90±0.86	90.87±0.98	92±0.62	92±0.68	91.37±1.26	91.25±1.27	91.75±1.22	91.87±1.07	92.25±0.99	94.12±0.66

*Significantly different from base value (P<0.05)
Values with different superscripts differ significantly (P<0.05) between the groups

Conclusion

It was concluded that dexmedetomidine (10µg/kg) with butorphanol 0.2 mg/kg and midazolam 0.2 mg/kg as preanaesthetic with ketamine hydrochloride induces effective surgical anaesthesia in healthy dogs and significantly depresses HR, RR and rectal temperature. Blood pressure decreases after initial increase. More intense changes were observed in DBK protocol.

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