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Comparative evaluation of propofol and ketamine total intravenous anaesthesia (TIVA) with dexmedetomidine and butorphanol in goats

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ABSTRACT

The present study was aimed to compare clinicophysiological, and haemodynamic effects of propofol and ketamine anaesthesia with dexmedetomidine-butorphanol premedication. Prospective, randomized clinical trial, with owner consent was performed on sixteen clinical cases of urolithiasis in goats. After sedation with dexmedetomidine (2.5 µg/kg body wt) and butorphanol (0.05 mg/kg body wt), anaesthesia was induced and maintained with either propofol or ketamine. For maintenance, continuous intravenous infusion (CII) at variable rate was used with respective drug. Infusion rate was adjusted in response to positive reactions to surgical nociceptive stimulation performed during tube cystostomy procedure. Clinicophysiological, and haemodynamic parameters were measured before treatment (baseline), after sedation and during anaesthesia. One way repeated measure analysis was used to compare the mean values at different intervals in each group for non-parametric observations. Mann whitney U test was used to compare median score between groups at corresponding intervals. Compared to baseline, HR (heart rate) improved at 15 min and onwards but remained significantly (P=0.030) lower than the baseline value in both groups. MAP (mean arterial pressure) decreased significantly (P=0.022) up to the end of the observation period in DBP (dexmedetomidine + butorphanol+ propofol); however, in DBK (dexmedetomidine + butorphanol + ketamine) improvement in MAP was observed at 15 min and onwards with significantly (P=0.018) lower values at 15 and 20 min and a non-significantly (P=0.080) lower value at 30 min as compared to the baseline value. Both drug combinations are suitable to induce and maintain anaesthesia for one hour, with good haemodynamic stability and analgesia. However, DBP is related with excellent sedation and muscle relaxation.

Key words: Anaesthesia, Butorphanol, Dexmedetomidine, Goats, Ketamine, Propofol.

Total intravenous anaesthesia (TIVA) is a well-established anaesthetic concept for some animal species, notably dogs and horses. Information on TIVA protocols for goats is very scarce at the moment; yet, there are situations (field anaesthesia, anaesthesia for MRI, research) when TIVA might be the only practically possible way to achieve general anaesthesia in goats (Larenza *et al.* 2005). In veterinary practice, intravenous anaesthetic drugs are commonly used as induction agents to facilitate endotracheal intubation; however, inhalation anaesthetic agents form the foundation for maintenance of general anaesthesia (McKenzi 2008). Inhalation anaesthesia may not be applicable in all situations where anaesthesia is required. General anaesthesia can then be maintained by intravenous drugs in those situations (Hofer *et al.* 2003).

α_2-agonist, reduces the dose requirements of opioids and anaesthetic drugs and attenuates the haemodynamic responses to tracheal intubation and surgical stimuli. Dexmedetomidine has been studied in goats, however, its clinical effects are presumed to be comparable with those of racemic medetomidine (Hayashi *et al.* 1991). Butorphanol, an opioid agonist-antagonist with sedative and analgesic properties is known to induce mild sedation accompanied by small decreases in arterial blood pressure, heart rate, and arterial oxygen tension. Synergistic interactions have been reported between α_2-agonists and opioids and benzodiazepines in earlier studies (Kojma *et al.* 2002). Intravenous anaesthetic agents used for induction and maintenance of anaesthesia in animals include propofol and ketamine (Lin *et al.* 1997) as variable or constant rate infusion. Propofol is a short-acting hypnotic agent and usually injected as a single bolus for induction to allow intubation and initiation of inhalant anaesthesia, a popular technique in small animals (Short and Bufalari 1999). Propofol has been investigated as intravenous anaesthetic in sheep (Lin *et al.* 1997), goats (Amarpal *et al.* 2002, Kumar *et al.* 2014) and buffaloes (Malik *et al.* 2011, Khattri *et al.* 2013). Ketamine has been used for maintenance of anaesthesia, either by intermittent bolus infusion or

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continuous intravenous infusion (Tranquilli *et al.* 2007). The present study was designed to compare the suitability of propofol or ketamine anaesthesia over the dexmedetomidine and butorphanol as premedication.

MATERIALS AND METHODS

Present study was performed on male goats presented to the polyclinic for the treatment of urethral obstruction and were divided randomly into groups DBP and DBK. The study was approved by the Institutional Animal Ethics Committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written and informed owner consent was obtained from the owners prior to subjecting the animals to the study.

The study was carried out as a prospective, randomized blinded clinical trial. Sixteen ASA (American Society of Anesthesiologists) physical status II or III goats, which were scheduled for emergency tube cystostomy, were included in the study. Animals were excluded if they were classified as ASA IV or greater, or if they were excessively nervous or aggressive for which the sedation protocol would be inappropriate. All the animals in present study completed clinical trial without any side effect. The animals were restrained in right lateral recumbency and intravenous catheter during trial was maintained for 0.9% normal saline and patients were randomly allocated to receive dexmedetomidine (2.5 µg/kg body wt) and butorphanol (0.05 mg/kg body wt) as premedication and after 10 minutes, induction was achieved by intravenous administration of 1% propofol and ketamine till effect. Both the treatment groups were designated as DBP and DBK. Anaesthesia was maintained with variable rate infusion of propofol (DBP) and ketamine (DBK) in respective groups. Administration of equipotent dose for propofol or ketamine during induction of anaesthesia, were determined by observing the abolition of pedal reflex. However, during maintenance, continuous infusion was adjusted in response to positive reactions to surgical nociceptive stimulation performed during tube cystostomy procedure. After completion of clinical trial, 5% dextrose was given, if required.

Clinical parameters (Table 1) and heart rate (HR), respiratory frequency (fR) and rectal temperature (RT) were measured at 5, 10, 15, 20, 30, 45, 60, 75 and 90 minutes. Recovery time (RET), sternal recumbency time (SRT), standing time (ST) and the doses of anaesthetic drugs were recorded after each experiment. Induction dose (mg/kg) and maintenance dose (mg/kg/min) of anaesthetics were calculated for propofol or ketamine in both groups. Recovery time (RET) was recorded as the time elapsed from discontinuation of injection of drugs to the reappearance of pedal reflex. Sternal recumbency time (SRT) was recorded as the time elapsed from discontinuation of injection of drugs until the spontaneous regaining of sternal recumbency. Standing time (ST) was recorded as the time elapsed from the time of discontinuation of injection of drugs until the spontaneous regaining of standing position and able to walk. Duration of anaesthesia was recorded as the time elapsed between abolition and reappearance of pedal reflex.

Mean arterial pressure (MAP), diastolic arterial pressure (DAP) and systolic arterial pressure (SAP) were recorded using a oscillometric non-invasive blood pressure monitor by placing the cuff in left forelimb (Equinox, EQ 101) at 5, 10, 15, 20, 30, 45, 60, 75 and 90 min after administration of the drug. Haemoglobin oxygen saturation (SpO2) was recorded by pulse oximeter (Traze Uno, Akas Medical, Chennai, India) at the same time intervals as for MAP.

Analysis of Variance (ANOVA) and Duncan's multiple range test (DMRT) were used to compare the means at different time intervals among different groups. One way repeated measure analysis was used to compare the mean

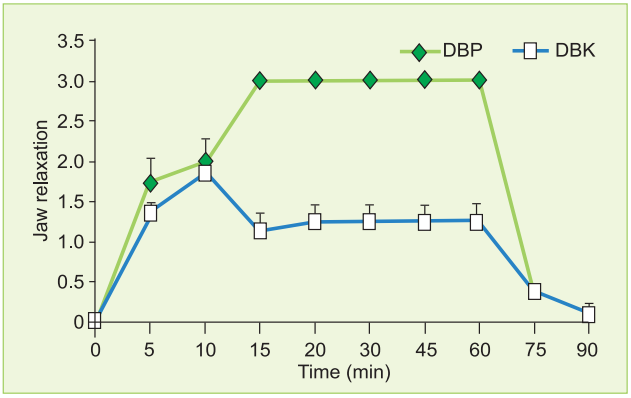

Fig. 1. Median±SD score for jaw relaxation in the animals of groups DBP and DBK at different time intervals.

Table 1. Numeric scoring system used for recording of various reflexes and responses (Adapted and modified after Amarpal *et al.* 1996)

Clinical parameter	Score			
	0	1	2	3
Jaw relaxation	Not allowing to open the jaw	Resistant to opening the jaws and closed quickly	Less resistance to opening the jaws and closed slowly	No resistance and jaws remain open
Palpebral reflex	Intact and strong (quick blink)	Intact but weak (slow response)	Very weak (very slow and occasional)	Abolished
Pedal reflex	Intact and strong (strong withdrawal)	Intact but weak (animal responding slowly)	Intact but very light (slow and occasional response)	Abolished completely
Salivation	No salivation	Mild salivation	Moderate salivation	Excessive salivation

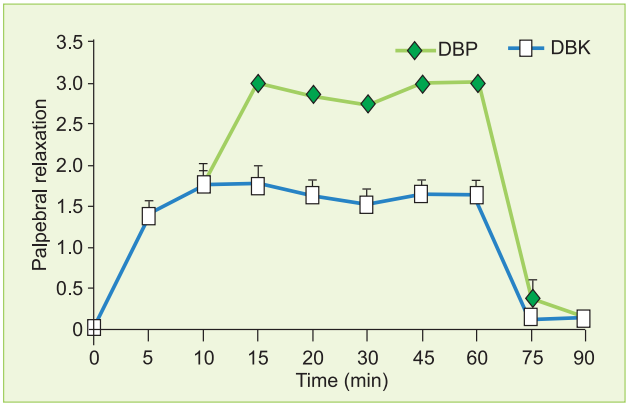

Fig. 2. Median±SD score for palpebral reflex in the animals of groups DBP and DBK at different time intervals.

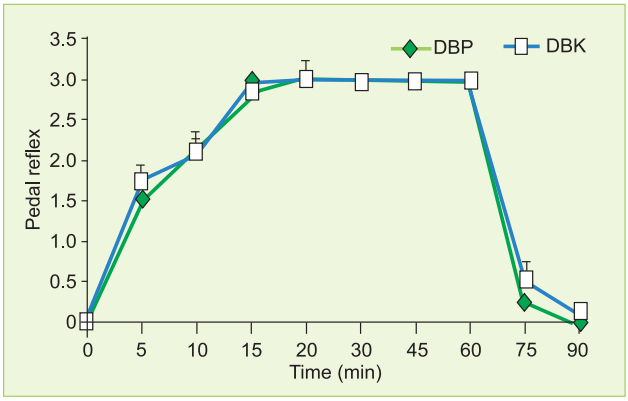

Fig. 3. Median±SD score for pedal reflex in the animals of groups DBP and DBK at different time intervals.

values at different intervals in each group (Snedecor and Cochran 1994). For non-parametric observations, Mann whitney U test (Siegel and Castellan 1988) was used to compare median score between groups at corresponding intervals. The SPSS v20.0 (IBM, IL, USA) software was used to analyze the data.

RESULTS AND DISCUSSION

Mild to moderate jaw relaxation was observed in all animals after premedication followed by excellent relaxation after induction in treatment DBP; however, jaws were mildly relaxed up to the end of anaesthetic period in DBK (Fig. 1). A mildly depressed palpebral reflex was recorded after premedication followed by completely abolished reflex up to the end of anaesthesia in DBP; however, in DBK, a mildly depressed plapebral reflex was present at most of the time intervals (Fig. 2). A mildly depressed pedal reflex was recorded after premedication; however, excellent depression of reflex after induction of anaesthesia was observed in both treatments up to the end of the anaesthetic period (Fig. 3). A very mild salivation was present in animals of both groups.

The median±SD values of recovery time recorded in groups DBP and DBK were 5.75±1.79 min and 7.67±1.77 min respectively. Group DBP recovered earlier than group DBK. The recovery time, however, did not differ significantly (P=0.087). The median±SD of sternal recumbency time was 3.50±3.19 min and 21.50±2.42 min respectively in both the groups. Group DBK took significantly (P=0.013) longer to resume sternal recumbency than group DBP. Standing time in group DBK (41.75±5.87 min) was significantly (P=0.028) longer than in group DBP (20.00±3.53 min). The mean values of induction and maintenance dose of propofol and ketamine recorded in groups DBP and DBK were 1.99±0.29 mg/kg and 9.63±0.60 mg/kg, and 0.14±0.04 mg/kg/min and

Table 2. Mean±SE of heart rate (HR), respiratory rate (f_R), rectal temperature (RT) and mean arterial pressure (MAP) values obtained before treatment (baseline), immediately after sedation (sedation) and during anaesthesia

Parameter	Treatment	Time (min)									
		0	5	10	15	20	30	45	60	75	90
HR (beats/min)	DBP	112.88^{A} ±9.05	86.37^{BC} ±5.17	80.75^{aC} ±5.25	88.37^{BC} ±4.93	92.00^{BC} ±3.65	94.62^{BC} ±4.42	94.25^{BC} ±3.74	91.50^{BC} ±4.01	99.00^{BC} ±6.10	103.62^{A} ±7.17
	DBK	110.00^{A} ±13.15	73.50^{DE} ±6.80	70.00^{bDE} ±7.26	84.87^{E} ±6.14	92.62^{BE} ±5.68	91.37^{BE} ±5.41	92.62^{BE} ±6.31	93.37^{AE} ±5.39	99.00^{AE} ±6.27	102.00^{AE} ±7.56
RR (breaths/min)	DBP	34.50^{A} ±1.76	23.50^{C} ±2.13	25.25^{aBC} ±2.10	28.75^{aBC} ±2.23	28.75^{aBC} ±2.33	28.00^{aBc} ±2.07	26.87^{aBC} ±1.33	34.62^{bA} ±1.93	30.12^{abA} ±0.85	28.00^{aBC} ±2.03
	DBK	38.75^{A} ±2.42	24.75^{CD} ±1.89	29.75^{bD} ±1.62	33.00^{bBD} ±1.00	36.25^{bA} ±2.99	37.75^{bA} ±3.41	34.75^{bAD} ±1.55	29.75^{aA} ±2.28	38.25^{bAD} ±1.33	34.87^{bA} ±2.17
RT (°C)	DBP	38.87^{bA} ±0.19	36.56^{A} ±0.65	36.72^{A} ±0.49	37.94^{bAD} ±0.17	37.79^{bACD} ±0.14	37.31^{CD} ±0.23	36.84^{D} ±0.23	36.31^{BD} ±0.29	35.35^{B} ±0.63	35.50^{B} ±0.30
	DBK	37.30^{aA} ±0.50	38.56^{A} ±0.23	38.30^{AC} ±0.21	36.45^{aAC} ±0.50	36.07^{aABC} ±0.47	36.08^{ABC} ±0.59	35.26^{CB} ±0.69	34.98^{B} ±0.66	35.84^{BD} ±0.29	34.95^{B} ±0.62
MAP (mmHg)	DBP	133.12^{A} ±9.27	102.12^{B} ±8.47	99.50^{B} ±8.63	99.25^{B} ±9.09	94.87^{B} ±9.03	95.62^{aB} ±7.78	92.87^{aB} ±7.73	93.00^{aB} ±8.87	-	-
	DBK	123.62^{A} ±6.10	103.12^{BC} ±4.50	100.25^{C} ±4.53	107.12^{BC} ±4.12	113.00^{BCD} ±3.55	120.75^{bAB} ±3.28	125.88^{bAD} ±4.00	130.88^{bAD} ±3.89	-	-

Means with different upper case superscript differ significantly within a group (P<0.05). Means with different lower case superscript differ significantly between groups (P<0.05).

0.45±0.04 mg/kg/min respectively.

Heart rate (HR) decreased gradually but remained significantly (P=0.033) lower than the baseline value in both groups until the end of the observation period (Table 2). Respiratory rate (fR) decreased significantly (P=0.0410) after premedication (Table 2). The fR continued to decrease significantly (P=0.022) lower than the baseline after induction of anaesthesia in DBP up to 45 min (Table 2). However, after induction of anaesthesia with ketamine, respiratory rate decreased significantly (P=0.019) only at 15 min thereafter, values were non-significantly (P=0.065) lower than the baseline value up to the end of the observation period. Comparison between both TIVAs revealed that the mean baseline respiratory rate in DBP was significantly (P=0.019) lower at 10 min and onwards up to the end of the observation period. Rectal temperature (RT) decreased non-significantly (P=0.063) after premedication with dexmedetomidine and butorphanol (Table 2). However, after induction of anaesthesia in both groups, RT decreased significantly (P=0.021) at most of the time intervals up to the end of the observation period.

Mean arterial pressure (MAP) decreased significantly (P=0.024) after premedication and induction of anaesthesia in both groups; however, MAP started to improve at 15 min and onwards in DBK. MAP in propofol TIVA was significantly (P=0.027) lower than that in ketamine TIVA at 30, 45 and 60 min (Table 2). SpO_2 values were non-significantly (P=0.085) higher in DBP than DBK at most of the time interval (Table 2).

α2-agonists have been reported to produce profound muscle relaxation when used alone or in combination with opioids agonist antagonists (Ahmad *et al.* 2011). Ketamine does not have muscle relaxant property and relaxation of jaw in the animals of both groups might be attributed to the action of dexmedetomidine and butorphanol. Dexmedetomidine induces a dose dependent sedation (Sabbe *et al.* 1994) but increasing the dose beyond a certain level does not cause a further increase in sedation (Kuusela *et al.* 2000). Palpebral, corneal and swallowing reflexes have been reported to be mildly active during ketamine anaesthesia in cattle (Wright 1982) and goats (Tadmor and Zukerman 1981). Similar findings have been reported in the present study.

Anaesthesia with propofol has been successfully induced after pre-medication with alpha$_2$-agonists (Kim and Jang 1999) and midazolam in dogs (Amarpal *et al.* 2002). Ketamine is a potent analgesic property but propofol is thought to have no or minimal intrinsic analgesic property (Tranquilli *et al.* 2007). However, in present study, dexmedetomidine and butorphanol both analgesic helped in producing better induction with propofol and subsequent maintenance of anaesthesia. Salivation after induction with either propofol or ketamine in the present study might be due to delayed effect of alpha$_2$-agonist, dexmedetomidine or due to decreased swallowing reflex (Kokkonen and Eriksson 1987) or due to partially opened jaw for application of sensor of pulse oximeter.

Lower RT, SRT and ST in propofol anaesthesia might be due to virtual lack of any cumulative effect either by repeated bolus injection or by continuous infusion (Adetunji *et al.* 2002). Propofol is an ultra-short acting drug and distribution and elimination of propofol are rapid after bolus injection or after constant infusion (Gepts *et al.* 1987). Our findings supported the observations.

Higher values of heart rate during ketamine infusion in comparison to post-sedation values in the present study could be attributed to its sympathomimetic action mediated within the CNS, inhibition of catecholamine re-uptake by peripheral sympathetic nerve endings and the subsequent effects of catecholamines on the myocardium (Kumar *et al.* 2014, Lin *et al.* 1997). Propofol caused a further decrease in mean fR by depressing central inspiratory drive and ventilatory response to arterial carbon-dioxide response (Goodman *et al.* 1987). Increase in respiratory rate recorded during induction and maintenance of anaesthesia with ketamine may be due to some degree of hyperventilation induced by ketamine (Waterman 1981). α-2 agonists induce prolonged depression of thermoregulation (Ponder and Clarke 1980) and depress hypothalamic noradrenergic α-2 adrenergic receptors to cause hypothermia (MacDonald *et al.* 1988). Decrease in RT had been reported after medetomidine administration in goats (Kinjavdekar *et al.* 2000) and sheep (Monsang 2011).

The changes in SpO_2 during propofol and ketamine infusion were inversely proportional to the rate of administration of drugs and could be adjusted easily by changing the rate of infusion. Ketamine infusion has been reported to cause significant respiratory depression with decrease in all measures of ventilation in animals (Kuusela *et al.* 2003). Reduced blood pressure after propofol administration has been reported in domestic animals and has been associated with arterial and venous vasodilatation and decreased contractility of the heart (Ilkiw *et al.* 1992). An increase in the arterial blood pressure after ketamine infusion might be due to the selective positive inotropic influence on heart muscles or reflexogenic autonomic nervous system changes (Adams *et al.* 1976).

In conclusion, after premedication with dexmedetomidine and butorphanol, a surgical plane of anaesthesia was reached with propofol (0.14±0.04 mg/kg/min) and ketamine (0.45±0.04 mg/kg/min) TIVAs for one hour. Both the treatments were suitable with excellent degree of analgesia. Ketamine TIVA was associated with better haemodynamic stability in comparison to propofol TIVA; however, propofol treatment had advantage of excellent muscle relaxation with improved time of recovery.

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