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COMPARISON OF KETAMINE-BUTOROPHANOL AND KETAMINE–DIAZEPAM-BUTOROPHANOL FOR TOTAL INTRAVENOUS ANAESTHESIA (TIVA) IN DROMEDARY CAMELS-A CLINICAL STUDY

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ABSTRACT

This study was conducted to evaluate and compare combinations of TIVA using ketamine-butorophanol (KB) and ketamine-butorophanol-diazepam (KBD) in eight dromedary camels (divided into two groups) and these underwent general surgeries and premedicated with intravenous (IV) 0.2 mg/kg^{-1} of xylazine. Anaesthesia was induced IV in KB group with 0.8 mg kg^{-1} of ketamine and 0.1 mg kg^{-1} of butorophanol, and maintained with constant rate infusion (CRI) of ketamine at 3.3 mg kg^{-1} hour^{-1} and by IV bolus injections of butorophanol at 0.1 mg kg^{-1}. Anaesthesia was maintained in KBD group as same with KB group but with including diazepam for induction at 0.1 mg kg^{-1} and as CRI at 0.3 mg kg^{-1} hour^{-1}. The quality of induction was rated as poor in KB group and as acceptable in the KBD group. Level of maintained surgical anaesthesia was rated in both groups as marginal for soft tissue surgeries and inadequate for orthopedic surgeries. The mean anaesthetic time was 62.0±20.5 minutes in KB group, and 72±43.2 in KBD group, while the recovery time was 21.8± 4.6 minutes in the KB group, and 28.3+5.2 with KBD group.

Key words: Anaesthesia, butorophanol, camel, diazepam, ketamine, TIVA

Ketamine is a dissociative anaesthetic, probably the most widely used injectable anaesthetic in veterinary practice due to its wide margin of safety and compatibility with other drugs (Fish, 1997). Ketamine alone in sheep (Thurmon *et al,* 1973) or in any other animals fails to produce satisfactory anaesthesia (Hall *et al,* 2001). It is usually combined with a variety of other compounds such as xylazine (Muir *et al,* 1977), detomidine (Taylor *et al,* 1995) and propofol (Flaherty *et al,* 1997) to induce balanced anaesthesia. Butorophanol is a synthetic kappa opioid agonist and mu opioid antagonist, comparable or superior in potency to morphine (Kamerling *et al,* 1989; Spadavecchia *et al,* 2007) and has been used extensively in a wide variety of veterinary species (Lamont and Mathews, 2007; Dos Santos *et al,* 2011). Diazepam is a benzodiazepine derivative used as sedative and usually administered with ketamine-xylazine combinations to enhance muscle relaxation and to control convulsions (Averill, 1970; Green *et al,* 1981). Xylazine and Ketamine have been used as total intravenous anaesthesia in dromedaries, previously (Al-Mubarak *et al,* 2008). There appears to be little information on the anaesthetic effects of ketamine-butorophanol-diazepam combination in spontaneously breathing camels. The goal of this study was to compare and evaluate the efficacy of co-administration of butorophanol alone or in combination with diazepam to ketamine for TIVA in dromedary camels.

Materials and Methods

Eight dromedary camels (five females and three males) of different breeds (four Magateer, three Majaheem, and one Hegin) with a mean body weight of 640 ± 139.9 and aged 9.6 ± 1.9 years were scheduled to undergo general surgery (3 ovarian cyst removal, 3 mastectomy, and 2 jaw fixation). Food, but not water, was withheld for 48-72 hours before surgery. Camels were restrained manually in sternal recumbency before an initial physical examination was performed. All camels received xylazine (Ilium-Xylazil-20, Troy Laboratories, Australia) @ 0.2 mg/kg^{-1} as preanaesthetic medication, intravenously. Camels were then positioned as required for surgery (laterally for ovarian cyst removal and mastectomy, and sternal recumbency for jaw fixation). The skin was prepared for aseptic surgery. Camels were

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divided into KB group or KBD group (n = 4 for each group). Approximately 30 minutes after pre-anaesthetic medication, anaesthesia in KB group was induced intravenously with combination of ketamine (Ketamil, Troy Laboratories, Australia) @ 0.8 mg kg^{-1} and butorophanol (Alvegesic, Cp-pharma, Burgdorf, Germany) @ 0.1 mg kg^{-1}. In KBD group anaesthesia was induced with combination of ketamine @ 0.8 mg kg^{-1}, butorophanol @ 0.1 mg kg^{-1}, and diazepam (Farcozepam, Pharco Co., Egypt) @ 0.1 mg kg^{-1} in KBD group. Anaesthesia was then maintained in KB group by CRI of ketamine @ 3.3 mg kg^{-1} $hour^{-1}$ using one special syringe (60 ml; BD, NJ, USA) mounted on syringe pump (AP 14, Ascor S.A, Poland) and by IV bolus injection of butorophanol @ 0.1 mg kg^{-1} every thirty minutes after induction. Anaesthesia was maintained in KBD group as same with KB group, but diazepam was simultaneously infused after induction using two special syringes mounted on multi-syringe pump (Stoelting Syringe Pumps, Wood Dale, IL, USA) @ CRI of 0.3 mg kg^{-1} $hour^{-1}$. Once the surgery was completed, infusions were then disconnected. Heart rate, respiratory rate, temperature and indirect blood pressure values using a cuff placed around the base of the tail connected to a patient monitor (Infinity Delta XL, Drager medical, Germany) were measured and recorded before preanaesthetic medication, 10 minutes after, and then continuously until the end of surgery. Pulse oximetry connected to the monitor with the probe placed on tongue was placed on animal immediately after induction. Clinical signs of anaesthesia including the quality of induction and maintenance, presence or absence of spontaneous movement, and palpebral reflex were evaluated at each group. The time from disconnection of infusions to sternal posture with the ability to support and raise the head was recorded.

Results

Time from induction of anaesthesia to disconnection from anaesthetic infusion was 62.0±20.5 minutes in KB group and 72±43.2 in KBD group. The

Table 1. Mean (± SD) values of respiratory rate (RR), heart rate (HR), body temperature (T), mean arterial blood pressure (MAP), systolic arterial blood pressure (SAP), and diastolic arterial blood pressure (DAP) at the baseline (BL) and 10 minutes after premedication with romifidine (AR) and 5−100 minutes after the induction of anaesthesia.

Parameters	Groups	BL (n:4) (n*:4)	AR (n:4) (n*:4)	The after induction of anaesthesia (in minutes)										
				5 (n:4) (n*:4)	10 (n:4) (n*:4)	20 (n:4) (n*:4)	30 (n:4) (n*:4)	40 (n:4) (n*:3)	50 (n:4) (n*:3)	60 (n:4) (n*:3)	70 (n:3) (n*:3)	80 (n:2) (n*:2)	90 (n:0) (n*:2)	100 (n:0) (n*:2)
RR	KB	13.6 ±2.6	12.4 ±3.5	13.0 ±3.2	13.6 ±4.3	18.2 ±4.8	18.6 ±5.5	22.0 ±3.7	19.8 ±6.8	20.8 ±6.2	24.0 ±2.8	23.0 ±1.4		
	KBD	12.0 ±1.3	9.2 ±1.2	12.0 ±1.8	13.8 ±1.9	13.8 ±1.6	18.0 ±1.2	19.5 ±4.1	18.3 ±4.7	20.0 ±4.6	18.6 ±3.5	20.5 ±5.5	22.5 ±5.5	23.0 ±7.0
HR	KB	37.2 ±6.6	28.8 ±6.6	49.2 ±29.9	55.8 ±28.1	53.4 ±26.8	59.2 ±25.7	65.6 ±30.2	77.0 ±31.0	83.6 ±27.2	71.0 ±4.6	70.0 ±0.0		
	KBD	44.0 ±6.9	34.4 ±7.3	68.4 ±16.9	68.0 ±19.0	70.0 ±15.4	72.0 ±18.1	76.5 ±21.3	82.0 ±26.1	74.7 ±32.3	82.6 ±24.4	94.0 ±2.8	96.0 ±5.7	109.5 ±24.7
T	KB	36.9 ±0.3	36.9 ±0.4	36.9 ±0.5	37.1 ±0.6	37.0 ±0.4	37.0 ±0.3	36.8 ±0.6	36.8 ±0.6	36.8 ±0.7	36.9 ±0.2	37.0 ±0.2		
	KBD	37.2 ±0.4	37.4 ±0.5	37.3 ±0.6	37.2 ±0.7	37.3 ±0.6	37.1 ±0.6	37.1 ±0.6	37.1 ±0.8	37.1 ±0.8	37.0 ±0.9	36.5 ±0.4	36.5 ±0.4	36.5 ±0.4
MAP	KB	153.8 ±32.8	129.8 ±25.2	133.8 ±15.9	146.8 ±18.7	167.3 ±41.0	142.0 ±29.0	158.3 ±34.9	151.0 ±13.7	153.3 ±29.8	155.0 ±5.6	167.0 ±9.9		
	KBD	150.5 ±12.3	136 ±17.9	124.5 ±10.6	139.7 ±19.4	135.5 ±16.8	156.3 ±2.5	166.7 ±12.9	164.5 ±16.3	153.5 ±10.6	160.5 ±10.6	142.0 ±16.9	150.0 ±25.4	158.0 ±12.7
SAP	KB	183.0 ±29.3	164.5 ±11.3	159.8 ±10.4	174.3 ±9.8	197.0 ±21.9	184.3 ±30.2	197.0 ±32.5	170.3 ±7.9	187.7 ±9.9	183.5 ±1.5	191.0 ±5.0		
	KBD	178.5 ±27.9	156.8 ±15.9	139.7 ±14.2	162.0 ±20.9	173.3 ±10.2	178.0 ±7.5	198.0 ±22.6	200.0 ±9.9	185.0 ±5.7	189.5 ±4.9	171.0 ±15.6	200.5 ±4.9	222.0 ±60.8
DAP	KB	124.3 ±15.9	112.5 ±26.5	113.3 ±13.5	125.5 ±11.3	150.5 ±42.4	99.0 ±31.1	121.3 ±12.1	113.3 ±40.4	133.7 ±22.5	129.0 ±4.2	150.5 ±13.4		
	KBD	124.0 ±11.7	115.3 ±23.3	107.0 ±11.3	121.0 ±14.9	114.0 ±26.0	124.0 ±20.7	154.7 ±13.3	142.5 ±10.6	124.5 ±0.7	136.5 ±2.1	104.0 ±35.3	134.0 ±16.9	131.0 ±5.6

-n; number of animals in KB group. -n*; number of animals in KBD group.

quality of induction was rated as poor in KB group as additional doses of ketamine were required by two camels, while rated as acceptable in the KBD group. Level of maintained surgical anaesthesia was rated as marginal in soft tissue surgeries (ovarian cyst removal and mastectomy) in both groups, while rated inadequate in orthopaedic surgeries (jaw fixation) as an adequate surgical plane of anaesthesia was not achieved in two camels (one from each group) and extra doses of ketamine were given. Two camels in KB group exhibited muscle tremors, started immediately after induction until end of anaesthesia in one camel and at 40 minutes after induction till end of anaesthesia in the other one. Eyes remained open with positive response to palpebral reflex throughout the anaesthesia in all groups. Mean heart rate, respiratory rate and arterial blood pressure measurements (see table 1) decreased after premedication with xylazine. Heart and respiratory rates were elevated after induction and during the maintenance, while the arterial blood measurements remained within the baseline limit. Body temperature was within the normal physiological limit during the anaesthesia. Camels in KB group were able to support and raise their head in sternal posture in 21.8±4.6 minutes and in 28.3±5.2 with KBD group.

Discussion

The increased knowledge of action and toxicity of anaesthetics and anaesthetic adjunct drugs, that is appropriate for camel practice, is essential to decrease the risks in camel anaesthesia. Cardiopulmonary effects of xylazine have been extensively studied in animals and these usually are decreased heart and respiratory rates, decreased cardiac output and stroke volume and profound systemic arterial hypotension (Campbell *et al,* 1979; Doherty *et al,* 1987; Mama *et al,* 1996). Mean heart rate, respiratory rate, and arterial blood pressure measurements in this study decreased after premedication with xylazine, similarly with the previous studies. Almubarak *et al* (2008) reported that induction of anaesthesia with the combination of xylazine and ketamine was generally rapid and smooth, and surgically satisfactory anaesthesia was achieved and maintained by IV xylazine (0.16 - 0.2 mg kg^{-1}) and ketamine (0.8 mg kg^{-1}) in 55 camels underwent major surgeries. In the current study, the quality of induction was rated as poor in KB group compared with xylazine-ketamine combination in the previous study. This is not in agreement with Demirkan *et al* (2002) who showed that when butorophanol followed by ketamine was comparable with xylazine-ketamine for the induction of anaesthesia in dogs. However, this could be attributed to the low dose of ketamine based for this study compared with induction dose of 5.5 mg kg^{-1} intramuscularly or 1-2 mg kg^{-1} intravenously in camels (White, l986). The quality of induction was acceptable in the KBD group since the diazepam provided useful combination, which is in agreement with previous studies (Hellyer *et al,* 1991; White *et al,* 2001). The quality of maintenance of anaesthesia was generally marginal for soft tissue surgeries in both groups, but inadequate for orthopeadic surgeries that are usually associated with severe pain. This may indicate that infusion rates based for this study was not appropriate to achieve adequate depth of anaesthesia and it could be useful to increase dosage rates of anaesthetic infusion in order to improve the quality of anaesthesia. Advantages and the analgesic efficacy of butorophanol have been evaluated extensively, specifically for the control of acute visceral pain (Reed and Bayly, 1980; Kohn and Muir, 1988) and as pre-anaesthetic adjunct to improve the quality of sedation and anaesthesia (Bennett and Steffey, 2002; Corletto *et al,* 2005). The Butorophanol has been used effectively in horses at doses of 0.02-0.4 mg kg^{-1}, and in dogs and cats at doses of 0.1-0.5 mg kg^{-1} (Hall *et al,* 2001). However, another study is needed to evaluate the effects and safety of different doses of butorophanol when used alone in camels. Muscle tremor was observed in this study in two camels of KB group. Several studies have related ketamine with tremors previously (Green *et al,* 1981; Clarke *et al,* 1982; Haskins *et al,* 1985). The addition of diazepam in the KBD group might have contributed to prevent tremor and improve muscle relaxation observed in this group. The sympathomimetic action of ketamine elevates heart rate, respiratory rate and arterial blood pressure (Clarke *et al,* 1982; Haskins *et al,* 1985), while butorophanol and diazepam promote minimal change in cardiopulmonary function (Trim, 1983; Becker and Schmidt-Oechtering, 1993). The elevated heart and respiratory rates in this study after induction and during the maintenance of anaesthesia is clearly associated with ketamine administration. However, arterial blood measurement in this study was within baseline limit after induction and during the maintenance of anaesthesia. This could be due to a different interaction between butorophanol and diazepam. When butorophanol combined with general anaesthetics decreases arterial pressure (Greene *et al,* 1990; Dos Santos *et al,* 2011), while the diazepam has been shown to minimise the

cardiovascular changes associated with ketamine administration (Haskins *et al*, 1986). Noninvasive blood pressure devices can be a very useful means of early warning of impending problems during anesthesia (Sawyer *et al*, 2004). The indirect oscillometric method of blood pressure measurement was used in this study as direct arterial blood pressure measurement could not be done due to thickened skin and muscle layers in this species. However, a comparative study between the direct and indirect oscillometric blood pressure measurement with recommendations for cuff placement should be conducted in camel to demonstrate that measurements are meaningful. This study was limited by the small number of subjects, but in conclusion, it has shown that the combinations of KB or KBD was safe to use in camels, and the quality of maintained anaesthesia was generally marginal for soft tissue surgeries but inadequate for orthopedic surgeries in both groups. This study also suggests that anaesthetic characteristics associated with KB combination for induction and maintenance in camel can be improved upon by combining with diazepam. Further work needs to be done with larger numbers of subjects, and with investigating pharmacokinetics of these combinations in camels.

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