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EFFICACY OF MIDAZOLAM-PROPOFOL COMBINATION ANAESTHESIA IN DROMEDARY CAMELS (*Camelus dromedarius*)

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ABSTRACT

Systematic studies on midazolam–propofol combination anaesthesia have been conducted to determine its efficacy in randomly selected 6 adult dromedary camels of either sex, aged 9-13 years and weighing 350-600 kg maintained at National Research Centre on Camel (NRCC) at Jorbeer, Bikaner. Pre-anaesthetic dose of midazolam (0.2 mg kg^{-1}) and propofol (0.75 mg kg^{-1}) administered intravenously, resulted in induction of satisfactory surgical anaesthesia in camels. Behavioural, physiological and haemato-biochemical parameters were studied. Propofol inducted satisfactory anaesthesia for 8-10 minutes in camels premedicated with midazolam. No significant alterations occurred in any of the studied parameters in camels anaesthetised with midazolam-propofol combination. The combination provided satisfactory surgical anaesthesia of ultra short duration. Adequate muscle relaxation with rapid, smooth and uneventful recovery was noted in camels.

Key words: Anaesthesia, camel, midazolam, propofol

General anaesthesia is routinely used as a means of chemical restraint for diagnostic procedures and major and minor surgery in camels. It is indeed one of the miracles of medicine without which modern techniques could have never developed in surgery (Thurmon *et al,* 1996). With the development of newer and effective anaesthetic combinations and sedatives, the camel surgery is becoming more promising. Various combinations of anaesthetics and pre-anaesthetics or tranquilisers have been studied and used in camels such as chloral hydrate, chloral-mag and intraval sodium as general anaesthesia (Sharma *et al,* 1984a; b), halothane (Bhargava *et al,* 1969), thiobarbiturates (Sharma, 1980), xylazine-ketamine combination (White *et al,* 1987 and Peshin *et al,* 1992) and detomidine (Kashyap, 1994).

Intravenous anaesthesia is favoured over inhalant anaesthetics in camels due to ease of administration and simplicity of the technique requiring no sophisticated equipments. With significant development in camel surgery, the anaesthetists continue to look for newer (drugs) anaesthetics which could be declared safe for use in camels with least cardiovascular and respiratory side effects.

Propofol (2, 6 - diisopropyl phenol) is a popular intravenous anaesthetic widely used because of its immediate onset and rapid recovery. In veterinary practice, it has largely been used in dogs (Mama et al, 2013) and horses. Propofol, when used alone in camels (Sharma, 2000) and combined with xylazine and xylazine-diazepam (Mohamed, 2013) and other sedatives/tranquilisers, provided dependable anaesthesia of short duration.

In veterinary practice, midazolam has been used as sedative/preanaesthetic in dogs (Greene *et al,* 1993), cattle calves (Bishnoi and Saini, 2005), alpacas (Aarnes *et al*, 2013) and in goats (Stegmann, 1998), found to have less side effects than diazepam (Conklin *et al,* 1980; Pieri, 1983). Midazolam has an early induction, short duration, rapid elimination and total body clearance (Court and Greenblatt, 1992; Thurmon *et al,* 1996). Systematic studies on midazolam –propofol combination anaesthesia have been conducted to determine its efficacy in dromedary camels.

Materials and Methods

The present study was conducted on randomly selected 6 adult healthy camels of either sex, aged 9-13 years and weighing 350-600 kg. These camels of an organised herd were kept under identical managemental conditions and on the standard ration prior to this investigation that was conducted on the National Research Centre on Camel (NRCC)

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at Jorbeer, Bikaner. These experimental trials were conducted while the Animals were in sternal recumbency. Food and water were withheld for 24 hrs prior to anaesthesia.

Experimental Procedure

Midazolam (0.2 mg kg^{-1} body weight) administered as i.v. bolus, 5 min. later, Propofol (0.75 mg kg^{-1} body weight) was administered intravenously for induction of surgical anaesthesia and determination of the behavioural, physiological and haemato-biochemical parameters.

Collection of blood samples

The blood samples (10 ml) were collected from the jugular vein in heparinised glass tubes for haematobichemical studies. Serum was separated using refrigerated centrifuge at different time intervals.

Behavioural Observations

Depth of sedation/anaesthesia was assessed by monitoring palpebral and corneal reflexes, position of eye ball, salivation, lacrimation, relaxation of jaw, limbs, tail, abdomen and anus, and response to pin-prick and bone-prick. These observations were graded as mild (+), moderate (++) and good (+++). Relaxation of jaw, tail, limbs, abdomen and anus were graded according to resistance observed. Response to pin-prick and bone-prick was graded mild when animal blinks its eye at the time of prick, moderate when animal shakes its skin and a movement of tail, eyelids or nostrils observed and good when animal moves its limbs, tail or head at the time of prick.

Physiological Parameters

Rectal temperature, pulse rate and respiration rate were recorded at base line, at 5 min, P (immediately after propofol administration), 10, 20, 40, 60 minutes and after 24 hrs of administration of midazolam-propofol combination.

Haematological Parameters

Haematological examination includes haemoglobin, packed cell volume, total erythrocyte count, total leucocyte count and differential leucocyte count. These parameters were analysed as per the methods described by Jain (1986).

Biochemical Parameters

Biochemical study of blood serum samples was performed for quantitative estimation of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH) enzymes. The methodology for estimation ALP, ALT and AST enzymes was based on International Federation of Clinical Chemistry (IFCC), Kinetic method on autoanalyser using standard kits. Lactic dehydrogenase (LDH - P) enzyme was analysed on autoanalyser using a standard kit. The method was developed by Henry *et al* (1960).

These parameters were recorded at base line, at 5 min, P (immediately after propofol administration), 10, 20, 40, 60 minutes and after 24 hrs of administration of midazolam-propofol combination.

Statistical Analysis

The recorded data were subjected to the statistical analyses for interpretation of results to the methods suggested by Snedecor and Cochran (1967). The data were subjected to a two way analysis of variance (ANOVA) followed by a critical difference test for the comparison of mean values. A probability level of $P<0.05$ was considered as statistically significant. The mean values and standard error (SEM) were presented in tabular form.

Results and Discussion

Midazolam (0.2 mg kg^{-1} body wt) and the propofol (0.75 mg kg^{-1} body wt.) administered intravenously in 6 camels to study the change in behavioural response and various physiological, haematological and biochemical parameters.

The change in behaviour after administration of midazolam (0.2 mg kg^{-1}) followed by propofol (0.75 mg kg^{-1}) intravenously in camels have been shown in table 1. The anaesthesia was exhibited by absence of palpebral reflex and weak corneal reflex, salivation and lacrimation. Swallowing reflex abolished with good relaxation of jaw, tail, limbs, abdomen and anus during anaesthesia. The analgesia was good as observed by no response to pin-prick and bone-prick and absence of limb movements. In the present study, propofol at the dose 0.75 mg kg^{-1} intravenously, resulted in induction of satisfactory anaesthesia in camels premedicated with midazolam (0.2 mg kg^{-1}), that lasted for 8 - 10 minutes The dose of propofol for induction of anaesthesia in unpremeditated camels is reported as 1 mg kg^{-1}, i.v. (Sharma, 2000) and 2 mg kg^{-1} (Mohamed, 2013). However, the quality of induction varied from poor to excellent in horses (Oku *et al,* 2003). The dose of propofol was reduced by 25% after premedication with midazolam. When administered in combination with sedative or analgesic agents as a part of a balanced technique, the propofol induction dose requirement be appropriately decreased by 20% to

80 % (Short and Bufalari, 1999). The decrease in the dose of propofol is a result of additive or synergistic interaction between midazolam and propofol. Similar interaction between midazolam and thiopentone was also reported by Bishnoi (2001) in calves. Reduction in the dose of propofol in premedicated dogs and cats had also been reported by Morgan and Legge (1989) and Weaver and Raptopolous (1990). Administration of midazolam before propofol reduced propofol requirements although caused mild excitement in dogs (Sánchez *et al,* 2013). However, Covey and Murison (2008) reported that midazolam did not reduce propofol requirements and caused excitement in dogs. The co-administration of midazolam with propofol decreased the total dose of propofol needed for induction of anaesthesia in sedated healthy dogs, caused some excitement (Hopkins *et al,* 2014).

Mean ± SE values of rectal temperature, pulse and respiration rate in camels have been shown in table 2. Non-significant increase in rectal temperature was observed till 20 min. However, significant increase in rectal temperature observed at 40 and 60 min. were 98.80 ± 0.32 and 98.91 ± 0.28 0F respectively, when compared with base line value of 97.68 ± 0.26° F. This significant increase in rectal temperature had no clinical significance. Rectal temperature remained stable in camels without any significant changes before and during propofol anaesthesia and after recovery as reported by Sharma (2000). However, in dogs, a significant decrease in rectal temperature was observed after midazolam ketamine combination (Hellyer *et al,* 1991) and in pigs after administration of midazolam, thiopentone and fentanyl (Softeland *et al,* 1995). Pulse rate showed non-significant increasing trend till 10 min. Thereafter, non-significant decreasing trend was observed. The pulse rate in dogs anaesthetised with propofol remained stable (Hammond and England, 1994; Gili *et al,* 1996) but substantially increased in sheep (Lin *et al,* 1997; Mama *et al,* 1996). Little cardiovascular depression had been observed in horses after detomidine-propofol anaesthesia, reported by Matthews *et al* (1999). No significant change in pulse rate had been observed in camels during and after recovery from propofol anaesthesia (Sharma, 2000). The co-administration of midazolam with propofol caused a clinically unimportant decrease in systolic arterial pressure (SAP) (Hopkins *et al,* 2014). The mean respiration rate was significantly higher immediately after administration of propofol, at 20, 40 and 60 min. i.e.13.5 ± 0.42, 13.83 ± 0.91, 12.16 ± 0.47 and 11.5 ± 0.34 respectively, when compared to base line value of 9.83 ± 0.47 beats per minute. This significant increase in respiration rate was not clinically important. Respiratory depression had been reported in animals anaesthetised with propofol, viz. dogs (Reid and Nolan, 1996; Gili *et al,* 1996) and horses (Flaherty *et al,* 1997). Non-significant increased respiratory rate was also observed in goats anaesthetised with propofol after premedication with diazepam (Kelawala and Parsania, 1992). Minimal cardio - pulmonary

Table 1. Behavioural observations after intravenous administration of midazolam - propofol anaesthesia in camels (n=6).

Observations	Time interval (min)							
	Base line	**5**	**P**	**10**	**20**	**40**	**60**	**24hrs**
Recumbency	Sitting	Sitting	Lateral	Lateral	Sitting (Lateral)	Sitting	Sitting	-
Palpebral Reflex	+++	++ (+++)	- (+)	- (+)	++	+++	+++	+++
Corneal Reflex	+++	+++	+	+	++ (+++)	+++	+++	+++
Eye ball position	C	C	C (D)	C (0)	C	C	C	C
Salivation	-	-	++ (+)	++ (+++)	+ (-)	-	-	-
Lacrimation	-	-	++ (+++)	+++	+ (++)	-	-	-
Swallowing Reflex	+++	+++	-	- (+)	++ (+++)	+++	+++	+++
Jaw relaxation	-	-	+++	+++	+	-	-	-
Tail relaxation	-	+	+++	+++	++	- (+)	-	-
Limb relaxation	-	- (+)	+++	+++	+ (-)	-	-	-
Anus relaxation	-	+	+++	+++	+	-	-	-
Abdomen relaxation	-	- (+)	+++	+++	-	-	-	-
Pin prick Response	+++	+++	-	-	++ (+++)	+++	+++	+++
Bone prick Response	+++	+++	-	-	+++	+++	+++	+++

P = Propofol (immediately after administration); - = absent; + = mild; ++ = moderate; +++ = good; C = central; D = downward rotation. Values in parentheses indicate variation from the response in 1 or 2 animals.

depression was also observed during propofol anaesthesia in llamas (Duke *et al,* 1997). Quandt *et al* (1998) also reported respiratory depression and apnoea as major adverse effects associated with propofol and thiopental anaesthesia in dogs. Significant depression of respiratory function was reported with induction and maintenance of propofol anaesthesia (Short and Bufalari, 1999). However, no significant change in respiration rate was observed in camels during anaesthesia and after recovery from propofol (Sharma, 2000) and propofol anaesthetic regimes with xylazine and xylazine-diazepam (Mohamed, 2013). Observations on the combination of midazolam with other anaesthetic agents have been quite varied. Midazolam and thiopentone caused a significant decrease in respiration rate in calves (Bishnoi, 2001). No significant change in respiration rate in dogs (Hellyer *et al,* 1991) and in ponies (Luna *et al,* 1993) during anaesthesia with midazolam and ketamine. Mean pulse rate was higher in dogs given midazolam-propofol (MP) than in control-propofol (CP) or fentanyl-propofol (FP) groups. No statistically significant difference was found between groups in mean RR (Covey and Murison, 2008). In horses, the respiration rate and heart rate decreased after induction with xylazine-midazolam-propofol anaesthesia in horses (Oku *et al,* 2003)

Mean ± SE values of Hb, PCV, TEC, TLC and DLC have been shown in table 3. Non-significant increase in haemoglobin was observed immediately after administration of propofol, at 10, 20 and 40 min. PCV, TEC, TLC and DLC did not show any relevant change in their values throughout the study. Sharma (2000) reported no significant change in haematological

Table 2. Mean± SE values of physiological parameters after intravenous administration of midazolam – propofol anaesthesia in camels (n=6).

Parameter	Time interval (min)							
	Base line	5	P	10	20	40	60	24hrs
Temperature (°F)	97.68±0.26	97.8±0.27	97.90±0.32	98.16±0.31	98.34±0.28	98.80*±0.32	98.91*±0.28	97.61±0.18
Pulse rate (min^{-1})	40.16±2.12	43.6±2.09	47.00±0.07	47.50±1.94	44.33±1.97	42.50±2.10	42.16±2.38	40.50±2.48
Respiration rate (min^{-1})	9.83±0.47	10.6±0.73	13.50*±0.42	13.83*±0.91	12.16*±0.47	11.50*±0.34	10.83±0.30	10.50±0.42

P = Propofol (immediately after administration); * Significantly different from base line value ($P < 0.05$).

Table 3. Mean± SE values of haematological parameters after intravenous administration of midazolam - propofol anaesthesia in camels (n = 6).

Parameter	Time interval (min)							
	Base line	5	P	10	20	40	60	24hrs
Hb (g/dl)	11.05±0.34	11.05±0.37	11.18±0.41	11.30±0.32	11.11±0.25	11.06±0.36	10.91±0.38	11.00±0.32
PCV(%)	25.83±1.60	26.00±1.09	26.16±1.13	26.00±1.34	25.66±1.22	25.66±1.49	26.00±1.46	25.50±1.47
TEC (x 10^6 μL^{-1})	9.33±0.33	9.50±0.62	9.83±0.60	9.83±0.49	10.20±0.30	9.91±0.41	9.75±0.44	10.08±0.41
TLC (x 10^3 μL^{-1})	13.21±0.98	13.46±0.92	13.26±0.94	13.20±0.85	13.38±0.86	13.26±0.89	13.36±0.87	13.30±0.95
DLC (%)								
Neutrophils	50.16±0.83	50.66±0.88	50.50±0.67	50.66±0.71	50.16±0.91	50.50±0.88	50.33±0.66	50.33±0.84
Lymphocytes	39.83±1.49	39.83±1.49	39.50±1.47	39.50±1.38	39.33±1.60	39.50±1.47	39.66±1.40	39.66±1.56
Monocytes	1.83±0.30	1.83±0.30	1.50±0.34	1.66±0.33	1.83±0.30	1.83±0.30	1.83±0.30	1.83±0.30
Eosinophils	1.66±0.33	1.66±0.33	1.85±0.30	1.66±0.33	1.66±0.33	1.83±0.30	1.83±0.30	1.66±0.33

P = Propofol (immediately after administration). All values were statistically non - significant ($P < 0.05$).

Table 4. Mean± SE values of biochemical parameters after intravenous administration of midazolam - propofol anaesthesia in camels (n=6).

Parameter	Time interval (min)							
	Base line	5	P	10	20	40	60	24hrs
ALP (IU/L)	75.51±6.41	79.37±6.14	81.93±5.57	81.45±4.61	80.14±5.69	78.20±5.87	77.47±6.21	76.94±6.36
ALT (IU/L)	13.13±1.39	14.26±0.99	15.42±0.80	14.04±0.70	14.32±0.98	13.66±1.36	13.08±1.47	12.98±1.30
AST (IU/L)	93.24±5.66	96.94±5.53	98.50±5.60	100.54±6.88	97.93±6.15	96.52±6.06	94.37±5.58	94.47±5.76
LDH (IU/L)	472.85±25.67	487.69±25.07	494.84±21.37	488.36±24.35	478.87±23.92	477.2±25.91	475.8±24.71	474.59±25.03

P = Propofol (immediately after administration); All values were statistically non-significant ($P < 0.05$).

parameters in camels during anaesthesia and after recovery from propofol. No significant change in haematology in dogs anaesthetised with propofol was also reported by David (1993). Haematological parameters remained within normal physiological range in sheep after administration of propofol (Brzeski *et al,* 1994). In a study conducted on camels administered detomidine alone and in combination with ketamine, no significant change in haematological parameter was noticed except for TLC (Kashyap, 1994). In the present study the TLC and other parameters did not showed any appreciable change from base line values. However, transient decrease in TLC had been reported after thiopentone administration in horses and camels (Tyagi *et al,* 1964; Singh, 1990) and after pentobarbitone administration in dogs and camels (Gilmore, 1965; Sharda *et al,* 1991). They were of the opinion that this might have been associated with the splenic and lung pooling.

No significant change was observed in the activity of ALP, AL T, AST and LDH enzymes have been noticed after administration of midazolam - propofol combination anaesthesia in camels of present study (table 4). Similar findings were also reported after midazolam and thiopentone sodium anaesthesia in calves by Bishnoi (2001) and after diazepam and thiopentone anaesthesia in calves by Mirakhur *et al* (1988). Similarly, no changes of clinical importance in plasma alkaline phosphatase were also reported after detomidine and detomidine - ketamine administration in camels (Kashyap, 1994).

No significant alterations occurred in any of the physiological, haematological and biochemical parameters in camels anaesthetised with midazolam-propofol combination, thus excluding the possibility of any systemic toxicity. The recovery was rapid, smooth and uneventful in all the camels. Calm and smooth recovery was also noticed with xylazine-midazolam-propofol anaesthesia in horses (Oku *et al,* 2003).

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