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Dexmedetomidine, ketamine and isoflurane anaesthesia in Bonnet Macaques (*Macaca radiata*)

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Abstract
The study was conducted to evaluate the efficacy of a combination of dexmedetomidine (10 µg/kg body weight) and ketamine (10mg/kg body weight) as induction agent and isoflurane as an maintenance agent in 12 Bonnet Macaques (*Macaca radiata radiata*) which were referred for vasectomy. The induction combination induced ataxia in 285 ± 34.42 seconds and induction of anaesthesia in 11.83 ± 1.92 minutes. Anaesthesia was maintained for a duration of 107 ± 4.289 minutes for the surgical procedure and the monkeys recovered in 27.83 ± 3.50 minutes without any complication. The cardiopulmonary, haematologica, biochemical and plasma cortisol levels fluctuated within the normal limits. The study revealed that the combination of dexmedetomidine (10 µg/kg body weight) and ketamine (10mg/kg body weight) intramuscularly could be used as chemical restraining and induction agents and isoflurane as a safe inhalant anaesthetic for maintenance.

Keywords: Dexmedetomidine, ketamine, isoflurane, Bonnet Macaques

Introduction
Among the primates, the macaque species are in abundance especially Rhesus while the Bonnet Macaques are denser and more distributed widely. The two sub-species of Bonnet Macaque have been morphologically recognized in India, they are *Macaca radiata radiata* and *Macaca radiata* Diluta (Mehu *et al*., 2006) [1]. Monkeys are commonly found in villages, living freely with the human environment, where food is offered by the villagers, worshippers and tourists. Human-monkey conflict starts when they seize food from houses, shops and crop raiding in cultivated area (Sharma *et al*., 2011 and Thierry, 2000) [2, 3] and is often noticed in public places. Indications for chemical restraining of Bonnet Macaques include, physical examination, blood collection, cardiac and urethral catheterization, treatment of wound, tattooing, tuberculosis testing, radiological examination, major surgical procedure and animal model studies. They are often immobilized for translocation and birth-control surgeries. While capturing and subjecting them for surgical procedure, their feeding status and health status is not known. The expected outcome of anaesthetic regimen for capturing and anaesthetizing for surgery is quick and smooth induction, good anesthetic plane, smooth recovery and post-operative analgesia.

Dexmedetomidine is an alpha-2 adrenergic agonist which has sedative and analgesic properties with long terminal half-life and plasma clearance. Dexmedetomidine does not require an antagonist for revival and it has minimal effect on cardiovascular and respiratory functions. Dexmedetomidine is an alpha-2 adrenergic agonist which lack extra pyramidal action and stimulation of cortical area. Combination of dexmedetomidine with ketamine reduces the convulsive threshold of ketamine and thereby reduces the incidence of convulsions with the added advantages of smooth induction, good muscle relaxation and stable vital signs (Sanders *et al*., 2010) [4].

Isoflurane has the highest safety margin and is a potent coronary vasodilator (Collins *et al*., 2013) [5]. Unlike halothane, isoflurane does not sensitize the myocardium to adrenaline; hence it can be used even in cardiomyopathy and in geriatric animals with hepatic and renal diseases. Isoflurane is suitable for conservative, diagnostic and surgical procedures with less stress and intra and post anaesthetic complication (Garzel *et al.*, 2009)

The study was planned to study the benefit of a combination of dexmedetomidine and ketamine as induction agent, which can also be used for chemical restraining and isoflurane as maintenance agent for diagnostic and surgical procedures.

Material and Methods

The study was conducted on 12 cases of male *Macaca radiata radiata* (Bonnet macaque) referred to vasectomy from Aringar Anna Zoological Park to Department of Veterinary Surgery and Radiology, Madras Veterinary College Teaching Hospital. The study was approved by the Dean, Faculty of Veterinary Sciences and Director of Clinics, Tamil Nadu Veterinary and Animal Sciences University. In the selected 12 male monkeys feed and water were withheld for about 12 hours and 6 hours respectively to reduce the risk of aspiration. (Alstrup *et al*., 2013; Kumar and Kumar, 2013) [6, 7]. The Bonnet macaques were administered dexmedetomidine at the dose rate of 10 µg/kg body weight and ketamine at the dose rate of 10mg/kg body weight intramuscularly for immobilization and induction. Following induction, endotracheal tube intubation was donw with Murphy cuffed endotracheal tube at the size 3 to 5 (Morris *et al*., 1997; Vnuk *et al*., 2009) [8, 9]. The Murphy cuffed endotracheal tube was selected based on body size and weight after induction. After intubation the monkeys were pre-oxygenated with 100 per cent oxygen for 5 minutes and maintained anaesthesia with 2.5 to 3 per cent isoflurane initially followed by 1 to 1.5 per cent isoflurane with adequate oxygen supplementation.

The anaesthetic parameters studied were time of ataxia, time of induction, quality of induction, duration of anaesthesia, quality of anaesthesia (scale 0 to 4), time for recovery and quality of recovery. Immediately after induction, during peak anaesthesia or during surgical intervention and before recovery the vital signs such as rectal temperature, intra ocular pressure, cardio-pulmonary, haematological, biochemical parameters and plasma cortisol level were recorded. Complication, if any occur during intra and post anaesthetic period were also recorded. The data obtained were subjected to statistical analysis using SPSS 20.00 windows using ANOVA.

Results

Intramuscular administration of dexmedetomidine at a dose of 10 µg/kg body weight and ketamine at the dose rate of 10mg/kg body weight was sufficient to induce ataxia in 285 ± 34.42 seconds. During the onset of ataxia the monkeys carefully drooped down from the top of cage to the ground by using the foreleg and assumed sitting posture with head bent forward and eyes closed in the groups. The mean time for induction was 11.83 ± 1.92 minutes. The time required for the entire anaesthetic procedure including vasectomy, from the point of induction to cessation of administration of isoflurane was 107 ± 4.289 minutes. The time required from onset of cutaneous reflexes, lifting the head and gripping the object with hand to unassisted standing was 27.83 ± 3.50 minutes

The quality of anaesthesia in terms of nature of induction, recovery, reflex status and muscle relaxation was smooth and uneventful. The corneal, palpebral and pupillary reflexes were weak and the quality of anaesthesia in terms of jaw tone was 3.50 ± 0.08 after induction. Isoflurane at the flow rate at 2 per cent/litter of oxygen supplementation was sufficiently maintained anaesthesia. No incremental doses were required during the procedure.

The mean ± SE of rectal temperature after induction, during peak anaesthesia and before recovery was 38.40 ± 0.09, 38.70 ± 0.10 and 38.01 ± 0.22 with a significant decrease before recovery (P<0.01). The mean intraocular pressure in mmHg assessed using indentation type of Schiotz tonometer, immediately after induction, during peak anaesthesia and before recovery was 17.60 ± 0.32, 18.70 ± 0.50, 18.36 ± 0.34 respectively. Statistical analysis revealed a significant increase (P<0.01) in the mean intraocular pressure during peak anaesthesia and before recovery in all monkeys.

The mean heart rate per minute immediately after induction, during peak anaesthesia and before recovery were 187.0 ± 11.63, 191.0 ± 7.37 and 188.16 ± 10.07 with significant increase during anaesthesia (P>0.05). The mean recorded systolic blood pressure in mmHg was 143.66 ± 6.95, 127.50 ± 13.19 and 136.50 ± 9.93 and diastolic blood pressure was 111.61 ± 6.95, 108.83 ± 9.01 and 111.0 ± 5.60 after induction, during anaesthesia and before recovery respectively with significant variation (P>0.05). The mean respiratory rate decreased significantly with a mean of 39.66±1.35, 31.66±1.40 and 29.66±1.90 after induction, during anaesthesia and before recovery. The saturated partial pressure of oxygen after induction, during anaesthesia and before recovery was 94.40±0.79, 93.71±0.56 and 95.55±0.25 with significant variation (P<0.01).

The mean ± SE values of haematological, biochemical and plasma cortisol vales were recorded immediately after induction, during peak anaesthesia and before recovery were shown in table 1. The mean haemoglobin, packed cell volume and total erythrocyte count after induction, during peak anaesthesia and before recovery showed reduction in mean values during anaesthesia, but with in clinical limits. The mean platelet count, total leucocytic count and differential counts also fluctuated within normal limits. The mean blood glucose level, blood urea, creatinine, serum protein, calcium and phosphorous level also fluctuated within the normal limits. The mean plasma cortisol in µg/dl immediately after induction, during peak anaesthesia and before recovery was 23.26±0.65, 25.25±0.63 and 25.98±0.62, respectively without any statistical variation.

Table 1: Mean±SE of Haematological parameters immediately after induction, during peak anaesthesia and before recovery in Bonnet macaque

S.no	Parameter	Mean±SE		
		After immobilization	During maintenance	During recovery
1	Haemoglobin (g/dl)	11.85±0.71^{aA}	11.60±0.71^{aA}	11.70±0.62^{aA}
2	Packed cell volume (%)	34.16±1.09^{aA}	34.98±0.77^{aA}	35.33±0.91^{abA}
3	Red blood cells (millions/ cumm)	5.59±0.29^{aA}	5.40±0.19^{aA}	5.57±0.19^{aA}
4	White blood cells (thousands/cumm)	18.41±2.55^{aA}	16.81±2.45^{aA}	19.11±2.09^{aA}
5	Platelets (laks/cumm)	4.53±0.17^{aA}	4.28±0.01^{aA}	4.37±0.19^{aA}
6	Neutrophils (%)	68.46±0.30^{aA}	71.50±0.25^{a}	71.30±0.07^{a}
7	Eosinophil (%)	1.73±0.16^{aA}	1.73±0.26^{aA}	2.10±0.00^{aA}
8	Monocytes (%)	1.85±0.06^{aA}	1.36±0.07^{aA}	1.69±0.09^{aA}
9	Lymphocytes (%)	26.76±0.24^{aA}	24.39±0.39^{aA}	24.60±0.14^{aA}

Mean bearing different superscripts differ significantly **- highly significant (P≤0.01), and ^{NS} –not- significant (P>0.05).

Table 2: Mean±SE of Biochemical parameters and stress parameters in Bonnet macaque

S. no	Parameters	Mean±SE		
		After immobilization	During maintenance	During recovery
1	Blood urea nitrogen (mg/dl)	18.40 ± 0.82^{aA}	22.46 ± 0.79^{abA}	21.88 ± 1.38^{abA}
2	Creatinine (mg/dl)	1.28 ± 0.15^{aA}	1.45 ± 0.15^{aA}	1.32 ± 0.13^{aA}
3	Total protein (g/dl)	7.10 ± 0.22^{bA}	$7.09\pm0.13^{Bb*}$	6.90 ± 0.13^{abA}
4	Albumin (g/dl)	3.42 ± 0.06^{aA}	3.45 ± 0.08^{aA}	3.41 ± 0.03^{aA}
5	Globulin (g/dl)	3.68 ± 0.18^{cA}	3.62 ± 0.12^{bcA}	3.48 ± 0.11^{bcA}
6	Glucose (mg/dl)	67.33 ± 2.26^{bA}	56.16 ± 1.83^{aA}	58.33 ± 0.66^{aA}
7	Alkaline phosphatase (mmol/dl)	186.16 ± 13.28^{aA}	217.00 ± 13.97^{abA}	205.00 ± 12.32^{abA}
8	Calcium (mg/dl)	10.81 ± 0.20^{bA}	9.73 ± 0.18^{aA}	10.05 ± 0.19^{abA}
9	Phosphorus (mg/dl)	3.68 ± 0.15^{aA}	3.68 ± 0.11^{aA}	3.73 ± 0.02^{aA}
10	Sodium mmol/dl	142.16 ± 2.42^{bA}	134.66 ± 1.68^{aA}	138.66 ± 1.41^{abA}
11	Plasma Cortisol	23.26 ± 0.655^{Aa}	25.25 ± 0.637^{abA}	25.98 ± 0.628^{bA}

Mean bearing different superscripts differ significantly**- highly significant (P≤0.01), *- significant (P≤0.05), ^{NS} –non- significant (*P*>0.05).

Discussion

The dose of dexmedetomidine (10 µg/kg) and ketamine (10mg/kg) was sufficient to induce smooth ataxia and induction within a period of 285±34.42 and 11.83±1.92 seconds and the longer duration for inducing could be attributed to the delayed absorption of dexmedetomidine as reported by Larsson *et al*., (2012) [10], Garzel *et al*. (2009) [11], Sanders *et al*. (2010) [4]. Kumar and Kumar (2013) [7] and Koo *et al*. (2014) [12] who had used ketamine with sedatives such as alpha-2 adrenergic agonists and benzodiazepines and phenothiazine derivatives. Lee *et al*. (2010) [13] attributed the delay in the action of dexmedetomidine to the high lipid soluble nature in the adipose tissue and slow drug release. The dissociative nature of anaesthesia in ketamine was attributed to the blocked of thalamic nuclei (White *et al.*, 1982; Crofoot *et al.*, 2009; Kumar and Kumar (2013) [14, 7, 15]. Smooth induction could be attributed to the effect of ketamine that altered the reactivity of the central nervous system to various sensory impulses without blocking sensory input at spinal or brain stem levels (Lee *et al.* (2010) [13]. Dexmedetomidine – ketamine - isoflurane combination produced good depth of anaesthesia without any complication. Similar results were reported in alpha-2 adrenergic agonist-ketamine-isoflurane anaesthetic combination by Ranen *et al*. (2006) [16] and Re *et al.* (2010) [17]. The depth of anaesthesia was adequately maintained due to the adjunct actions of dexmedetomidine and ketamine during isoflurane anaesthesia (Nolosco *et al*. (2009) [18].

The normal body temperature of macaques ranged from 38.5ºC to 40.0ºC (Frank, 1976). In the present study the rectal temperature reduced following induction with dexmedetomidine-ketamine combinations during peak anaesthesia and before recovery. The lowest temperature recorded was 38.16±0.22ºC following administration of dexmedetomidine and ketamine which concurred with the findings of Brady (2000) [19], Williams *et al.* (2003) [20] and De-Zhang *et al*. (2012) [21]. The reduction in rectal temperature in dexmedetomidine – ketamine combination could be attributed to the anxiolytic action and reduction in skeletal muscle metabolism (Nolosco *et al*., 2009) [18]. The intraocular pressure is maintained by the dynamic movement of aqueous and vitreous humour and choroidal vascular volume. Increase in arterial blood pressure after induction could also increase intra ocular pressure drastically (Bito *et al.*, 1979) [22]. Ketamine significantly increased the intra – ocular pressure in humans which could be due to the increase in extra-ocular muscle tone (Gelatt, 1981) [23] and increase in blood pressure due to the sympathomimetic effect of ketamine (Laforcade and Rosanki, 2001) [24].

The mean heart rate elevate when ketamine alone was administered in animals due to the stimulation of sympathetic nerve trunks, vagolytic action and positive ionotropic action (Thurmon *et al.*, 1996, Larsson *et al*., 2012, Nolosco *et al*., 2009 and Lee *et al*., 2010) [25, 10, 18, 13]. Dexmedetomidine as an alpha-2 adrenergic agonist could reduce the heart rate due to increase vagal tone (Nolosco *et al*., 2009; Larsson *et al*., 2012) [18,10], but ketamine moderated the reduction (Kontak *et al*. (2013) [26]. Pypendop *et al*. (2011) [27] reported that the heart rate reduced when dexmedetomidine was administered with isoflurane. In the present study, an insignificant increase in heart rate was noticed in dexmedetomidine-ketamine combination which would be attributed to the adjunct action of ketamine (Lee *et al*., 2010; Kim *et al*., 2014) [13, 28]. No clinically significant alteration was observed in the systolic and diastolic blood pressure during peak anaesthesia or recovery and the findings were similar to that of Fahlman *et al*. (2006) [29] and Lee *et al*. (2010) [13] which could be attributed to the moderation between vasodilatation induced by dexmedetomidine and sympathomimetic action of ketamine. The normal respiratory rate in non-human primates is 30 to 50 respirations per minute (Frank, 1976) [30]. The respiratory rate decreased significantly when dexmedetomidine was combined with ketamine from 39.66±1.35 to 29.66 (immediately after induction) to 29.66 ± 1.90 (before recovery) (*P*<0.05). Various authors reported inconclusive findings such as decreased respiratory rate (De-Zhang *et al*., 2012, Vaughan *et al*., 2014 and Kim *et al.*, 2014) [21, 31, 28] both bradypnea and tachypnea (Sleeman *et al*., 2000) [32] and non-significant effect on respiratory rate (Fahlman *et al*., 2006 and Lee *et al*., 2010) [29, 13].

The mean ± SE of haemoglobin level, packed cell volume and total erythrocyte count, total leucocytic count and differential count (Table 1) throughout the study were within the clinical limits (Thierry *et al*., 2000) [3]. The blood urea nitrogen, creatinine, serum protein, blood glucose, serum phosphorus and sodium (Table 2) remained within the normal range revealing good fluid maintenance, lack of respiratory acidosis, acid base balance and renal perfusion (Rahaman *et al.*, 1975; Thierry *et al*., 2000; De-zhang *et al*., 2012) [33, 3, 21]

The plasma cortisol values fluctuated between 23.26±0.65 to 25.98±0.62 µg per dl in dexmedetomidine-ketamine-isoflurane anaesthesia. Benston *et al*. (2003) [34] reported low dose of ketamine could be inducing cortisol elevation which could be overcome by increasing the dose of ketamine to achieve surgical plane of anaesthesia. Increase in plasma cortisol level is often considered as a marker of physiological or physical stress and cortisol had wide ranging effects on many physiological systems. The insignificant increase in

plasma cortisol values in the study could be attributed to stress induced corticotrophin release. The neuroendocrine stress response was mediated continuously through adrenal cortex stimulation and caused production of cortisol (Benston *et al*., 2003) [34].

The present study was designed to evolve a safe and reliable anaesthetic regimen for immobilization, induction and maintenance with less stress and minimal alterations in homeostasis for chemical immobilization and maintenance of anaesthesia for surgical procedure. The study revealed dexmedetomidine at a dose of 10 µg/kg body weight and ketamine at the dose rate of 10mg/kg body weight intra muscularly provided safe and reliable immobilization and induction and isoflurane at a concentration of 2 per cent in oxygen provided good maintenance in Bonnet macaque.

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