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Comparison between the anaesthetic effects of xylazine–ketamine and diazepam–ketamine: physiological and blood parameters in young hamadryas baboons (*Papio hamadryas*)

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Abstract: The objective of this study was to evaluate the anaesthetic effects on young hamadryas baboons (*Papio hamadryas*) of xylazine–ketamine (XK) compared to diazepam–ketamine (DK). Six healthy young male hamadryas baboons were first premedicated with xylazine HCl (0.5 mg/kg, IM) and anaesthetised 20 min later with ketamine (10 mg/kg, IM). After a 10-day washout period, the hamadryas baboons were premedicated with diazepam (1 mg/kg, IM) and anaesthetised 20 min later with ketamine (10 mg/kg, IM). The onset, duration, and the depth of anaesthesia were determined by recording palpebral, corneal, and jaw reflexes. The results showed a significant decrease in heart rate and rectal temperature after XK injection, while a significant reduction in respiratory rate was seen when using the DK protocol. A highly significant increase in the levels of glucose was observed with the XK regimen. Blood pressure decreased when using both anaesthetic regimens, but this reduction did not reach significant levels. The quality of recovery was better when using XK compared to DK. In conclusion, major complications including bradycardia, hypothermia, and hyperglycaemia should be considered with a combination of XK. However, no complications other than bradypnea and hypercapnia should be expected when immobilising young hamadryas baboons with DK. No significant difference was observed in CBC, electrolytes, or lactate level between the anaesthesia protocols.

Key words: Xylazine, diazepam, ketamine, hamadryas baboons, anaesthesia

1. Introduction

The wide range of body size and weight of nonhuman primates plays an important role in the selection of an appropriate anaesthetic agent and the dosage of the drug to be administered. Primate species differ in their responses to certain anaesthetic agents. Several studies have used young nonhuman primates as experimental animal models for human paediatric research (1–4). Baboons are the largest old world nonhuman primates. Five species of baboons (genus *Papio*) have been identified; four are considered savanna baboons and the remaining one is referred to as a desert baboon (5). The hamadryas baboon (*Papio hamadryas*) or desert baboon is a common species found in many countries including Saudi Arabia, Somalia, Ethiopia, and Yemen (5). Weaning begins at 6 months and the young become independent at 2 years of age. Males and females reach sexual maturity at 4–7 and 4–5 years old, respectively (5). Baboons are frequently utilised as experimental animal models for a wide variety of research in humans such as in studies of coronary heart disease, chronic lung disease, atherosclerosis, hypertension, osteoporosis, and spinal disorders, and for development of HIV and hepatitis C vaccines as well as for neonatal research (5–8).

Injectable anaesthesia is preferred for conducting short-term experiments with baboons. Ketamine, a short-acting dissociative anaesthetic, has a wide margin of safety in many species of nonhuman primates and has been used for restraining and induction of anaesthesia in various species including primates. However, poor muscular relaxation and tonic–clonic movements or psychotomimetic emergence reactions are associated with ketamine administration in nonhuman primates (9–11). Thus, in order to achieve complete immobilisation and reduce the undesirable effects of injecting ketamine alone, administration of a premedication agent in combination with the ketamine is recommended. Xylazine (α2 adrenoceptor agonist) and diazepam (benzodiazepine agent) have been used widely as premedication drugs given with or prior to ketamine administration in animals, including nonhuman

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primates (12–18). The administration of xylazine provides the added effects of increased sleep time, good muscle relaxation, prevention of voluntary muscle movement, and substantial analgesia (19). Diazepam has been used in combination with ketamine in hamadryas baboon for minor procedures requiring muscle relaxation (16). To the best of the authors' knowledge, the effects of xylazine, diazepam, and ketamine have not previously been studied using young hamadryas baboons. Therefore, the aim of the present study was to evaluate the anaesthetic effects of xylazine–ketamine (XK) in young hamadryas baboons (*Papio hamadryas*) and compare them with the effects of a diazepam–ketamine (DK) regimen.

2. Materials and methods

The experimental protocol was approved by the Ethics Committee (No. 367) for Animal Research of the Scientific Research Deanship, Qassim University, Saudi Arabia

2.1. Hamadryas baboons

Six young male hamadryas baboons (*Papio hamadryas*) were used in this study. These hamadryas baboons were considered healthy on the basis of a physical examination. Their mean body weight was 3.4 kg (range = 3–3.8) and their mean age was 11 months (range = 10–12 months). Food (fruits and vegetables) and water were withheld for 6 h before the beginning of the study. The experiments were performed in a temperature-controlled room maintained at 25 °C.

2.2. Anaesthesia

Twenty-gauge intravenous catheters (Mais Co., Riyadh, Saudi Arabia) were placed in the left or right cephalic vein. Combinations of XK and DK were administered with a washout period of 10 days between the 2 anaesthetic protocols. The hamadryas baboons were first premedicated with xylazine HCl (0.5 mg/kg, IM, Rompun 2%, Bayer Health Care, Monheim, Germany). Twenty minutes later, general anaesthesia was induced with ketamine (10 mg/kg, IM, ketamine 10%, Alfasan, Woerden, Holland). After 10 days, the hamadryas baboons were premedicated with diazepam (1 mg/kg, IM, Valium, F. Hoffmann La Roche Ltd., Basel, Switzerland) and anaesthetised 20 min later with ketamine (10 mg/kg, IM).

The onset and duration of anaesthesia were recorded. Rectal temperature (RT), respiratory rate (RR), heart rate (HR), haemoglobin oxygen saturation (OHS), and mean arterial blood pressure (MBP) were measured before and 20 min after the administration of xylazine or diazepam and then every 10 min until recovery. RT was recorded using a digital thermometer and respiratory rate was counted by watching the movement of either the thoracic or the abdominal wall. A pulse oximeter (504DX Digital Oximeter, Criticare Systems Inc., Waukesha, WI, USA) with a probe attached to the tip of the ear was used to assess the concentration of OHS and HR. The values of MBP were indirectly measured by oscillometer (Accutorr Plus Recorder, Datascope, Datascope Corp., Paramus, NJ, USA) using a cuff placed around the arm. The depth of anaesthesia was determined by monitoring various reflexes including palpebral, corneal, and jaw reflexes. The onset time and signs of recovery were determined.

2.3. Sampling

Cephalic blood samples (approximately 1–1.5 mL) were collected from each hamadryas baboon and transferred to EDTA- and heparin-containing Vacutainer tubes (Venoject, Leuven, Belgium) immediately before and 20 min after the injection of xylazine or diazepam, 20 and 30 min after the injection of ketamine, and at the onset of and full recovery from anaesthesia. The blood samples with EDTA were used to determine the red blood cell (RBC) and white blood cell (WBC) counts, differential leucocytic counts (dWBC), packed cell volume (PCV), haemoglobin concentration (HGB), haematocrit (HCT), and platelets (PLT) using an automated machine (VetScan HM5, ABAXIS, Union City, CA, USA). The blood samples with heparin were used for measurement of concentrations of oxygen (PO_2), carbon dioxide (PCO_2), pH, sodium (Na), potassium (K), calcium (Ca), and lactate immediately in venous blood using a blood gas analyser (GEM Premier 3000, Instrumentation Laboratory Co., Bedford, MA, USA). The levels of glucose were measured before and 20 min after the administration of xylazine or diazepam and then every 10 min until recovery. This test was performed by using the traditional home blood glucose monitoring method, which involved pricking the hamadryas baboon's finger with a lancet, putting a drop of blood on a test strip, and then placing the strip into a meter that displays the blood glucose level.

2.4. Statistical analysis

The data were analysed and comparisons were made between the two groups with a commercial statistical software package (SAS version 8, SAS Institute Inc., Cary, NC, USA). A repeated measures analysis of variance (ANOVA) was used as the statistical model to evaluate the differences over time in the dependent variables, including the parameters of physiological and haematological functions. Duncan's test was used to calculate multiple comparisons. Results were considered significant at $P < 0.05$.

3. Results

The RR was significantly ($P < 0.05$) depressed in the DK hamadryas baboons group (Figure 1A) 10 min following ketamine administration. The HR and RT significantly decreased ($P < 0.01$) during anaesthesia in the hamadryas baboons belonging to the XK group (Figures 1B and 1C). The MBP decreased during anaesthesia in both groups

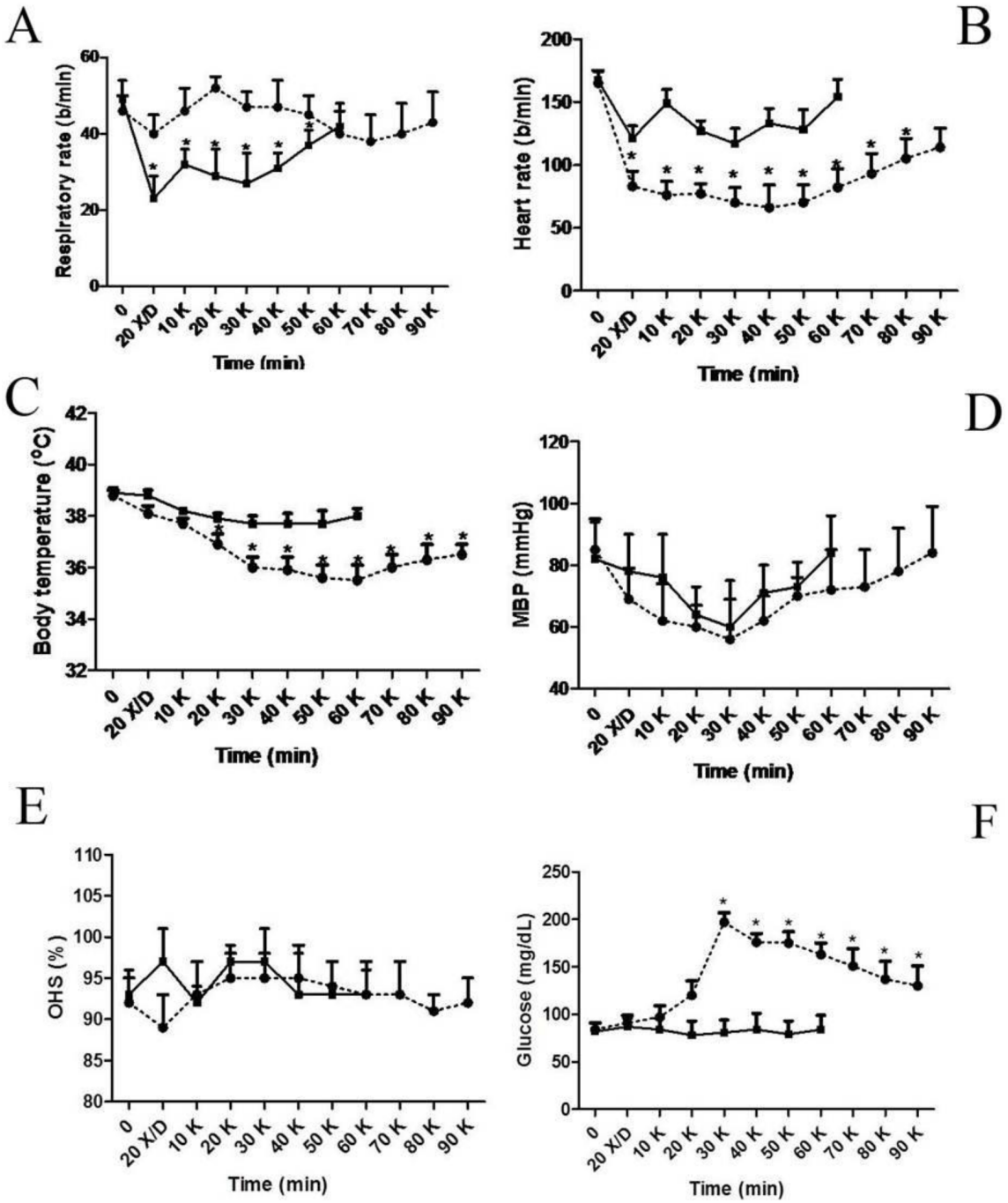

Figure 1. Changes in (A) respiratory rate, (B) heart rate, (C) body temperature, (D) mean arterial blood pressure (MBP), (E) oxygen haemoglobin saturation (OHS) and (F) glucose in young hamadryas baboons (n = 6) anaesthetised with xylazine–ketamine (dotted lines) and diazepam–ketamine (solid lines) at 0 time and 20 min (0, 20 X/D) after xylazine/diazepam injection and 10, 20, 30, 40, 50, 60, 70, 80, and 90 min after ketamine administration (*indicates significant values compared to baseline value (these values were obtained before administration of anaesthetic protocols)).

(Figure 1D). The OHS did not significantly ($P > 0.2$) change in either group (Figure 1E). Hyperglycaemia was observed after XK administration, but not after DK (Figure 1F) ($P < 0.01$). There were significant changes in the levels of PCO_2 between the two groups at 20 min after premedication injection ($P < 0.05$) and 20 min after ketamine injection ($P < 0.05$). In addition, within the DK group, levels of PCO_2 were significantly increased following diazepam

and ketamine administration ($P < 0.05$). Otherwise, no significant difference was observed in CBC (Tables 1 and 2), blood gases, electrolytes, or lactate level (Tables 3 and 4) between the anaesthesia protocols.

Within 2.5 (±0.4) min following the xylazine injection, the animals showed signs of decreased spontaneous activity by sitting on the sternum and sometimes lying down. Within 2 (±0.5) min of diazepam administration, the hamadryas baboons were awake, but with some signs associated with ataxic movement (e.g., falling down, lack of coordination), minor skin rubbing, and yawning. In both groups, within 1.5 (±0.9) min postadministration of ketamine, the hamadryas baboons were lying down, and the jaw reflex was absent within 3 (±0.6) min. In the hamadryas baboons of both groups, palpebral and corneal reflexes disappeared 5 (±0.4) min after the administration of ketamine (Table 5). The duration of anaesthesia was 40 (±6) and 34 (±4) min for XK and DK, respectively.

The first sign of recovery in the XK hamadryas baboons appeared 40 (±5) min after the ketamine injection and was characterised by movement of the tail. Subsequently, the signs of recovery gradually appeared, with palpebral and corneal reflexes returning in 45 (±6) min, moving the head while still lying on the ground in 47 (±6) min, raising the head in 48 (±2) min, moving the limbs in 50 (±4) min, sitting on the sternum in 58 (±6) min, and walking in a creeping posture 60 (±5) min after ketamine administration. Urination was observed during the recovery period in 3/6

Table 1. Mean (±SEM) values of complete blood count in young hamadryas baboons (n = 6) after xylazine and ketamine administration.

Time Parameter	Before injection (T0)	20 min after xylazine injection (T1)	20 min after ketamine injection (T2)	30 min after ketamine injection (T3)	At the beginning of recovery (T4)	At full recovery (T5)
WBC ($\times 10^9$/L)	9.3 (±0.3)	9.4 (±1.3)	10.7 (±1.7)	9.3 (±1.3)	9.2 (±2.3)	9.3 (±2.6)
Lymphocytes (%)	58.4 (±5.3)	56.7 (±3.6)	55.6 (±2.3)	56.8 (±1.8)	59.3 (±2.6)	57.4 (±3.8)
Monocytes (%)	1.5 (±0.3)	0.9 (±0.4)	1.1 (±0.3)	0.9 (±0.7)	0.6 (±0.3)	0.7 (±0.2)
Neutrophils (%)	39.0 (±3.3)	41.2 (±6.3)	42.1 (±7.6)	41.5 (±10.4)	39.7 (±13.2)	40.4 (±7.9)
Eosinophils (%)	1.1 (±1)	1 (±0.5)	1.2 (±0.5)	0.7 (±0.2)	0.4 (±0.2)	1.4 (±0.4)
Basophils (%)	0 (±0)	0.2 (±0.07)	0 (±0)	0.1 (±0.05)	0 (±0)	0.1 (±0.03)
RBCs ($\times 10^{12}$/L)	6.15 (±0.6)	5.9 (±0.8)	5.4 (±0.5)	5.8 (±0.6)	6.51 (±0.8)	6.38 (±0.9)
HGB (g/dL)	12.3 (±1.1)	11.5 (±1.2)	11.1 (±0.9)	12.4 (±1.5)	13.3 (±2.3)	13.8 (±1.7)
HCT (%)	40.9 (± 3)	36.9 (±4.3)	36.6 (±7.2)	37.3 (±5.6)	39 (±6.3)	38.1 (±6.4)
Platelets ($\times 10^9$/L)	461 (±30)	420 (±37)	380 (±39)	340 (±29)	445 (± 32)	456 (± 45)

White blood cell; Red blood cells; Haemoglobin concentration; Haematocrit.

Table 2. Mean (±SEM) values of complete blood count in young hamadryas baboons (n = 6) after diazepam and ketamine administration.

Time Parameter	Before injection (T0)	20 min after diazepam injection (T1)	20 min after ketamine injection (T2)	30 min after ketamine injection (T3)	At the beginning of recovery (T4)	At full recovery (T5)
WBC ($\times 10^9$/L)	9.4 (±0.3)	9.6 (±1.8)	9.6 (±3.2)	10.2 (±5.2)	11.4 (±3.4)	10.4 (±3.2)
Lymphocytes (%)	60.1 (±5)	56.4 (±7.3)	54.8 (±10)	57.7 (±6)	57.6 (±9.2)	58.2 (±9.6)
Monocytes (%)	1.2 (±2)	0.9 (±0.3)	1.4 (±0.6)	1.1 (±0.3)	1.2 (±0.2)	1.3 (±0.6)
Neutrophils (%)	38.7 (±3)	41.3 (±10.3)	43.5 (±9.2)	40.2 (±7.8)	40.1 (±10.2)	39.5 (±12.2)
Eosinophils (%)	0 (±0)	1.2 (±0.7)	0.2 (±0.1)	1 (±0.6)	1.1 (±0.5)	1.0 (±0.4)
Basophils (%)	0 (±0)	0.2 (±0.1)	0.1 (±0.05)	0 (±0)	0 (±0)	0 (±0)
RBCs ($\times 10^{12}$/L)	6.81 (±0.4)	6.51 (±0.3)	5.3 (±1.2)	6.4 (±1.3)	6.7 (±1.2)	6.8 (±1.1)
HGB (g/dL)	12.7 (±0.2)	12.6 (±0.6)	11.6 (±0.4)	12.2 (±3.2)	12.7 (±0.8)	12.7 (±1.5)
HCT (%)	42.8 (±4.2)	37.2 (±3)	31.4 (±7.2)	42.4 (±5.3)	42.5 (±6.3)	42.6 (±3.3)
Platelets ($\times 10^9$/L)	450 (±20)	400 (±30)	300 (±30)	315 (±35)	401 (±30)	405 (±34)

White blood cell; Red blood cells; Haemoglobin concentration; Haematocrit.

Table 3. Mean (±SEM) values of venous blood gases, electrolytes, and lactate in young hamadryas baboons (n = 6) after xylazine and ketamine administration.

Time Parameter	Before injection (T0)	20 min after xylazine injection (T1)	20 min after ketamine injection (T2)	30 min after ketamine injection (T3)	At the beginning of recovery (T4)	At full recovery (T5)
pH (mol/L)	7.50 (±0.3)	7.50 (±1.2)	7.52 (±1.0)	7.47 (±1.4)	7.51 (±0.3)	7.51 (±1.1)
PCO_2 (mmHg)	23 (±2.6)	25 (±1.6)	21 (±1.3)	30 (±3.5)	21 (±1.6)	22 (±1.8)
PO_2 (mmHg)	50 (±20)	53 (±12)	61 (±11)	55 (±15)	53 (±13)	53 (±14)
Na (mmol/L)	148 (±2)	149.5 (±1)	148 (±2)	149 (±0.8)	149 (±0.6)	149 (±1.9)
K (mmol/L)	4.3 (±1)	4.3 (±0.2)	4.4 (±2)	4.1 (±0.7)	4.2 (±0.2)	4.1 (±0.2)
Ca (mmol/L)	0.95 (±0.5)	0.84 (±0.4)	0.93 (±0.5)	1 (±0.1)	0.95 (±0.2)	0.95 (±0.3)
Lactate (mmol/L)	4.3 (±0.2)	3.9 (±0.3)	4.0 (±0.4)	3.7 (±0.3)	3.8 (±0.3)	4.0 (±0.4)

PCO_2: Concentration of carbon dioxide; PO_2: Concentration of oxygen; Na: Sodium; K: Potassium; Ca: Calcium. Results were considered significant at $P < 0.05$.

Table 4. Mean (±SEM) values of venous blood gases, electrolytes, and lactate in young hamadryas baboons (n = 6) after diazepam and ketamine administration.

Time Parameter	Before injection (T0)	20 min after diazepam injection (T1)	20 min after ketamine injection (T2)	30 min after ketamine injection (T3)	At the beginning of recovery (T4)	At full recovery (T5)
pH (mol/L)	7.50 (±0.3)	7.47 (±0.4)	7.47 (±0.5)	7.46 (±0.2)	7.48 (±0.2)	7.50 (±0.5)
PCO_2 (mmHg)	24 (±0.5)	35 (±2.3)*	36.5 (±4.2)*	35.3 (±3)*	25.6 (±2.2)	25.2 (±2.6)
PO_2 (mmHg)	50 (±12)	47 (±10)	55 (±13)	53 (±10)	53 (±12)	50 (±11)
Na (mmol/L)	149 (±.5)	149 (±1)	148 (±1.2)	148 (±2)	150 (±3.2)	149 (±2.2)
K (mmol/L)	4.3 (±0.2)	4.3(±0.5)	4.3 (±0.3)	4.5 (±1.6)	4.5 (±0.8)	4.4 (±0.7)
Ca (mmol/L)	1 (±0.3)	0.95 (±0.5)	1 (±0.3)	0.95 (±0.4)	0.94 (±0.5)	0.96 (±0.6)
Lactate (mmol/L)	4.4 (±0.6)	3.8 (±0.4)	3.6 (±0.4)	3.5 (±0.3)	3.6 (±0.4)	3.9 (±0.3)

PCO_2: Concentration of carbon dioxide; PO_2: Concentration of oxygen; Na: Sodium; K: Potassium; Ca: Calcium. Results were considered significant at $P < 0.05$.

Table 5. Parameters of anaesthesia in young hamadryas baboons after administration of xylazine–ketamine and diazepam–ketamine.

Parameters of anaesthesia	Xylazine–ketamine	Diazepam–ketamine
Time of disappearance of jaw reflex	3 (±0.6) min	3 (±0.6) min
Time of disappearance of eye reflex	5 (±0.4) min	5 (±0.4) min
Beginning of recovery	40 (±5)	34 (±6)
Full recovery	91 (±10) min after ketamine injection	60 (±10) min after ketamine injection
Duration of anaesthesia	40 (±6)	34 (±4)

of the hamadryas baboons in the XK group 43 (±7) min postketamine injection. Full recovery occurred 91 (±10) min after ketamine administration.

In the DK group, the first sign of recovery was seen 34 (±6) min after the ketamine injection. This was characterised by either moving the head and hands together (3/6 hamadryas baboons) or by minor jerking over the entire body (3/6 hamadryas baboons). The palpebral and corneal reflexes returned 36 (±5) min after the ketamine injection. Afterwards, the hamadryas baboons suddenly stood up and then fell down while trying to walk 38 (±6) min after the ketamine injection. Urination was observed

during recovery in 2/6 hamadryas baboons 40 (± 4) min after administration of ketamine. Full recovery occurred 60 (±10) min after the administration of ketamine.

Highly significant hyperglycaemia ($P < 0.05$) was observed in all hamadryas baboons when using the XK combination and, on the other hand, the administration of DK did not significantly ($P > 0.05$) alter the levels of sugar in the blood. A significant elevation ($P < 0.05$) in the concentration of PCO_2 was seen in the DK group after ketamine administration (Table 4). Otherwise, no significant difference was observed in CBC, electrolytes, or lactate level between the anaesthesia protocols.

4. Discussion

This study was conducted to analyse the effects of anaesthesia with XK and DK on the physiological and haemodynamic parameters of young baboons. Baboons are frequently used as experimental animal models for a wide variety of human research (5–8). In fact, the baboon is considered an ideal experimental model because of genetic similarity to humans of approximately 89%. They have an immune system similar to that of humans and are relatively large in size, and thus capable of providing ample fluid and tissue samples (7,20). In the present study, both XK and DK produced a depth of anaesthesia and analgesia in the young baboons sufficient for surgical procedures. The duration of anaesthesia was longer (40 min) and recovery was smoother for XK compared to DK (34 min). Minor skin rubbing was observed in baboons after the DK regimen was applied. This might be due to the intramuscular injection of the diazepam, which is usually painful in nonhuman primates (14).

This study found a significant reduction in the respiratory rates of hamadryas baboons in the DK group. Respiratory depression has been reported in humans following diazepam administration (21–24). In children with seizures, the overall incidence of respiratory depression following diazepam administration intravenously, rectally, or both was 20%, 5%, and 9%, respectively (25,26). Respiratory depression has also been reported in adult humans following the use of diazepam (27). It has been thought that diazepam causes respiratory depression due to direct suppression of the central respiratory drive (22). In addition, benzodiazepines including diazepam exhibit some muscular relaxation properties capable of depressing the respiratory muscle strength (22) and causing CO_2 retention (24). The levels of CO_2 in the present study were significantly higher in the DK group 20 min following diazepam and ketamine administration. Even though ketamine stimulates respiration in various species, diazepam-induced respiratory depression might have masked this stimulation in the DK group.

In the XK group, the HR significantly decreased 20 min after the injection of xylazine. This study is in agreement with other studies using nonhuman primates (28) and other species (29–33). It has been reported that xylazine-induced bradycardia is associated with a decreased outflow of sympathetic nervous system impulses to the periphery and with increased vagal activity (34). In the present study, the levels of HR gradually increased after the administration of ketamine, but were not enough to show significant improvement. In most species, including hamadryas baboons, the administration of ketamine stimulates HR (18,32,35). In the present study, the continuous reduction of HR encountered in the XK group indicated that xylazine overrides the stimulatory effects of ketamine.

Body temperature is regulated by both the central and the peripheral thermoregulatory mechanisms. The rectal temperature was a reliable, noninvasive approximation of the internal core body temperature of the young baboons. Hypothermia was observed in both groups; however, it was significant in the XK group. Similar results have been reported in primates (36) and other animals including rats (37,38), rabbits (39), cattle (40), and goats (41). Both xylazine and ketamine have been reported as producing a hypothermic response (17,42–45). The central control of body temperature is located in the hypothalamus, and α-2 agonists-induced hypothermia is associated with a presynaptic inhibition of noradrenaline (46,47). The blockade of N-methyl-D-aspartate (NMDA) receptors is credited as being the mechanism by which ketamine produces the hypothermic response (44,48). Others have suggested that ketamine-produced hypothermia is due to the release of serotonin in the hypothalamus (49).

Highly significant hyperglycaemia was observed in all hamadryas baboons when using the XK combination. Xylazine-induced hyperglycaemia has been reported previously in various species, including humans (50), rhesus hamadryas baboons (51), rats (52), mice (53), dogs (54,55), cats (56), horses (57), and cattle (58–60). It has been stated that the acute hyperglycaemic effect of XK administration is associated with decreased plasma levels of insulin, adrenocorticotropic hormone (ACTH), and corticosterone and increased levels of glucagon and growth hormone (52,61). Recent studies have shown that xylazine can cause hyperglycaemia in nonhuman primates with no significant alterations in blood insulin and glucagon. The stimulation of α2-adrenoceptors and subsequent decreasing tissue sensitivity to insulin lead to the reduction of tissue glucose uptake and utilisation (51). On the other hand, the administration of DK did not significantly alter the levels of sugar in the blood. In fact, oral diazepam has been used in humans to

attenuate the hyperglycaemic response resulting from surgical stress (62).

In conclusion, major complications including bradycardia, hypothermia, and hyperglycaemia should be considered when anaesthetising young hamadryas baboons with a combination of xylazine–ketamine. However, no complications other than bradypnea and hypercapnia should be expected when immobilising young hamadryas baboons with diazepam–ketamine. Therefore, it was concluded that anaesthesia using diazepam–ketamine is better than that using xylazine–ketamine.

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