Article — Artikel

Xylazine, diazepam and midazolam premedicated ketamine anaesthesia in White Leghorn cockerels for typhlectomy

S K Maiti[a*], R Tiwary[a], P Vasan[b] and A Dutta[a]

ABSTRACT

Thee different combinations of ketamine hydrochloride were used to induce general anaesthesia for surgical operations (typhlectomy) in 30 adult, single-comb White Leghorn cockerels. They were randomly divided into three groups, each comprising 10 birds. Birds in Group I received xylazine-ketamine combinations at the dose rate of 2 mg xylazine and 10 mg ketamine per kg i.v., whereas birds of Group II received diazepam (2.5 mg/kg i.v.) and 5 min later ketamine (75 mg/kg i.m.). In the Group III, midazolam (2 mg/kg i.m.) and 5 min later ketamine (50 mg/kg i.v.) was administered. The onset of sedation/anaesthesia was shortest (1.60 ± 0.27 min) in Group I, followed by Group II (8.40 ± 0.83 min) and Group III (17.10 ± 1.71 min). Recovery period was shortest in the Group I (65–75 min) followed by Group II (80–85 min) and Group III (92–105 min). Sedation, muscle relaxation and surgical anaesthesia was optimal and excellent in Group I compared with the other two groups. Torticollis, salivation and dyspnoea were observed in Group III. Short-term limb contractions were present in all birds in Groups II and III, up to 20 min of observation. Recovery from anaesthesia was smooth in all three groups. A Surgical procedure (typhlectomy) was performed on all birds. Hypothermia was observed in Group II, whereas heart and respiratory depression was recorded in Group I. Blood sugar level did not vary significantly in any anaesthetic regime. The reduction of haemoglobin was maximum in Group II compared with Groups I and III. Hypoxaemia and hypercapnaea were elevated in all birds in Groups II and III. Blood electrolytes did not vary significantly from the baseline values among the three groups of birds during the period of observation (120 min). The xylazine-ketamine combination was found to be the best anaesthesia for surgical intervention in chickens.

Key words: anaesthesia, diazepam, ketamine, midazolam, poultry, typhlectomy, xylazine.

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INTRODUCTION

General anaesthesia is necessary in birds before performing surgical intervention on them because it induces complete unconsciousness, insensitivity to pain, freedom from reflex responses, good muscle relaxation, and loss of motor control[25]. Inhalation anaesthetics, including halothane, methoxyflurane and isoflurane have been used in birds[4,14]. However, the physiological and anatomical characteristics of birds render the use of inhalant anaesthetics more hazardous than in mammals[9]. Further, a disadvantage of inhalant anaesthetics is that the delivery of the inhalants requires special equipment such as a source of oxygen, a vaporiser, a breathing circuit and a mechanism for scavenging waste anaesthetic gases[24]. Alternatives to inhalant anaesthetics for diagnostic and surgical procedures include the use of different injectable drugs, which have been used either alone or in combination, with variable results[38,43]. There are many advantages associated with the use of injectable drugs, including their low cost, ease of use and the rapidity with which anaesthesia can be induced. In addition, expensive equipment is not required for delivery or maintenance of anaesthesia[24]. The use of anaesthetics in birds has generally indicated that the tolerance of birds to most anaesthetics between a surgical plane of anaesthesia and death is relatively narrow and that extreme care should be exercised when anaesthetics are administered either by an inhalation or by an injectable route[10,34].

Several investigators have recommended ketamine hydrochloride as a suitable injectable anaesthetic agent for birds, especially for physical examinations[6,17,27]. However, there is a paucity of literature on the effect of ketamine anaesthetic premedicated by different sedatives for surgical intervention in birds. Ketamine has been used as an anaesthetic for a number of avian species, mostly raptors[7,37]. Generally, a dose of 15–20 mg per kg given intramuscularly was sufficient to produce immobilisation. However, pigeons were resistant to this drug, as much as 400 mg/kg did not produce surgical anaesthesia[8]. For 'parakeets' 10 mg/kg ketamine produced muscular relaxation and the lethal dose was 460 mg/kg body weight[28].

Investigation of the effects of ketamine on chickens has apparently been limited. The dissociative anaesthetic ketamine induces a state of catalepsy with open eyes, occasional purposeful skeletal movements and hypertonus independent of stimulation. Duration of maximal effect is dose-dependent with poor muscle relaxation and little analgesia[5,20], and incoordination, excitement, head shaking and wing flapping characterise recovery[5,20,22]. Different pre-anaesthetic combinations usually result in rapid induction, uneventful maintenance and smooth recovery compared with ketamine alone. Boever and Wright[6] reported that ketamine hydrochloride alone may cause convulsions, especially during the recovery phase and that birds require physical restraint to protect them from injuries. The aims of anaesthesia in birds should be to provide a smooth, reliable induction with adequate restraint, muscle relaxation and analgesia, followed by a fast, but full, uneventful recovery[21]. The objective of the present study was therefore to compare three commonly used ketamine combination anaesthetic regimes for surgical intervention in White Leghorn cockerels.

MATERIALS AND METHODS

Adult White Leghorn (*Gallus domesticus*) cockerels of 25 weeks of age and weighing between 1.5 and 2.5 kg were used. Birds were housed in individual cages. A commercial poultry grower ration and water *ad libitum* were provided to all birds. Experiments were carried out between February and March and all experiments were started at the same time of the day. *i.e.* at 10:00 and conducted in the same operating theatre to avoid

[a]Division of Surgery, Indian Veterinary Research Institute, Izatnagar – 243122, (Uttar Pradesh) India.

[b]Division of Animal Nutrition, Madras Veterinary College, Tamil Nadu, India.

*Author for correspondence. E-mail: maiti@ivri.up.nic.in

differences resulting from possible daily variability in the responses of chickens to ketamine.

Animals and anaesthetic regimes

The study was carried out at the Indian Veterinary Research Institute on 30 adult, single-comb White Leghorn cockerels that were randomly divided into three groups (I–III), each consisting of 10 birds. The birds in Group I were injected with a xylazine and ketamine combination in which an equal volume of xylazine (20 mg/ml) and ketamine (100 mg/ml) were mixed in single syringe (final concentration: xylazine 10 mg/ml; ketamine 50 mg/ml) and injected at 0.2 ml (2 mg xylazine and 10 mg ketamine) per kilogram body weight intravenously. In Group II, diazepam (2.5 mg/kg body weight) was injected intravenously and 5 min later ketamine was administered (75 mg/kg body weight) intramuscularly. In Group III, midazolam (2 mg/kg body weight) was administered intramuscularly and 5 min later ketamine was administered (50 mg/kg body weight) intravenously. These drug combinations were injected using 24 gauge needles for intramuscular injection in the *pectoralis major* muscle, whereas a 1 ml tuberculin syringe was used for intravenous injection in the wing vein. The Institute (IVRI) Animal Ethics Committee approved this experiment.

Surgical procedure

Birds were deprived of solid food and water for 12 h before surgery. After achieving complete anaesthesia, a laparotomy was performed though a horizontal incision in the body wall, at a position approximately midway between the pelvic and distal ends of the breastbone. Initially, the two distal ends of the caeca were carefully detached by hand from the mesentery. Careful detachment was continued in a proximal direction along the sides of the cloacae. When both caeca were completely detached, each was transected near to the ileo-caeco-colic junctions and the cut surface was sutured. After the caeca were removed, the exposed intestine was returned to the peritoneal cavity and the peritoneum, muscular layer and skin was closed in a routine manner. Broad-spectrum antibiotic, analgesic and local wound dressing was performed for four days post-caecectomy.

Evaluation of action of drug

Before the induction of anaesthesia (time 0) and 15, 30, 60 and 120 min after anaesthesia, we measured the heart rate, respiration rate and body (cloacal)
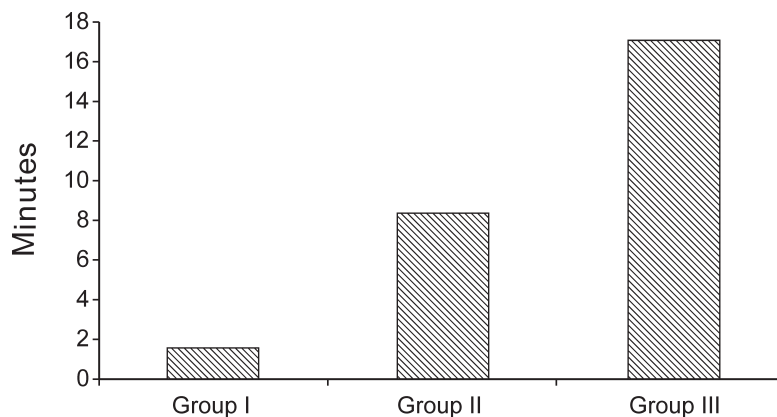

Fig. 1: **Mean of onset of anaesthesia in three groups of birds.**

temperature, blood glucose and response to a moderate toe-pinch. To test the response to toe-pinch pain reflex, moderate pressure to the bottom surface of the middle toe on the left foot was applied with a haemostat. Subjective assessment of the response to this external stimuli was scored on a scale of 0–3 as follows: 0 = no response to the stimulus, 1 = a delayed response with minimal retraction force of the leg, 2 = an immediate response but with reduced reflex force or a delayed response with normal retraction force of the leg, and 3 = an immediate and forceful retraction of the leg in response to the stimulus.

Degree of sedation/anaesthesia was scored on a scale of 0–3: 0 = standing alert, 1 = standing with a tired look, 2 = lying down but able to sit without support and 3 = not able to sit without support, or recumbent.

Degree of muscle relaxation/jaw reflex was scored on a scale of 0–3: 0 = tightly closed jaw (full tone), 1 = moderate resistance to opening the jaw, 2 = mild resistance to opening the jaw, and 3 = no resistance to opening the jaw. Degree of muscle relaxation was also assessed by whether it was difficult or easy to pluck feathers from the abdominal area .

We also recorded weak time, down time, sleep time and recovery time after induction of anaesthesia in all groups of birds. Weak time was the time elapsed from the time of injection of the drug to the time when the bird showed signs of incoordination (ptosis of head). Down time was the time from the administration of anaesthetic drug to sternal/lateral recumbency. Sleep time was recorded as the time spent by the bird in lateral/sternal recumbency. Recovery time was recorded in all the three groups as the time elapsed between the time of administration of the drugs and the time when the bird was able to walk unassisted.

Venous blood was collected in heparinised sterile syringes before and at 30- and 60-min intervals after injection of the

drugs. The blood was used for haemato-biochemical analyses such as blood pH, total carbon dioxide pressure (TCO$_2$), carbon dioxide tension (pCO$_2$), oxygen tension (pO$_2$), oxygen saturation percentage (SO$_2$) and blood electrolytes sodium (Na$^+$), potassium (K$^+$), chloride (Cl$^-$), calcium (Ca^{++}), and bicarbonate (HCO$_3^-$).

Statistical analysis

The data pertaining to clinical parameters and laboratory values were analysed using analysis of variance for repeated measurements. Results were considered significant if the *P*-value was <0.05. All data were expressed as mean ± SD. A subjective scoring system of weak time, down time, recovery time, response to toe-pinch, degree of sedation/anaesthesia and degree of jaw reflex was used and data were analysed using Wilcoxon's signed rank test.

RESULTS

A significant ($P < 0.05$) difference in onset of sedation/anaesthesia was observed among the different treatment groups. The onset of anaesthesia was significantly ($P < 0.05$) shortest in Group I and all the birds in this group immediately gained lateral recumbency after administration of anaesthetics and exhibited a good degree of analgesia. The onset of sedation/anaesthesia in the Group I birds was shortest (1.60 ± 0.27 min) followed by Group II (8.40 ± 0.83 min) and Group III (17.10 ± 1.71 min) (Fig. 1). Weak time was shortest in Group I (15–30 sec) and longest in Group III (5–8 min). Similarly, down time was shortest in Group I (25–45 sec) followed by Group II (3–5 min) and Group III (8–10 min). The recovery period recorded was significantly ($P < 0.05$) different among the three groups. Recovery period in Group I was shortest followed by Groups II and III (Fig. 2). Sedation, muscle relaxation and analgesia were optimal and excellent in Group I. A surgical plane of anaesthesia was achieved within 5–10 min of administration of

xylazine-ketamine in Group I. However, the diazepam-ketamine or midazolam-ketamine combinations failed to produce a surgical plane of anaesthesia up to 20 min after induction of anaesthesia. A Surgical plane of anaesthesia was recorded at 20–25 min and 25–35 min in Groups II and III, respectively.

A significant (P < 0.05) difference in toe-pinch reflex was observed among the three ketamine combination groups. In the case of xylazine-ketamine, the response to toe-pinch stimuli decreased significantly (P = 0.028) within 5 min of injection and a surgical plane of anaesthesia was achieved within 10 min. Decreases in toe-pinch responses manifested as decreased strength of leg contraction. At the 10-min interval, in Group I no response to the toe-pinch stimuli was observed (score 0). In the diazepam-ketamine group, a delayed response with minimal retraction force of the leg (score 1) was observed at the 20-min interval, whereas in Group III an immediate response but with reduced reflex (score 2) to toe-pinch stimuli was observed.

Muscle relaxation and analgesic effect of these anaesthetic combinations was evidenced by smooth and easy feather plucking from the abdominal area. The tone of the jaw became less tense as the bird entered a medium plane of anaesthesia, whereas no resistance to opening the jaw (score 3) was recorded when the birds entered a deep plane of anaesthesia. Muscle relaxation was excellent during maximum effect of drugs. Torticollis, salivation and dyspnoea were observed in Group III. Short-term myotonic limb contractions were present in all birds in Groups II and III up to 15 min. No remarkable events occurred during recovery phase of the birds, regardless of the anaesthetic regimes used. Sedate behaviour (eyes closed), a tendency to sleep in sternal recumbency and inactivity characterised the recoveries. No birds showed flapping, violent behaviour, vocalisation or involuntary muscle or limb movements during recovery. Birds were able to stand without assistance with slight ataxia at recovery time.

Body (cloacal) temperature began to drop in response to all anaesthetic regimes within 15 min of administration, but returned to normal at the 120-min interval, except in the group of birds anaesthetised with diazepam-ketamine (Fig. 3). The respiratory rate of Group I birds decreased significantly (P < 0.05) from baseline at the 15- and 30-min intervals, thereafter a significant (P = 0.018) rise at the 60-min interval, followed by a significant (P = 0.032) decrease at the 120-min interval, was observed. In Group II, the
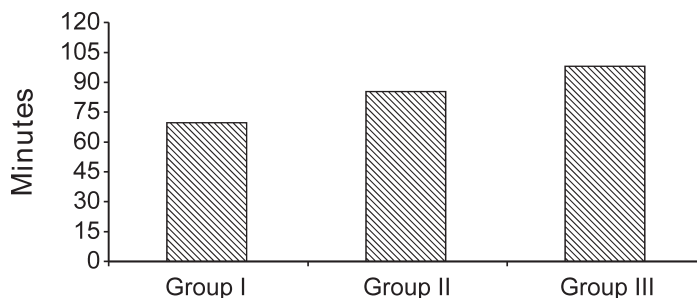

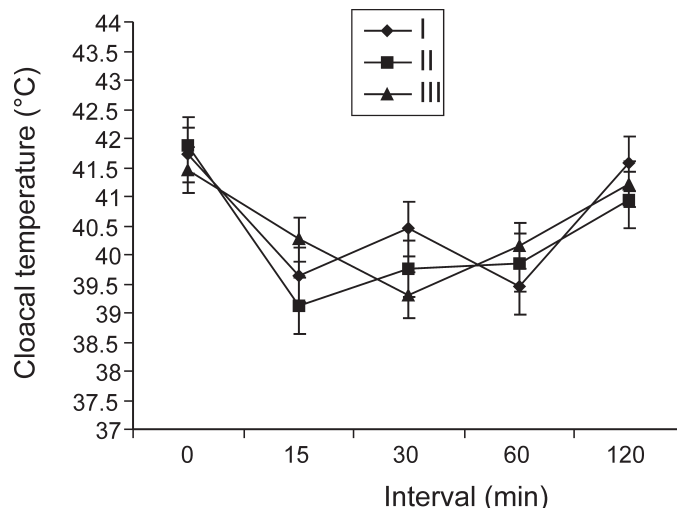Fig. 2: **Mean of recovery time from anaesthesia in three groups of birds.**

Fig. 3: **Cloacal temperature** (mean ± SE) **at different intervals in three groups of birds.**

respiration rate was significantly (P = 0.028) higher than baseline values at the 30-min interval. Later, it gradually decreased at the 60- and 120-min intervals. A similar trend was also observed in Group III birds (Fig. 4). The heart rate of Group I birds showed significant (P < 0.05) depression from baseline values at different time intervals. In the Group II, heart rate was significantly (P < 0.05) higher from the baseline value at the 15-, 30- and 60-min intervals. The post-anaesthetic heart rate of the midazolam group (III) of birds fluctuated non-significantly at different intervals (Fig. 5).

Blood glucose concentrations did not vary significantly from the pre-anaesthetic value in response to any anaesthetic regime at any time, although, in all

groups, non-significant hypoglycaemia was observed. The average pre-anaesthetic blood glucose values were 230 ± 14, 244 ± 18 and 225 ± 22 mg/dℓ for the xylazine-ketamine, diazepam-ketamine and midazolam-ketamine regimes, respectively. At the 120-min interval the blood glucose values were 215 ± 16, 226 ± 22 and 210 ± 20 mg/dℓ, respectively.

The haemoglobin values (g/dℓ) decreased significantly (P < 0.05) in Groups II and III at 1 h after induction of anaesthesia (Table 1). A significant decrease (P = 0.026) in blood pH at the 30-min interval followed by a significant rise (P = 0.033) after 1 h was observed in Group I, while a significant decrease (P = 0.024) at 1 h after induction of anaesthesia was recorded in Group II. The TCO$_2$ values in

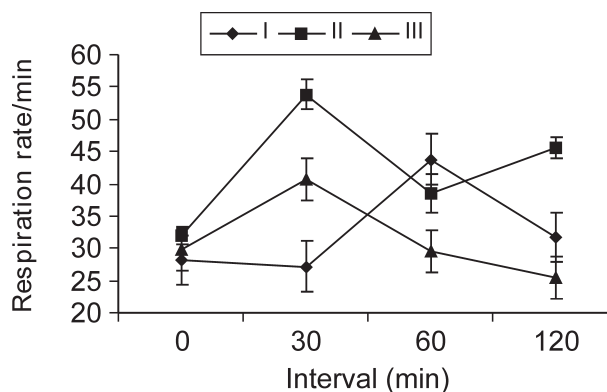Fig. 4: **Respiration rate** (mean ± SE) **at different intervals in three groups of birds.**

Groups I and II fluctuated non-significantly throughout the observation period, whereas in the Group III, the TCO_2 value rose significantly ($P = 0.036$) 30 min after induction of anaesthesia. The pCO_2 value in all the three groups increased significantly ($P < 0.05$) from the baseline value 30 min after induction of anaesthesia, thereafter it decreased at 60 min. The pO_2 values in all the three groups decreased at both the 30- and 60-min intervals; however, this reduction was significant ($P < 0.05$) only at the 30-min interval in Groups II and III. The SO_2 values (%) were significantly ($P < 0.05$) reduced at the 30-min interval in the Groups II and III (Table 1).

The Na+ concentration (mmol/ℓ) decreased from the baseline values in all the three groups of birds at the 30- and 60-min intervals (Table 1), but the reduction was significant ($P < 0.05$) only in Groups I and III at 60 min. Similarly, a reduction in K^+ concentration (mmol/ℓ) was observed in all three groups and the decrease was significant ($P < 0.05$) in Group II (at 30 and 60 min) and Group III (at 60 min). The Cl^- concentration (mmol/ℓ) decreased significantly ($P = 0.044$) at the 60-min interval in Group II, whereas it increased significantly ($P = 0.018$) at same interval in Group III. The blood Ca^{++} concentration decreased significantly ($P = 0.026$) in Group III at 60 min after anaesthetic induction. A significant ($P = 0.030$) reduction in HCO_3^- concentration was observed at the 60-min interval in Group II, whereas, it increased significantly ($P < 0.05$) at the 30-min interval in Group III (Table 1).

DISCUSSION

Onset of sedation and analgesic effects after xylazine-ketamine administration was rapid compared to the diazepam-ketamine and midazolam-ketamine combinations. In Groups I and II the induction was smooth except for occasional head shaking. The toe-pinch reflex was decreased in all three groups after administration of anaesthesia; however, it was completely absent in Group I within 10 min, whereas in the other two groups of birds it decreased but had not completely disappeared at the 20-min interval. Depression of pinprick response at various parts of the body has been reported after xylazine-ketamine administration in cattle[33] and diazepam-ketamine in horses[30]. A number of sites, including the supraspinal and spinal sites, modulate the transmission of nociceptive signals in the CNS. The alpha₂-agonists may act on any of these sites to reduce nociceptive transmission, leading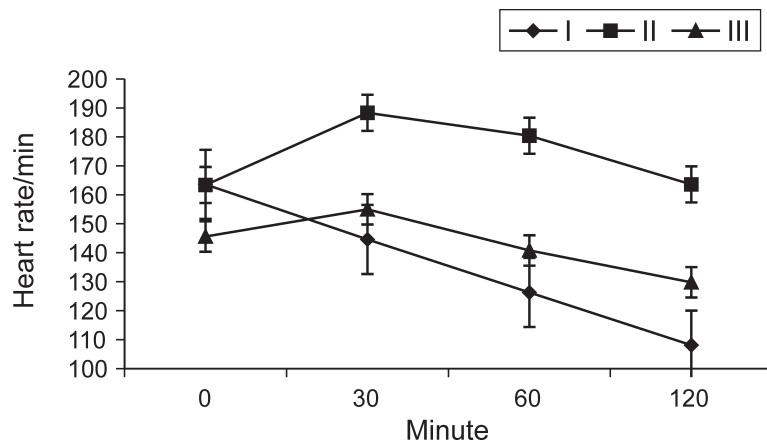 to analgesia[1]. Analgesia is also thought to be the result of stimulation of central and peripheral α-receptors *via* opiate pathways[39]. A combination of xylazine and ketamine does appear to improve the surgical analgesia produced by the latter. Opioid analgesics produce analgesia though opioid receptors present primarily in the CNS[4,16].

Muscle relaxation was rapid and excellent in Group I as evidenced by easy plucking of abdominal feathers and no resistance to opening the jaw, followed by Group II; however, it was poor in Group III. The benzodiazepines provide muscle relaxation when used in conjunction with

Fig. 5: **Heart rate** (mean ± SE) **at different intervals in three groups of birds.**

Table 1: **Effect of pre-anaesthetic xylazine, diazepam and midazolam in combination with ketamine anaesthesia on acid-base parameters** (mean ± SE) **of White Leghorn adult cockerels.**

Parameters	Group	Drug	Baseline	30 min	60 min
Haemoglobin (Hb) (g/dℓ)	I	X+K	11.7 ± 0.27	11.3 ± 0.74	$_Y$11.06 ± 0.33
	II	D+K	11.53 ± 0.52^b	10.38 ± 0.25^b	$_X$8.34 ± 0.05^a
	III	M+K	11.67 ± 0.36^a	11.29 ± 0.28^{ab}	$_Y$10.78 ± 0.19^b
Blood pH	I	X+K	7.44 ± 0.01^b	7.36 ± 0.02^a	$_Y$7.52 ± 0.03^c
	II	D+K	7.46 ± 0.01^b	7.44 ± 0.14^b	$_X$7.38 ± 0.03^a
	III	M+K	7.46 ± 0.01	7.42 ± 0.30	$_X$7.44 ± 0.01
T CO_2 (mmol/ℓ)	I	X+K	25.98 ± 1.48	26.63 ± 1.45	26.82 ± 1.93
	II	D+K	25.93 ± 0.83^{ab}	27.77 ± 1.41^b	24.21 ± 0.35^a
	III	M+K	24.11 ± 0.75^a	26.53 ± 0.45^b	23.65 ± 0.23^a
PCO_2 (mmHg)	I	X+K	36.82 ± 2.61^a	44.33 ± 3.78^b	38.09 ± 2.98^a
	II	D+K	33.43 ± 0.85^a	40.77 ± 2.19^b	37.08 ± 0.28^{ab}
	III	M+K	33.69 ± 1.77^a	39.55 ± 0.45^b	35.19 ± 0.51^a
PO_2 (mmHg)	I	X+K	$_x$33.21 ± 3.55	$_x$30.95 ± 3.56	25.90 ± 4.49
	II	D+K	$_{xY}$35.02 ± 1.47^b	$_Y$31.04 ± 2.33^c	27.99 ± 0.15^a
	III	M+K	$_Y$41.24 ± 1.33^b	$_{xY}$35.51 ± 2.55^a	33.12 ± 0.30^a
SO_2 (%)	I	X+K	$_x$47.44 ± 5.78	48.21 ± 5.83	$_x$44.48 ± 6.77
	II	D+K	$_x$65.04 ± 2.25^b	52.14 ± 4.29^a	$_Y$57.32 ± 0.34^{ab}
	III	M+K	$_Y$67.02 ± 2.15^a	56.78 ± 4.79^b	$_{xY}$54.83 ± 0.24^b
Na^+ (mmol/ℓ)	I	X+K	142.20 ± 2.22^b	137.40 ± 2.16^{ab}	$_x$133.10 ± 1.79^a
	II	D+K	144.80 ± 2.06	141.30 ± 0.91	$_z$141.10 ± 0.82
	III	M+K	141.50 ± 0.72^b	139.30 ± 0.91^{ab}	$_Y$137.60 ± 0.62^a
K^+ (mmol/ℓ)	I	X+K	5.21 ± 0.68	$_Y$4.99 ± 0.46	$_z$4.99 ± 0.12
	II	D+K	4.83 ± 0.35^b	$_x$4.08 ± 0.20^a	$_Y$4.13 ± 0.12^a
	III	M+K	4.30 ± 0.13^b	$_x$4.05 ± 0.05^b	$_x$3.72 ± 0.04^a
Cl^- (mmol/ℓ)	I	X+K	107.10 ± 1.16	$_x$106.20 ± 1.53	$_x$104.70 ± 0.56
	II	D+K	108.30 ± 0.93^{ab}	$_Y$111.50 ± 2.24^b	$_x$105.80 ± 1.16^a
	III	M+K	106.70 ± 0.56^a	$_{xY}$106.80 ± 0.81^a	$_Y$116.70 ± 1.17^b
Ca^{++} (mmol/ℓ)	I	X+K	0.742 ± 0.06	$_x$0.64 ± 0.05	$_{xY}$0.68 ± 0.06
	II	D+K	0.837 ± 0.08	$_Y$0.877 ± 0.09	$_Y$0.748 ± 0.03
	III	M+K	0.666 ± 0.02^b	$_{xY}$0.698 ± 0.02^b	$_x$0.583 ± 0.09^a
HCO_3^- (mmol/ℓ)	I	X+K	$_Y$24.80 ± 1.43	25.19 ± 1.37	26.62 ± 1.78
	II	D+K	$_Y$25.15 ± 0.79^b	26.95 ± 1.39^b	22.36 ± 0.39^a
	III	M+K	$_x$21.90 ± 0.08^a	24.02 ± 0.45^b	22.65 ± 0.39^{ab}

X = xylazine, D = diazepam, M = midazolam and K = ketamine.
a, b, c – means bearing different superscripts in a row differ significantly ($P < 0.05$).
X, Y, Z – means bearing different subscripts in a column differ significantly ($P < 0.05$).

ketamine[22,40]. The effect of muscle relaxation may be attributed to inhibition of intraneural transmission of impulses in the CNS.

No remarkable events occurred during the recovery phase of the birds, regardless of the anaesthetic regimens used. Muscle tremors, which were unrelated to painful stimulation, and flapping of wings, were common during recovery from ketamine-only anaesthesia in chickens[31]. Diazepam and midazolam can reduce anxiety during anaesthetic induction and recovery. The sedative effect of these drugs is evident during recovery, which is slow and smooth[40,43]. Alpha$_2$-adrenergic agonists (xylazine) are usually used in combination with ketamine. These drugs provide muscle relaxation, analgesia and sedation during the peak effect of the drug, along with smooth induction and recovery, whereas ketamine alone causes rough recovery in birds[35]. Ketamine alone is rarely used in birds because it is associated with poor muscle relaxation, muscle tremors, myotonic contractions, opisthotonus and rough recoveries[10,38]. Paul-Murphy and Fialkowski[35] recommended that ketamine not be used alone in birds and should be combined with benzodiazepines or alpha$_2$-adrenergic agonists to improve relaxation and depth of anaesthesia.

Ketamine produces profound analgesia without muscle relaxation, salivation and mild respiratory depression in animals[13]. Ketamine is used in combination with drugs such as the benzodiazepines (diazepam or midazolam) and/or α_2-adrenoceptor agonists (xylazine) in order to reduce the dose of ketamine, improve muscle relaxation and to increase the effectiveness of the dissociative agent as an anaesthetic[13]. The synergic action of the combination of xylazine with ketamine produces a smooth induction and improved muscle relaxation, without difficulties in recovery due to a residual ketamine effect in birds[12]. Petruzzi et al.[36] found 18.5 mg/mℓ ketamine and 1.5 mg/ml xylazine to be effective in raptors. Xylazine-ketamine given intramuscularly (1–10 mg/kg) rapidly induced a consistent level of anaesthesia (induction time 5.4 ± 1 min; duration 109 ± 25.4 min) in Turkey vultures[2].

Diazepam improved muscle relaxation, anaesthetic duration and recovery. Surgical anaesthesia was not as good as with the xylazine-ketamine combination, but adverse cardiopulmonary effects were less. Chistensen et al.[10] used this combination in same route and dose and observed rapid tranquillisation and loss of rigidity reflex, with recovery in 90–100 min. They observed behavioural changes like opisthotonus and short-term myotonic limb contractions during anaesthesia of birds, which was also observed in this study. A combination of diazepam and ketamine given intravenously was successfully utilised to induce anaesthesia for various surgical procedures in raptors[37]. Similar to our study, prolonged recovery was also found in pigeons given diazepam-ketamine anaesthesia[26].

Laweighton[21] reported that diazepam or midazolam are good combinations with ketamine anaesthesia in birds, which allow a smooth induction and recovery compared with ketamine by itself. The benefit of midazolam is that it can be mixed in the same syringe as ketamine, while diazepam has to be given as a separate injection. Mandelker[29] considered these combinations as the most effective anaesthesia in birds for diagnostic procedures. Midazolam at 2.0 mg/kg i.m. in Canada geese induced moderate sedation 15 and 20 min after administration of the drug; however, it was sufficient for performing diagnostic procedures, with minimal cardiopulmonary changes[43]. However, in this study, the midazolam-ketamine combination did not prove as effective as either the xylazine-ketamine or the diazepam-ketamine combinations for anaesthesia in chickens.

Body temperature began to drop within 15 min in all three groups after administration of three different ketamine combinations. However, it returned to normal after the 120-min interval in Groups I and III, but not in Group II. Hypothermia was significant in Group II and may have been due to the additive effect of the drugs. Reduction in temperature may be attributed to an inhibitory effect of the drugs on metabolism, leading to a decrease in metabolic rate, which finally causes inhibition of skeletal muscle activity. Varner et al.[44] reported similar results after administration of xylazine-ketamine and diazepam-ketamine combinations for anaesthesia in chickens. Among the three groups, respiratory depression was pronounced in the xylazine-ketamine-anaesthetised birds. Xylazine is well known to cause profound respiratory depression due to a direct depressive effect of the drug on respiratory centres[3,4,16], although this effect can be reversed with intravenous injection of yohimbine[12] or tolazoline[19]. Ketamine with xylazine given to chickens can result in anaesthetic mortality at doses below what is necessary for induction of general anaesthesia[44]. The chickens anaesthetised with xylazine-ketamine had depression of the heart rate during the entire 120-min observation period. However, anaesthesia using either diazepam-ketamine or midazolam-ketamine resulted in early tachycardia followed by a normal base value after the 120-min interval. Several mechanisms contribute to the alpha$_2$-agonist (xylazine)-induced bradycardia, which includes decreased sympathetic outflow from the CNS, inhibition of noradrenaline release from sympathetic nerve terminals, direct depression of cardiac pacemaker and conduction tissue, increased vagal tone and direct increase in the release of acetylcholine from parasympathetic nerves in the heart[32]. Xylazine-ketamine anaesthesia caused post-operative depression that may result in the bird being unable to perch properly or be unable to feed, leading to bradycardia, hypothermia, hypoglycaemia and even death[20]. In our study, post-operative bradycardia was observed in the Group I birds, but no death was recorded in any group. Varner et al.[44], however, observed unaffected heart rate during xylazine-ketamine anaesthesia in chickens. Initial increase in heart rate in Groups II and III may be due to the action of ketamine in the CNS, which causes an overflow of increased electrical activity in the limbic hypothalamic centres of the autonomic nervous system via medullary centres. Chistensen et al.[10] used similar doses of diazepam-ketamine anaesthesia in the domestic fowl and observed stable blood pressure, body temperature and respiration rate.

Blood sugar level did not vary significantly from the baseline value in response to any anaesthetic regime at any time as observed by Varner et al.,[44] who administered xylazine-ketamine, diazepam-ketamine and isoflurane anaesthesia in chicken. However, in all three groups of birds, a non-significant hypoglycaemia was observed. Under anaesthesia, hypoglycaemia may manifest as non-responsive bradycardia, hypotension, and pulmonary dilation[4,16]. Birds are very prone to hypoglycaemia when anaesthetised[21].

The effect of different combination of ketamine anaesthesia on different electrolytes such as sodium, potassium and chloride in birds has not yet been studied. In general, none of the groups showed significant differences in electrolyte values from baseline during anaesthesia. Although, there were some significant alterations in some groups at particular intervals, all these values remained within the normal physiological limit.

Reduction in values of haemoglobin (Hb) of variable degrees was recorded in all the three groups. Pooling of the circulating blood cells in the spleen or other reservoirs secondary to decreased sympathetic activity may explain the

decrease in the values of Hb, as reported with other tranquillisers as well[41]. Cross *et al.*[11] also reported reduction in values of Hb following administration of xylazine sedation in red deer. The decrease in Hb levels during the period of anaesthesia or sedation may also be due to shifting of fluid from the extravascular compartment to the intravascular compartment[45] in order to maintain normal cardiac output in the animal.

The measurement of blood gas values and pH are useful for the evaluation of ventilation, oxygen transport and delivery, and metabolic status. Blood gas values in birds are corrected to body temperature for easy interpretation. Blood gas values of birds are similar to those obtained in mammals[42]. In this study both the pCO_2 and TCO_2 values increased in all three groups of birds 30 min after induction of anaesthesia, then it decreased towards base values after the 60-min interval. Increased pCO_2 (hypercapnia) is a direct consequence of hypoventilation during anaesthesia. Hypercapnea in birds during anaesthesia may cause stimulation of the sympathetic nervous system, increased blood pressure and cardiac output[13]. A state of hypercapnea was more prominent in Groups II and III than in Group I. The partial pressure of oxygen/oxygen tension (pO_2) decreased in all three groups after induction of different combinations of ketamine anaesthesia; however, this hypoxaemia was significant in Groups II and III after 30 min of induction of anaesthesia. The hypoxaemia that developed in these birds during anaesthesia might be due to hypoventilation when breathing air. A non-significant increase in HCO_3^- concentration was observed in Groups I and II after 30 min of induction of anaesthesia; however, it returned towards baseline values after 60 min. The SO_2 values decreased significantly at 30 min in Groups II and III, and then it increased non-significantly in Group II after 60 min of observation. The SO_2 values reduced non-significantly during the whole period of anaesthesia in the ketamine-xylazine group. The fluctuation of HCO_3^- and SO_2 values in different intervals was within the physiological limit and these changes did not significantly affect the anaesthetic response of the birds.

An increase in $PaCO_2$ and decreased PaO_2 has been seen following ketamine administration in the cat, along with a fall in pH, reflecting a shift towards metabolic and respiratory acidosis[15]. In Pekin ducks, xylazine-ketamine i.v. produced respiratory depression and acidaemia and hypoxaemia[23], which was similar to this study. In Red-tailed hawks, xylazine-ketamine i.v. also induced bradypnoea,

hypoventilation and bradycardia[12] as observed in this study. However, Kollias and McLeish[18] reported that ketamine alone did not significantly affect arterial blood gas or acid-base values in Red-tailed hawks at a dosage of 30 mg/kg i.m.

CONCLUSION

Among the three different premedicants of ketamine anaesthesia, the xylazine-ketamine combination induced anaesthesia within 3 min with excellent analgesia and muscle relaxation. Surgical plane of anaesthesia was achieved within 10 min of induction of xylazine-ketamine anaesthesia, whereas the diazepam-ketamine and midazolam-ketamine combinations failed to produce a surgical plane of anaesthesia up to 20 min after induction. Acid base and blood electrolytes did not cause any significant adverse effects on the birds during the course of anaesthesia.

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