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The effects of ketamine-midazolam and isoflurane induction along with or without butorphanol premedication in birds

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Abstract
This study aimed to evaluate the comparative effects of ketamine-midazolam combination and isoflurane induction agents along with or without butorphanol premedication in birds. In this study, birds (N=24) were selected randomly and divided into 4 groups. In present study, ketamine-midazolam combination and isoflurane were used as induction agents, with and without butorphanol premedication in birds. All birds were maintained by isoflurane. Different physiological parameters were evaluated, namely, cloacal temperature, heart rate, respiratory rate and SpO_2 were recorded at 0, 10, 20 min. and at a recovery time. The quality of anesthesia was assessed on the basis of induction time & quality, analgesia, muscle relaxation, body reflexes, recovery time & quality, sitting, standing and complete recovery time. Shorter mean induction time was observed into ketamine-midazolam induction agents as compared to isoflurane agents. Quality of induction was observed to be excellent to the tune of 100% in the birds under Group-I. The mean±SE values of sitting, standing and complete recovery time was recorded to be lower in birds induced with isoflurane induction as compared to ketamine-midazolam combination, with the differences being significant ($P<0.05$) while comparing between Group-I vs. III and Group-II vs. IV.

Keywords: birds, inhalation, injectable, isoflurane, ketamine-midazolam

Introduction

Avian probably the most easily recognized of all animal species. There are many obvious differences in size, ranging from the humming birds to the ostrich in varying forms of the bill and in the color and profusion of the plumage occurring in the different species of bird[3]. Birds have unique anatomical and physiological characteristics that have significant impacts on anesthesia [6]. Ornithological research in the field and laboratory may often require the use of anesthesia [11]. Understanding and knowing the distinctive features of the cardio respiratory system of birds is important in terms of the method of administering anesthetics and selecting suitable anesthetics [1].

Butorphanol is a mixed agonist/antagonist opioid that has low activity at mu receptors and strong agonist activity at kappa-receptors which has lead to suggestions that it is an appropriate opioid for avian species based on receptor selectivity. Adverse effects seen in mammals, such as dysphoria, have not been reported in avian species [18]. It exerts its agonistic effect on kappa receptors, which induce analgesia and has antagonistic effects on mu receptors, which are responsible for opioid induced respiratory depression [2].

Ketamine is a dissociative anesthetic agent leading to CNS depression and lack of pain sensation. It was frequently used in domestic species [10]. Midazolam is a short acting water soluble sedative-hypnotic that belongs to benzodiazepine group of drugs. It has shorter onset and duration and minimal cardiopulmonary depression [5]. Ketamine-midazolam combination produces adequate sedation and analgesia in parakeet studies [20]. Combinations of ketamine and benzodiazepines were administered to improve muscle relaxation, depth of anesthesia and quality of recovery [6].

Isoflurane is an anesthetic of choice in birds because of rapid induction, rapid recovery and minimal myocardial depressant effect. Isoflurane is reported to provide less arrythmogenic effects as compared to halothane [15]. Isoflurane do not potentiate epinephrine induced cardiac arrhythmias [9].

Materials and Methods

This study was conducted in the Department of Veterinary Surgery and Radiology, College of Veterinary Science and A. H., AAU, Anand-388 001. In the present study, injured birds (N=24) were selected and divided into four groups. In Group-I (N=6) butorphanol tartrate @ 1.5 mg/kg, intramuscular (IM) was given 10 minutes before anesthesia followed induction with ketamine-midazolam combination (@ 25 mg/kg and 0.5 mg/kg, respectively) and maintenance with isoflurane (@ 2.5%). In Group-II (N=6), anesthesia was induced by ketamine-midazolam combination (@ 25 mg/kg and 0.5 mg/kg, respectively) and maintenance with isoflurane (@ 2.5%). In Group-III (N=6) butorphanol tartrate @ 1.5 mg/kg, IM was given 10 minutes before anesthesia followed by induction (@ 4%) and maintenance (@ 2.5%) with isoflurane. In Group-IV (N=6), anesthesia was induced (@ 4%) and maintained (@ 2.5%) with isoflurane. Mask induction was performed by modified custom made face masks in the all birds under Groups-III and IV. Endotracheal intubation with uncuffed endotracheal tube was performed immediately after induction. Physiological parameters were recorded *i.e.*, cloacal temperature, heart rate, respiratory rate and SpO_2. The quality of anesthesia was assessed by the induction time & quality, analgesia, body reflexes, muscle relaxation, recovery time & quality, sitting time, standing time and complete recovery time.

Fig 1: Comb Duck intubated by uncuffed

Results

Sedation of milder degree was observed after intramuscular administration of butorphanol tartrate in the birds. Ketamine-midazolam combination produced smooth and successful induction of anesthesia in Group-I and II. Larger sized avian patients, induced anesthesia using a combination of ketamine and midazolam, covered under the group evinced formation of mucus plug and salivation. However, birds having smaller size under these groups had a minor degree of salivation and minute quantity of mucus secretion during induction. Mask induction was carried out in avian patients (N=12) with 4.0% isoflurane in group-III and IV, while oxygen flow rate was kept at 0.5 to 1.5 liter/minutes depending on size of avian patients and tidal volume. Mild and severe degree of struggling was shown by the avian patients during initial stages of induction of anesthesia using mask for isoflurane under Groups-III and IV, respectively. All avian patients were induced safe and successful. Formation of salivation and mucus plug were not observed, when avian patients induced by isoflurane and with or without premedication in avian patients.

Fig 2: White Goose induced by face mask

Table 1: Mean (±SE) induction time, recovery time, sitting time, standing time and complete recovery time of anesthesia in avian patients (N=24)

Groups (N=6, each)	Group-I	Group-II	Group-III	Group-IV	LSD*
Induction Time*(sec.)	$150.00{\pm}25.69^{d}$	$190.00{\pm}10.00^{bdc}$	$230.00{\pm}32.55^{bac}$	$280.00{\pm}25.29^{a}$	71.74
Recovery time*(sec.)	$310.00{\pm}42.19^{a}$	$270.00{\pm}33.76^{ba}$	$220.00{\pm}42.89^{bdac}$	$190.00{\pm}28.63^{bdc}$	90.27
Sitting time* (sec.)	$620.00{\pm}45.60^{a}$	$590.00{\pm}36.05^{ba}$	$380.00{\pm}42.89^{dc}$	$340.00{\pm}36.87^{d}$	118.54
Standing time* (sec.)	$870.00{\pm}72.24^{a}$	$840.00{\pm}40.98^{a}$	$590.00{\pm}39.24^{bcd}$	$510.00{\pm}55.31^{cd}$	163.32
Complete recovery time* (min.)	$35.83{\pm}2.13^{a}$	$32.50{\pm}1.72^{ba}$	$25.83{\pm}1.24^{dc}$	$20.66{\pm}1.38^{e}$	4.60

*Least significant difference

*Means bearing different superscripts (a, b, c, d) in a horizontally differ significantly (P<0.05).

The mean time of induction in avian patients was found to be significantly (P<0.05) difference between Group-I vs. III and II vs. IV. Shorter mean induction time was observed into ketamine-midazolam induction agents as compared to isoflurane agents. The palpebral reflex was found when the level of induction was light and when induced with ketamine-midazolam combination. The feather plucking, pharyngeal and toe pinching reflexes were noticed when the birds were passing through the light plane of anesthesia using isoflurane agents for induction.

Table 2: Grading of quality of induction of anesthesia in avian patients (N=24)

Quality	% of Induction	Ketamine-midazolam induction		Pooled value	Isoflurane induction		Pooled Value
		Group-I	Group-II		Group-III	Group-IV	
Excellent	54.16 (13)	100.00 (06)	83.33 (05)	91.66 (11)	33.33 (02)	-	16.66 (02)
Very Good	8.33 (02)	-	16.66 (01)	8.33 (01)	16.66 (01)	-	8.33 (01)
Good	12.5 (03)	-	-	-	33.33 (02)	16.66 (01)	25.00 (03)
Fair	8.33 (02)	-	-	-	-	33.33 (02)	16.66 (02)
Poor	16.66 (04)	-	-	-	16.66 (01)	50.00 (03)	33.33 (04)
Total (N=24)	(100.00)(24)	6	6	-	6	6	

Figures in parenthesis include number of birds

Quality of induction was observed to be excellent to the tune of 100.00% in the avian patients under Group-I, indicative of identical induction results obtained by premedication with butorphanol tartrate followed by induction using ketamine-midazolam combination. Based on the details of the results presented in the Table 2, the anesthetic protocols comprising ketamine-midazolam combination seemed to be meritorious for induction of anesthesia in comparison to isoflurane anesthetics.

Table 3: Mean (±SE) cloacal temperature (˚F) following anesthesia using different protocols in avian patients (N=24)

Groups (N=6)	Time Intervals			
	0 min. (Mean±SE)	**10 min. (Mean±SE)**	**20 min. (Mean±SE)**	**Recovery (Mean±SE)**
Group-I	103.63±0.46^{bac}	102.93±0.57^{bac}	102.26±0.58^{bac}	100.31±0.53^{bdc}
Group-II	103.61±0.27^{bac}	102.98±0.24^{bac}	102.38±0.28^{ba}	100.56±0.32^{bac}
Group-III	103.91±0.29^{bac}	103.48±0.35^{ba}	103.01±0.29^{a}	101.16±0.28^{ba}
Group-IV	104.46±0.58^{a}	103.81±0.61^{a}	103.25±0.64^{a}	101.38±0.31^{a}

Least significant difference: 0 min.=1.24; 10 min.=1.32; 20 min.=1.22; R=0.95
Means bearing different superscripts (a, b, c, d) in a column differ significantly (*P*<0.05).

Table 4: Mean (±SE) heart rates (beats/minutes) during anesthesia using different protocols in avian patients (N=24)

Groups (N=6, each)	Time Interval			
	0 min.* (Mean±SE)	**10 min.* (Mean±SE)**	**20 min.* (Mean±SE)**	**Recovery* (Mean±SE)**
Group-I	123.00±17.40^{bc}	119.16±17.13^{a}	116.50±16.36^{a}	123.33±18.01^{a}
Group-II	167.66±14.91^{a}	132.33±14.65^{a}	126.16±13.51^{a}	126.83±14.14^{a}
Group-III	108.00±7.59^{c}	104.66±7.43^{a}	108.00±7.99^{a}	118.00±7.95^{a}
Group-IV	156.16±6.46^{ba}	126.33±5.76^{a}	121.50±5.45^{a}	136.00±5.62^{a}

Least significant difference: 0 min.=38.05, 10 min.=37.51, 20 min.=36.16 and R=37.89
*Means bearing different superscripts (a, b, c, d) in a column differ significantly (*P*<0.05).

Table 5: Mean (±SE) respiratory rate (breaths/minutes) during anesthesia using different protocols in avian patients (N=24)

Groups (N=6, each)	Time Interval			
	0 min.* (Mean±SE)	**10 min.* (Mean±SE)**	**20 min.* (Mean±SE)**	**Recovery* (Mean±SE)**
Group-I	28.33±2.82^{ba}	26.00±2.38^{ba}	21.83±2.34^{ba}	22.00±1.39^{bac}
Group-II	27.33±1.33^{ba}	24.66±1.22^{bac}	22.66±1.80^{ba}	22.16±1.70^{bac}
Group-III	25.83±2.31^{b}	23.50±2.56^{bac}	20.83±2.02^{bac}	22.50±1.14^{ba}
Group-IV	32.50±1.58^{a}	27.83±2.35^{a}	25.00±2.32^{a}	24.50±1.25^{a}

Least significant difference: 0 min.=5.52, 10 min.=5.50, 20 min.=5.09 and R=3.29
*Means bearing different superscripts (a, b, c, d) in a column differ significantly (*P*<0.05).

Table 6: Mean (±SE) SpO_2 (%) during anesthesia using different protocols in avian patients

Groups (N=6, each)	Time Interval			
	0 min.* (Mean±SE)	**10 min.* (Mean±SE)**	**20 min.* (Mean±SE)**	**Recovery* (Mean±SE)**
Group-I	82.33±0.71^{f}	73.83±0.70^{e}	65.50±1.31^{e}	80.00±0.73^{d}
Group-II	89.33±0.84^{cb}	83.16±0.65^{bcd}	76.00±1.12^{d}	83.00±1.52^{dc}
Group-III	85.66±0.49^{ed}	81.16±1.19^{d}	75.66±0.71^{d}	85.50±0.95^{bac}
Group-IV	89.66±0.88^{b}	85.00±0.44^{ba}	81.66±0.49^{ba}	87.16±0.79^{a}

Least significant difference: 0 min.=2.01, 10 min.=3.04, 20 min.=3.48 and R=3.27
*Means bearing different superscripts (a, b, c, d) in a column differ significantly (*P*<0.05).

The Mean±SE value of heart rates and respiratory rates in avian patients found to be differing non-significantly between Group-I vs. III and Group-II vs. IV. The mean±SE values of% SpO_2 values found in the birds induced for anesthesia using ketamine-midazolam and isoflurane induction agents varied significantly (*P*<0.05) at the time of recovery. Whereas, the mean SpO_2 value were recorded to be higher in the birds induced with isoflurane as compared to ketamine-midazolam combination. Adequate muscle relaxation and analgesia was observed during surgery in all avian patients.

Fig 3: Maintenance of anesthesia by isoflurane in Kite.

Table 7: Quality of recovery of avian patients from anesthesia (N=24)

Group No. (N=6, each)	I	II	III	IV
Quality				
Excellent	50.00 (3)	50.00 (3)	100.00 (6)	100.00(6)
Very good	33.33 (2)	33.33 (2)	-	-
Good	16.66 (1)	16.66 (1)	-	-
Fair	-	-	-	-
Poor	-	-	-	-

Figures in parenthesis include number of birds

The mean±SE values of time of recovery from anesthesia was recorded to be longer in avian patients under anesthetic protocol with ketamine-midazolam anesthetic induction as compared to isoflurane induction protocols, with the differences being non-significant. The present finding with regards to faster onset of recovery of birds from anesthesia in isoflurane anesthesia as compared to the birds recovered for injectable anesthesia can be attributed to lower solubility of anesthetic gas in the blood. Excellent quality of recovery of birds from anesthesia was recorded in all the birds covered under anesthetic groups-III and IV, where all the birds under different groups were induced and maintained by isoflurane anesthetics, with and without butorphanol tartrate premedication in avian patients. Avian patients induced for anesthesia by the combination of ketamine and midazolam and maintained with isoflurane had excellent, very good and good recovery in 50.00, 33.33 and 16.66% cases, respectively. The mean±SE values of sitting, standing and complete recovery time was recorded to be higher in avian patients induced with ketamine-midazolam combination as compared to isoflurane induction, with the differences being significant ($P<0.05$) while comparing between Group-I vs. III and Group-II vs. IV.

Discussion

Butorphanol tartrate is an opioid with mixed action and act as a µ-opioid antagonist and as a κ-receptor agonist. It is regarded as the drug of choice for treatment of pain in avian species [19]. In this study, the induction of anesthesia was found to be smooth and without any complications in the premedicated birds as compared to without premedicated birds. No befitting literature could be traced while screening the reference to substantiate the present findings.

In the present study, ketamine and midazolam combination produced fast and smooth induction of anesthesia in Group-I and II. The present findings corroborated well with the similar results reported by [20, 21] in birds. Combinations of ketamine and midazolam are administered to improve muscle relaxation, depth of anesthesia and quality of anesthesia. Midazolam produced minimal cardiovascular side effects and reversibility make ideal for administration in conjunction with either induction and maintenance anesthetics. Ketamine not be used alone in birds and should be combined with midazolam to improve muscle relaxation and depth of anesthesia [17].

In this study, shorter mean induction time was observed into induction along with ketamine-midazolam combination as compared to isoflurane. These findings corroborated well with the observations reported by [13, 8]. According to the results of our study, the ketamine-midazolam combination used as an induction agents, which produced 91.66% excellent quality of induction in birds. Ketamine-midazolam combination can be used for safe and effective induction agents in birds.

Ketamine produces profound analgesia without muscle relaxation, salivation and mucus secretion reported by [12] in white leghorn cockerels. The presence of palpebral reflex in the ketamine anesthetics was reported previously by [7, 4]. The present findings corroborated well with the observed in our study.

The mean±SE values of cloacal temperature was found to be comparatively higher at the time of recovery in the birds induced with isoflurane under groups-III and IV as compared to those of birds induced with ketamine-midazolam combination under groups-I and II, with the difference being non-significant between Group-I vs. III and II vs. IV. These findings corroborated well with the observations reported by [14, 6, 16]. Isoflurane can be attributed to lower solubility of anesthetic gas in the blood. Observations on the same line have also been reported by [6] in birds.

Conclusions

Ketamine-midazolam combination produced rapid, smooth and excellent quality of induction of anesthesia in avian patients as compared to isoflurane anesthetic agents. The quality of sedation, analgesia and muscle relaxation was observed to be quite satisfactory in all the birds induced with ketamine and midazolam combination, irrespective of premedication of birds with butorphanol tartrate. Birds induced with isoflurane anesthetic agents observed lower sitting, standing and complete recovery time as compared to ketamine-midazolam combination, where 100% of birds reported safe and excellent quality of recovery.

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