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Effects of zoletil, midazolam-ketamine and dexmedetomidine-ketamine on hemato-biochemical parameters in chickens

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Abstract
The purpose of this study was to document the hematological and biochemical changes that observed during anesthesia following the intramuscular administration of zoletil (15 mg/kg), midazolam (0.5 mg/kg) in combination with ketamine (40 mg/kg) and dexmedetomidine (5 µg) in combination with ketamine (20 mg/kg) in eighteen (18) White Leghorn chickens which were randomly allocated in three different groups. No significant differences were observed in the haemato-biochemical parameters except for decreased glucose values in all the three groups.

Keywords: Chickens, dexmedetomidine, ketamine, midazolam, zoletil

1. Introduction

Anaesthesia is essential for safe and effective handling of birds for any clinical examination or surgical procedure while minimizing stress, trauma or discomfort (Clarke *et al*., 2001) [4]. Zoletil is a non-opioid, non-barbiturate injectable anaesthetic which is a combination of equal concentrations of tiletamine and zolazepam. Tiletamine is a long-acting dissociative anaesthetic agent which is more potent than ketamine (Dugassa and Fromsa, 2018) [5]. Zolazepam is a sedative belonging to benzodiazepine group that provides anxiolysis, muscle relaxation as well as effective anticonvulsant effect. Midazolam is currently the most often prescribed benzodiazepine with a wide margin of safety. Midazolam is a water soluble and short acting benzodiazepine with sedative, muscle-relaxing, anxiolytic, amnestic and appetite-stimulating properties in birds (Araghi *et al*., 2016) [1]. Ketamine is a dissociative anaesthetic used to induce and maintain general anaesthesia. Ketamine has a high margin of safety and any negative effects won't manifest until up to 10 times the therapeutic dose for birds (Athar *et al*., 1996) [2]. Dexmedetomidine is analpha2 adrenoceptor agonist and active sterioisomer of the racemic mixture medetomidine commonly used as sedative and tranquilizer in veterinary (Clarke *et al*., 2001) [4]. Not much information is available about their effects on hematological and biochemical parameters. Therefore, the present study evaluated several hematologic changes during anesthesia after injectingzoletil, midazolam-ketamine and dexmedetomidine-ketamine in chickens.

2. Materials and Methods

Eighteen numbers of one year old male White Leghorn chickens with mean body weight 1.60±.03kg were used in this study. All the chickens were kept in uniform environmental and managemental condition. The chickens were housed in pairs in cages in a quiet room in the Department of Veterinary Surgery and Radiology, to avoid possible stress-inducing factors during the study and fed a commercial diet. The chickens had free access to food and water. The chickens were adapted for one week before the study and the experiment was carried out in an operation theatre having temperature controlled environment. The chickens were fasted for 3-6 hours before the anaesthetic trials. The chickens were randomly divided into three groups, *viz*., Group-A, B and C, comprising six chickens in each. Zoletil @ 15 mg/kg body weight was administered intramuscularly in Group A; midazolam @ 0.5 mg/kg combined with ketamine @ 40 mg/kg body weight was administered intramuscularly in Group B and dexmedetomidine @ 5 µg/kg in combination with ketamine @ 20 mg/kg body weight was administered intramuscularly in Group C. Blood samples were collected at 0 minutes (prior to administration of any anaesthetic drug), 30 and 40 minutes after administration of anaesthetics. Haematological parameters *viz*., haemoglobin (g/dL), total erythrocyte count (million/cu.mm) and total leucocyte count (thousand/cu.mm) were estimated using automatic haemato-analyzer. Blood glucose (mg/dL) was estimated using glucometer immediately after the collection of blood. Serum biochemical parameters *viz*., gamma glutamyltransferase (U/L) creatinine (mg/dl) and uric acid (mg/dL) were estimated by automatic biochemical analyzer. General Linear Model of one way and two way ANOVA based on Fisher's Least Significant Difference method was used to determine the significant difference among time points for different treatment groups as well as among treatment groups for different time points. The Duncan multiple range test was used for analyzing the significant values noticed in the ANOVA. Results are presented as mean ± SE and differences were considered significant when $p<0.05$. The data obtained were analyzed using SPSS version27.0.

3. Results

3.1 Haematological parameters

The haematological parameters were shown in Table 1. In Group A and C, the mean haemoglobin values increased non-significantly ($p>0.05$) throughout the period of observations whereas a non-significant ($p>0.05$) decrease in the haemoglobin values were recorded in Group B throughout the period of observations. In Group A, the total erythrocyte count increased non-significantly ($p>0.05$) at 30 minutes and then decreased non-significantly ($p>0.05$) at 60 minutes towards the baseline. In Group B, a non-significant increase ($p>0.05$) in total erythrocyte count were observed at 30 minutes and then decreased non-significantly at 60 minutes. In Group C, the total erythrocyte count increased non-significantly ($p>0.05$) throughout the observation period. In Group A and B, a non-significant ($p>0.05$) increase in the total leucocyte count were observed throughout the observation periods while in Group C, a non-significant ($p>0.05$) increase in total leucocyte count were reported at 30 minutes time interval and thereafter non-significant ($p>0.05$) decrease at 60 minutes towards the baseline values were observed. There was no significant ($p>0.05$) variation in mean haemoglobin, total erythrocyte and total leucocyte count at different time intervals between the Group A, B and C.

Table 1: Mean±SE values of haematological parameters at different time interval in chickens

Parameters	Group	0 minute	30 minutes	60 minutes	P Value
Haemoglobin (g/dL)	A	13.67±.55	13.77±.53	14.00±.47	.898^{NS}
	B	13.77±.39	13.17±.42	12.54±.45	.157^{NS}
	C	12.63±.36	13.22±.39	14.02±.50	.101^{NS}
	P Value	.167^{NS}	.597^{NS}	.071^{NS}	
Total Erythrocyte Count (million/cu.mm)	A	3.02±.17	3.28±.19	3.12±.12	.521^{NS}
	B	2.80±.18	3.24±.66	2.38±.28	.398^{NS}
	C	2.80±.08	2.91±.12	3.14±.11	.145^{NS}
	P Value	.087^{NS}	.777^{NS}	.927^{NS}	
Total Leukocyte Count (thousand/cu.mm)	A	15.93±.94	16.07±1.04	16.10±1.08	.993^{NS}
	B	14.97±1.86	15.67±2.13	17.12±1.51	.709^{NS}
	C	17.75±1.92	18.20±2.01	18.17±2.04	.984^{NS}
	P Value	.492^{NS}	.573^{NS}	.664^{NS}	

$p>0.05$= non-significant (NS).

3.2 Biochemical parameters

The biochemical parameters were presented in Table 2. The biochemical parameters values recorded before the administration of drugs did not show any significant variation among the groups. The GGT values in Group A, were observed to increase non-significantly ($p>0.05$) in at 30 minutes time period and thereafter decreased non-significantly at 60 minutes time interval towards the baseline values. In Group B, the GGT values increased non-significantly ($p>0.05$) throughout the period of observation. In Group C, the GGT values decreased non-significantly ($p>0.05$) at 30 minutes and thereafter increased non-significantly ($p>0.05$) at 60 minutes time interval. In Group A, a non-significant increase ($p>0.05$) in creatinine values were observed at 30 minutes time period and subsequently no significant variations were detected at 60 minutes observation. In Group B, the creatinine values did not show any significant variations ($p>0.05$). In Group C, the creatinine values increased non-significantly ($p>0.05$) at 60 minutes time period. In Group A and B, the glucose values decreased significantly ($p\leq0.01$) at 30 minutes time interval and thereafter increased significantly ($p\leq0.01$) at 60 minutes observation towards the baseline values. In Group C, the glucose level decreased significantly ($p\leq0.01$) at 30 minutes time interval and afterwards decreased non-significantly ($p>0.05$) at 60 minutes observation. Between the Group A, B and C, there was no significant ($p>0.05$) differences at 30 minutes time interval but significant ($p\leq0.01$) variations in glucose values were observed at 60 minutes time intervals. In Group A, the level of uric acid raised non-significantly ($p>0.05$) at 30 minutes time period and thereafter, elevated significantly ($p\leq0.01$) at 60 minutes time interval. In Group B, the uric acid values increased non-significantly ($p>0.05$) throughout the period of observation.In Group C, the uric acid values increased non-significantly at 30 minutes time interval and then decreased non-significantly ($p>0.05$) at 60 minutes time period towards the baseline values. However, the values were within the physiological range. There were mean significant ($p\leq0.05$) difference between the groups at 30 minutes time interval but no significant variations ($p>0.05$) at 60 minutes observation.

Table 2: Mean±SE values of biochemical parameters at different time interval in chickens

Parameters	Group	0 minute	30 minutes	60 minutes	P Value
Gamma glutamyltransferase (U/L)	A	45.67±.61	52.67±1.69	47.33±3.78	.136[NS]
	B	42.00±4.17	43.17±3.93	49.00±4.91	.493[NS]
	C	44.33±2.17	43.33±4.34	50.00±2.11	.281[NS]
	P Value	.640[NS]	.126[NS]	.882[NS]	
Creatinine(mg/dL)	A	0.15±.03	0.18±.04	0.18±.03	.746[NS]
	B	0.17±.03	0.17±.03	0.17±.03	1.0[NS]
	C	0.17±.03	0.17±.03	0.18±.03	.916[NS]
	P Value	.922[NS]	.930[NS]	.912[NS]	
Glucose (mg/dL)	A	204.33±2.44[a]	162.00±2.67[b]	175.50±2.60[cA]	.001**
	B	203.33±1.17[a]	150.67±1.12[b]	196.33±1.61[cB]	.001**
	C	206.50±4.39[a]	154.67±8.35[b]	134.50±9.01[bC]	.001**
	P Value	.748[NS]	.309[NS]	.001**	
Uric acid (mg/dL)	A	5.43±.02[a]	5.70±.19[aA]	6.23±.10[b]	.001**
	B	5.87±.41	6.13±.34[B]	6.55±.46	.503[NS]
	C	6.98±.66	7.28±.57[B]	7.27±.29	.904[NS]
	P Value	.069[NS]	.034*	.098[NS]	

*or $p \leq 0.05$ = significant at 5%, ** or $p \leq 0.01$ = significant at 1%, $p > 0.05$= non-significant (NS). Values in the same row and the same column with different superscripts i.e. small font and capital font respectively differ significantly.

4. Discussion

4.1 Haematological observations

In the present study, there were no statistically significant changes in the haemoglobin values, total erythrocyte count and total leucocyte count. Similarly, non-significant changes in haemoglobin values, total erythrocyte and total leucocyte count was observed by Li *et al.* (2012) [11] following tiletamine-zolazepam-xylazine-tramadol combination in cats. Non-significant change in haemoglobin values was observed byKumar *et al*. (2014) [10] after the administration of midazolam-ketamine in buffalo calves. Non-significantchange in the total leucocyte counts were also reported with medetomidine in pigeons (Sani and Onifade, 2012) [14]. During sedation and anaesthesia, pooling of circulating blood cells in the spleen and other reservoirs secondary to decreased sympathetic activity might be the reason for the change values in the blood parameters and also might be due to shifting of fluid from the extravascular compartment to the intravascular compartment with the aim of maintaining the normal cardiac output (Vasan *et al.,* 2006) [15].The effect of catecholamines on α-adrenergic receptors in the splenic capsule and the release of erythrocytes into the blood circulation caused an increase in the erythrocyte count, PCV, and Hb concentration during the capture in mammals. The spleen of the birds does not serve as a storehouse for erythrocytes and studies have demonstrated that they recover quickly from experimentally-induced blood loss (Lopez-Olvera *et al.,* 2007) [12]. Physical restraint might result in a rise in total erythrocyte count because it releases catecholamines, which cause the spleen to contract (Volpato *et al*., 2015) [16]. An increase in the total leucocyte count might occur in birds that have an excess of endogenous glucocorticoids because of the excitement brought on by handling (Jain, 1993) [8].

4.2 Biochemical observations

In the present findings, there were insignificant fluctuations in GGT values throughout the period of observation in Group A, B and C. Similar findings were also reported midazolam-ketamine in pigeons by Hajizadeh *et al*. (2018) [6]. It indicated that none of the drug used in this study leads to hepatic microsomal changes (Ismail *et al*., 2010) [7]. The serum creatinine values did not show any significant changes throughout the observation period and remained within the acceptable physiological limits. This result was in accordance with the findings of Ismail *et al.* (2010) [7] following xylazine–ketamine–diazepam anaesthesia in sheep and goats; Kumar *et al*. (2014) [10] following midazolam-ketamine in buffalo calves.The insignificant variations of creatinine values might be indicative of the short-term effect of the anaesthetic agents on the renal blood flow (Li *et al*., 2012) [11]. In Group A, B and C, the glucose level decreased significantly at 30 minutes time interval thereafter increased significantly at 60 minutes observation except in Group C, where the blood glucose level decreased insignificantly till 60 minutes observation. A decrease in blood glucose values were also reported with xylazine-ketamine, diazepam-ketamine, midazolam-ketamine combinations in chickens (Vasan *et al*., 2006) [15] and with ketamine-tramadol, ketamine-midazolam, ketamine-hyoscine, and ketamine-atropine in broiler chickens (Javdani *et al*., 2014) [9]. When under anesthesia, birds are particularly vulnerable to hypoglycemia (Vasan *et al*., 2006) [15]. When birds are subjected to stressors like restraint, they get excited causing release of catecholamines and the corticostrone from the adrenal cortex which aids in boosting metabolism (Javdani *et al*., 2014) [9]. A non-significant elevation in the uric acid values were recorded at 30 minutes in all the groups. In Group B and C, the uric acid values increased non-significantly and in Group A, the level of uric acid increased significantly at 60 minutes observationbut the uric acid values remained within the physiologicallimits for all the groups. Similarly, a non-significant variation in the uric acid values was observed by Camkerten *et al*. (2013) [3] following the xylazine-ketamine combinationin Bozova greyhounds.It seemed that none of the drugs used in the study had any detrimental effects on the kidney functions of the chickens.

5. Conclusions

The anaesthetic protocols used in this study did not show statistically significant effects on the studied hematobiochemical parameters in chickens except for the decreased glucose during anaesthesia and all the three protocolos are found to be safe for use in chickens.

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