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Comparative evaluation of clinical efficiency of intramuscular diazepam-ketamine, medetomidine-ketamine, and xylazine-ketamine anaesthesia in Ring-necked pheasants (*Phasianus colchicus*)

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Summary

Background: Several injectable anaesthetics and sedatives are used in various avian species for general anaesthesia. Birds are very sensitive animals and any mismanagement in a crisis can lead to immediate shock and death. Therefore, careful selection of the safest possible anaesthetic agent and dose is very important. **Aims:** The aim of this study was to examine the clinical efficiency of diazepam-ketamine (DK), medetomidine-ketamine (MK), and xylazine-ketamine (XK) combinations anaesthetic regimens in pheasants. **Methods:** Twenty-four pheasants were divided into three equal groups and received one of three anaesthetic combinations by intramuscular injections: 9.0 mg/kg diazepam and 150.0 mg/kg ketamine, 0.20 mg/kg medetomidine and 80.0 mg/kg ketamine, and 3.0 mg/kg xylazine and 80.0 mg/kg ketamine. Each pheasant was pre-medicated with sedative drugs and 5 min later, anaesthesia was induced with ketamine injection. **Results:** The weak time (2.50 ± 1.07 min; mean±SD) and down time (6.13 ± 1.25 min) were shortest in group XK. The sleep time was longest (73 ± 20.24 min) while the recovery time (157 ± 13.61 min) was shortest in group MK. Muscle relaxation was excellent during the anaesthesia in all groups. The recovery phase of the birds was uneventful. Heart rate (HR) in DK group was statistically higher than MK and XK groups. Body temperature (BT) decreased in all groups compared to baseline values and those of MK group were lower than DK and XK groups. Respiratory rate (RR) in XK group was significantly lower than DK and MK groups. **Conclusion:** In conclusion, the MK combination shows better anaesthetic outcome compared to DK or XK combinations in pheasants.

Key words: Diazepam, Ketamine, Medetomidine, Pheasant, Xylazine

Introduction

General anaesthesia is used for diagnostic or therapeutic purposes in birds (Sinn, 1994). As in other species, general anaesthesia in birds can be provided either by inhalational or injectable agents. Inhalant anaesthetic agents have the advantage of predictable and rapid changes in depth of anaesthesia, as well as minimal or no need for metabolic breakdown. However, the use of inhalant anaesthetics requires more precautions or attention in birds than mammals due to physiological and anatomical characteristics of birds. Another disadvantage is that this anesthetic regimen restricts surgical operations on the head, neck, and air sac (Hall *et al*., 2001; Gunkel and Lafortune, 2005; Lierz and Korbel, 2012).

Ketamine, a dissociative anaesthetic, has been recommended by many researchers as a suitable agent for many different bird species (Hall *et al*., 2001). However, ketamine is rarely used as a single agent because of poor muscle relaxation, induction of muscular tremors, myotonic contractions, opisthotonus, and rough recoveries (Gunkel and Lafortune, 2005; Lierz and Korbel, 2012). Therefore, according to various authors (Paul-Murphy and Fialkowski, 2001; Gunkel and Lafortune, 2005; Durrani *et al*., 2008; Lierz and Korbel, 2012) ketamine should not be used as a single agent and needs to be combined with benzodiazepines or alpha-2 adrenergic agonists to minimize the adverse effects, improve the relaxation, and the depth of anaesthesia.

Pheasants with injuries that require general anaesthesia for necessary treatment may be frequently presented to veterinarians. Practitioners face situations in which anaesthesia is required for surgical treatment of injured pheasants, where the most confusing part of the puzzle is the determination of the method and the dose to be administrated.

To our knowledge, there are no published reports describing the anaesthetic outcome of diazepam, medetomidine or xylazine in combination with ketamine in pheasants. The aim of this study was therefore to compare the clinical efficiency of three commonly used ketamine combinations as an anaesthetic regimen in the pheasants.

Materials and Methods

Animals and grouping system

In this study, a total of 24 healthy adult pheasants (*Phasianus colchicus*) aged between 8-12 months of both sexes were used. Pheasants were obtained from the Gelemen Pheasant Production Station, Samsun (41°13′ N, 36°28′ E). The study was carried out at the Physiology Department, Faculty of Veterinary Medicine,

Ondokuz Mayis University, Turkey. Pheasants received commercial feed mixtures and water *ad libitum*. This study was approved by the Animal Experimentation Ethics Committee at Ondokuz Mayis University (approval number: 2015/07).

The pheasants were divided into three groups considering their body weight (BW), with four males and four females in each group. The BW of the birds in group Diazepam + Ketamine (DK), Medetomidine + Ketamine (MK), and Xylazine + Ketamine (XK) were 1110 ± 71, 939 ± 130, and 1067 ± 47 g, respectively. There was no statistical difference among three groups for BW.

Anaesthetic methods

Pilot study

Initially, a pilot study was carried out to establish appropriate dose rates for each trial group. The birds were deprived of water and fed 30-60 min prior to sedative injections to minimize the risk of vomiting. To minimize stress, all the procedures were carried out in a quiet and dim room and birds' heads were covered with a thin cloth until full sedation was observed.

Minimal starting doses for the sedatives [Diazepam (D, Diazem, DEVA, Turkey, 10 mg/2 ml), medetomidine (M, Domitor, Orion Pharma, Finland, 1 mg/ml), and xylazine (X, Rompun, Bayer, Turkey, 20 mg/ml)], and ketamine (K, Ketalar, Pfizer, Turkey, 50 mg/ml) were determined by the evaluation of dosages applied for other bird species in the previous reports (Paul-Murphy and Fialkowski, 2001; Lumeij and Deenik, 2003; Uzun *et al*., 2003; Gunkel and Lafortune, 2005; Lierz and Korbel, 2012). The initial doses of anaesthetic combinations were: diazepam at 4 mg/kg/BW and ketamine at 60 mg/kg/BW for DK group, medetomidine at 0.2 mg/kg/BW and ketamine at 60 mg/kg/BW for MK group, and xylazine at 2 mg/kg/BW and ketamine at 60 mg/kg/BW for XK group. All drugs were diluted before use with sterile water to provide a suitable volume for accurate dosing (0.5-1.0 ml/bird). The sedative drugs were injected to the deep left pectoral muscles and 5 min later, ketamine was injected to the deep right pectoral muscles. The sedative and ketamine combinations were not injected at the same time to be able to observe the possible effects of sedatives alone (Uzun *et al*., 2003; Maiti *et al*., 2006; Mostachio *et al*., 2008).

The sedatives and ketamine doses were gradually increased until an adequate anaesthesia was provided. Adequate anaesthesia for this study was defined as the ability to place the bird in dorsal recumbency without the bird struggling for at least 30 min and lack of response to toe pinch. The doses which provided adequate anaesthesia for birds and an uneventful recovery were considered safe and were used in the main study.

Main study

The twenty-four birds without a history of drug administration were used for the main study. Sedative drugs and ketamine were administered to all birds in each group as described above. The drug combinations were injected as follows:

Group DK: Diazepam at 9 mg/kg and ketamine at 150 mg/kg

Group MK: Medetomidine at 0.20 mg/kg and ketamine at 80 mg/kg

Group XK: Xylazine at 3 mg/kg and ketamine at 80 mg/kg

Hearth rate (HR), respiratory rate (RR), and body temperature (BT) were recorded just before the sedative drug administration to determine base line values (time 0). Then the sedative drug was injected and all physiologic parameters and reflexive responses were recorded 4 min later to determine the effects of sedative drugs. Ketamine injections were administrated 5 min after sedative injections, and then all the parameters, except for electrocardiography (ECG), were recorded with 15 min intervals until the bird wakes up or up to 120 min. The ECG records were carried out at 30 min intervals for the HR calculation.

Electrocardiograms were recorded with a portable electrocardiograph (Cardiette, ar600adv, Italy). Animals were located on a rubber surface as reported in a previous study (Kaya and Soylu, 2013). The RR was determined by directly observing the movement of pectoral muscles. The BT was measured by placing a digital clinical thermometer into the cloaca.

In this study, the leg-withdrawal reflex after a toe pinch was used to assess the depth of anaesthesia. All body reflexes evaluated in this study were determined as described by Maiti *et al*. (2006). Briefly, to test the response to toe pinch pain reflex (TR), moderate pressure was applied with a haemostat to the middle toe and the subjective assessment of the response to external stimuli was scored at 0-2 scale. The degree of muscle relaxation was assessed by jaw reflex (JR) scored on a scale of 0-2. The degree of nictitating membrane reflex (NR) was scored on a scale of 0-2. Palpebral reflexes (PR) were tested by touching the eye's periphery with a cotton tip bar. Presence or lack of the reflexes were scored as (+) or (-), respectively.

In addition, the weak time, down time, sleep time, and recovery time were recorded during the experiment in all groups. Weak time was determined as the period from the injection time of the drug to the time when the bird showed signs of incoordination. The time from the administration of anaesthetic drug to sternal/lateral recumbency was considered as the down time. Sleep time was recorded as the period spent by the bird in lateral/sternal recumbency. The recovery time was defined as the period starting from the emergence from anaesthesia to the moment when the bird was able to walk unassisted and to hold the head in normal, alert position.

During the study, after ketamine injection, apnoea was observed in 1, 2, and 5 birds in groups DK, MK and XK, respectively. Therefore, we had to apply resuscitation to 3 birds in XK group. Other cases were resolved unaided or by slightly changing the positions of pheasants' head or neck.

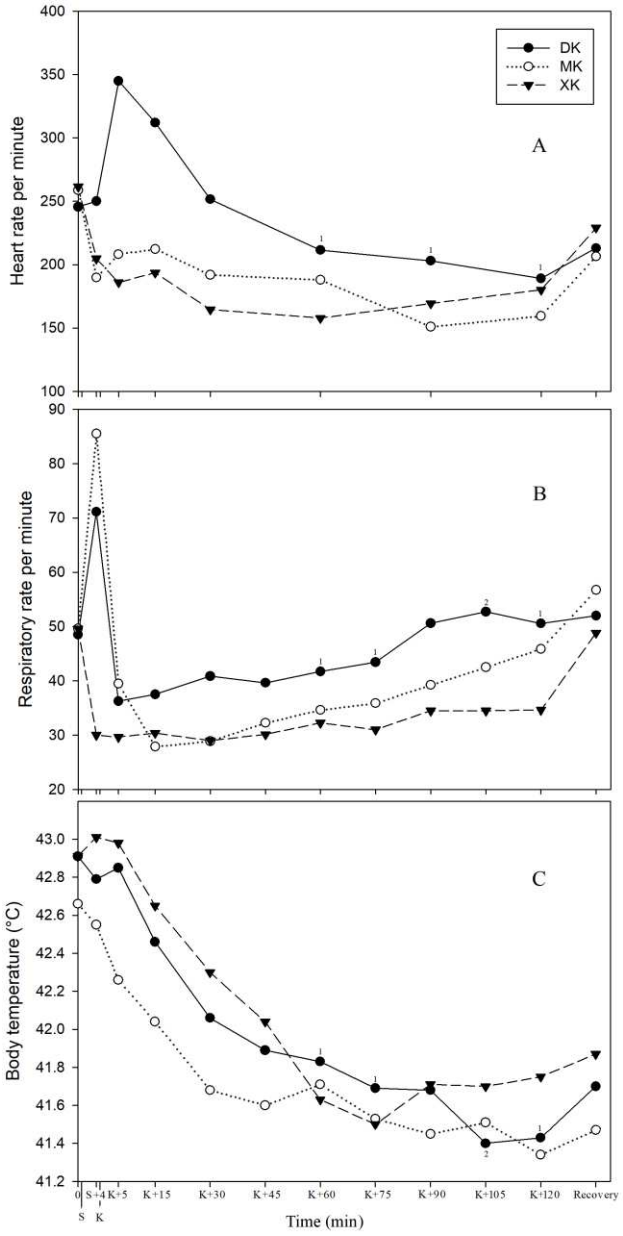

Fig. 1: Physiological parameters: the mean of heart rate (**A**), respiratory rate (**B**), and body temperature (**C**) of 3 groups of 8 pheasants. Group DK received diazepam (9.0 mg/kg IM) and ketamine (150 mg/kg IM) group, MK received medetomidine (0.2 mg/kg IM) and ketamine (80 mg/kg IM), and group XK received xylazine (3.0 mg/kg IM) and ketamine (80 mg/kg IM). S: Time of sedatives injection, K: Time of ketamine injection (5 min after S). The numbers indicate the missing data for that measurement time. The standard deviations were presented as positive bars for DK and XK groups, a negative error bar for MK group in one direction to avoid overlapping

Statistical analysis

The recorded data were analyzed using SPSS Statistical Package (ver. 21) and expressed as mean±SD. The GLM Univariate Analysis of Variance procedure was used to determine effect of drug (as fixed factor), time (as random factor) and drug × time (as covariate) on HR, RR, and BT. One way ANOVA was also used to compare the reflexive responses among groups. Tukey's post-hoc multiple comparison test was used to determine where there was difference in means. Differences were considered significant when $P<0.05$. There were some missing data in some birds in each group because some measurements coincided with the resuscitation of birds. The missing data were marked on chart in Fig. 1.

Results

Physiological parameters

The fixed drug effect was significant ($P<0.001$) but random time effect and drug × time effect was insignificant on HR. There was statistically difference between DK and MK ($P<0.001$), and DK and XK groups ($P<0.001$). The baseline HR values of birds in all three groups were similar. Although there was no statistical difference, compared to baseline values the HR decreased suddenly in MK and XK groups within 4 min after sedative drug injections, while it increased in the DK group 5 min after the ketamine injection. In all the groups, the HR continued to decrease moderately up to 120th min and there was an increase towards baseline values during recovery (Fig. 1A).

It was determined that fixed drug effect ($P=0.007$), random time effect ($P=0.005$) and drug × time effect ($P=0.013$) were statistically significant on RR. The difference was statistically significant between DK and XK ($P<0.001$), and MK and XK groups ($P<0.001$). The RR of group DK and MK increased significantly ($P<0.05$) from baseline within 4 min after sedative drug administration, thereafter a fall below the baseline was observed in RR during the ketamine injection, followed by a steady course up to 120th min. Tachypnea was observed in 5 animals in group MK after medetomidine injection and normalized shortly after ketamine injection. After ketamine injection, transient apnoea was observed in 13% (at 2nd min), 25% (within first 5 min), and 63% (within first 10 min) in groups DK, MK, and XK, respectively. In group XK, the RR was significantly ($P<0.001$) lower than baseline values at just before ketamine injection and remained at a constant level up to 120th min. The RR increased to approximate baseline values at recovery time in all groups (Fig. 1B).

The fixed drug effect was significant ($P=0.006$) but random time effect and drug × time effect were insignificant on BT. The BT values in MK group were lower than those of DK and XK groups throughout the experiment ($P<0.05$ and $P<0.01$, respectively). The BT began to decrease in response to all anaesthetic regimes, within 15 min of administration in group DK, MK, and 30 min in group XK. The BT remained almost constant between 45-120 min, and rose a bit at the recovery time but did not reach the starting value (Fig. 1C).

Reflexive responses

The weak time, down time, sleep time, and recovery time of each group are presented in Table 1. There were significant differences in weak time, sleep time, and recovery time among groups. The weak time was

Table 1: The weak time, down time, sleep time, and recovery time obtained from treatment groups (mean±SD)

Parameters	Treatment groups			P-value
	DK	MK	XK	
Weak time (min)	5.75 ± 0.89[a]	3.75 ± 1.49[b*]	2.50 ± 1.07[b**]	0.008[*] 0.001[**]
Down time (min)	11.00 ± 8.67[a]	7.63 ± 1.69[a]	6.13 ± 1.25[a]	0.177
Sleep time (min)	41.50 ± 19.37[b]	73.00 ± 20.24[a]	52.00 ± 19.62[ab]	0.014
Recovery time (min)	195 ± 21.35[a]	157 ± 13.61[b]	190 ± 42.72[ab]	0.029

DK: Diazepam+Ketamine group, MK: Medetomidine+Ketamine group, XK: Xylazine+Ketamine group. [a, b] Different letters at the same row denote statistical difference (P<0.05)

statistically similar in MK and XK groups, and it was shorter than DK group. The sleep time was longest in MK group and shortest in DK. The recovery period was shortest in MK group and longest in DK group. There was no statistical difference in down time among groups.

All birds in each group had all the reflexes (TR, JR, PR, and NR) from the start of sedative injections to the start of ketamine injections. The reflexes begin to disappear after ketamine administration. The reflexes were absent throughout the anaesthesia in all three groups. The JR, PR, and NR were lost in all birds in three groups within the first 5 min after ketamine injection. The disappearing time of TR was statistically similar in all groups with 10 ± 5.35, 6 ± 1.93, and 7.5 ± 4.63 min for groups DK, MK, and XK, respectively. There was statistical difference among groups to regain time of TR (P=0.008), JR (P=0.039), and PR (P=0.015) but no difference for NR (Fig. 2).

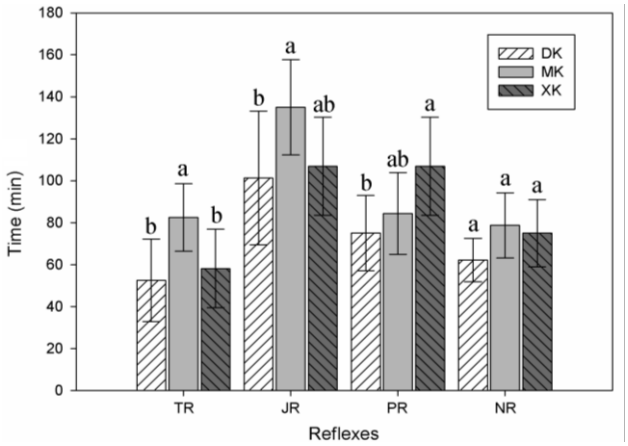

Fig. 2: Regaining time of reflexes (mean±SD). DK: Diazepam+Ketamine group, MK: Medetomidine+Ketamine group, XK: Xylazine+Ketamine group. TR: Toe pinch pain reflex, JR: jaw reflex, PR: Palpebral reflex, and NR: Nictitating membrane reflex. P<0.05 was considered as statistically significant which is indicated by different letters ([a, b]) for each parameter

The resistance to opening the jaw disappeared immediately after the ketamine injection. Muscle relaxation was excellent during the anaesthesia in all groups. Hypersalivation was present in 25%, 63%, and 13% in group DK, MK, and XK, respectively. Short-term convulsions with duration of approximately 10-15 s were determined in two birds of each group towards the end of the anaesthesia.

No noticeable events were observed during the recovery phase of the birds. During the recovery, the pheasants changed their positions from lateral recumbency to sternal and then were able to stand without assistance with slight ataxia. In any of the birds, flapping, violent behaviour, vocalization, and involuntary muscle or limb movements were not observed during the recovery phase.

Discussion

The doses of sedative drugs and ketamine used in this study for pheasants were higher than those previously reported for various species (Gunkel and Lafortune, 2005; Durrani *et al*., 2008; Gandomani *et al*., 2011; Lierz and Korbel, 2012). Although it is significantly higher compared with the dose found in the literature for birds, this dose provided good anaesthesia and there was no death in pheasants. A similar situation has been reported by other researchers before (Sandmeier, 2000; Lumeij and Deenik, 2003; Uzun *et al*., 2003; Muresan *et al*., 2008). Researchers stated that they used the previously recommended doses at the beginning but since the anaesthesia was not adequate they increased the doses gradually. These authors did not discuss the possible causes of using of anaesthetics at higher doses. But some researchers (Lichtenberger and Ko, 2007) had argued that the use of anaesthetics at higher doses might be related to interspecies differences in receptor populations within the spinal cord and central nervous system.

In our study, the onset of sedation and anaesthetic effects of MK and XK was more rapid than DK combination, and furthermore, the use of ketamine combination with medetomidine and xylazine allowed a longer surgical time (approx. 73 and 52 min, respectively) compared to the combination of DK in pheasants (approx. 41 min).

Similarly, Maiti *et al*. (2006) reported that a XK combination was effective for induction of surgical anaesthesia and that this provided better anaesthesia in chickens compared to a benzodiazepine/ketamine combination. Forbes (1998) obtained good surgical anaesthesia for 30 min when ketamine was used in combination with medetomidine in avian species. Mahmud *et al*. (2004) also investigated the efficiency of DK combination in cockerel chickens and found that the duration of induction period was shorter and the duration of sedation/anaesthesia period was longer than those of our findings in DK group.

In our study, in all anaesthetic groups, proper muscle relaxation similar to that reported in chickens (Maiti *et al*., 2006; Mostachio *et al*., 2008); in pigeons (Uzun *et al*., 2003), and in ducks (Machin and Caulkett, 1998) was observed.

All body reflexes disappeared in all three groups over the entire course of anaesthesia. The TR was ceased in all three groups within 10 min after ketamine injection. This result differs from those reported by Varner *et al*. (2004) and Maiti *et al*. (2006) for chickens anaesthetized with XK or DK combinations. The presence of the PR in the ketamine-treated pigeons was reported previously by many studies (Durrani *et al*., 2008; Mostachio *et al*., 2008) but it was not observed in our study.

Curro (1998) noted that disorientation and wing flapping are common and are usually more prominent during recovery from injectable anaesthetics. Self-induced trauma is most potential complication during the recovery and bird's restraint is essential to prevent postanesthetic injury. This approach is supported by researchers who reported that the stormy recovery when the ketamine is used alone is caused by the dissociative characteristics of ketamine anaesthesia (McGrath *et al*., 1984; Atalan *et al*., 2002; Mahmud *et al*., 2004). No pheasants showed wing flapping, violent behaviour, vocalization or involuntary muscle or limb movements during recovery in our study. These findings were consistent with previous studies in birds (Atalan *et al*., 2002; Maiti *et al*., 2006; Durrani *et al*., 2008).

The recovery period in birds is important because of relatively poor hepatic glycogen stores and high metabolic rate compared to mammals (Curro, 1998). For this reason, the longer the recovery time is, the higher the risk of lethal hypoglycaemia. In the present study, the recovery period recorded was significantly different among the three groups ($P<0.05$). Recovery period in group MK was shortest followed by groups XK and DK (Table 1). These results are similar to those reported by Forbes (1998) and Lumeij and Deenik (2003) but differ from those reported by Maiti *et al*. (2006) who reported that the XK combination provided the fastest recovery in chickens. However, Gandomani *et al*. (2011) reported that there was no difference between the recovery times in the budgerigars anesthetized with XK or DK combinations.

In our study, the HR suddenly decreased in MK and XK groups in the 4th min after preanesthetic injections, and then the decline continued until 120th min. In the DK group, the HR increased dramatically up to 5th min after ketamine injection. Thereafter, it fell steadily up to 120th min. The HR increased insignificantly in all birds between 120th and 150th min (Fig. 1A). Bradycardia occurred in group MK and XK, which is a characteristic response to alpha-2 adrenergic agonist drugs (Uzun *et al*., 2003). Machin and Caulkett (1998) reported bradycardia in ducks after administration of medetomidine-midazolam-ketamine combination. Similarly, Uzun *et al*. (2003) and Maiti *et al*. (2006) found significant decreases in HR using combinations of MK and XK, respectively on birds. The tachycardia after K injection in group DK occurred probably due to the effect of ketamine. The result was in line with the earlier studies carried out in ducks (Machin and Caulkett, 1998), pigeons (Sandmeier, 2000; Uzun *et al*., 2003; Durrani *et al*., 2008), and parrot (Sandmeier, 2000). Thus, ketamine causes an increase in HR attributable to stimulation of the central nervous system (Morgan and Curran, 2012).

Although xylazine and medetomidine have been reported to cause decreases in RR, because of a direct depressive effect of the drugs on respiratory centres in avian species (Machin and Caulkett, 1998; Uzun *et al*., 2003; Maiti *et al*., 2006; Durrani *et al*., 2008), and mammalians (rewieved by Sinclair, 2003), the RR increased in MK group pheasants in our study (Fig. 1B). While the RR data obtained from group DK was similar to those reported in the aforementioned studies, those of MK group were not. The author was able to find only one article, in which the reported medetomidine-induced RR decreases in rhesus macaques (Capuano *et al*., 1999). In our study, the RR values in group DK, as similar to MK group, were increased after diazepam injection and decreased after ketamine injection and then remained regular during anaesthesia. The results were in agreement with the findings of Maiti *et al*. (2006) who carried out general anaesthesia in pigeons using a combination of DK. Christensen *et al*. (1987) and Varner *et al*. (2004) also reported that no depression of the RR was observed in domestic fowl and chickens injected with a combination of ketamine and diazepam, respectively.

There were many reports expressing a significant reduction in BT during use of many anaesthetic agents in birds (Uzun *et al*., 2003; Maiti *et al*., 2006). In our study, there was a decrease in the BT in all groups until 45th min of anaesthesia and remained almost constant between 45-120 min (Fig. 1C). The decreased BT gradually increased to near baseline values at recovery time. Atalan *et al*. (2002) strongly advised that warming devices should be used in order to prevent dangerous decreases in BT. Therefore, heating pads were used in the current study to prevent hypothermia in anaesthetized pheasants.

In conclusion, intramuscular injection of MK combination in healthy pheasants provides a safe and long lasting anaesthesia with an excellent induction and recovery period when compared to DK or XK combinations. XK combination leads to a more serious respiratory depression and apnoea than the other drug combinations. The authors strongly recommend that XK combination should not be used in pheasants at the doses used in the current study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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