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An analysis of oxidative stress indices and clinical parameters in budgerigars (*Melopsittacus undulatus*) treated with medetomidine-ketamine and midazolam-ketamine

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Abstract

Various companion birds, including budgerigars, are anesthetized with injectable anesthesia. The current study aimed to evaluate oxidative stress indices including malondialdehyde (MDA), total antioxidant capacity (TAC), total oxidant status (TOS), and oxidative stress index (OSI) along with clinical parameters such as the time required to induce, maintain and recover from medetomidine-ketamine anesthesia and midazolam-ketamine anesthesia in budgerigars. Among 20 mature and healthy budgerigars, three groups were assigned as follows: Control (n = 4) to determine baseline oxidative stress indices medetomidine + ketamine (n = 8) anesthetized by intramuscular injections of medetomidine (0.04 mg kg^{-1}) and ketamine (30.00 mg kg^{-1}) in the pectoral muscles, midazolam + ketamine (n = 8) anesthetized by intramuscular injections of midazolam (1.00 mg kg^{-1}) and ketamine (50.00 mg kg^{-1}). Half of birds (n = 4) in the second and third groups were euthanized by cervical dislocation 1 hr after anesthesia induction, blood samples were collected directly from the heart, and sera were extracted. Additionally, the remaining birds were euthanized 24 hr later, and their serum was analyzed for oxidative stress indices. Clinical parameters were recorded during the study. Compared to the medetomidine + ketamine group, the midazolam + ketamine group experienced shorter induction, anesthetic, and recovery times. Administering medetomidine and ketamine elevated TOS levels compared with midazolam + ketamine. No significant difference was found between the test groups for TAC, MDA, or OSI. Therefore, the midazolam + ketamine regimen appears superior to medetomidine + ketamine when performing minor surgeries on budgerigars.

Introduction

General anesthesia plays a critical role in performing routine and elective surgical procedures on various animals. Typically, avian anesthesia is induced using injectable agents, as inhalation anesthesia requires specific equipment. In addition, using a mask on the bird's beak and head restricts the scope of operations on the head, neck, and respiratory system. The use of inhalants in birds should be approached with greater caution than in mammals due to their anatomical and physiological characteristics.[1,2] It is common for companion birds to receive injectable anesthetics, such as alpha-2 agonists, benzodiazepines, dissociatives, alfaxalone, and propofol.[3-6]

In addition to produce a strong somatic analgesia, ketamine is a derivative of phencyclidine and functions as dissociative anesthetic. However, due to its poor muscle relaxation and tendency for excitatory recovery, it is not commonly used alone for a balanced anesthesia.[1,2,7,8] Instead, it is often combined with alpha-2 agonists, like xylazine, detomidine, and medetomidine, or benzodiazepines, including diazepam and midazolam, to mitigate these side effects.[2,9-12] Medetomidine, when administered in low doses, produces sedation, analgesia, and muscle relaxation in small animals by binding to alpha-2 adrenergic receptors. Atipamezole, a specific reversal agent for medetomidine, and an alpha-2 adrenoceptor antagonist, can effectively reverse deep sedation and cardiovascular side effects in animals.[13,14]

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Benzodiazepines such as midazolam increase the binding of γ-aminobutyric acid (GABA) to $GABA_A$ receptors, leading to increased suppression of the central nervous system (CNS) by GABA. Midazolam possesses anxiolytic, sedative, hypnotic, and anticonvulsant properties. Compared with other benzodiazepines, midazolam has a shorter duration of action due to its water solubility. The drug also has the following advantages: rapid onset of anesthesia and minimal cardiovascular and respiratory effects.[4,8,15]

During oxidative stress, the body produces excessive amounts of reactive oxygen species (ROS) that the cells' antioxidative defenses cannot conteract.[16] It has been widely demonstrated that preoperative risk factors are associated with oxidative stress. Anesthetics play a major role in this regard. In different species, anesthetics have been shown to affect oxidative stress differently.[17-20] A thorough understanding of the role of anesthesia in diagnostic and clinical approaches and surgical procedures for ornamental birds makes it imperative that drugs are introduced to create appropriate and safe anesthesia, reducing the risk of oxidative damage.

To date, no study has been conducted to evaluate the effects of medetomidine-ketamine anesthesia in budgerigars compared to midazolam-ketamine anesthesia. Therefore, the present study aimed to examine the clinical efficiency and oxidative stress indices in budgerigars after anesthesia with medetomidine-ketamine and midazolam-ketamine.

Materials and Methods

Animals. The 20 mature and healthy budgerigars were selected based on similar weights ranging from 25.00 - 35.00 g, regardless of gender or age. These birds were kept in suitable conditions for one week after purchase, including appropriate lighting, heating, and a comfortable environment with a free access to food and water. They were acclimated to these new conditions, and any stress from handling and transportation stress was alleviated. Moreover, the birds were handled daily and returned to their cages during this period to minimize stress from the study. The experimental protocol was approved by the Institutional Animal Ethics Committee, Razi University, Iran (Ethics No. IR.RAZI.REC.1400.084).

Pilot study. First, a pilot study was conducted to determine the appropriate dosages of medetomidine (Syva, Leon, Spain), midazolam (Exir Pharmaceutical Co., Boroujerd, Iran), and ketamine (Bremer, Warburg, Germany). Based on previous studies,[11,21-23] various dosages of the drugs were administered. A dosage was then selected that would allow the birds to remain in dorsal recumbency for at least 30 min, and not respond to a withdrawal reflex. Table 1 illustrates the dosages used in the pilot study.

Study design. The 20 mature and healthy budgerigars were divided into three groups. These groups included the control group (n = 4) to assess the baseline oxidative stress indices and the medetomidine + ketamine group (n = 8) to be anesthetized by injecting medetomidine (0.04 mg kg^{-1}) and ketamine (30.00 mg kg^{-1}) into the pectoral muscles, intramuscularly. Also, the midazolam + ketamine group (n = 8) was the third group to be anesthetized by intramuscular injection of midazolam (1.00 mg kg^{-1}) and ketamine (50.00 mg kg^{-1}). The sedatives, containing medetomidine/midazolam were administered, and the birds were anesthetized by ketamine 5 min later. Later, half of the birds in each group (n = 4) were euthanized by cervical dislocation 1 hr after anesthesia induction in the second and third groups. Further, blood samples were directly taken from the heart, and sera were harvested. In addition, the rest of the birds were euthanized and sera were analyzed for the oxidative stress indices including malondialdehyde (MDA), total antioxidant capacity (TAC), total oxidant status (TOS), measured by colorimetric method with Navand Salamat Laboratory assay kits (Urmia, Iran), and oxidative stress index (OSI; TOS/TAC ratio) 24 hr after anesthesia induction among the mentioned groups. Ultimately, the clinical parameters, including duration of induction, anesthesia, and recovery were recorded during the study. The duration of induction was defined as the time between the injection of ketamine (5 min after the sedatives) and the beginning of dorsal recumbency. The anesthesia period referred to the duration of dorsal recumbency, characterized by the absence of the righting reflex and unresponsiveness to withdrawal reflex. Recovery time was determined as the interval between the disappearance of the withdrawal reflex and the moment when the birds were able to stand up.

Table 1. Dosage of drugs used to reach dorsal recumbency in the pilot study.

	Medetomidine	Ketamine	Time (min)	Midazolam	Ketamine	Time (min)
Dosages (mg kg^{-1})	0.20	30.00	100.00	2.00	50.00	70.00
	0.10	30.00	85.00	1.00	25.00	10.00
	0.05	30.00	55.00	1.00	50.00	30.00
	0.04	30.00	30.00	2.00	25.00	12.00
	0.03	30.00	20.00	2.00	40.00	45.00

The grey shaded cells represent the selected dosage that would allow the birds to remain in dorsal recumbency for at least 30 min, and not respond to withdrawal reflex.

Statistical analysis. Data were analyzed using SPSS software (version 22.0; IBM Corp., Armonk, USA). Normality and homogeneity of data were assessed by the Kolmogorov–Smirnov and Shapiro-Wilk tests. Analyses were done with two-sample independent t-test conducted to determine significance at $p < 0.05$. For oxidative stress indices, the data was analyzed using the Kruskal-Wallis test due to non-normal data distribution and small group sizes. Additionally, the Multiple Comparison Test (MCT) was conducted, with significance reported at $p < 0.05$.

Results

The induction and anesthetic times in the midazolam + ketamine group were significantly shorter than that of the birds receiving medetomidine + ketamine ($p < 0.05$; Fig. 1). Also, the recovery was significantly faster following administration of midazolam + ketamine compared to medetomidine + ketamine ($p < 0.05$).

Figure 2 depicts the changes in oxidative stress indices including MDA, TAC, TOS and OSI in the sera of control, medetomidine + ketamine and midazolam + ketamine groups.

Figures 2A and B show that the content of serum MDA and TAC did not statistically significant change following the administration of medetomidine + ketamine or midazolam + ketamine as compared to the control group. In addition, there was no significant difference between the different groups at 1 hr after anesthesia induction (T1) and 24 hr after anesthesia induction (T24), ($p > 0.05$).

As Figure 2C shows, TOS in the medetomidine + ketamine group was significantly higher than that of the midazolam + ketamine group at T1 ($p = 0.014$) but this indicator was statistically the same between the studied groups at T24 ($p > 0.05$).

Additionally, regarding OSI (Fig. 2D), there was no significant difference between the different groups at T1 and T24 ($p > 0.05$).

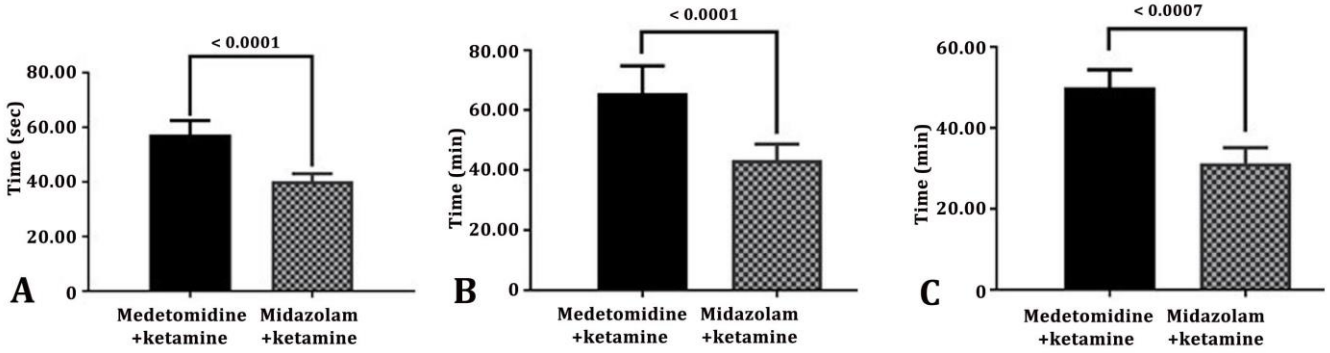

Fig. 1. The duration of **A)** induction, **B)** anesthesia, and **C)** recovery time in the medetomidine + ketamine group in comparison to the midazolam + ketamine group. The data is presented as mean ± SD.

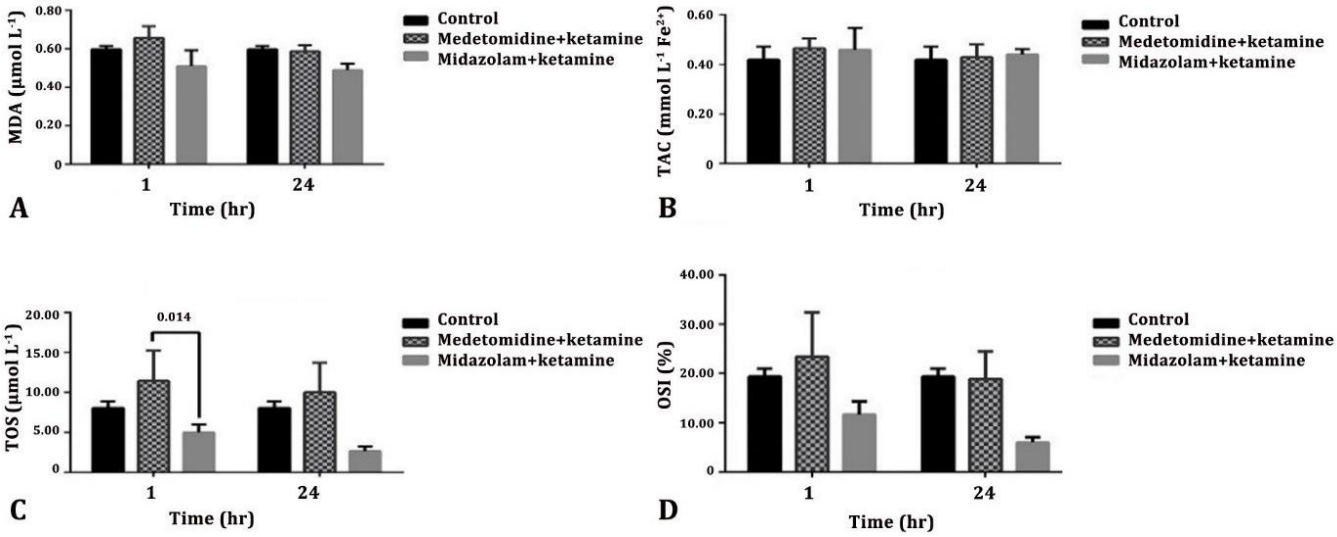

Fig. 2. A) Serum malondialdehyde (MDA), **B)** total antioxidant capacity (TAC), **C)** total oxidant status (TOS) concentration, and **D)** oxidative stress index (OSI) in different groups at 1 hr and 24 hr after anesthesia induction. Data are expressed as mean ± SD.

Discussion

In the current study, the anesthesia produced by medetomidine (0.04 mg kg^{-1})-ketamine (30.00 mg kg^{-1}) and midazolam (1.00 mg kg^{-1})-ketamine (50.00 mg kg^{-1}) was compared and evaluated in budgerigars for the first time. The doses used in this study were lower than those in other studies conducted on birds.[5,11,24,25] This difference may be due to variations in pharmacokinetics between species or variations in the number of relevant receptors in the CNS among different bird species. Despite the lower doses, the duration and depth of anesthesia were not negatively impacted. Using lower doses was considered advantageous due to the direct effects of anesthesia on the CNS and its potential side effects.

The anesthetic drugs in this study were administered intramuscularly. It has been claimed that the duration of anesthesia induced by intramuscular injection of midazolam-ketamine is longer than that of oral and intranasal methods in birds. Surgeons are advised to use the intramuscular administration method to ensure adequate anesthesia, reserving oral and intranasal methods for clinical examination and diagnostic methods.[25]

In this study, the induction, anesthetic, and recovery times were found to be longer in the medetomidine + ketamine group compared to the midazolam + ketamine group. Midazolam is water-soluble unlike other benzodiazepines, and its imidazole ring is rapidly oxidized by the liver. Moreover, it has been stated that this drug has a rapid onset and minimal cardiovascular and respiratory effects.[4,8,26] Therefore, the regimen of midazolam and ketamine used in this study resulted in shorter induction, anesthetic, and recovery times.

Many researchers examined and compared anesthesia induced by benzodiazepines and alpha-2 agonists in birds. In a study carried out by Zamani Moghadam *et al*, midazolam, diazepam, and xylazine were administered intranasally to pigeons. The results revealed that the induction speed of anesthesia was faster in birds treated with midazolam compared to the other drugs. Besides, the duration of lying on their backs was shorter with midazolam than with diazepam.[4]

Javdani *et al*. compared the effects of intramuscular injection of ketamine-diazepam with ketamine-xylazine in budgerigars. They found that birds receiving diazepam and ketamine had a shorter onset duration of action, maintenance, and recovery from anesthesia.[5] In another study, midazolam, diazepam, and xylazine were administered intranasally to budgerigars, and the duration of induction and dorsal recumbency were compared. The results showed that the onset time of anesthesia and maintenance with midazolam was shorter than with the other two drugs.[27] The results of this research were consistent with the mentioned studies.

In addition to the trauma caused by surgery, anesthetics can also disrupt the antioxidant defense system, leading to oxidative stress. The magnitude of this stress relies on the animal species and the specific anesthetic used.[28]

Malondialdehyde, the major product of lipid peroxidation and one of the most important markers of oxidative stress can be easily measured in serum, plasma, and various tissue homogenates.[29] Moreover, measuring TAC alone facilitates examining the activity of all factors and enzymes that inhibit oxidative stress. The results of this study indicated that there was no significant difference in serum MDA and TAC concentrations among the different groups (control, medetomidine + ketamine, and midazolam + ketamine) at T1 and T24 ($p > 0.05$). According to previous studies, it has been found that the administration of ketamine increases lipid peroxidation and induces oxidative stress.[30-32] This stress has been greatly suppressed by administrating midazolam and medetomidine, simultaneously. As a result, the levels of MDA and TAC parameters were not significantly different from those of the control group in the treated birds. The suppression of oxidative stress has been proved by medetomidine/midazolam in previous studies.[33-38] Ketamine easily distributes in adipose tissue,[39] leading to lipid peroxidation and increased oxidative stress. Besides, administering medetomidine/midazolam, and increasing antioxidants, may simultaneously neutralize the oxidative stress induced by concomitant ketamine.[36-38]

Another parameter evaluated in this study was TOS, which measures the concentration of various ROS such as superoxide anion and hydrogen peroxide. Measuring these indicators individually can be time-consuming, require complex techniques, and be costly. Therefore, TOS is used as a more practical alternative.[40,41] The results of this research indicate that the serum content of TOS in the group receiving medetomidine-ketamine is significantly higher than that of the birds anesthetized by midazolam-ketamine. This finding can be related to the clinical evaluation findings directly. As mentioned, the induction, anesthetic, and recovery duration, following anesthesia by medetomidine-ketamine was significantly higher than the values of these indicators after midazolam-ketamine administration. In addition, the recovery quality among birds anesthetized by medetomidine-ketamine was lower than that of the other group, and it was associated with more stress and frequent flapping. Moreover, the most common side effects of medetomidine are reported to be bradycardia and hypothermia.[42] However, midazolam is very fast-acting and short-lasting, resulting in minimal cardiovascular and respiratory effects.[43] These differences can also directly influence the TOS induced by medetomidine in comparison with midazolam. It can be argued that TOS is the result of all oxidant factors, considering the molecular mechanisms behind the

increased TOS in the birds anesthetized with medetomidine-ketamine compared to those given midazolam-ketamine. However, only the level of MDA was measured in this study. The medetomidine or medetomidine-ketamine regimen likely led to an increase in other oxidant factors, including glutathione, nitrogen, or other oxidative stress-inducing proteins, which were not measured in this study. Furthermore, the administration of medetomidine-ketamine may have caused more ROS, compared to midazolam-ketamine, resulting in increased TOS. While MDA only shows lipid peroxidation, it does not reflect the damage caused by oxygen free radicals to other macromolecules.

Regarding the results of TAC and especially TOS, the OSI, obtained by dividing the TOS level by TAC level (TOS/TAC ratio) revealed an increase in the medetomidine + ketamine group compared to the birds that received midazolam-ketamine. However, this difference was insignificant, which may be due to the similar TAC values among the different groups.

The midazolam-ketamine regimen is preferred over the medetomidine-ketamine regimen for budgerigars based on the parameters of measured clinical evaluation. This includes a shorter duration of induction and anesthetic times, as well as faster recovery of birds in the midazolam + ketamine group compared to the other. Additionally, the higher TOS content in the birds receiving medetomidine-ketamine compared to the midazolam +ketamine group was another reason for this preference when performing short-term anesthesia before quick surgeries.

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Conflict of interest

The authors declare no conflict of interest.

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