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Comparative Evaluation of Intramuscular, Intranasal, Oral and Intraosseal Administration of Midazolam, Ketamine Combination in Quail (Coturnix coturnix japonica)

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Abstract

This study was aimed to compare the effects of different delivery routes of midazolam ketamine combination in quails. Thirty two adult male quails (Coturnix coturnix japonica) with a mean weight of 180-220 gr and a 25-week-old were used in this study. The birds were divided into four groups of eight animals each. In group I (Group IM), 6 mg/kg midazolam-100 mg/kg ketamine combination was injected intramuscularly. It was given the same dose of this combination intranasal in the group II (Group IN) and orally in the group III (Group O). In the last group (Group IO), 2 mg/kg midazolam-20 mg/kg ketamine was administered intraosseally. Induction, recovery time and depth of anesthesia were evaluated. Pulse, systolic blood pressure, diastolic blood pressure, respiratory rate and cloacal temperature were also monitored. The anesthesia durations were determined as 28.88±5.87 min in group IM, 13.75±5.18 min in group IN, 14.88±4.79 min in group O and 38.13±8.84 min in group IO, respectively. There were statistically significant differences between groups in terms of both anesthesia duration and physiological values. As a result, intramuscular and oral administration of the midazolam ketamine combination may be preferred to many operative interventions, but intranasal use can be used for clinical examination or diagnostic procedures because it does not provide adequate anesthesia. It can be said that oral and intraosseous use may be preferred in cases requiring longer duration of anesthesia in birds.
Key Words: Intranasal, Intraosseal, Midazolam-ketamine, Oral, Quail

Bıldırcınlarda (Coturnix coturnix japonica) Midazolam-Ketamin Kombinasyonunun İntramusküler, İntranasal, Oral ve İntraosseal Olarak Uygulanmasının Karşılaştırmalı Olarak Değerlendirilmesi

Öz

Bu çalışmada midazolam ketamin kombinasyonunun farklı veriliş yollarının etkilerinin karşılaştırmalı olarak değerlendirilmesi amaçlandı. Çalışmada toplam 32 adet erkek, ortalama 180-220 gr ağırlığında ve 25 haftalık erişkin bıldırcın (Coturnix coturnix japonica) kullanıldı. Kuşlar her birinde 8 hayvan olacak şekilde dört gruba ayrıldı. Grup I'de (Grup IM) 6 mg/kg dozunda midazolam-100 mg/kg ketamin kombinasyonu intamusküler olarak enjekte edildi. Grup II'de aynı dozdaki kombinasyon intranasal (Grup IN), III. gruba ise oral (Grup O) olarak uygulandı. Son gruba da 2 mg/kg midazolam-20 mg/kg ketamin intraosseal (Grup IO) olarak uygulandı. Anesteziye giriş ve çıkış süreleri ve anestezi derinliği değerlendirildi. Ayrıca nabız, sistolik ve diastolik kan basınçları ile solunum sayısı ve kloakal ısı takip edildi. Anestezi süreleri sırasıyla grup IM'de 28.88±5.87, grup IN'de 13.75±5.18, grup O'da 14.88±4.79 ve grup IO'de 38.13±8.84 olarak belirlendi. Gruplar arasında hem anestezi süreleri hem de fizyolojik değerler bakımından istatistiksel olarak anlamlı farklılıklar bulundu. Sonuç olarak midazolam ketamin kombinasyonun intramusküler ve oral kullanımı birçok operatif girişim için tercih edilebilir, fakat intranasal kullanım yeterli derinlikte anestezi sağlayamadığından dolayı sadece klinik muayene ve diagnostik işlemler için kullanılabilir. Oral ve intraosseal kullanımın daha uzun süreli bir anestezi gerektiren olgularda tercih edilebileceği söylenebilir.
Anahtar Kelimeler: Bıldırcın, İntranasal, İntraosseal, Midazolam-Ketamin, Oral.

INTRODUCTION

Inhalation agents such as halothane, methoxyfluran, and sevoflurane are used to general anesthesia in birds, but inhalation anesthesia is more dangerous in birds than in mammals due to the anatomical and physiological structures of the birds (1,2). In addition, inhalation anesthesia requires special equipment and the risk of gas waste is a disadvantage (1). For this reason, as an alternative to inhalation anesthesia in birds, different injectable anesthetic agents are used alone or in combination (1,3).

Many investigators recommend ketamine as an appropriate anesthetic agent in birds (1,4,5-8). Despite the widespread use of ketamine in birds, many different sedative agents such as xylazine, detomidine, medetomidine, and midazolam are used for premedication (5-9).

In birds, injectable anesthetics or sedatives can be injected intravenously, intramuscularly or intraosseously, but each of these routes of administration is an invasive procedure and may cause pain during administration, especially intravenous and intrathecal administration. In addition, pain is inevitable during intramuscular injections when the drug used is in irritant or increased volumes (10).

Although intranasal use of sedatives used in birds has been reported to be rare, literature has been found on the use of sedatives such as midazolam or xylazine in some species of birds (11-14).

It was aimed to compare the effects of intramuscular, intranasal, oral and intraosseal applied midazolam/ketamine combination on anesthesia and some physiological values in this study in which quail was preferred for being a suitable model for many avian species.

MATERIAL AND METHOD

This study was carried out on 32 clinically healthy mature (25 weeks old) male quails (Coturnix coturnix japonica) with 180-220 g body weight from farm of the Kafkas University Veterinary Faculty.

The birds were adapted to their environment for a week before starting work. They were hosted at constant room temperature with a 12-12 h light-dark cycle and fed with a wheat-based diet in accordance with the previous feeding regimen. All experiments were performed in quails deprived of food for 60 min, but allowed free access to water.

The University of Kafkas at Animal Research Ethics Committee of Veterinary Medicine approved all experiments before studies were conducted (KAU-HADYEK 2018/058).

For general anesthesia, the combination of Midazolam HCl (Zolamid® 5mg/5 ml, Defarma-Turkey) and ketamine HCl (Ketasol® 10 ml, Richter Pharma-Austria) was used.

Study Protocols: The birds were divided into four groups on the basis of their exposure route of anesthetics as intramuscular (IM), intranasal (INS), oral (O) and intraosseal (IO). Quails in IM Group (n=8) was anesthetized with combination of 6 mg/kg midazolam and 100 mg/kg ketamine by insulin syringe. Deep pectoral muscle was used for intramuscular injection. In INS group (n=8) the same dose combination was applied intranasally while in group O (n=8) administered orally. Quails in IO Group (n=8) was received combination of 2 mg/kg midazolam and 20 mg/kg ketamine. In IO Group, this combination was diluted in 1:1 ratio with 0.9 % NaCl solution. The left tibia was chosen for intraosseous administration using 17x32 mm needle. After aseptic conditions, it was positioned at flexion to knee joint of quails laid on lateral recumbency. Needle was inserted to medulla of tibia. Loss of resistance against the needle proved that needle was in medullary region. After the injector is kept in the palm of the hand for a short time, intraosseous injection was performed.

Measurements: Heart rate (HR), respiratory rate (RR), cloacal temperature (CT) and ECG were recorded for each quail before drug administration and at the 1, 5, 10, 20, 30, 40 and 50th minutes after injection. A multi-parametric monitor (Veterinary Monitor® MMED6000DP S6-V, MVM-Hamburg, Germany) was used for these measurements.

Induction time, anesthesia duration and recovery time were assessed by standard painful stimuli as pin-prick and sensory function as righting reflex, feather plucking reflex, palpebral reflex, pharyngeal reflex and eyelid status.

Anesthesia duration was identified as passing time from loss of consciousness to reappearance of sensory function. Standard painful stimuli used for this reason, performed in two ways as superficial (needle used to prick the skin) and deep pin-prick (needle inserted into the muscle). Needle was applied to muscle in different body parts such as neck, pectoral, wings and legs. Also, other body reflexes (righting reflex, feather plucking reflex, pharyngeal reflex) were recorded as previously reported (3-8). In addition, eyelids scored as 0 for closed, 1 for half-opened and 2 for opened.

Statistical analysis; Statistical analysis was performed using the commercial Minitab-16 software program. All results were expressed as the mean±standard deviation (SD). After the parameters were subjected to normality test, nonparametric data (as analgesic scores) was evaluated by the Kruskal-Wallis test and Mann-Whitney U test. Also, parametric data with time were analyzed using ANOVA (for One-way analysis of variance and Post Hoc Tukey). Differences were considered significant at P<0.05.r.

RESULTS

There was a statistically significant difference between groups in terms of onset and duration of anesthesia (P<0.05), in contrast there is no significant difference within groups (Table 1).

All body reflexes disappeared in four groups during anesthesia.

Changes between groups in that HR, RR, CT during anesthesia were shown in Table 2. When compare to baseline values in HR of the groups, there was significant decreased at the 5 to 20 minute in both group IM and group IN, at the 5 to 10 in group O and at the 1 to 40 minute in group IO (P=0.000). There were also significant statistical differences between the groups during anesthesia (1, 5, 10, 20, 30 and 40th min after anesthesia).

In all four groups, RR values decreased from the 5th minute after anesthesia and statistically significant differences were found in each group according to the baseline value (p=0.000, Table 2). In addition, there were significant statistical differences at the 5, 10, 20, 30 and 40th min between the groups (p=0.000).

There was no different significantly between groups in that CT, but there were significantly differences between baseline values and the 10, 20, 30, 40, 50th min within each groups.

Table 1. Body weight, anesthesia onset time and duration of anesthesia of the groups

Groups	Body weight (gram)	Anesthesia onset (second)	Anesthesia duration (minute)
IM (n=8)	199.13±9.05	111.8±11.6 [a]	28.88 ± 5.87 [a]
IN (n=8)	194.88±10.97	184±21.62 [a]	13.75 ± 5.18 [b]
O (n=8)	193.00±10.60	14.88±4.79 [b]	14.88 ± 4.79 [b]
IO (n=8)	197.13±9.36	4.75±3.33 [c]	38.13 ± 8.84 [c]
P	0.643	0.000	0.000

a-c: The differences between the means of time carrying various letters in the same column are statistically significant

Table 2. Effect of HR, RR, CT via the IM, IN, O and IO injections of midazolam/ketamine combination at different time

Values	Groups	Time								P
		0	1	5	10	20	30	40	50	
HR	IM	356.25±6.27 [a]	347.50±3.82 [ab]	333.63±4.27 [b]	334.88±3.98 [b]	347.88±4.29 [ab]	354.88±6.96 [a]	355.00±6.87 [a]	355.88±5.82 [a]	0.000
	IN	360.50±5.78 [a]	352.50±5.35 [a]	332.63±3.58 [b]	352.38±6.50 [a]	358.63±5.68 [a]	360.50±6.05 [a]	360.25±5.85 [a]	360.00±5.40 [a]	0.000
	O	360.50±5.95 [a]	330.75±15.79 [b]	317.88±12.54 [b]	331.25±15.54 [ab]	358.38±5.68 [a]	360.00±6.21 [a]	360.75±5.92 [a]	360.50±5.40 [a]	0.000
	IO	361.00±4.47 [a]	299.38±14.99 [b]	295.25±13.44 [b]	309.8±37.30 [b]	310.50±3.66 [b]	330.63±5.88 [b]	345.88±6.94 [ab]	360.00±4.46 [a]	0.000
P		0.329	0.000	0.000	0.003	0.000	0.000	0.000	0.229	
RR	IM	17.12±0.35 [a]	16.87±0.64 [ab]	16.62±0.74 [ab]	15.00±1.06 [b]	14.25±1.98 [b]	15.25±1.03 [b]	15.87±0.83 [ab]	16.87±0.64 [a]	0.000
	IN	17.25±0.46 [a]	17.12±0.65 [a]	16.87±0.83 [ab]	15.12±1.35 [b]	15.62±1.18 [b]	15.75±0.70 [b]	16.50±0.75 [ab]	17.00±0.75 [a]	0.000
	O	17.35±0.51 [a]	17.25±0.70 [a]	16.87±0.99 [a]	14.75±0.46 [b]	15.25±1.16 [ab]	15.25±0.70 [ab]	16.75±0.46 [a]	17.25±0.92 [a]	0.000
	IO	17.50±0.53 [a]	17.25±0.88 [a]	13.88±3.23 [b]	10.25±1.38 [c]	9.62±0.74 [c]	10.87±0.83 [c]	13.62±1.50 [b]	17.12±0.99 [a]	0.000
P		0.438	0.702	0.005	0.000	0.000	0.000	0.000	0.949	
CT	IM	41.21±0.25 [a]	41.06±1.82 [a]	39.82±0.41 [ab]	38.82±0.12 [ab]	38.41±0.13 [b]	37.56±1.23 [c]	36.90±0.27 [c]	36.20±0.28 [c]	0.000
	IN	41.13±0.51 [a]	39.98±2.14 [a]	39.63±0.52 [ab]	38.75±0.58 [ab]	38.22±0.24 [b]	37.25±0.96 [c]	36.82±1.83 [c]	36.50±1.33 [c]	0.000
	O	41.07±0.27 [a]	39.94±0.28 [a]	39.00±0.37 [a]	38.96±0.64 [ab]	38.33±0.56 [ab]	37.36±1.08 [b]	36.73±0.23 [b]	36.92±0.48 [b]	0.000
	IO	41.46±0.86 [a]	40.10±1.36 [a]	39.25±0.74 [a]	38.25±0.75 [ab]	37.98±0.47 [ab]	37.09±0.85 [ab]	36.50±0.64 [b]	36.45±1.27 [b]	0.000
P		0.526	0.418	0.752	0.345	0.218	0.486	0.971	0.705	

a-c: The differences between the means of time carrying various letters in the same line are statistically significant
HR: Heart rate, RR: Respiratory rate, CT: Cloacal temperature

DISCUSSION

In birds, ketamine which is a suitable injectable anesthetic agent is widely used for effective and safe general anesthesia. Sedative agents such as xylazine, detomidine, medetomidine, and midazolam may also be used for premedication or short-term procedures as clinical examination and radiodiagnostic process in birds. These sedative agents can be used alone or in combination with ketamine (7,8,15). In this study, it was aimed to compare the effects of midazolam/ketamine combination administered via intramuscular, intranasal, oral and intraosseal on anesthesia and some physiological values in quail in that a suitable model for many avian species.

The midazolam in the benzodiazepine class has an inhibitory effect on the central nervous system (13). Midazolam is increasingly used in birds to sedation produce, centrally moderate muscle relaxation and anticonvulsant activity. It can be used in different ways such as intramuscular, intravenous and intranasal (16). The midazolam has many advantages such as water solubility, a shorter duration of action and stronger than diazepam and minimal cardiopulmonary side effects (13). It has been reported as 5 mg/kg intravenously dose in broiler chicken, turkeys, ring-necked pheasants and bobwhite quail by Guzman (2014). In our study, intramuscular, intranasal, oral and intraosseal applications were preferred as the route of use. It was used as a combination of midazolam at a dose of 6 mg/kg with ketamine at a dose of 100 mg/kg for intramuscular, intranasal and oral administration. Although the duration of anesthesia and anesthesia onset were different between groups, this combination was sufficient for anesthesia. We recommend intranasal or oral administration for short-term surgical procedures. Because it is known that birds will suffer from pain during intramuscular injection.

Earlier studies have shown that intraosseus route is a good alternative to the intravenous route for drug administration such as allowed anesthesia and fluid therapy in birds (7,8,15,17). On the other hand, for intraosseal applications, anesthetic dose should be reduced (7,8,15). Therefore, in this study combination of 2 mg/kg midazolam and 20 mg/kg ketamine was used via intraosseal in group IO. Anesthesia in this group was onset faster (4.75±3.33 second) and lasted longer (38.13±8.84 minute) than other groups. Therefore, intraosseal administration of midazolam/ketamine combination for long-term operations can be considered. In addition, bones in communication with air sacs for intraosseal injection should not be used. We think that tibia is a suitable bone for this purpose in terms of its structure and ease of manipulation in birds. In addition, it should not be forgotten that bones may fracture during application.

Midazolam can be given intranasal and it is safe and effective when intranasal administered. In addition, cardiopulmonary changes are insignificant, when the midazolam is intramuscularly administered. However, it was reported that intranasal midazolam decreased respiratory rate but had no effect on hemoglobin saturation and blood gas (13). The changes in HR and RR values in our study were statistically significant among the groups. But the amount of this decline is expected during anesthesia. So it cannot be said that respiration or circulation is depressed. On the other hand, thermoregulation during anesthesia may be largely depending on respiratory and cardiovascular decrease (7,18). Hypothermia or hyperthermia can contribute to complication and postoperative physiological chance. Therefore, changes in CT are minimized by appropriate anesthetic combinations and proper fluid therapy (7). In our study, there was no difference between the groups in CT, but the decrease in CT depending on anesthesia was seen in all groups. Similarly, studies using different sedatives as xylazine, detomidine, medetomidine, and midazolam (3,4,6,8,9) have also shown that the body temperature is lower.

The route of administration of the drug for anesthesia is important. The route of administration is determined by the type of bird, the type of agent to be applied and the duration of the operation. According to the results of our study, the combination of midazolam and ketamine can be used for safe and effective anesthesia in the quail. But the route of administration has significantly changed the duration of anesthesia. So, the veterinary surgeon should decide which of the routes of use. Intranasal or oral use is very easy, but duration of action is shorter than intramuscular and introsseal.

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