



Anesthesia and Sedation in Chough (*Pyrrhocorax pyrrhocorax*) Following Intranasal Administration of Diazepam, Midazolam, Xylazine with or without Ketamine: Clinical Evaluation

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Abstract

Objective- This study aimed to compare sedation efficacy in intranasal administration of xylazine, diazepam and midazolam with or without ketamine in Chough.

Design- To determine the sedation efficacy, an experimental in vivo study was employed.

Animals- Seven healthy Choughs were examined in the current study.

Procedures- With an interval of one week, seven healthy adult non domesticated Choughs of either genders, weighing 232.54 ± 14.5 grams, were sedated or anesthetized by xylazine (8 mg/kg), diazepam (8mg/kg) and midazolam (8mg/kg) with or without Ketamine (30 mg/kg).

Results- Following intranasal administration of the subjects, sedation or anesthesia was produced in all groups.

Conclusion and Clinical Relevance- This study revealed that intranasal use of xylazine, diazepam and midazolam alone or combined with ketamine provides reliable sedation in Chough; however all anaesthesia protocols are not perfect to be used in surgical procedures.

Keywords- Anesthesia, Sedation, Intranasal administration, Chough.

Introduction

When avian patients are suffering from surgical intervention and painful conditions, an appropriate use of a perfect anesthesia and an analgesia technique is of paramount importance.

Inhalation anesthesia is the veterinarian's technique of choice; however, the anesthetic machines with calibrated vaporizers may not always be available.

Some advantages of injectable anaesthesia in comparison with inhalant anaesthetics are better induction speed of anaesthesia, demanding less equipment and low cost.¹

Intravenous injection is challenging in birds. Hence, intramuscular (IM) injection or subcutaneous routes are preferred in this regard. For IM administration, pectoral muscle injection is usually used; however, injecting

needle to pectoral muscle may cause inadvertent intravascular or intracoelomic drug administration.²

Injections into the thigh muscles of small birds are not recommended since it may lead to nerve injury. Furthermore, an irritant drug being administered intramuscularly may result in pain. To avoid pain and anxiety caused by IM injections in children, intranasal route have been evaluated for the induction of sedation or analgesia.^{3,4} Intranasal administration of xylazine, midazolam and diazepam has been reported in some species of bird such as pigeons and canaries.^{5,6}

This study aimed to determine the effect of ketamine and its combination with benzodiazepines (midazolam and diazepam) and $\alpha 2$ -agonists (xylazine) on Choughs (*Pyrrhocorax pyrrhocorax*) and to design the best drug protocol for IN anaesthesia and sedation.

Materials and Methods

Animal

The protocol for this project was approved by the Institutional Animal Care and Use Committee of Lorestan University. Seven healthy adult non-domesticated Choughs of both genders, weighing

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232.54±14.5 grams, were included in this study. The birds were kept in a temperature-controlled environment (18–20 °C) in the cage. Prior to the study, they were acclimatized for at least 4 weeks. The birds were provided with water and fed with a variety of seeds, vegetables, and fruits ad libitum. They were not fasted before the administration of medication.

Anaesthetic protocols

Ketamine(30 mg/kg, Daroupakhsh, Iran) (K) , xylazine (8 mg/kg, Daroupakhsh, Iran)(X), diazepam(D) (8mg/kg, Daroupakhsh, Iran) , midazolam (8mg/kg, Daroupakhsh, Iran)(M), ketamine–diazpame(KD), ketamine-midaolam(KM) and ketamine-xylazine(KX) were administered intranasally using a micropipette (Varipet 4810; Eppendorf, Hamburg, Germany) with an interval of one week (Fig.1).



Figure 1. Photograph illustrating the technique of intranasal drug administration in a cough. Equal volumes of drug are administered slowly into each nostril using a micropipette.

To determine the optimum dose of the sedatives administered to birds, we used the technique employed by Vesal and Eskandari.⁷ Briefly, three doses (from 3, 5 and 8 mg/kg) of Xylazine, diazepam and midazolam were injected into the naris of three birds. One dose was used that the bird did not have movement in dorsal recumbency for at least 5 minutes.

All drugs were administered over approximately 30 seconds in each nostril.^{5,8} Immediately, after drug administration, each bird was placed in dorsal recumbency in separate cages in order for him to be monitored. Closure of the eyelids, drooping wings and tail and decrease of other stimuli observed after drug administration. The onset time, the duration of dorsal recumbency time and complete recovery time were subjectively evaluated based on standard tests.^{5,9} The onset time was defined as the time between drug

administration and early signs of the bird's reaction to sedation, (including closure of the eyelids, falling wings and tail). The duration of dorsal recumbency was defined as the time from moderate sedation (the birds did not move when placed in dorsal recumbency) to mild sedation (the onset of head and neck voluntary movements and attempt of bird for placing in sternal position). Complete recovery time was defined as the time from placing in sternal recumbency to complete standing of birds. In addition to these parameters, the quality of recovery was achieved individually as excellent, good and poor.¹⁰ Excellent recovery was defined as a type in which the bird showed early sternal position with little or no struggle, walking without assistance or struggle, not to fall to sternal recumbency once standing, minimal ataxia when walking. Good recovery was defined as a type in which the birds showed sternal position with little or no struggle, premature standing without weakness in hind limbs, not to fall to sternal recumbency unlikely once standing, slight ataxia. Poor recovery was defined as a type in which the birds showed some struggling, repeated attempts to move from lateral to sternal recumbency, premature standing with splayed and weak hind limbs, repeatedly falls to sternal recumbency once standing, manual restraint required to avoid injury.¹⁰

Statistical analysis:

Regarding the onset and duration of sedation, duration of dorsal recumbency, and respiratory rate, the data collected were analyzed using One-way ANOVA followed by a Duncan Test, if necessary. All results are expressed as mean ±SD and differences were considered significant at a value of $P < 0.05$.

Results

Following intranasal administration of the agents, sedation or anesthesia was produced in all groups. The onset time, duration time and full recovery time are shown in Table 1. The longest onset time was observed in K (10±2.9), KX (6.6±3.6) and X (6.4±2.8) groups, respectively. There were significant differences among groups at the onset of induction. Briefly, using ketamine alone, xylazine and ketamine –xylazine combination revealed longer induction than other treatment protocols. The duration of dorsal recumbency was short for the groups having been treated with diazepam (13.6±4.22) and midazolam (15.6±12.9) alone. However, the longest duration of dorsal recumbency was observed in X (51.2±22.25) group. Full-recovery time in the KD (30.0±12.39) group was longer than those of other treatment groups $p < 0.05$.

Quality of recovery for experimental groups is represented in Table 2. Briefly, D, M, KD and KM groups enjoyed good quality of recovery; however, K, X and KX were of moderately poor quality of recovery.

The birds accepted IN administration of drugs without resistance. A decreased appetite was not observed in

birds after sedation of all treatment protocols. However, an increased appetite was observed in groups receiving midazolam and diazepam following the termination of

sedation and anaesthesia. No adverse reactions or complications were revealed after IN drug administration in this study.

Table 1. onset of action, duration of dorsal recumbency and complete recovery time after intranasal administration of xylazine, midazolam and diazepam (with or without ketamine)

Groups	The onset time(min)	duration of dorsal recumbency(min)	complete recovery time(min)	Respiratory rate
K (ketamine)	10±2.9	33±25.7	9±4.7	48.6 ± 27.83
X (xylazine)	6.4±2.8	51.2±22.25	10.4±3.13	99.0 ± 31.42
D (diazepam)	3±1.58ab	13.6±4.22b	10.4±6.1	29.8 ± 5.45
M (midazolam)	3.8±2.9a	15.6±12.9b	9±6.7	30.8 ± 7.26
KD (ket+diz)	2.2±0.84abe	27.2±12.03c	30.0±12.39abcde	38.6 ± 10.14
KM (ket+mid)	4±2.9a	27.4±7.16c	18.2±7.5b	51.2 ± 15.02
KX (ket+xyl)	6.6±3.6	37.6±30.34	14.2±8.5	36.0 ± 7.07

a P<0.05 vs K group, b P<0.05 vs X group, c P<0.05 vs D group, d P<0.05 vs M, e P<0.05 vs KX. Values are given as mean ± SD

Table 2. The evaluation of recovery quality for coughs anesthetized after intranasal administration of xylazine, midazolam and diazepam (with or without ketamine)

	Excellent	Good	Poor
Ketamine (No.cough)	0	1	6
xylazine	0	2	5
diazepam	2	4	1
midazolam	1	5	1
Ketamine + diazepam	2	5	0
Ketamine + midazolam	2	4	1
Ketamine + xylazine	0	3	4

Discussion

This study revealed that intranasal use of xylazine, diazepam, and midazolam alone or combined with ketamine provides reliable sedation in Chough; however all anaesthesia protocols are not perfect to be used in surgical procedures. Our data suggested that intranasal administration of midazolam or diazepam can provide adequate sedation for diagnostic and minor therapeutic procedures. This finding suggested that intranasal administration of midazolam or diazepam could provide adequate sedation for diagnostic and minor therapeutic procedures such as other studies.⁵⁻⁷

In this study, the onset of action for ketamine, xylazine and ketamine-xylazine combination was longer than that for other drugs. It is well-known that, in order to induce anaesthesia, fast induction and smooth recovery are preferred variables. Hence, these results showed that the use of ketamine- xylazine and ketamine-midazolam are the best protocols for surgical procedures in *Pyrrhocorax pyrrhocorax*. Recovery times of IN administration of Ketamine-diazepam combination was longer, compared to other groups.

Respiratory rate in the birds treated with xylazine alone was significantly higher than that of birds treated with other drugs. This can be caused by the physiological response of birds to suppress effect of xylazine on cardiovascular and respiratory systems. Therefore, the use of xylazine alone is not recommended for IN administration.

Ketamine as a dissociative agent, inducing a cataleptic state, was administered alone and in combination with sedative drugs in birds. It is now rarely used as the sole anesthetic agent.¹¹

The IN administration of other anesthetic drugs, such as midazolam, ketamine, xylazine, and diazepam have been examined in humans, dogs, cats, birds, rabbits and turtle.^{12-14, 5-7, 15, 16} Midazolam in these studies produced adequate levels of sedation.

Administration of different drugs into the nose can result in short induction periods because the nasal mucosa is a highly permeable port; however, many reports have confirmed that IN administration has a large potential surface of fast absorption and it is near to the brain.^{17,18}

Conclusion

The results of this study showed that IN drug administration was an acceptable, minimally invasive alternative method of drug delivery for birds. This method requires no special technical skills, and only a brief physical restraint is required to deliver the drugs into the nares. Intranasal drug administration has the potential to become a viable clinical option in exotic animal medicine and may be an alternative to the conventional IM or subcutaneous injections. The non-domesticated birds such as chough have different age ranges (one year to seventy year). Hence, the intranasal sedation and anaesthesia can be safe for young and old birds. Further studies are necessary to

evaluate different doses and drugs and to determine their safety in compromised patients, their usefulness, and best drug protocol in other bird species.

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References

- Forbes N-A: Avian anesthesia. *Vet Q.* 1998; 20:265-266.
- Kamiloglu A, Atalan G, Kamiloglu N-N. Comparison of intraosseous and intramuscular drug administration for induction of anaesthesia in domestic pigeons. *Research in Veterinary Science.* 2007; 85:171-175.
- Weber F, Wulf H, Saeidi G. Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. *Canadian Journal of Anesthesia* 2003;50:470-475.
- Malinovsky JM, Populaire C, Cozian A, Lepage JY, Lejus C, Pinaud M. Premedication with midazolam in children. Effect of intranasal, rectal and oral routes on plasma midazolam concentrations. *Anaesthesia.* 1995; 50(4):351-354.
- ZamaniMoghadam A, BighamSadegh A, Sharifi S, Habibian S. Comparison of intranasal administration of diazepam, midazolam and xylazine in Pigeons: Clinical evaluation. *Iranian Journal of Veterinary Science and Technology.* 2009 ;1(1):19-26
- Vesal N, Zare P. Clinical evaluation of intranasal benzodiazepines, α_2 -agonists and their antagonists in canaries. *Veterinary Anaesthesia and Analgesia.* 2006; 33:143-148.
- Vesal N, Eskandari M-H. Sedative effects of midazolam and xylazine with or without ketamine and detomidine alone following intranasal administration in Ring-necked Parakeets. *Journal of the American Veterinary Medical Association.* 2006;228(3):383-388.
- Weiland L C, Kluge K, Kutter A P, Kronen WP. Clinical evaluation of intranasal medetomidine-ketamine and medetomidine-S(+)-ketamine for induction of anaesthesia in rabbits in two centres with two different administration techniques. *Veterinary Anaesthesia and Analgesia.* 2016; doi:10.1111/vaa.12408
- Araghi M, Azizi S, Vesal N, Dalir-Naghade B. Evaluation of the Sedative Effects of Diazepam, Midazolam, and Xylazine After Intranasal Administration in Juvenile Ostriches (*Struthio camelus*). *Journal of Avian Medicine and Surgery.* 2016;30(3):221-226.
- Kilic N, Pasa S. Cardiopulmonary effects of propofol compared with those of a medetomidine-ketamine combination in the common buzzards (*Buteo buteo*). *Revue de Médecine Veterinaire.* 2009;160(3):154-159.
- Ludders J-W, Matthews N. Anesthesia and immobilization of birds. In: Thumson JC, Tranquilli WJ, Benson GJ, eds. *Lumb and Jones' veterinary anesthesia.* 3rd ed. Baltimore: The William & Wilkins Co, 1996
- Walbergh E-J, Wills R-J, Eckhart J. Plasma concentrations of midazolam in children following intranasal administration. *Anesthesiology.* 1991; 74(2):233-235.
- Robertson S-A, Eberhart S. Efficacy of the intranasal route for administration of anesthetic agents to adult rabbits. *Laboratory Animal Science.* 1994; 44(2):159-165.
- Cattet M-R, Caulkett N-A, Wilson C, Vandenbrink T, Brook RK. Intranasal administration of xylazine to reduce stress in elk captured by net gun. *Journal of wildlife diseases.* 2004;40(3):562-565.
- Mans C, Guzman D, Lahner L- L, Paul-Murphy J, Sladky KK. Intranasal midazolam induces conscious sedation and attenuates the acute stress response in manually restrained Hispaniolan amazon parrots (*Amazona ventralis*). *Journal of Avian Medicine and Surgery.* 2012; 26(3):130-139.
- Schnellbacher R-W, Hernandez S-M, Tuberville T-D, Mayer J, Arnold RD. The Efficacy of Intranasal Administration of Dexmedetomidine and Ketamine to Yellow-Bellied Sliders (*Trachemys scripta scripta*). *Herpetological Medicine and Surgery.* 2012;22(3-4):91-94.
- Louon A, Reddy V-G. Nasal midazolam and ketamine for pediatric sedation during computerised tomography. *Acta anaesthesiologica Scandinavica.* 1994;38:259-261.
- Klein E-J, Brown J-C, Kobayashi A, Osincup D, Seidel K. A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. *Annals of Emergency Medicine.* 2011; 58(4):323-329.

چکیده

بیهوشی و آرام بخشی زایلازین، دیازپام و میدازولام در ترکیب با کتامین یا بدون آن به روش تزریق داخل بینی در کلاغ نوک قرمز (*Pyrhacorax pyrrhacorax*): ارزیابی بالینی

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هدف- مقایسه اثر آرام بخشی و بیهوشی زایلازین، دیازپام و میدازولام در ترکیب با کتامین یا بدون آن به روش تزریق داخل بینی در کلاغ نوک قرمز

طرح مطالعه- مطالعه تجربی در شرایط زنده

حیوانات- هفت کلاغ سالم

روش کار- هفت عدد کلاغ سالم غیراهلی از هر دو جنس با میانگین وزنی $232/54 \pm 14/5$ گرم با زایلازین (۸ mg/kg)، دیازپام (۸ mg/kg)، میدازولام (۸ mg/kg) به تنهایی یا ترکیب با کتامین (۳۰ mg/kg) یک هفته در میان آرام یا بیهوش شدند.

نتایج- با تزریق داخل بینی داروها آرام بخشی یا بیهوشی در تمام گروه‌ها ایجاد شد.

نتیجه‌گیری و کاربرد بالینی- این مطالعه نشان داد که استفاده از داروهای زایلازین، دیازپام و میدازولام به تنهایی یا همراه با کتامین می‌توانند آرام بخشی قابل قبولی به صورت داخل بینی در کلاغ ایجاد کنند. هرچند که تمامی این پروتکل‌ها برای اعمال جراحی مناسب نیست.

کلمات کلیدی- بیهوشی، آرام بخشی، تزریق داخل بینی، کلاغ نوک قرمز.