

Clinical Evaluation of General Anesthesia with a Combination of Ketamine HCL and Diazepam in Pigeons

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Abstract: This study was performed to investigate the clinical effects of ketamine, diazepam and ketamine/diazepam combination in general anesthesia. Total of 32 pigeons with body weight ranged from 280-300 g were randomly designed in four groups with 8 birds. In the group D:0.5 mL mixture of diazepam (0.2 mg kg⁻¹) and normal saline. In the group K:0.5 mL mixture of ketamine 5% (30 mg kg⁻¹) and normal saline. In the group KD:0.5 mL combination of ketamine 5% (10 mg kg⁻¹), diazepam (0.2 mg kg⁻¹) and normal saline and in the group C:0.5 mL of normal saline was administered intramuscularly. Standard thermal conditions of operating room demonstrated that general anesthesia have not been observed in group C. In group D, sedative effect and a muscle relaxation of diazepam without complete loss of general anesthesia was observed. Onset time of anesthesia in group KD was significantly quicker than group K (p<0.05). Duration of anesthesia in group KD was significantly higher than group K (p<0.05). Recovery was longer in group KD as compared to group K but the difference was not statistically significant (p>0.05). The birds in group KD were calm and sedated with more muscle relaxation during the study but in group K the birds were excited and behavioral incoordination and also drop of temperature were recorded. The results of this study showed that the combination of ketamine HCL by low dose and diazepam overcome the side effects of ketamine alone and caused more rapid induction, increase in duration of anesthesia, smooth and slow recovery and more muscle relaxation. Use of ketamine HCL 10 mg kg⁻¹ + diazepam 0.2 mg kg⁻¹ for current anesthesia in pigeons is recommended.

Key words: Ketamine, diazepam, anesthesia, recovery, pigeons, Iran

INTRODUCTION

Avian anaesthetic and surgical techniques have progressed greatly in the last decade. The choice of anaesthesia and route of administration is often as important as the surgical procedure itself (Forbes, 1998). General anaesthesia in various avian species may be produced by administration of either inhalant or parenteral injectable agents (Athar *et al.*, 1996). Injectable anaesthetics and sedatives can be placed in vein, muscle or intraosseous (Harrison, 1986). Although, inhalation anaesthesia is preferred for birds but requires expensive equipment. The use of an injectable agent in comparison with an inhalant anaesthetic agent may have the advantage of increased speed of induction of anaesthesia, the need for minimal equipment and low cost (Athar *et al.*, 1996; Durrani *et al.*, 2009). Several injectable drugs were used in birds. Include barbiturates, chloral hydrate, phenothiazine derivatives, alpha₂ agonists, ketamine and propofol (Hall *et al.*, 2001; Krajka and Juranova, 1994; Machin and Caulkett, 1998). Ketamine is a dissociative anaesthetic which can be used for induction of general

anaesthesia in many species by either the intravenous, intramuscular or intraosseous route (Atalan *et al.*, 2002; Athar *et al.*, 1996; Durrani *et al.*, 2008). When ketamine is used as sole anesthetic agent, it tends to cause poor muscle relaxation, muscle tremors, myotonic contractions, opisthotonus, persistent pain reflex responses and rough recoveries (Patrick, 2005; Valverde *et al.*, 1993; Wright, 1982). It is most often combined with other agents (alpha₂ agonists, diazepam or azaperone), depending on the species involved (Atalan *et al.*, 2002; Durrani *et al.*, 2009; Lumeij and Deenik, 2003; Valverde *et al.*, 1993). Diazepam has a potent, muscle relaxant and anticonvulsant effects that has been used in a wide range of wild and domestic animals and birds (Lees, 1991; Lumeij and Deenik, 2003). Diazepam and ketamine have synergistic effect, results in smooth recovery and better muscle relaxation (Patrick, 2005; Varner *et al.*, 2004). Their efficacy is enhanced while minimizing their untoward effects. The purpose of this study was to compare the clinical effects (time to onset, duration of anesthesia, duration of recovery, excitement, muscular relaxation, palpebral and pedal reflexes and cloacal temperature) of

intramuscular administration of a diazepam/ketamine combination with individual sedative and anaesthetic efficacy of diazepam and ketamine in pigeons, respectively.

MATERIALS AND METHODS

Birds: About 32 healthy adult pigeons of either sex (9 males and 23 females) with body weight ranged from 280-300 g were used in the study. All the pigeons were from a same flock and their ages were between 1 and 2 years. All birds were kept for 2 weeks in a quiet room (with groups of 8 birds per cage) to acclimatize to the new environment and fed with a wheat-based diet in accordance to the previous feeding regimen. The pigeons had free access to water and food except 1 h prior to drug administration to minimise the chances of vomiting. Just before the commencement of experiment, the birds were judged to be in good health based on complete physical examinations and clinical evaluation.

Experiment procedure: Birds were divided randomly into four equal groups: D, Diazepam (0.2 mg kg^{-1}), K, Ketamine (30 mg kg^{-1}), KD, Ketamine/Diazepam combination ($10 \text{ mg kg}^{-1} + 0.2 \text{ mg kg}^{-1}$, respectively) and C (Control) 0.5 mL of normal saline. All treatments were administered intramuscularly in to the deep pectoral muscle using an insulin syringe. The medications dosage in groups D, K and KD was diluted in normal saline to a final volume of 0.5 mL.

Post-treatment monitoring: After drug administration each bird was placed in sternal recumbency in separate cages for observation. Noise, movement and other stimuli were minimized after drug administration. The clinical parameters were evaluated for each pigeon as follows:

- The severity of opisthotonus was scored 0-4; lack of opisthotonus was scored 0 and those with opisthotonus, based on its severity was scored 4 at the maximum
- Onset of anesthesia; time interval (in minute) from administration of drug to ataxia, falling and loss of consciousness
- Duration of anesthesia; time interval (in minute) from loss of consciousness to reappearance of sensation
- Eyelids conditions; based on closed, half-opened and opened, eyelids were scored -, + and ++, respectively
- Duration of recovery; time interval (in minute) from the return of responses to complete consciousness and standing without ataxia

- The severity of excitements and behavioral incoordination such as wing fluttering were scored 0-1; the loss of excitement were scored 0 and the birds showed positive response to this parameter were scored 1 at the maximum based on its volume and intensity
- Muscular relaxation was recorded in the muscles of the neck, wings and legs. The ease with which the wings of birds could be opened, their hind limbs could be bent without resistance and the flaccid neck could be pressed was recorded as the extent of muscle relaxation. It was graded on a 0-3 scoring scale as: 0 (weak relaxation) = Almostly closed wings and stiff limbs; 1.5 (moderate relaxation) = mild resistance to pressing of neck, opening of wings and bending of limbs; 3 (excellent relaxation) = flaccid neck, no resistance to opening of wings and bending of limbs
- Pedal reflex was evaluated by using a towel clamp forceps. The presence of the reflex was scored based on its severity from 0-4
- Palpebral reflex were tested by touching the eyelids with sterile cotton tip swap; lack and presence of palpebral reflex were scored - and +, respectively
- Cloacal temperature was measured by a digital thermometer before and 10 min after induction of anesthesia

Statistical analysis: Data were expressed as mean \pm SE for each group. Analysis of Variance (one-way ANOVA) and Duncan's multiple-range test were used to compare the means among different groups. An independent t-test was used to compare the mean scores of two groups. For nonparametric observations Chi-square (χ^2) test was used to compare the means among groups. All statements of significance were based on the 0.05 level of probability.

RESULTS

According to the results of this study in groups C and D no anesthesia were recorded. Opisthotonus in ketamine/diazepam combination was more severe than ketamine but the difference was not statistically significant ($p > 0.05$) while this parameter in control and diazepam were not observed during the study (Table 1). The onset of anesthesia after injection was significantly quicker with ketamine/diazepam combination ($1.5 \pm 0.23 \text{ min}$) than ketamine ($4.5 \pm 0.41 \text{ min}$) ($p < 0.05$) (Table 1). The duration of anesthesia in group KD ($14.1 \pm 1.48 \text{ min}$) was significantly higher than group K ($8.13 \pm 1.41 \text{ min}$) ($p < 0.05$) (Table 1). There were significant differences in eyelids conditions between groups KD and

Table 1: Rate of opisthotonus and times (min) for onset of anesthesia duration of anesthesia and recovery period in control treated birds (C), Ketamine treated birds (K), Diazepam treated birds (D) and Ketamine/Diazepam combination treated birds (KD)

Groups	Opisthotonus	Onset of anesthesia	Duration of anesthesia	Recovery period	Excitement
K	3.5±0.21	4.5±0.41 ^a	8.13±1.41 ^a	19.25±2.69	0.9±0.05 ^a
KD	3.8±0.35	1.5±0.23 ^b	14.1±1.48 ^b	23.12±2.85	0.2±0.04 ^b

^{a,b}Mean presented in column with different superscripts differ significantly (p<0.05); K: Birds treated with Ketamine; KD: Birds treated with Ketamine/Diazepam combination

Table 2: Rate of opisthotonus, the status of eyelids, excitement rate and response of palpebral reflex during study in pigeons of different groups

Groups	Eyelids	Palpebral reflex	Cloacal temperature (°C)
C	++	+	41.30±0.72 ^a
K	++	+	39.17±0.59 ^b
D	++	+	38.52±1.04 ^b
KD	-	+	40.93±0.86 ^a

+: Palpebral reflex present; -: Palpebral reflex absent; ++: Eyelids opened; +: Eyelids half-opened; -: Eyelids closed

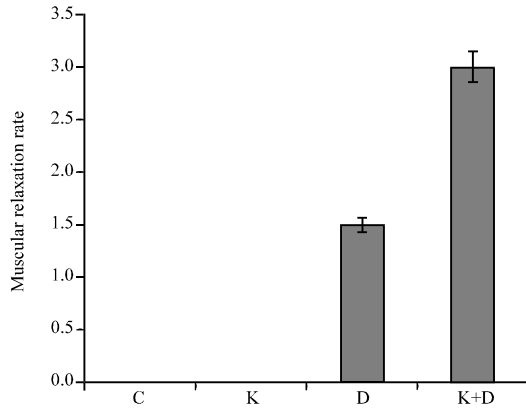


Fig. 1: The comparison of muscular relaxation in normal saline (C), Ketamine (K), Diazepam (D), Ketamine/Diazepam combination (KD)

C, K and D (p<0.05). In ketamine/diazepam treated birds the eyelids were entirely closed as compared to ketamine during the anesthesia (Table 2). The recovery was longer with ketamine/diazepam combination (23.12±2.85 min) than ketamine (19.25±2.69 min) but the difference was not statistically significant (p>0.05) (Table 1).

The excitements was significantly less in group KD as compared to group K (p<0.05) during the recovery but the birds that treated with diazepam were calm and sedated (Table 1). In current study, muscular relaxation in administration of ketamine with diazepam was significantly doubled as compared to diazepam alone during the study (p<0.05) while the relaxation effect on muscles was not observed in ketamine and control (Fig. 1). The pedal reflex was significantly lower in ketamine and diazepam/ketamine combination as compared to control and diazepam during the study

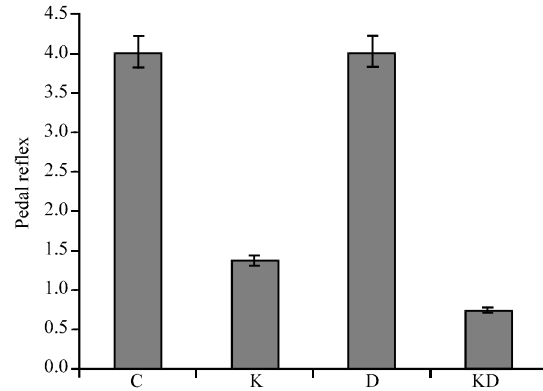


Fig. 2: The comparison of Pedal reflex in normal saline (C), Ketamine (K), Diazepam (D), Ketamine/Diazepam combination (KD)

(p<0.05). This reflex was markedly decreased with ketamine/diazepam combination than ketamine alone (Fig. 2).

There were no significant differences in palpebral reflex among groups. It was present in control, ketamine, diazepam and ketamine/diazepam combination during the study (Table 2). The cloacal temperature which was 41.30±0.72°C at the beginning of anaesthesia, significantly decreased in ketamine and diazepam 10 min after drugs administration (p<0.05) while in Ketamine/Diazepam combination remained at 40.93±0.86°C (Table 2).

DISCUSSION

Pigeons are very sensitive birds and any mishandling can lead to immediate shock and death. Many times pigeons are referred to the hospital with critical condition, requiring a safe and painless surgery. In such situations, careful selection of an anaesthetic agent at safest dose is very important. There are many anaesthetic agents to be chosen for pigeons as sole agents or combinations, e.g., alpha₂ agonists as sedatives (detomidine, xylazine), pentothal sodium, isoflurane, ketamine and diazepam (Atalan *et al.*, 2002; Durrani *et al.*, 2008, 2009; Lumeij and Deenik, 2003). Combination of ketamine and diazepam or xylazine was routinely administered for general anesthesia in birds (Durrani *et al.*, 2009; Patrick, 2005; Varner *et al.*, 2004).

The benzodiazepines provide muscle relaxation, sedation and smooth recovery. Diazepam and midazolam are usually used in combination with ketamine in birds (Lumeij and Deenik, 2003; Varner *et al.*, 2004). Ketamine is rarely advised for use alone in birds. According to Athar *et al.* (1996), ketamine has a wide margin of safety up to 10 times the usual dose normally required for

toxicity. Since, respiratory depression may occur following toxicity, supportive ventilation and administration of doxapram are suggested in such cases. However, myoclonic contraction is an adverse complication commonly associated with ketamine that can be controlled by ultra-short-acting barbiturates, diazepam or midazolam but the use of combinations to avoid this effect is preferable.

It is important to use an adequate amount of ketamine in birds because of dosages and anesthetic response are variable among species (Wright, 1982). Dosage of ketamine is approximately 10-60 mg kg⁻¹ IM or IV with larger birds (>1000 g) requiring a lower dose per kilogram (10 mg kg⁻¹). The adequate dose for intramuscular and intravenous diazepam administration in birds is 0.2-1 mg kg⁻¹ (Patrick, 2005). In present study, the determined dosage for ketamine was as well as half determined dose of this drugs in pigeons (Durrani *et al.*, 2008, 2009; Lumeij and Deenik, 2003). There is a few document in current literature about ideal intramuscular dosage of diazepam/ketamine combination in light anesthesia of pigeon.

This is the reason for using low dosage of ketamine and diazepam in this current study. In current study, ketamine/diazepam combination induced a fast and smooth induction of anaesthesia while ketamine induced a slow and smooth anaesthesia. Duration of anesthesia with ketamine/diazepam combination (14.1±1.48 min) obtained in the study is long than 8.13±1.41 min obtained with ketamine. Diazepam is highly lipid-soluble and is widely distributed throughout the body after administration and it can be redistributed into muscle and adipose tissue (Bateson, 2002). Researchers proposed that diazepam accumulates in adipose tissues and redistributes through the body therefore duration of anaesthesia was longer in diazepam administration in comparison with ketamine. The increase in anesthesia time by this is a new composition that provides an ideal and suitable time for current surgeries. This finding is approximately in agreement with Paul-Murphy *et al.* (1999) who reported the average of 15 min is needed in current operations of birds, although these researchers referred to other related parameters such as the experience of surgeon and operation condition. In present study, the recovery was smooth but slow in ketamine/diazepam combination treated birds.

This observation is similar to those reported by Lumeij and Deenik (2003) and Varner *et al.* (2004). In ketamine treated birds, recovery was rough (severe convulsions and wing fluttering) that is the same with the findings of Atalan *et al.* (2002) who reported rough recovery is due to dissociative characteristics of

ketamine anesthesia. The excitements and behavioral incoordination such as wing fluttering was due to dissociative effect of the ketamine (Hall *et al.*, 2001). In combination of ketamine and diazepam, the reduction of side effects during the recovery could be the result of a low dose of ketamine in this group as compared to ketamine alone as well as administering sedatives like diazepam. In this study, muscular relaxation was significantly higher ketamine/diazepam combination than diazepam ($p < 0.05$). Significant increasing of muscular relaxation in this combination associated to diazepam with muscle relaxant properties (Lumeij and Deenik, 2003; Varner *et al.*, 2004). Poor muscle relaxation could be expected in the pigeons because of pharmacological effects of the ketamine alone (Atalan *et al.*, 2002; Wright, 1982).

The presence of palpebral reflex in ketamine administered birds is previously reported by many researchers (Durrani *et al.*, 2008, 2009) which was also observed in the study. In current study, interestingly, cloacal temperature dropped to 39.17±0.59°C in ketamine while it remained 40.93±0.86°C in ketamine/diazepam combination within 10 min of administration of anaesthetic agents.

Based on the results of current study, addition of muscular injection of diazepam/normal saline mixture could not induce any anesthesia but sedative effect and muscle relaxation were observed during the study. This finding is in accordance with former investigations (Lumeij and Deenik, 2003; Varner *et al.*, 2004).

CONCLUSION

Consequently, in this study solution volume did not play any role for induction of anesthesia. The addition of diazepam to ketamine provides a better condition for the surgeon to do a current operation because of sedative effect of diazepam and its prolongation effect in general anesthesia.

Furthermore, ketamine/diazepam combination caused more rapid induction, increase in duration of anesthesia, smooth recovery and more muscle relaxation without any side effects that it can be considered as an important protocol in light anesthesia of pigeons.

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