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The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2021; SP-10(7): 79-83

www.thepharmajournal.com
Received: 10-05-2021
Accepted: 12-06-2021

Varun Sastry
Department of Veterinary Surgery and Radiology, Veterinary College, Hebbal, Bangalore, Karnataka, India

BN Nagaraja
Department of Veterinary Surgery and Radiology, Veterinary College, Hebbal, Bangalore, Karnataka, India

KM Srinivasa Murthy
Department of Veterinary Surgery and Radiology, Veterinary College, Hebbal, Bangalore, Karnataka, India

V Mahesh
Department of Veterinary Surgery and Radiology, Veterinary College, Hebbal, Bangalore, Karnataka, India

Corresponding Author:
Varun Sastry
Department of Veterinary Surgery and Radiology, Veterinary College, Hebbal, Bangalore, Karnataka, India

A study on sedation, induction and recovery characteristics observed on usage of midazolam is used as preanesthetic, etomidate as the induction agent under isoflurane maintenance in renal compromised dogs

Varun Sastry, BN Nagaraja, KM Srinivasa Murthy and V Mahesh

Abstract
The objective of the present research was to study the sedation, induction and recovery characteristics of the anesthetic protocol consisting of Midazolam as the pre-anesthetic, Etomidate as the induction agent and Isoflurane for maintenance in renal compromised dogs. The study was conducted on six clinical cases of dogs with either acute or chronic kidney disease (stage-I and stage-II) undergoing the required surgical procedure using the anesthetic protocol under study. Ceftriaxone was administered intravenously @ 25 mg/kg BW, 30 minutes prior to induction. Butorphanol tartrate was administered @ 0.3 mg/kg BW,15 minutes before induction as a pre-emptive analgesic. Midazolam Hydrochloride was administered as the sedative @ 0.3 mg/kg BW. Etomidate was administered for induction of anesthesia @ 1.5-3 mg/kg BW, ten minutes after the administration of Midazolam. 1/10th of the dose was administered every six seconds till the desired plane of anesthesia sufficient to intubate the dog was achieved. Intubation was performed soon after the jaw tone and swallowing reflexes were abolished. Inhalation anesthesia was administered along with oxygen throughout the surgery. Tramadol hydrochloride was administered @ 4 mg/kg BW, IV, post-operatively. The goal was to achieve satisfactory level of anesthesia, enough to allow the surgical procedure to be carried out while maintaining all the hemodynamic parameters as close to the normal limits as possible so as to minimally influence the already compromised renal function. Quantitative parameters like time taken for onset of sedation, time taken for induction of anesthesia with Etomidate, recovery time, extubation time, time for sternal recumbency and time for unassisted standing were studied and qualitative evaluation of sedation, induction and recovery using scoring systems was carried out. In conclusion, the anesthetic protocol was found to be safe and effective for use in renal compromised dogs and provided fair quality of sedation, rapid and smooth induction and a quick and fairly smooth recovery while minimally influencing renal function.

Keywords: midazolam, etomidate, isoflurane, renal compromised dogs

Introduction
Dogs with compromised renal function may require anesthesia for many reasons like planned dental and orthopedic procedures, mass and tumor excisions, diagnostic procedures or in emergencies such as trauma and pyometra. A dog presented for surgery may be clinically normal and may also not show significant changes in the hematological parameters but may have only a small percentage of functional kidney tissue left and when these patients are challenged by highly stressful stimuli like anesthesia and surgery, it might lead to anesthetic complications and an iatrogenic cause of clinically evident renal failure. The effects of anesthesia on renal function may occur through direct action of some anesthetics that are nephrotoxic or through indirect responses on neuroendocrine and hemodynamic parameters with relatively nontoxic drugs (McKelvey and Hollingshead, 2000) [11]. Alpha-2 adrenoceptor agonists and Barbiturates which are commonly used anesthetics owing to their desirable sedative, induction and recovery characteristics have been shown to alter the hemodynamics. Alpha-2 adrenoceptor agonists initially raise the mean arterial blood pressure followed by a long-lasting decrease, therefore, decrease sympathetic outflow and reduce cardiac output which greatly affect the renal perfusion and result in consistent changes in renal function (Newell *et al*., 1997) [14] and hence is vindicated in dogs with compromised renal function.
Benzodiazepines such as Diazepam and Midazolam are favored for their rapid onset of action, minimal negative cardiovascular effects and anticonvulsant properties (Olkkola and Ahonen

2008) [15] but produce undesirable behaviour during sedation and recovery. High doses of Midazolam (i.e., 10 mg/kg, BW) is known to cause agitation in normovolemic dogs but induces unconsciousness or sleepiness in acutely hypovolemic dogs and healthy dogs have a higher incidence of paradoxical reactions (Adams *et al*., 1985) [1] whereas it is diminished in pediatric, geriatric, and systemically ill dogs (Muir *et al*., 2011) [13]. The paradoxical effect of transient agitation after administration of Benzodiazepines may be caused by the 'disinhibitory' effects of Benzodiazepines on suppressed behavior (Booth, 1988) [3] or loss of muscle tone and co-ordination that was experienced following administration of Midazolam (Court and Greenblatt, 1992) [4]. Butorphanol as an opioid along with Midazolam minimizes excitation and enhances tranquilization in dogs (Kojima *et al*. 2002) [8]. The various paradoxical behavioral reactions observed after Midazolam administration includes agitation, excitation, hyper-responsiveness to noise, restlessness, change in handling behavior, aggression, ataxia, increased appetite, drooling, licking, chewing, vocalization, and nosing (Sano *et al*., 2003) [18]. Etomidate is a non-barbiturate imidazole derivative induction agent for general anesthesia which causes minimal change in hemodynamic stability, initially used for the induction of anesthesia in risky patients (Pascoe *et al.*, 1992) [16]. The side-effects of Etomidate administration in dogs include excitement, myoclonus, pain on injection, vomiting, and apnea during induction and these seem get attenuated or eliminated by the administration of Diazepam, Acepromazine, or Morphine prior to Etomidate administration (Muir and Mason, 1989) [12]. Isoflurane is a popular anesthetic agent in Veterinary practice because of its cardiovascular stability, low blood/gas partition coefficient, minimal dependence on hepatic metabolism and renal clearance (Topal *et al.*, 2003) [19] and is virtually non-toxic to the kidneys and liver (Werner, 1987) [20]. Signs characterized by excitement, some paddling, vocalization, trembling, or vomiting is a common observation during recovery from Isoflurane anesthesia (Lozano *et al*., 2009) [10].

Materials and Methods

The study was conducted on six clinical cases of dogs with either acute or chronic kidney disease, which were presented for various surgical conditions to Department of Surgery and Radiology, Veterinary College Hospital, KVAFSU, Hebbal, Bangalore. All the dogs which had acute kidney injury and stage-I, stage-II chronic kidney disease were subjected to the required surgical procedure using the anesthetic protocol under study. Butorphanol tartrate was administered @ 0.3 mg/kg BW, IV, 15 minutes before induction of anesthesia and before the administration of Midazolam. Midazolam Hydrochloride was administered @ 0.3 mg/kg BW, IV, ten minutes before induction. Ceftriaxone was administered intravenously @ 25 mg/kg BW, IV, 30 minutes prior to induction. Tramadol hydrochloride was administered @ 4 mg/kg BW, IV after the end of surgical procedure and orally @ 4 mg/kg, as part of post-operative analgesia. Etomidate was administered for induction of anesthesia @ 1.5-3 mg/kg BW, IV. 1/10th of the dose was administered every six seconds till the desired plane of anesthesia sufficient to intubate the dog was achieved. Intubation was performed soon after the jaw tone and swallowing reflexes were abolished. Inhalation anesthesia was administered along with oxygen till the animal reached surgical plane of anesthesia, marked by absence of pedal reflex, ventro-medial deviation of eyeball and deep abdominal breathing with decreased respiratory rate. Surgical plane of anesthesia was maintained throughout the period of surgery. The goal was to achieve satisfactory level of anesthesia, enough to allow the surgical procedure to be carried out while maintaining all the hemodynamic parameters as close to the normal limits as possible. Quantitative parameters like time taken for onset of sedation, time taken for induction of anesthesia with Etomidate, recovery time, extubation time, time for sternal recumbency and time for unassisted standing were recorded. All the cases were clinically evaluated for quality of sedation based on the criteria given by Jimenez *et al.* (2012) [6] (Table 1), for quality of induction based on the criteria given by Saini (2017) [17] (Table 2) and the scale provided by Lozano *et al*. (2009) [10] was used to score the recovery of dogs (Table 3).

The surgical procedures performed using the anesthetic protocol were mammary tumour excision and mass excision. An elliptical incision was made around the tumour or mass after aseptic preparation of the surgical site. A combination of blunt and sharp dissection of the subcutaneous fascia was performed to isolate the tumour or mass. Hemostasis was achieved using hemostats and ligatures and the mass or tumour was excised. The wound was closed routinely in three layers using absorbable sutures for muscles and subcutaneous tissue and non-absorbable sutures for closure of the skin.

Physiological parameters namely rectal temperature, respiratory rate, heart rate and pulse rate were measured just before administration and monitored throughout the period of anesthesia. Soon after the completion of the surgical procedure, the dogs were shifted to the recovery room and left undisturbed till the dog stood on its own and qualitative characteristics during recovery were observed and recorded. Recovery phase of anesthesia was marked from the point of turning the vaporizer to 'OFF', which was done after the last skin suture was completed. Recovery time was the time elapsed between termination of Isoflurane anesthesia to return of pedal reflex and central positioning of the eyeball from ventromedial position. The time taken by the dog to lift its head and neck while in lateral recumbency after the termination of Isoflurane anesthesia (turning the vaporizer setting to 'OFF') was marked as time taken for return of head righting reflex.

Table 1: Simple Descriptive Scale of sedation scoring in dogs used during the study (Jimenez *et al.*, 2012) [6]

Score	Description
1	**Not very/not sedated**: Able to stand up and walk. Fully responsive. No signs of depression, drowsiness, ataxia or altered character with respect to how it was without any medication
2	**Slightly sedated**: Able to stand up and walk. Fully responsive but slow to react. Mild signs of depression, drowsiness, ataxia or mild changes in character
3	**Sedated**: Able to stand up but reluctant to walk. Slow reaction to stimuli. Signs of depression, drowsiness, ataxia and changed character
4	**Deeply/very sedated**: Unable to stand up and walk. Unresponsive to stimuli. Depressed, drowsy and sleepy

Table 2: Induction scoring system used in the study (Saini, 2017) [17]

Grade	Quality of induction
Excellent (4)	Rapid disappearance of laryngeal reflex with smooth induction
Good (3)	Intubation with depressed laryngeal reflex or mild body movement during intubation
Fair (2)	If it is necessary to use Lignocaine spray to control laryngeal spasms
Poor (1)	Difficult to intubate. Dog shows obvious signs of distress

Table 3: Simple Descriptive Scale of Recovery Scoring in dogs used during the study. (Lozano *et al.*, 2009) [10]

Grade	Quality of Recovery
1	Very smooth, no excitement, vocalization, trembling or vomiting. No convulsions
2	Quite smooth, a little excitement. No paddling, vocalization, trembling or vomiting. No convulsions
3	Moderately smooth with excitement. Some paddling, vocalization, trembling or vomiting observed. No convulsions
4	Not smooth and with excitement. Paddling, vocalization, trembling or vomiting observed. No convulsions
5	Extreme excitement observed with aggression, vocalization, violent movements or convulsions observed. Rescue sedation or anticonvulsant therapy needed

Results

The mean ± SE value of duration to attain sedation after administration of Midazolam was 109.33 ± 19.14 seconds. After the onset of sedation, the dogs were lying down but still able to rise with stimulus of noise and touch, paradoxical excitement was noticed in one case characterized by vocalization, paddling of the legs, chewing movement of the jaws and horizontal nystagmus. The mean sedation score obtained during the study was 2.33 ± 0.49.

Table 4: Evaluation of sedation using the simple descriptive scale during the study period.

Sedation Score	
Category	**No. of dogs**
1	n = 2
2	n = 1
3	n = 2
4	n = 1
Mean ± SE - 2.33 ± 0.49	

The quality of induction achieved was given a score of 3.50 ± 0.33. The mean ± SE value of duration required to attain optimal level of induction with Etomidate was 57.4 ± 5.06 seconds. The plane of anesthesia attained was sufficient to intubate the dog and characterized by an absence of palpebral reflex, sluggish pedal reflex, ventromedial positioning of the eyeball, abolishment of jaw tone and the gag reflex. Vomiting was noticed in one out of the six dogs, pain on injection was observed in three out of the six dogs and myoclonus was observed in two of the six dogs during induction.

Table 5: Evaluation of quality of anesthetic induction during the study period.

Quality of Induction	
Grade	**No. of dogs**
Excellent (4)	n = 4
Good (3)	n = 1
Fair (2)	n = 1
Poor (1)	n = 0
Mean ± SE - 3.50 ± 0.33	

The recovery was fairly smooth and quick in most of the dogs under the study. Two dogs showed mild involuntary limb movements. Vocalization was observed in one dog and nystagmus was noticed in two dogs. Vomiting, tremors, seizures, or death during recovery phase were not observed in any of the dogs. The quality of recovery was scored and the mean ± SE recovery score was 2.50 ± 0.24.

Table 6: Evaluation of quality of Recovery from anesthesia during the study

Quality of Recovery	
Grade	**No. of dogs**
1	n = 1
2	n = 2
3	n = 2
4	n = 1
5	n = 0
Mean ± SE	2.50 ± 0.24

The mean duration for return of pedal reflex, regaining head righting reflex, attainment of sternal recumbency and the duration to stand without assistance were 107 ± 15.67 seconds, 6.33 ± 1.3 minutes, 10.8 ± 1.62 minutes, and 19.83 ± 1.60 minutes, respectively (Table 7)

Table 7: Mean ± SE values of various quantitative recovery parameters recorded during the study period.

Sl No.	Parameter	Value
1	Time taken for return of pedal reflex from the point of termination of anaesthesia (Recovery Time)	107.00 ± 15.67 seconds
2	Time of extubation from the point of termination of anaesthesia	130.40 ± 15.09 seconds
3	Time taken for return of head righting reflex from the point of termination of anaesthesia	6.33 ± 1.3 minutes
4	Time for sternal recumbency from the point of termination of anaesthesia.	10.8 ± 1.62 minutes
5	Time taken to stand from the point of termination of anaesthesia.	19.83 ± 1.60 minutes

Discussion

The mean duration to attain sedation after administration of Midazolam was 109.33 ± 19.14 seconds. Similar behavioural changes within five minutes after intravenous administration of Midazolam were also observed by Court and Greenblatt (1992) [4]. Paradoxical excitement which was observed in one dog after the administration of Midazolam in the present study was also noted by Booth (1988) [3] and Court and Greenblatt (1992) [4]. The sedation score obtained using the scale given by Jiménez *et al*. (2012) [6] was 2.33 ± 0.49 and agreed with the findings of Kropf and Hughes (2018) [9]. The mean duration to attain optimal level of induction with Etomidate was 57.4 ± 5.06 seconds. Gopal (2015) reported induction time of around 27.6 ± 4.2 seconds when Xylazine was co-administered with Midazolam. Saini (2017) [17] recorded the induction time of 70.0 ± 4.3 seconds using Etomidate in Glycopyrrolate and Midazolam premedicated dogs which finding was slightly longer compared to the findings of this study. The shorter induction time observed in the present study might be attributed to the use of Butorphanol as pre-emptive analgesic which also caused mild sedation.

The mean recovery score obtained using the simple descriptive scale (SDS) in the present study was 2.50 ± 0.24 which represented a slightly lower quality of recovery and was in approximation with the findings of Lozano *et al.* (2009) [10]. The relatively low recovery score observed in the present study could be attributed to the use of Midazolam as the pre-anaesthetic (Kropf and Hughes, 2019). Hampton *et al.* (2019) [5] also reported emergence delirium which manifested as a hyperactive motor behaviour in the immediate post-anaesthetic period, occasional paddling, flailing of short duration, brief excitement when Isoflurane was used for maintenance of anaesthesia after induction with Tiletamine-Zolazepam, Alfaxalone, Ketamine-Diazepam or Propofol. Various quantitative recovery characteristics recorded in the present study like the mean duration for return of pedal reflex, regaining head righting reflex, attainment of sternal recumbency and the duration to stand without assistance could be due to the relatively low depth of sedation provided by Midazolam (Kropf and Hughes, 2019), rapid clearance of Etomidate (Kay, 1976) [7] and Isoflurane owing to its low blood-gas solubility (Auer, 1978) [2], and minimal dependence of Isoflurane on body metabolism for clearance.

In conclusion, although the anaesthetic protocol provided only a fair quality of sedation, induction and recovery, it was found to be safe and effective for use in renal compromised dogs and minimally influenced renal function. However, the anesthetic protocol was found to be less effective on ferocious and excited dogs because the fair quality of sedation achieved was not sufficient to carry out the necessary pre-operative procedures.

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