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Sodagar BN
Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

Patel PB
Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

Barot HM
Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Anand, Gujarat, India

Sutaria PT
Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

Chaudhari JD
Department of Animal Genetics and Breeding, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

Corresponding Author
Sodagar BN
Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India

Assessment of atropine-tiletamine-zolazepam and dexmedetomidine-ketamine-butorphanol anaesthesia for ovariohysterectomy in non-descript cats

Sodagar BN, Patel PB, Barot HM, Sutaria PT and Chaudhari JD

Abstract
This study was performed to assess clinical efficacy of two anaesthetic protocols Atropine-Tiletamine-Zolazepam (ATZ) and Dexmedetomidine-Ketamine-Butorphanol (DKB) anaesthesia for spaying in domestic felines. Patients were monitored for 120 minutes to study anaesthetic intervals, depth of anaesthesia and quality of anaesthesia. ATZ provided rapid sedation and induction compared to DKB while duration of antinociception and degree of muscle relaxation was better in DKB. In conclusion, ATZ renders surgical anaesthesia providing smaller window for completion of surgery in comparison to DKB.

Keywords: Feline surgery, anaesthetic parameters, tiletamine-zolazepam, dexmedetomidine-ketamine-butorphanol

Introduction
An intramuscular (IM) anaesthetic protocol renders obvious benefits in small veterinary clinical facilities with limited availability of anaesthetic equipment. Moreover, fractious nature of some cats, adds-on to the reason for devising an anaesthetic protocol that is well absorbed via IM route and offer reliable sedation, loss of consciousness, muscle relaxation and analgesia, sufficient enough to perform an operative procedure (Parra *et al.*, 2017) [21].
Tiletamine-zolazepam combination was developed in late 1960s and have been in use ever since. It is frequently used for feline sedation and anaesthesia during minor procedures or surgery alone or in combination with other agents like various alpha-2-agonists, phenolic compounds, dissociative agents or opioids (Simon and Steagall, 2020) [25].
Alpha-2-agonists provide reliable sedation and short-term analgesia, hence are a widely used group of sedatives in feline medicine (Cullen and Reynoldson, 1997; Nagore *et al*., 2013) [4, 18]. It is a common practice to combine alpha-2-agonists in low doses (Ossipov *et al*., 1990) [19] with opioids for achieving good sedation and synergistic analgesia (Selmi *et al*., 2003; Slingsby and Taylor, 2008) [24, 28]. Butorphanol, after IM administration, produces rapid and variable analgesia lasting for short period (Lascelles and Robertson, 2004; Johnson *et al*., 2007) [14, 11] and when combined with dexmedetomidine, results into greater sedation and more profound muscle relaxation. Ketamine is often used to combine with opioids and alpha-2-agonists because of its high bioavailability, rapid absorption, short onset of action, analgesia and amnesia after IM administration (Hanna *et al*., 1988; Kohrs and Durieux, 1998) [11, 12] and has been found to have increased duration of anaesthesia when combined with dexmedetomidine and butorphanol (Selmi *et al*., 2003) [24].
To date, several intramuscular drug combinations have been investigated for feline anaesthesia. The purpose of this study was to evaluate the clinical efficacy of Atropine + Tiletamine + Zolazepam (ATZ) and Dexmedetomidine + Ketamine + Butorphanol (DKB) anaesthesia in cats undergoing spaying.

Material and methods
Study animals and treatments
This study was performed on 12 female cats of non-descript origin, presented for ovariohysterectomy. These cats were randomly allotted in Group I and Group II, each consisting six cats named (TZ-1, TZ-2….and so on upto DKB-6). All cats were kept off food and water for atleast 8 hours prior to administration of anaesthesia.

Cats in group I were premedicated with calculated dose of atropine sulphate [1] @ 0.04 mg/kg body weight subcutaneously, 15 minutes later tiletamine and zolazepam combination administrated at dose rate of 14.5 mg/kg body weight [2], whereas cats in group II were directly anesthetized using combination of dexmedetomidine, ketamine and butorphenol at a dose rate of 22 mcg/kg, 5 mg/kg, 0.5 mg/kg body weight, respectively. Elective ovariohysterectomy was performed using left lateral flank approach.

Time of injection, head down, onset of sternal and/or lateral recumbency, raising of head few centimetres above the ground for the first time, standing on its feet in mouse-sitting posture while trying to walk and complete return of normal mobility, temperament and wakefulness was observed and recorded to estimate time periods for onset of sedation, period of induction, duration of antinociception or surgical anesthesia, total duration of anaesthesia, duration of anaesthetic recovery and duration of anaesthetic hangover. Duration of anaesthetic hangover was classified as short (0 to 8 hours), long (8 to 16 hours), moderately long (16 to 24 hours) and very long (more than 24 hours).

Quality of anaesthesia was assessed subjectively by determining parameters local tolerance to intramuscular administration, quality of induction, degree of muscle relaxation, degree of analgesia and quality of recovery (Appendix 1).

Depth of anaesthesia was graded subjectively at 10, 15, 30, 60, 90, 120 minutes following administration of anaesthesia. Clap stimulus, ear flicker reflex, muscle tone of jaw and tongue, palpebral reflex, corneal reflex, eyeball position, status of pupils, pedal reflex and anal tone were assessed (Appendix 2) to judge the depth of anaesthesia.

Results and Discussion

Onset of sedation was typical with all cats exhibiting mydriasis, licking of nose and swaying of head before sedation, sufficient enough to cause a head down position. There were no significant differences in onset of sedation between both groups ($P>0.05$). Sedation was found to be rapid but accompanied with effects like salivation, head and neck rocking and excitatory muscular activity following tiletamine-zolazepam premedication which made (IV) injection difficult in a study conducted by Cullen and Reynoldson (1997) [4]. Volpato *et al*. (2015) [29] encountered more number of cats in dexmedetomidine-butorphanol-ketamine (DBK) group appeared well sedated compared to those in dexmedetomidine-butorphanol (DB) and noted the onset of sedation was a median value of 11 minutes and 12 minutes in combinations DBK and DB, respectively; however, the doses used in their study were much lower than those used in present study.

Although the induction appeared to have achieved faster in group I, there was no significant difference between induction times of both groups. However, 3 cats (TZ-3, TZ-4 and TZ-6) were sedated but did not appear adequately induced even after 10 minutes of anaesthetic administration, hence, inj. Propofol was administered intravenously @ 3 – 3.5 mg/Kg BW to induce and maintain anaesthesia. Similar findings were reported in pigs by Heinonen *et al*. (2009) [9], where tiletamine-zolazepam failed to induce surgical anaesthesia in 50 per cent of azaperone premedicated pigs. Cat TZ-3 exhibited lordosis (Plate 26) and positive reaction to tactile stimulation because of insufficient surgical anaesthesia hence 2% isoflurane was administered in addition to intravenous propofol to achieve surgical anaesthesia. Both Lin *et al*. (1993a) [15] and Williams *et al*. (2002) [30] noted a delayed induction requiring additional doses for sufficient anaesthetic depth in Tiletamine + Zolazepam combination. Selmi *et al*. (2003) [24] discovered time for lateral recumbency did not differ following dexmedetomidine alone or in combination with ketamine or butorphanol. Their study demonstrated lateral recumbency in maximum 3.9 ± 2.1 minutes; however, this was in contrast with findings of present study where the time to lateral recumbency was higher than that. This can be due to the fact that present study included feral cats in addition to domestic cats, which get stressed and excited easily and could have delayed induction (Sinclair, 2003) [26].

Duration of antinociception or surgical anaesthesia was significantly shorter in ATZ compared to DKB. Lin *et al*. (1993a) [15] confirms that muscle relaxation is optimum following administration Telazol® during the initial 20-25 minutes and diminishes later on suggesting that anaesthesia might not be adequate for procedures lasting longer than 25-minute duration. Chen and Chee (2005) [2] elucidated that antinociception was present for approximately 16.51 ± 6.35 minutes in low dose group containing ketamine (T_2X) and for 43.83 ± 8.4 minutes in high dose group containing ketamine and xylazine (T_4KX).

Total duration of anaesthesia was not significantly different between groups, although the period of antinociception or surgical anaesthesia was over, cats still continued to be in lateral recumbency. This effect was mainly due to delayed excretion of zolazepam which provides prolonged tranquilization effects but fails to provide surgical anaesthesia (Lin *et al*., 1993a) [15]. Heinonen *et al*. (2009) [9] demonstrated that anaesthesia lasted longer in pigs administered DBK as compared to those injected TZ.

Period of anaesthetic recovery was found to be significantly shorter following DKB anaesthesia mainly due to effect of zolazepam causing delay in anaesthetic recovery period as explained by Lin *et al*. (1993a) [15]. Biermann *et al*. (2012) [1] revealed that cats administered ketamine-dexmedetomidine achieved sternal recumbency (46 ± 8 minutes) earlier than those injected midazolam-butorphanol-dexmedetomidine (77 ± 33 minutes). These findings were similar to those achieved in present study elucidating the fact that presence of a benzodiazepine (in group I) delays the time to recovery in cats. Alike in present study, Reader *et al*. (2018) [23] encountered administration of dexmedetomidine-butorphanol led to recovery within a median time of 111.6 minutes.

Anaesthetic hangover period was found to be short in both groups. Similar findings were reported by Dhopatkar (1998) [5] where, cats anaesthetized using ketamine-xylazine and ketamine-midazolam were observed to have short anaesthetic hangover.

The reaction to intramuscular injection was moderate in both groups of cats. Lin *et al*. (1993b) [16] and Porters *et al*. (2014) [22] reported pain and vocalization in cats following intramuscular administration of anaesthetic while Granholm *et al*. (2007) [7] and McSweeny *et al*. (2012) [17] found moderate to no reaction. Degree of muscle relaxation and analgesia was found to be significantly better in group II

[1] Atropine Sulphate: Inj. Atropine sulphate, (1 mg/ml), Morvel Laboratories Pvt. Ltd., Mehsana, Gujarat.

[2] Tiletamine and zolazepam: Inj. Zoletil 50, (125 mg/vial of tiletamine and zolazepam each), Virbac Animal Health India Pvt. Ltd., Borivali, Maharashtra.

while quality of induction and recovery did not show significant differences. Pablo and Bailey (1999) [20] reported good muscle relaxation in only 60% of cats operated for ovariohysterectomy at 15mg/Kg BW of tiletamine-zolazepam while Lin *et al*. (1993a) [15], observed no improvement in muscle relaxation on increasing the dose of tiletamine-zolazepam.

Pablo and Bailey (1999) [20] stated that analgesia produced following tiletamine-zolazepam was inadequate in female kittens for ovariohysterectomy when administered at 12.3 mg/Kg body weight, respectively. Analgesia in group II was superior to group I with median score of 4 and 2.5, respectively, obviating the fact that duration of antinociception was prolonged due to presence of alpha-2-agonists. This however might also be due to deep sedative action which masked response to pain stimulus (Fernandez-Parra *et al*., 2017) [21] or increased its threshold (Slingsby and Taylor, 2008) [28].

Similarly, Pablo and Bailey (1999) [20] reported better quality of recovery in cats as compared to dogs due to extended effect of zolazepam which provided long term tranquilizing effect. Quality of recovery in a study carried out by Hunt *et al*. (2013) [10] was good in most cats but 27 % cats were reported to have poor or rough recoveries. Recovery was observed to be excellent in cats anaesthetized using ketamine, dexmedetomidine and butorphanol by Cremer and Ricco (2017) [3].

Most anaesthetic reflexes including clap stimulus, ear flicker reflex, eyeball position did not exhibit significant difference between group variation but muscle tone of jaw and tongue, palpebral reflex, corneal reflex, status of pupils and anal tone showed significantly higher median scores indicative of deeper anaesthesia following DKB protocol.

Conclusion

Onset of sedation and onset of induction was faster in Tiletamine-Zolazepam (TZ) compared to Dexmedetomidine-Ketamine-Butorphanol (DKB) anaesthesia. Quality of induction was better in TZ while quality of recovery was smoother in DKB protocol. Duration of surgical anaesthesia was significantly shorter after TZ protocol compared to DKB, where ample amount of surgical anaesthesia was observed allowing larger window for completion of surgery. Superior quality of muscle relaxation and analgesia following DKB combination compared to TZ. Anaesthetic parameters including palpebral reflex, pedal reflex, corneal reflex, muscle tone of jaw and tongue, swallowing reflex and anal sphincter tone were diminished in DKB anaesthesia compared to TZ. The tranquilizing effect of zolazepam delayed anaesthetic recovery but did not prolong anaesthetic hangover period when compared to DKB.

Table 1: Mean ± SE values of anaesthetic intervals

Anaesthetic intervals (minutes)	Group I (A-TZ)	Group II (DKB)	p-Value
Onset of sedation	1.50 ± 0.500	3.33 ± 0.760	0.158
Period of induction	2.33 ± 0.76	5.16 ± 1.077	0.127
Duration of antinociception	31.0 ± 3.214	76.5 ± 6.232	0.002
Total duration of anaesthesia	106.333 ± 9.207	99.166 ± 6.881	0.561
Period of anaesthetic recovery	161.33 ± 6.887	118 ± 9.957	0.025
Period of anaesthetic hangover	199.67 ± 8.11	265 ± 8.64	0.002

Table 2: Median scores of anaesthetic quality assessment parameters

Anaesthesia quality (median score)	Group I (A-TZ)	Group II (DKB)	p-Value
Quality of induction	2.5	3	0.240
Degree of muscle relaxation	3	4	0.041
Degree of analgesia	2.5	4	0.015
Quality of recovery	3	2	0.310

Appendix 1: Anaesthesia quality assessment

Score	Description
Quality of induction (Singh et al., 2012)	
1	Marked excitement, struggling, vocalization, urination or defecation. Firm restraint required.
2	Moderate excitation, gross movement, vocalization, urination or defecation. Restraint required.
3	Transition associated with some movements requiring restraint by a single assistant.
4	Smooth and rapid transition from conscious to anaesthetized state.
Degree of muscle relaxation (Dhopatkar, 1998) [5]	
1	Tenderness during incision; Cat tightly coiled; difficult retrieval of uterus and ovary; assistance required to hold legs apart.
2	Abdominal musculature not relaxed, Difficult retrieval of uterus and ovary.
3	Abdominal musculature a little relaxed; easy retrieval of uterus and ovary
4	Whole body gone limp; atonic abdominal musculature; very satisfactory surgical anaesthesia
Degree of analgesia (Dhopatkar, 1998) [5]	
1	Movement and/or vocalization during incision, handling of ovaries, uterus and suturing; assistance required to hold the cat; supplemental dose anaesthesia required for maintaining depth of anaesthesia
2	Muscle twitching during incision, movement and/or vocalization during handling of ovaries and uterus and while suturing
3	Slight increase in depth and rate of respiration during incision, handling of ovaries, uterus and suturing
4	No movement or vocalization or change in quality and quantity of respiration throughout the procedure; very satisfactory surgical anaesthesia
Quality of recovery (Ko et al., 2011)	

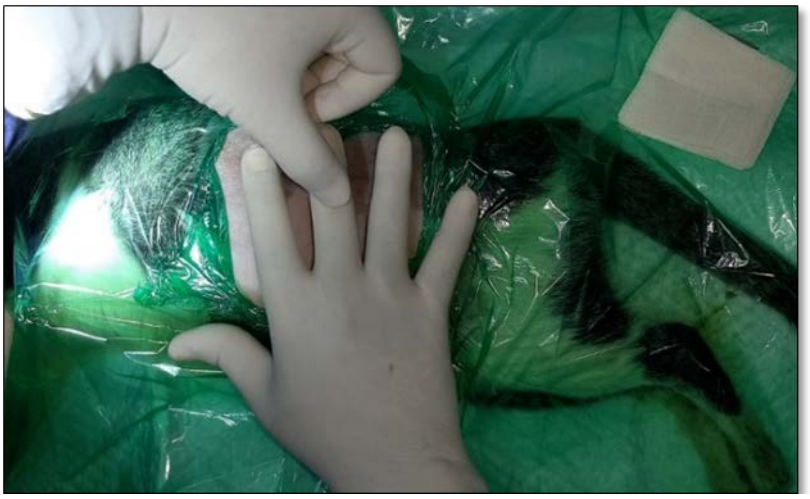
1	Prolonged struggling; unable to stand without assistance; hyperkinesis in response to manual assistance; increased rectal temperature associated with increased struggling resulting in increased metabolism
2	Some struggling; repeated attempts to stand and requires assistance to stand; very unstable when walking and unable to maintain balance; some signs of rough recovery (i.e., residual effects of anesthetic)
3	Some struggling; requires some assistance to stand; able to maintain balance once standing; minimal signs of residual effects of anesthetic
4	Assumes sternal recumbency with little or minimal struggling; stands and walks with minimal effort; no signs of residual effects of anesthetic

Appendix 2: Anaesthesia depth assessment

Score	Description
Clap stimulus: Observing response to clapping sound near head region	
0	No response to the clap stimulus
1	Occasional ear and head movement
2	Slight head or ear movements, trying to move the head
3	Rapid movements after the stimulus, turning of the head to where the stimulus originated.
Ear flicker reflex: observing response to stimulation of ear whiskers using an ear bud	
0	No response to stimulus
1	Occasional ear movement
2	Slight ear movement
3	Rapid ear movement, lowering the pinnae
Muscle tone of jaw and tongue: opening of jaws and pulling of tongue to observe muscle tone	
0	Very weak - Jaw stays open. Tongue can be easily pulled out and the cat is not able to withdraw it.
1	Weak - Jaws close partially after opening. Tongue can be pulled out, but the cat is able to withdraw it.
2	Moderate - Jaws closed after opening. Tongue cannot be pulled out, or can be pulled out only with difficulty.
3	Normal - Not allowing to open the jaws and pull tongue.
Palpebral reflex: response to gentle touching at medial canthus of eye	
0	Abolished reflex
1	Very weak reflex (very slow and occasional)
2	Intact but weak reflex (slow response)
3	Intact and strong reflex (quick blink)
Corneal reflex: response to touching corneal surface with cotton wick or ear bud	
0	Abolished reflex
1	Very weak reflex (very slow and occasional)
2	Intact but weak reflex (slow response)
3	Intact and strong reflex (quick blink)
Eyeball position: position of eyeball during anaesthesia was observed	
0	Complete ventromedial rotation
1	Moderate rotation ventrally
2	Slight rotation ventrally
3	No rotation of eyeball
Status of pupils: pupillary dilation in response to anaesthesia was graded subjectively	
0	Extremely constricted (Miosis)
1	Mildly dilated
2	Moderately dilated
3	Extremely dilated (Mydriasis)
Pedal reflex: pinching of interdigital skin to observe withdrawal response	
0	Absent or completely abolished or no withdrawal
1	Clearly weak or occasional withdrawal
2	Slightly impaired or slow and delayed withdrawal
3	Hypersensitive or normal withdrawal response
Anal tone was judged as present or absent by observing the relaxation of anal sphincter	

Drugs used in Group I (A-TZ)

Drugs used in Group II (DKB)



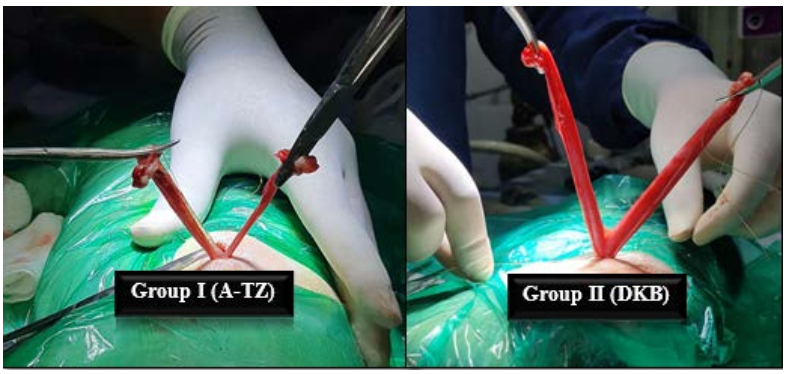
Determining site of incision using landmarks *(Dashed Yellow line – site of incision)*

Mydriasis following administration of anaesthetic combination

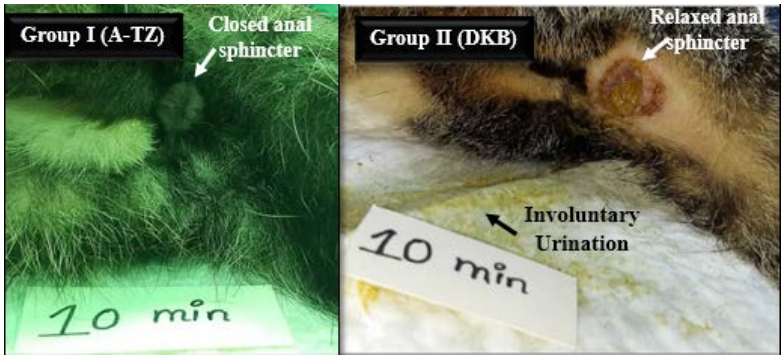
Head down position in sterno-lateral recumbency following induction

Lifting of head few centimetres above the ground for the first time

Trying to walk in mouse sitting posture



Better muscle relaxation score in Group II compared to Group I



Anal tone in Group I (present) and Group II (absent) at 10 minutes. Involuntary urination present in Group II

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