Clinical Efficacy of Tiletamine-Zolazepam and Ketamine-Diazepam Combination on Quality of Anesthesia for Ovariohysterectomy in Dog

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Abstract

The present study was undertaken to compare the anesthetic efficacy of tiletamine-zolazepam and ketamine-diazepam combination in 12 bitches presented to the TVCC, PGIVAS, Akola for ovariohysterectomies. These 12 dogs were randomly divided into two equal groups. Group I dogs were anaesthetized with tiletamine-zolazepam and Group II dogs were anaesthetized with ketamine-diazepam combination. In both the groups xylazine was used as a pre-anaesthetic. Quality of anaesthesia, assessment of anaesthesia and clinico-physiological parameters were recorded at different time intervals during the study period. The quality of anaesthesia was found to be superior in group I as compared to group II. Induction of anaesthesia was rapid and smooth in both the groups. However, duration of anaesthesia and recovery time was longer in group I as compared to group II. Smooth recovery was observed in both the groups. Rectal temperature and respiration rate was showing decreasing trend in both the groups however, these values were within normal physiological range. Heart rate in both the group was showing decreasing trend with the appearance of bradycardia during recovery in both the groups. SpO₂ level was fluctuating within normal physiological limit in both the groups. Quality of muscle relaxation of tiletamine was better than ketamine and overall quality of anaesthesia of tiletamine-zolazepam was found to be superior as compare to ketamine-diazepam combination.

Keywords: Dog; Ovariohysterectomy; Tiletamine-Zolazepam; Ketamine-Diazepam; Xylazine

Introduction

Ovariohysterectomy of bitches is routinely performed as an animal birth control programme in most of the cities which needs to be undertaken under general anaesthesia. The surgical proce-

dures are painful and therefore require an ideal anaesthetic protocol which produce sleep, amnesia, analgesia and muscle relaxation. General anaesthesia is defined as optimum induced drug intoxication of CNS which produces a reversible state of unconsciousness that provides immobilization, loss of sensation, analgesia and

muscle relaxation [1]. Two critical stages of general anaesthesia are induction and recovery, therefore most of the life-threatening hazards can occur during these two stages. Hence, anaesthetic agent must possess a quality of short onset and smooth recovery from anaesthesia. An ideal anaesthetic drug should produce sleep, amnesia, analgesia and muscle relaxation [2]. However, all these characteristics cannot be provided by a single agent and therefore a combination of drugs is used. Every drug has some unfavourable effects and therefore the combination of various drugs is employed to reduce the side effects of a single drug and thus the anaesthesia is produced with more satisfactory outcomes [3]. Premedication should always include an analgesic drug to control the peri and post-operative pain associated with surgical procedures [4]. Xylazine and ketamine are the main anaesthetic agents that has been used in veterinary surgery. Xylazine is a α_2 -adrenoceptor agonist which has sedative and analgesic effect while the ketamine is a dissociative anesthetic agent. Diazepam belongs to the benzodiazepine group, acts as central muscle relaxant and it reduces the muscle tone associated with the ketamine [5]. The combination of ketamine-diazepam has been used in veterinary surgery as a dissociative anaesthetic agent. Ketamine possesses poor visceral analgesic property. However, it can be used in combination with xylazine and/or diazepam to provide good visceral analgesia in case of abdominal surgery including ovariohysterectomy [6]. Zoletil is a combination of tiletamine hydrochloride which belongs to the class dissociative anesthetics and zolazepam hydrochloride which belongs to the benzodiazepine group. The basic descriptive pharmacology of tiletamine (2-(ethylamino)-2-(2-thienyl) cyclohexanone hydrochloride) was first reported in 1969 [7]. Tiletamine when used alone, produces cataleptic dissociative state which is associated with muscle spasm and convulsive seizure. To avoid these side effects, it is often combined with zolazepam which is a tranquilizer in action. Basic pharmacology of zolazepam HCl is 4-(0-fluorophenyl) 6,8-dihydro-1,3,8, trimethyl pyrazolo-3, 3e₁, 4 diazepam-7(14)-one HCl. The combination was found to be useful for the induction of anesthesia as well as a sole anesthetic agent for a wide variety of diagnostic and surgical procedures. In canids zolazepam metabolizes rapidly than the tiletamine and hence there can be transient tachycardia, athetoid movements and rough recovery [8,9]. Combination of Tiletamine-Zolazepam-Ketamine-Xylazine (TKX) has been used for the sterilization of street dogs in field clinics [10] and to compare TKX with tiletamine-zolazepam [11].

Materials and Methods

All the dogs selected for study were kept on fasting for 12 hours and water was with-held for 4 hours prior to surgery. The surgical site was prepared aseptically by clipping, shaving and scrubbing with antiseptic solution.

The dogs were randomly divided into two equal groups irrespective of age, breed and body weight. In group I induction was achieved using Tiletamine-Zolazepam combination @ 3 mg/Kg BW I/V and anaesthesia was maintained by intravenous administration of half of the induction dose of anaesthetic agent, whereas in group II induction was achieved using Ketamine @ 3 mg/Kg BW, I/V preceded by administration of Diazepam @ 0.25 mg/kg BW I/V and anaesthesia was maintained by administering the same dose as that of induction dose of anaesthetic agent.

Quality of anaesthesia includes palpebral reflex, pedal pinch reflex, position of the eyeball and mandibular muscle tone was assessed and recorded during anaesthetic period. Assessment of anaesthesia includes induction time (seconds), duration of anaesthesia (minutes) and recovery time (minutes) was recorded. Induction time was recorded from the administration of induction dose of anaesthetic agent to the disappearance of body reflexes. Duration of anaesthesia was recorded from the disappearance of body reflexes to the return of first righting reflex and recovery time was recorded from the administration of last bolus of anaesthetic agent during the surgery to the return of first righting reflex. Clinico-physiological parameters includes rectal temperature, respiration rate, heart rate and SpO₂ were recorded before sedation (0 min), at 15, 30, 45 min and at the time of recovery from anaesthesia. Rectal temperature was recorded with the help of digital thermometer and was measured in degree Fahrenheit. Respiratory rate was recorded in breaths/minutes by observing the insufflation and deflation of thorax and abdominal wall. Heart rate was calculated from the lead II of ECG paper. The ECG was recorded at speed 50 mm/sec and amplitude at 10 mV. Peripheral blood oxygen saturation level (SpO₂) was recorded with the help of NEW GEN MEDICAL SYSTEMS Pulse Oximeter by applying the probe to the upper lip of the dog.

The data was statistically analysed using the ICAR WASP 2.0 software's Two Way Factorial Experimental Design.

The Analysis of Variance (ANOVA) was used to compare the means of both the groups and different intervals.

Results and Discussion

Quality of anaesthesia

Quality of anaesthesia was assessed by monitoring palpebral and pedal pinch reflex, position of eyeball and mandibular muscle tone and has been shown in table 1.

	Group I	Group II
Palpebral reflex	Weak (3)	Weak (3)
	Absent (3)	Absent (3)
Pedal pinch reflex	Absent (6)	Absent (6)
Eyeball position	Central (5)	Central (6)
	Ventromedial (1)	
Mandibular muscle tone	Excellent (6)	Excellent (3)
	Moderate (0)	Moderate (3)

Table 1. Evaluation of body reflexes to assess quality of anaesthesia.

The number of animals with the various reflexes present or absent is indicated in parentheses.

In both the groups, palpebral reflex was weak in three dogs, whereas it was absent in three dogs. Presence of palpebral reflex in both the groups might be due to the characteristic of dissociative anaesthetic agent [12], whereas absence of it indicates that dogs were in a medium or deep plane of anaesthesia [12]. Pedal pinch reflex was absent in all dogs of both the groups. Absence of pedal pinch reflex indicates that quality of analgesia was excellent in both the groups. This might be due to visceral analgesia produced by the α -2 agonist as the dissociative anaesthetic agents are poor analgesic. Xylazine acts on the CNS and inhibits interneural transmission which results into depression of CNS, muscle relaxation and visceral analgesia [13]. Eyeball was positioned centrally in all the dogs of both the groups, except in one dog from group I where it was positioned ventromedially at the time of recovery from anaesthesia. The eyeball does not rotate in the animals anaesthetized with dissociative anaesthetic agents. When the eyeball is located at centre, it indicates that the level of anaesthesia is deep, whereas when it is located ventromedially, it indicates that the level of anaesthesia is medium [12]. In all the dogs of group I the mandibular muscle tone was excellent and it was moderate in three dogs and excellent in three dogs of group II. Muscle hypertonus can be a feature of dis-

sociative anaesthetic agents [12] and therefore benzodiazepines should be added to dissociative anaesthetic protocols. The quality of muscle relaxation was excellent in group I compared to group II. This might be due to the tiletamine having more muscle relaxation quality than ketamine [14]. The muscle relaxation was due to diazepam and zolazepam induced inhibition of internuncial neurons at the spinal level [15]. Similar observation regarding quality of anaesthesia has been reported by [6,14,16-19].

Assessment of anaesthesia

Assessment of anaesthesia was evaluated on the basis of induction time, duration of anaesthesia and recovery time and has been shown in table 2.

Group	Induction Time (seconds) ^{NS}	Duration of Anaesthesia (Minutes)*	Recovery Time (seconds)*
Group I	48.16 $\pm$ 4.90	125.33 $\pm$ 12.52	78.83 $\pm$ 10.08
Group II	36.55 $\pm$ 7.03	88.00 $\pm$ 9.35	36.83 $\pm$ 9.67

Table 2: Mean $\pm$ SE of Induction Time (seconds), Duration of Anaesthesia (Minutes) and Recovery Time (Minutes).

* Significant at 5%, NS - Non-Significant.

In group I, mean induction time was 48.16 $\pm$ 4.90 whereas it was 36.55 $\pm$ 7.03 in group II. Mean duration of anaesthesia and recovery time in group I was 125.33 $\pm$ 12.52 and 78.83 $\pm$ 10.08 respectively whereas in group II mean duration of anaesthesia and recovery time was 88.00 $\pm$ 9.35 and 36.83 $\pm$ 9.67 respectively. There was significant ($p < 0.05$) difference between the groups in duration of anaesthesia and recovery time. Longer period of duration of anaesthesia in group I could be due to the feature of tiletamine being more potent than ketamine and its duration of action is longer than ketamine [5,14]. Similar observations were recorded by [6,14,20-22]. Longer period of recovery time in group I as compared to group II might be due to the high potency of tiletamine compared with ketamine [5]. In dissociative anaesthetic recovery time is dose dependent. Higher dose of tiletamine-zolazepam was used by [23] and reported longer period of recovery time whereas lower dose of tiletamine-zolazepam was used by [18] and reported shorter period of recovery time. Ketamine was used at high dose by [6] and reported longer period of recovery time.

Clinico-physiological parameters

Clinico-physiological parameters includes rectal temperature, respiration rate, heart rate and SpO₂ were recorded at 15, 30, 45

min and during recovery from anaesthesia and has been shown in table 3.

	Group	Time (min)				
		0	15	30	45	At Recovery
Rectal Temperature	Group I	101.8 ± 0.29	100.7 ± 0.36 ^{NS}	99.65 ± 0.46 ^{**}	99.07 ± 0.51 ^{**}	99.43 ± 0.39 ^{**}
	Group II	101.81 ± 0.27	100.9 ± 1.03 ^{NS}	100.3 ± 0.95 ^{**}	99.33 ± 0.93 ^{**}	98.05 ± 0.78 ^{**}
Respiration Rate	Group I	25.50 ± 3.27	16.00 ± 4.76 ^{**}	18.00 ± 2.09 ^{**}	17.16 ± 2.42 ^{**}	17.00 ± 1.86 ^{**}
	Group II	26.16 ± 2.46	14.16 ± 0.74 ^{**}	15.00 ± 1.09 ^{**}	16.83 ± 1.62 ^{**}	20.16 ± 1.47 ^{**}
Heart Rate	Group I	124.50 ± 9.34	80.00 ± 9.30 ^{**}	73.16 ± 7.93 ^{**}	69.83 ± 9.13 ^{**}	64.16 ± 4.16 ^{**}
	Group II	107.00 ± 8.79	62.16 ± 6.92 ^{**}	79.83 ± 7.37 ^{**}	76.33 ± 4.52 ^{**}	63.00 ± 4.03 ^{**}
SpO ₂	Group I	98.50 ± 0.76	94.66 ± 0.71 ^{**}	95.16 ± 1.13 ^{**}	95.50 ± 0.84 ^{**}	98.33 ± 0.71 ^{NS}
	Group II	98.66 ± 0.33	95.16 ± 0.70 ^{**}	95.50 ± 0.50 ^{**}	95.66 ± 0.95 ^{**}	97.00 ± 1.48 ^{NS}

Table 3: Mean ± SE of Rectal Temperature (°F), Respiration Rate (breaths/min), Heart Rate (beats/min) and SpO₂ (%).

^{**} Significant at 1% level, NS-Non significance.

Rectal Temperature was decreased significantly ($p < 0.01$) at 30 min, 45 min and during recovery from anaesthesia in both the groups when compared to base value (0 min). The decreased in rectal temperature might be attributed to depression of thermo-regulatory centre in the hypothalamus [6,24,25] or due to muscle relaxation, decreased in metabolic rate and thermoregulatory centre depression as a sequel of anaesthesia [26,27]. The observations regarding rectal temperature are comparable with the observations reported by [6,24-28].

Respiration rate was decreased significantly ($p < 0.01$) at 15, 30, 45 min and during recovery from anaesthesia in both the groups when compared to base value (0 min). The respiration rate in both the groups was depressed could be due to depression of respiratory centre located in medulla oblongata by anaesthetic agents [6,16,27,29]. Similar observation has also been reported by [24,27,29,30] where they found significant declined in respiration rate. However, [6] in their study reported that respiration rate decreased non-significantly. Non-significant difference in the respiratory rate between the two groups was recorded by [16].

In both the groups heart rate was declined significantly ($p < 0.01$) at 15, 30 and 45 min when compared with base value (0 min). Bradycardia was observed in both the groups during recovery from anaesthesia. The heart rate might be decreased due to depression

of sympathetic activity and increase in parasympathetic effect on virtue of α_2 agonist's property [31]. This ubiquitous significantly reduced heart rate could be due to the anaesthetic effect which inhibits the CNS and excites the vagus nerve [32] and eventually causes the drop-in heart rate. Furthermore, the anaesthetic agent and sedative can simultaneously suppress the cardiac electrical stimulation [22]. These findings related to heart rate are corroborated with the findings reported by [16,22,28,31-33]. However, [6] in their study observed that decreased in heart rate was non-significant.

SpO₂ level was decreased significantly ($p < 0.01$) in both the groups at 15, 30 and 45 min when compared with its base value (0 min) but during recovery from anaesthesia it was elevated in both the groups. However, SpO₂ level was found to be fluctuating within normal physiological range throughout anaesthetic period in both the groups. The marginal decreased in the value of SpO₂ during anaesthesia might be attributed to the effect of xylazine which reduced the depth of respiration, but not the rate, leading to lowered oxygen saturation values [34] or it might be due to the anaesthetic agent's effects on the ventilator function of the lungs. Low SpO₂ indicates a decreased in peripheral oxygenation and tissue perfusion [25]. The observations related to the SpO₂ in this study are in accordance with [18,24,27].

Conclusion

Duration of anaesthesia and recovery time is longer in tiletamine-zolazepam combination compared with ketamine-diazepam combination. However, smooth recovery was observed without crying in both the anaesthetic protocols. Muscle relaxation was excellent in group I whereas it was moderate in group II. Therefore, it can be concluded that muscle relaxation quality of tiletamine-zolazepam combination is superior than ketamine-diazepam combination.

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