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Comparative evaluation of clinico-physiological effect of total intravenous anaesthesia of etomidate in midazolam and dexmedetomidine premedication in dogs

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Abstract
The present study was conducted to evaluate the efficacy of use of etomidate as total intravenous anesthesia in dogs. The research was conducted on 16 dogs of either sex, age group 7-12 years, presented to the TVCC and Department of Surgery & Radiology, Durg. Animals were randomly divided into two equal groups Group I and Group II consisting eight animals in each group. All the animals of both the groups premedicated with Inj. atropine sulphate @ 0.04 mg/kg intramusculary. In Group I dogs premedicated with Inj Midazolam @ 0.4 mg/ kg body weight and Group II premedicated with Dexmedetomidine @ 0.010 µg/kg body weight intravenously after 10 minutes. For induction after 10 minutes anaesthesia was induced by Inj. Etomidate @ 1.5mg/kg body weight intravenously to each animal of both the groups. Maintenance of anaesthesia for 2 hrs was achieved with repeated bolus with Injection of etomidate @ 0.5mg/kg body weight at different time intervals in both the groups. Anaesthetic combination were evaluated by clinical and physiological observations. The clinical parameters were recorded at different time interval in minutes and physiological parameters at 0, before induction, 15, 30, 45, 60, 90 and 120 minutes intervals were recorded. Induction quality was excellent, smooth and sternal recumbency and complete recovery was observed smoothly without struggling in both the groups after induction. The quality of anaesthesia was recorded on a scale 1 to 4 as shown score 1 – Poor, score 2 -Fair, score 3- Good and score 4- Excellent in both the groups. In both the groups provided satisfactory surgical plane of anaesthesia in dogs but it was excellent in Group II which was premedicated with Inj. Dexmedetomidine than Group I which was premedicated with Inj. Midazolam.

Keywords: midazolam, dexmedetomidine, premedication, etomidate, dogs, clinical and physiological parameters

Introduction
General anesthesia is widely used in veterinary practice especially in dogs; it is used to facilitate routine minor surgical procedures and even for complete life-saving surgeries. Balanced anaesthesia is used in the anaesthetic protocol to mask the side effects of one drug by another, so as to render minimal toxicity of the drugs used (Hall *et al.*, 2001). Recently, in surgical management a major emphasis has been laid to develop new and safe injectable anaesthesia technique, especially the 'Total Intravenous Anaesthesia' (TIVA), for the veterinary subjects primarily because of the fact that veterinary healthcare units are located outside the major cities. A technique of general anaesthesia which uses a combination of agents given exclusively by the intravenous route without the use of inhalation agents is called Total intravenous anaesthesia (TIVA). Total intravenous anaesthesia involves the use of drugs given solely by repeated or continuous intravenous injection for induction and maintenance of anaesthesia (Murrell *et al.*, 2007) [19]. The principle of TIVA is a plasma concentration needed to produce anaesthesia has to be reached quickly and maintained over the period of time that anaesthesia has been planned. Preanaesthetic drugs are administered to minimize the undesirable effects and the number of anaesthetic drugs as well as to prepare the animal for induction. These also contribute to smooth recovery from anaesthesia (Liptak *et al.*, 2012) [16]. Midazolam, is a benzodiazepine medication used for anesthesia, procedural sedation, trouble sleeping and severe agitation. It works by inducing sleep, decreasing anxiety and causing a loss of ability to create new memories.

Midazolam is routinely used at low doses via subcutaneous injection to help with agitation, myoclonus, restlessness or anxiety in the last hours or days of life. Midazolam as preanaesthetic used to reduce the total dose of propofol (Mohammad *et al.,* 2009) [20] and also decreases requirement of volatile anaesthetic agent after intravenous administration in both human and different animal species (Malik and Singh 2008) [17]. Dexmedetomidineis an alpha-2 adrenergic receptor agonist used for sedation, analgesia and also as an adjunct in anesthesia to reduce anesthetic requirements in procedures requiring total intravenous anesthesia (Miller, 2009) [18]. It provides sedation without risk of respiratory depression and cooperative or semi rousable sedation.

Etomidate is an ultrashort acting, non-barbiturate hypnotic intravenous anaesthetic agent, imidazole derivative that works in a fashion similar to that of propofol and thiopental since it enhances the action of the inhibitory neurotransmitter γ-aminobutyric-acid (GABA) (Branson, 2007) [3]. A continuous rate infusion of etomidate after medetomidine premedication produces anaesthesia with only minimal hemodynamic changes and smooth recovery (Ko *et al.,* 1994) [14]. It has been used in patients with evidence of allergy to the barbiturates and in combination with nitrous oxide in patients about to undergo short operations (Jeffrey *et al.,* 1983) [10]. A single bolus of etomidate reduces the adrenocortical response to anaesthesia and surgery for up to six hours (Dodam *et al*., 1990) [4].

Materials and Methods

The present study was conducted on 16 healthy dogs of both the equal sexes, there age ranged from 7 to 12 years presented for various surgical procedures in TVCC, Durg and Department of Surgery & Radiology, Anjora, Durg. All the animals included in research was fasted for 12 hours before anesthesia, while water was withheld for 6 hours before anesthesia. The dogs were premedicated with Inj. Atropine sulphate @ 0.04 mg/kg intramuscularly 10 minutes later Inj. Midazolam (0.4 mg/kg body weight intravenously) and 10 minutes after Inj. Etomidate 1.5 mg/kg body weight was given intravenously and maintained with Inj. Etomidate (0.5 mg/kg body weight intravenously in Group I upto complete surgical procedure. In Group II dogs were premedicated with Inj. Atropine sulphate @ 0.04 mg/kg IM. 10 minutes later Inj. Dexmedetomidine (0.010µg/kg intravenously and 10 minutes after Inj. Etomidate 1.5 mg/kg body weight was given intravenously and maintained with Inj. Etomidate 0.5 mg/kg body weight intravenously.

Clinical parameters were recorded viz. induction time (The time elapsed from administration of etomidate to the induction of anaesthesia (adjudged by the pedal reflex and it was recorded in minutes). The duration of anaesthesia (The time elapsed from the induction of anaesthesia to the spontaneous movement of any body part by the animal (after discontinuation of etomidate and it was recorded in minutes). The recovery time (The time from discontinuation of etomidate to the first spontaneous movement of any body part by the dog which was recorded in minutes). The complete recovery time (Time elapsed from discontinuation of the etomidate administration to the time when the animal can stand. It was recorded in minutes). The quality of anaesthesia was recorded on a scale 1 to 4 as shown score 1 – Poor, score 2 - Fair, score 3- Good and score 4- Excellent were recorded in both the groups.

Physiological parameters were recorded before induction, 15, 30, 45, 60, 90 and 120 minutes interval in both the groups i.e. rectal temperature (˚F) was monitored by the veterinary thermometer, respiratory rate was counted and recorded by observing the excursion of thoraco- abdomen per minute at different time intervals (breaths/min) and heart rate was monitored by auscultation of heart with stethoscope at different time intervals (beats/min).

Statistical analysis: The data was collected during the present study at different intervals for different parameters. The mean and standard error of all parameters were computed as per the Snedecor and Cochran (1994) [33].

Results and Discussion

In the present study different drugs Inj. Atropine sulphate @0.04 mg/kg intramuscularly injected all animals in both the groups. In Group I Inj. Medazolam and Group II Inj. Dexmedetomidine has been used as a premedicant in the animals as per the protocol shown earlier, at different dose rates i.e. Inj. Medazolam @ 4 mg/kg body weight, Inj. Dexmedetomidine @ 10 µg/kg body weight intravenously. The dose of the induction agents i.e. Inj. Etomidate @1.5 mg/kg were administered to achieve the induction of anaesthesia just sufficient for the facilitation of endotracheal intubation and maintenance of anaesthesia with Inj. Etomidate @t 0.5 mg/kg body weight intravenously in order to assess the effects on the various parameters observed in both the groups.

Induction Time (Min): Mean±SE values of induction time in both groups of animals premedicated with at the different dose rate of Group I Inj. Medazolam @ 0.4 mg/kg body weight and Group II Inj. Dexmedetomidine @ 10 µg/kg body weight are given in Table 1. The mean values of induction time were 2.02 ± 0.18 and 1.37±11.33 minutes in group I and II respectively. The induction time was significantly (P<0.05) lower in the animals of group II as compared to the animals of group I.

Induction time of 6.4±2.30 minutes was reported by Jadon *et al.* 1995 after administration of atropine – dexmidineketamine in dogs premedicated with atropine. The mean values of induction time was 167.83±7.45 seconds, 125.11±11.33 seconds, 179.00±23.05 seconds, 108.00±7.73 seconds, 60.83±8.76 seconds and 55.33±5.70 seconds in the animals of groups A1, A2, B1, B2, C1 and C2 respectively, reported by (Bisht, 2017) [2] and he was observed that an increase in the dose of dexmedetomidine from 10 µg/kg body weight to 15 µg/kg body weight had caused a reduction in the induction time of animals in all the groups of animals. Saini (2018) [29] noted the mean anaesthetic induction time was 70.2±4.03 seconds when he used etomidate. According to Hareesh (2016) the mean values of induction time were 21± 0.516 (seconds) and 22 ± 0.408 (seconds) in group I and group II respectively and induction quality was excellent, smooth and attained recumbency rapidly without struggling in all animals in group I with etomidate anaesthesia compared with propofol.

Table 1: Mean±SE Induction times (Minutes) in various groups of animals treated with their respective anaesthetic protocols.

Parameters	Groups	
	Group I	Group II
Induction Time (Min)	2.02 ± 0.18^{B}	1.37 ± 0.18^{A}

Duration of Anaesthesia

Mean±SE values of induction time in both groups of animals premedicated with at the different dose rate of Group I Inj. Medazolam @ 0.4 mg/kg body weight and Group II Inj. Dexmedetomidine @ 10 µg/kg body weight are given in Table 2. The duration of anaesthesia was 48.37±0.81 minutes in the animals of Group I and 77.25±1.84 minutes in Group II. The duration of anaesthesia was more in group II due to the reason that dexmedetomidine had caused dose dependent sedation in the dogs administered.

Rafee *et al.* (2015a) [24] have recorded longer duration of anaesthesia with atropine-dexmedetomidine-midazolam-ketamine as compared to atropine-dexmedetomidine-butorphanol-midazolam-ketamine in dogs. Bisht (2017) [2] reported the duration of anaesthesia was higher in the groups administered with dexmedetomidine at the dose rate of 15µg/kg body weight (A2, B2 and C2) as compared to the animals in which dexmedetomidine was administered at the dose rate of 10µg/kg body weight (A1, B1 and C1). Hui (2018) [8] observed that the total duration of anaesthesia in groups A and B were 83.24 ± 3.35 min and 86.42 ± 2.99 min respectively which was similar to our findings.

Table 2: Mean±SE Duration of Anaesthesia (Minutes) in various groups of animals treated with their respective anaesthetic protocols.

Parameters	Groups	
	Group I	Group II
Duration of Anaesthesia (Min)	48.37 ± 0.81^{A}	77.25± 1.70^{C}

Quality of Anaesthesia

Mean±SE values of induction time in both groups of animals premedicated with at the different dose rate of Group I Inj. Medazolam @ 0.4 mg/kg body weight and Group II Inj. Dexmedetomidine @ 10 µg/kg body weight are given in Table 3. The quality of anaesthesia was 1.75 ± 0.16 in the animals of Group I and in Group II it was 3.37 ± 0.18 respectively. The quality of anaesthesia was excellent in Group II which was premedicated with Dexmedetomidine in present study than the Group I.

According to Sharma (2019) [30] a fixed criterion was followed for evaluation of quality of anaesthesia. Scoring was done to assign numerical values; starting from 1 to 4 (1-poor, 2-fair, 3-good, 4-excellent) for premedication quality, induction quality, maintenance quality and recovery quality. Panzer *et al.*, 2011 [21] observed that Dexmedetomidine is a potent and selective α_2-adrenergic agonist, the active enantiomer of medetomidine [10] and clinical effects are presumed are better than other drugs in canines. Similar findings were recorded during the study and observed the in Group II the quality of anaesthesia to was excellent were used the Dexmedetomidine.

Table 3: Mean±SE Score of Quality of Anaesthesia Score in various groups of animals treated with their respective anaesthetic protocols.

Parameters	Groups	
	Group I	Group II
Quality of Anaesthesia	1.75 ± 0.16^{A}	2.37 ± 0.18^{C}

Recovery Time: Mean±SE values of induction time in both groups of animals premedicated with at the different dose rate of Group I Inj. Medazolam @ 0.4 mg/kg body weight and Group II Inj. Dexmedetomidine @ 10 µg/kg body weight are given in Table 4. The recovery time of animals in Group I was 55.12±0.47 and in Group II was 86.25± 2. 04 minutes respectively. The recovery time was significantly (P<0.05) higher in the animals of group II as compared to that of animals of Group I. The recovery was longer in group II which was premedicated with Dexmedetomidine. The recovery time in the dogs anaesthetized with propofol was found to be shorter than that of dogs anaesthetized with etomidate (Sams *et al*., 2008) [26]. Hui (2018) [8] also reported that the recovery time in group A and B was 5.37 ± 1.14 min and 9.12 ± 1.02 min respectively when he was used as etomidate in group B and Propofol in group A for induction and maintenance in all the dogs.

Sternal Recumbency Time: Mean±SE values of induction time in both groups of animals premedicated with at the different dose rate of Group I Inj. Medazolam @ 0.4 mg/kg body weight and Group II Inj. Dexmedetomidine @ 10 µg/kg body weight are given in Table 4. The sternal recumbency times (in minutes) in the animals of Groups 1 was 64.12±0.12 and in Group II was 98.12±2.23 minutes respectively. The sternal recumbency time was significantly (P<0.05) higher in the animals of Group II as compared to that of animals of Group I. The sternal recumbency time was more in Group II which was premedicated with Dexmedetomidine. Longer sternal recumbency time with etomidate as compared to propofol has been reported by Sams *et al.* (2008) [26] in dogs and in the present study the same has been observed as dexmedetomidne in combination with etomidate must have caused the longer sternal recumbency time. The sternal recumbency time in the present study increased with increase in the dose of dexmedetomideine which confirms the findings of Santosh *et al.* (2012) [27] in dogs.

Standing Time: Mean±SE values of induction time in both groups of animals premedicated with at the different dose rate of Group I Inj. Medazolam @ 0.4 mg/kg body weight and Group II Inj. Dexmedetomidine @ 10 µg/kg body weight are given in Table 4. The standing time in the animals of Group 1 was 72.12±0.69 and in Group II was 109.12±1.25 minutes respectively. The standing time was significantly (P<0.05) higher in the animals of Group II as compared to that of animals of Group I. The standing time was more in Group II which was premedicated with Dexmedetomidine. Sams *et al.* (2008) [26] have reported that the standing time noted with etomidate were significantly longer than those noted with the use of propofol in dogs. Similar findings have been observed in the present study. Singh *et al.* (2013) [31] have reported that the standing times were similar in animals administered with dexmedetomidine or medetomidine however the standing time increased in animals subjected to premedication with medetomidine/dexmedetomidine as compared to another group in which dexmedetomidine/medetomidine were not used as premedicants. The findings of the present study are in agreement with the observations of Santosh *et al*. (2013) [28] who have reported that higher dose of dexmedetomidine with ketamine vis-a-vis a lower dose of dexmedetomidine with ketamine caused the standing times to increase and decrease in proportion to the dose rate of dexmedetomidine.

Complete Recovery Time: Mean±SE values of induction time in both groups of animals premedicated with at the different dose rate of Group I Inj. Medazolam @ 0.4 mg/kg body weight and Group II Inj. Dexmedetomidine @ 10 µg/kg body weight are given in Table 4. The complete recovery time in the animals of Group 1 was 79.12±0.51 and in Group II

was 116.87± 0.61 minutes respectively. The complete recovery time of Group II was significantly (P<0.05) higher than the Group I. The standing time was more in Group II which was premedicated with Dexmedetomidine. The complete recovery time was longer with the use of etomidate observed in the present study confirms the findings of Sams *et al.* (2008) [26] in dogs anaesthetized with midazolam-propofol (18.1minutes) or midazolam-etomidate (48.8 minutes). The findings reported by Santosh *et al.* (2012) [27] and Santosh *et al.* (2013) [28] were similar to the findings of the present study wherein an increase in the dose of dexmedetomidine resulted in an increase in the complete recovery time in dogs anaesthetized with dexmedetomidine (at low and higher dose) with midazolam-ketamine and fentanyl.

Table 4: Mean±SE Recovery Time (Minutes), Sternal Recumbency (Minutes), Standing Time (Minutes) and Complete Recovery Time (Minutes) in various groups of animals treated with their respective anaesthetic protocols.

Parameters	Groups	
	Group I	Group II
Recovery Time (Min)	55.12 ±0.47 ^{A}	86.25 ±2.04^{B}
Sternal Recumbency Time (Min)	64.12±0.12^{A}	98.12± 2.23^{B}
Standing Time (Min)	72.12±0.69^{A}	109.12±1.25^{B}
Complete Recovery Time (Min)	79.12±0.51^{A}	116.87±0.61^{B}

Physiological Parameters

Rectal Temperature: The mean±SE values of rectal temperature in both groups of animals premedicated with Inj. Medazolam @ 0.4 mg/kg body weight and Inj. Dexmedetomidine @ 0.010 µg/kg body weight are given in Table 5. The mean rectal temperature in the animals of both the groups showed gradual decline in its values at different time intervals and then rose to gain the base level values at 2 hours interval. In the animals of Group I the mean rectal temperature decreased non significantly (P<0.05) at 60 minutes. Thereafter it showed slight increase in its values at 90 minutes to 2 hrs, however these were still significantly (P<0.05) lower as compared to the base values. The animals of Group II showed a non significant (P<0.05) decrease at 30 minutes interval followed by an increase in its value at 2 hours. Decrease in rectal temperature was more pronounced for a longer period in the animals of Group II as compared to the animals of Group I, Comparison between both the groups suggests that there was non significant (P<0.05) decrease in rectal temperature and then gradual increase which remained below the baseline.

Decrease in rectal temperature as observed in the present study can be a result of the reduced heat production consequent to decreased muscle activity or by action of the drug on the hypothalamus (Virtanen 1989) [34] or by the thermoregulatory center being affected by central alpha-2 adrenoceptors (Sabbe *et al.*, 1994) [25]. Kuusela *et al.* (2001b) [13], Sinclair *et al.* (2003) [32] and Lemke *et al.* (2004) have also recorded that the rectal temperature decreases with the administration of dexmedetomidine. The findings in the present study are in accordance with the findings of Hui (2018) [8] and Bisht (2017) [2] of the studies indicating decrease in body temperature after some time and again increase at baseline after the administration of different premedicants along with etomidate as induction and maintenance agent. Perk *et al.* (2002) [22] also recorded decrease in rectal temperature following etomidate – alfentanil anaesthesia in dogs.

Table 5: Mean±SE Rectal Temperature (°F) in various groups of animals treated with their respective anaesthetic protocols.

Parameters	Groups (n=8)	0 (Min)	Before Induction (Min)	15 (Min)	30 (Min)	45 (Min)	60 (Min)	90 (Min)	120 (Min)
Rectal Temperature (°F)	I	101.33±0.54^{A}	100.82±0.37^{A}	100.50±0.47^{A}	100.22±0.50^{A}	99.81±0.48^{A}	100.33±0.59^{A}	100.90±0.48^{A}	101.08±0.38^{A}
	II	101.27±0.26^{A}	100.93±0.27^{A}	100.76±0.27^{A}	99.88±0.27^{A}	99.50±0.28^{A}	99.35±0.36^{A}	100.30±0.23^{A}	100.63±0.13^{A}

Heart Rate (HR): The Mean±SE values of heart rate in various groups of animals premedicated with Medazolam @ 0.4 mg/kg body weight and Dexmedetomidine @ 0.010 µg /kg body weight are given in Table 6. The mean heart rate in the all the Groups showed gradual decline in its values at different time intervals and then rose to gain the base level. In the animals of Group I the mean heart rate was non significantly (P<0.05) lower after 15 min to 90 minutes interval then increases at base values. In the animals of Group II it was also non significantly (P<0.05) lower at after induction to 90 minutes interval and increased at 2 hrs.

In a study conducted by Pypendop *et al.* (1998) [23] heart rate remained at a low level for up to 120 minutes after the administration of medetomidine. The decrease in heart rate and other cardiovascular parameters were proportional to the dose rates of medetomidine used in the study, being lower for low doses (1-2µg/kg) and higher for the high doses. In the present study similar results were obtained with the use of different premedicants. Alpha-2 agonist action of drug was thought to be the reason for a drop in the heart rate. Gertler *et al.* (2001) [5] have reported a maximum reduction of 18% in the value of heart rate with the use of dexmedetomidine and clonidine in human patients. Similar findings have been observed in the present study.

Table 6: Mean±SE Heart Rate (Beats Per Minute) in various groups of animals treated with their respective anaesthetic protocols.

Parameters	Groups (n=8)	0 (Min)	Before Induction (Min)	15 (Min)	30 (Min)	45 (Min)	60 (Min)	90 (Min)	120 (Min)
Heart rate (Beats Per Min)	I	112.62±1.03^{A}	105.87±2.89^{A}	104.62±2.77^{A}	104.00±1.45^{A}	106.25±1.83^{A}	110.37±1.46^{A}	112.00±1.81^{A}	112.75±2.06^{A}
	II	115.50±0.70^{B}	108.12±1.39^{A}	107.12±1.31^{A}	106.37±1.60^{A}	112.75±1.06 ^{B}	113.25±1.50^{A}	114.87±1.20^{A}	116.87±0.69^{A}

Respiration Rate (RR): The Mean±SE values of the respiration rate in the animals of various groups premedicated with Medazolam @ 0.4 mg/kg body weight and Dexmedetomidine @ 0.010 µg /kg body weight are given in Table 7. In Group I there was a significant (P<0.05) decrease upto 30 minutes interval and then increases until the end of the observation period, where it remained lower than the base value. In Group II, respiration rate decreased non significantly (P<0.05) lower than the base value.

There was a decrease in respiration rate after the administration of dexmedetomidine in the present study which confirms the findings of Gertler *et al.* (2001) [5] who

have reported that respiration rate was lower in the patients treated with dexmedetomidine. Kuusela *et al.* (2001a) [12] have reported significant decrease in the respiratory rate in animals after the administration of dexmedetomidine or medetomidine at the dose rates ranging from 2-40µg/kg body weight. Kushiro *et al.* (2005) [11] and Bisht *et al.,* 2016 [1] have reported that respiratory rate decreased after the administration of anaesthetic protocol involving midazolam-ketamine-medetomidine-sevoflurane for the whole duration of the anaesthetic period, this could have been due to the stimulation of prejunctional alpha-2 receptors present in the sympathetic nervous system.

Table 7: Mean±SE Respiration Rate (Breaths Per Minute) in various groups of animals treated with their respective anaesthetic protocols.

Parameters	Groups (n=8)	0 (Min)	Before Induction (Min)	15 (Min)	30 (Min)	45 (Min)	60 (Min)	90 (Min)	120 (Min)
Respiration Rate	I	22.00 ± 0.37^{A}	20.25 ± 0.36^{A}	18.25 ± 0.16^{B}	17.00 ± 0.26^{B}	14.87 ± 0.47^{A}	16.50 ± 0.50^{A}	19.00 ± 0.50^{A}	21.12 ± 0.47^{A}
(Breaths Per Min.)	II	22.25 ± 0.36^{A}	19.87 ± 0.22^{A}	16.87 ± 0.29^{A}	16.00 ± 0.18^{A}	14.25 ± 0.25^{A}	16.62 ± 0.32^{A}	19.37 ± 0.37^{A}	21.50 ± 0.37^{A}

Conclusion

It imparts a smooth induction and recovery to the animals without any undesirable side effects in both the groups due to the induction agent. In both groups there was transient changes within physiological limits were observed in the haematological parameters which reached to the base levels by 2 hrs. as the Inj. Etomidate used for the induction and maintenance agent. Both preanaesthetic are good for the major and minor surgeries but the most efficacious, smooth and safe anaesthetic combination was Inj. atropine sulphate (0.04mg/kg im)-dexmedetomidine (10 µg/kg i.v.) and Inj. Etomidate used for induction and maintenance for surgical anaesthesia. Quality of anaesthesia was excellent in group II and and time of recovery in both groups was appreciable without any complication.

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