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Comparative studies on medetomidine and dexmedetomidine as pre-anaesthetics for propofol-isoflurane general anesthesia in dogs

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Abstract
The research was conducted in 18 clinical cases presented to Department of Veterinary Surgery and Radiology, Veterinary College Hospital, Hebbal, Bengaluru. Animals were randomly divided into three groups *viz*., Group I, Group II and Group III consisting of six dogs in each group. Dogs of all the groups were atropinised (@0.04 mg/kg) subcutaneously except Group I dogs. Dogs in Group I directly induced with propofol (@6mg/kg) intravenously. In dogs of Group II Medetomidine was administered @ 20mcg/kg IV, ten minutes later the anesthesia was induced by administering Propofol @ 3 mg/kg IV. In dogs of Group II Dexmedetomidine was administered @ 10mcg/kg IV, ten minutes later the anesthesia was induced by administering Propofol @ 3 mg/kg IV. Maintenance of anesthesia was done by isoflurane in all the three groups. Anaesthetic combinations were evaluated by clinical and physiological observations. The fast onset of sedation was observed in Group II and Group III dogs. The induction time was significantly slower in Group I dogs followed by Group III and Group II dogs. Smooth recovery in Group II and Group III dogs without any side effect. Excellent muscle relaxation and good analgesia were observed in Group II and Group III dogs as compared to Group I. Physiological parameters fluctuated within the normal limits. The anesthetic protocol carried out in Group II and Group III given satisfactory results with respect to sedation, analgesia, muscle relaxation, smooth induction and recovery without any untoward events or complications as compare to directly induced Propofol Group.

Keywords: Anesthesia, dog, medetomidine, dexmedetomidine, propofol, isoflurane

Introduction
Many minor and major surgical procedures are routinely performed in small animal practice that required short term sedation, analgesia or anaesthesia. Reversible production of insensibility to pain is known as anaesthesia. In veterinary practice, anaesthesia has to satisfy two requirements, humane handling of animals and technical efficiency. Anaesthesia is a indispensable pre-requisite for many surgical interventions with maximum technical efficiency and accuracy, so that surgeon can perform surgeries at ease. An ideal anaesthetic is one which produces sleep, amnesia, muscle relaxation and analgesia. However, all these effects cannot be produced by the single agent and therefore a combination of drugs is used which is known as the balanced anaesthesia (Thurmon and Short, 2007) [44].

Alpha-2 adrenoreceptor agonists are the another class of drugs widely used as pre-anaesthetics in dogs and other species for their sedative, analgesic, muscle relaxant, anxiolytic and anaesthetic sparing effects. Medetomidine is a potent and selective alpha2-adrenoceptor agonist that contains equal parts of two optical enantiomers, dexmedetomidine and levomedetomidine. It rapidly produces dose-dependent, reliable sedation and analgesia with good muscle relaxation. Potent anaesthetic-sparing effects of medetomidine allow the use of lower doses of anaesthetics as a part of balanced anesthesia. Dexmedetomidine is the dextro-isomer of medetomidine that posses the selective alpha-2-agonist action because of its pharmacological activity. It has approximately 7 to 8 times the alpha-2 selectivity than that of clonidine. It produced the reliable sedation, analgesia, chemical restraint and also reduced the requirement of isoflurane when administered as a bolus in dogs (Weitz *et al*., 1991) [48] and was a preferred sedative and analgesic in critically ill patients because of its least cardio-pulmonary depression (Shukry and Miller, 2010) [40].

Materials and Methods

The study was carried out in 18 clinical cases of dogs presented for elective surgeries to the Department of Veterinary Surgery and Radiology, Veterinary College Hospital, Hebbal, Bengaluru. The study was conducted to evaluate anaesthetic combinations of propofol-isoflurane, medetomidine-propofol-isoflurane and dexmedetomidine-propofol-isoflurane. All the animals were kept off feed for 12hrs and water was withheld for six hours prior to the anaesthesia. Eighteen clinical cases were randomly divided into three groups *viz*., Group-I, Group-II and Group-III with 6 animals in each group. All the dogs were atropinised at the dose rate of 0.04mg/kg body weight subcutaneously except in Group I dogs. The dogs of Group I anesthesia was induced by administering Propofol at the dose rate of 6mg/kg body weight intravenously. In dogs of Group II Medetomidine was administered at the dose rate of 20mcg per kg body weight intravenously, ten minutes later the anesthesia was induced by administering Propofol intravenously, at the dose rate of 3mg per kg body weight. In the dogs of Group III Dexmedetomidine was administered at the dose rate of 10 mcg per kg body weight intravenously, ten minutes later the anesthesia was induced by administering Propofol intravenously, at the dose rate of 3mg per kg body weight. After induction, maintenance of anaesthesia was carried under isoflurane inhalant anaesthetic. Clinical parameters *viz*., Onset of sedation (noted with the onset of symptoms such as ataxia, drooping of eyelids and drowsiness), induction time (time taken for induction of general anaesthesia after propofol administration), duration of anaesthesia (time between the abolition and reappearance of pedal reflex), recovery time (time taken for animal to stand voluntarily after the cessation of anaesthesia).All the clinical and physiological parameters were recorded before the administration of premedicants, immediately after administration (0 min) and at 5, 10, 15, 30, 45, 60 and 90 minutes after the administration of premedicants and induction of anesthesia. The variations in clinical and physiological parameters were recorded at different time intervals within the group and between the groups were calculated using T test: paired two sample for means and T test: two sample assuming equal variences respectively as described by Snedecor and Cochran (1994) [43].

Results and Discussion

Onset of sedation was characterized by lowering of head, drooping of eyelids, mild drowsiness and ataxia. Similar signs of sedation were earlier recorded by Vainio (1991) [46], Kuusela *et al*. (2001) [21] and Arunkumar (2017) [3] during their studies on Medetomidine and Dexmedetomidine used as a premedicants in dogs. Onset of sedation in Group II dogs was 1.36 ± 0.15 minutes. Where as, Vainio (1989), Tiwari *et al.* (1998) [45], Ko *et al.* (2001) [18] and Ozaydin *et al.* (2001) [30] also used the same drug and reported onset of sedation as 1.9 ± 0.22 minutes, 1.98 ± 0.26 minutes, 3.5± 1.2 minute and two minutes respectively. The variations in the onset of sedation could be due to change in the route of administration and lower dose of Medetomidine used in their studies. In the present study the onset of sedation was faster as compared to above authors which could be attributed to intravenous administration of the Medetomidine and higher dose selected for sedation. Onset of sedation in Group III was 1.36 ± 0.13 minutes. Similarly, Arunkumar (2017) [3] reported 2.05 ± 0.19 minutes of sedation time after intravenous administration of dexmedetomidine however, Ahmad *et al*. (2013) [1] and Sahoo *et al*. (2018) [36] reported a longer duration of onset with the same drug of 4.50 ± 0.96 minutes and 3.00 ± 0.89 minutes respectively. The variations in the onset of sedation could be due to intramuscular route of administration and lower dose of Dexmedetomidine used in their studies. In the present study fast onset of sedation could be due to intravenous administration of the Dexmedetomidine and higher dose range selected for sedation. The time taken for induction of anesthesia in Group I was 129 ± 13 seconds. This was in accordance with Shaaban *et al.* (2018) [38] who reported induction time as 120.00 ± 0.05 seconds with Propofol anesthesia in dogs. The time taken for induction of anesthesia in Group II was 44 ± 5.30 seconds and Raszplewicz *et al.* (2013) [35] reported similar induction time with Medetomidine-Propofol anesthesia in dogs. The time taken for induction of anesthesia in Group III also was 45 ± 4.46 seconds. This was in accordance with Asaramji (2018) [4]. On the contrary Arunkumar (2017) [3] reported induction time of 57.33 ± 0.99 seconds during Dexmedetomidine-Propofol-Isoflurane anesthesia in dogs. In the present study the induction time was slightly faster which might be due to the general anaesthetic sparing effects of the pre-anaesthetic used in the study as reported by (Kuusela, 2001a) [20]. All the dogs in Group I had excitation and apnoea for 11 to 18 seconds immediately after the administration of Propofol which was also found earlier by Gurmita (2010) [11] who observed apnoea for 13 to 20 seconds. Similar findings were recorded by Claeys *et al.* (1988) [7], Morgan and Legge (1989) [27], Smith *et al.* (1993) [42], Bufalari *et al.* (1995) [5] and Hofmeister *et al.* (2009) [13] the apnoea might be due to direct induction of anesthesia with Propofol without premedication and its respiratory depressant effects as earlier reported by Gurmita, (2010) [11] and it might be due to total calculated dose of propofol administered as a bolus dose. No excitement during induction in dogs was observed in Group II and III compared to Group I could be due to premedicants help to relieve anxiety and decrease stress before induction of anesthesia had earlier reported by Lukasik (1999) [24]. Similar findings were also observed by Vainio (1991) [46], Cullen and Reynoldson (1993) [8] and Jagtap (2003) [14] who reported excitement free induction with Propofol in alpha 2 agonist premedicated dogs. The induction time was significantly slower in Group I dogs followed by Group III dogs when compared to Group II dogs. Slower induction time in Group I could be due to direct induction with Propofol without premedication as reported by Bufalari *et al.*, (1995) [5]. The time taken for duration of anesthesia in Group I, Group II and Group III were 38.33 ± 2.31 minutes, 42 ± 6.14 minutes and 44.5 ± 4.86 minutes respectively for elective surgical procedures (OHE and castration) conducted during the study. No significant difference in the duration of anesthesia was noticed between the groups and within the group as the duration of anesthesia was almost similar in the present surgeries conducted in all the three groups. The variations in the duration of anesthesia was depends upon time and length of the surgery. Similarly, Arunkumar (2017) [3] reported duration of anesthesia as 67.17 ± 12.50 minutes under Dexmedetomidine-Propofol-Isoflurane anesthesia for Radius and ulna fracture repair in dogs. Chonde (2002) [6] reported duration of anesthesia as 43.40 ±3.12 minutes under Medetomidine-Ketamine anesthesia for enterotomy in dogs. Lozano *et al.* (2009) [23] reported duration of anesthesia as 105.3 ± 27.48 minutes under Propofol anesthesia for Magnetic Resonance Imaging in dogs. The time

taken for recovery in Group I was 10.33 ± 1.20 minutes. However, Bufalari *et al.* (1995) [5] and Shaaban (2018) [38] reported a longer recovery time of 43 minutes and 91.67 ± 3.71 minutes respectively with Propofol anesthesia. Faster recovery in the present study could be due to Isoflurane anesthesia as compared to injectables used by other authors for the maintenance of anesthesia. The time taken for recovery in Group II was 18.33 ± 2.23 minutes. Similar recovery time observed by Kuusela *et al*. (2000) [19] reported recovery time was 20 minutes after Medetomidine-Propofol-Isoflurane anesthesia. However, Bufalari *et al.* (1995) [5], Tiwari *et al.* (1998) [45], Ozaydin *et al.* (2001) [30] and Monsang (2011) [26] and reported 72 minute, 94.14 ± 6.18 minute, 86.1minutes and 60.75 ± 18.71 minutes for recovery respectively, this could be attributed to maintenance of anesthesia with injectables. The faster recovery in the present study is attributed maintenance of anesthesia with Isoflurane. Jena *et al*. (2014) [15] stated that the faster recovery during Isoflurane anesthesia was due to low blood gas solubility of the Isoflurane which facilitated fast elimination from the body. The time taken for recovery in Group III was 18.16 ± 2.15 minutes. This was in concurrence with Kuusela *et al.* (2000) [19] and Arunkumar (2017) [3] who reported recovery time of 18.17 ± 1.83 minutes and 20 minutes after Dexmedetomidine-Propofol-Isoflurane anesthesia in dogs. Kuusela *et al*. (2003) [22] reported a significantly lesser recovery time after Isoflurane anesthesia in comparison to Propofol infusion in Dexmedetomidine premedicated dogs. However, Monsang (2011) [26] reported longer recovery time of 29.75 ± 2.66 minute which could be attributed to maintenance of anesthesia with injectables. The faster recovery in the present study attributed to maintenance of anesthesia with Isoflurane. Jena *et al*. (2014) [15] stated that the faster recovery during Isoflurane anesthesia was due to low blood gas solubility of the Isoflurane which facilitated fast elimination from the body. All the dogs in Group I showed salivation, muscle twitches, increased muscle tone, paddling with the forelegs during recovery period. The above findings were in concurrence with the observations made by Cullen and Reynoldson (1993) [8] who observed the similar signs during recovery period when Propofol alone was used. Smooth recovery in Group II and Group III dogs were recorded without any side effect. Similar findings were observed by Amarpal *et al*. (1996) [2] Sharma *et al.* (2014) [39] and Patond (2016) [32] who observed good to excellent quality of recovery in their study of Medetomidine and Dexmedetomidine premedicants. The recovery time was non-significantly faster in Group I compared to Group II and Group III dogs which could be attributed to mechanism of extensive redistribution of the drug to the tissues and rapid metabolism that might have played a key role in early recovery from Propofol anesthesia. Prolonged recovery in other groups might be due to the synergistic effect of the premedicant drugs used prior to Propofol anesthesia. This was in agreement with Monsang (2011) [26] and Jena *et al*. (2014) [15] and this could also be attributed to the low blood gas solubility of the Isoflurane which facilitated fast elimination from the body. Further, similar findings had also been reported earlier by Hellebrekers (1984) [12], Meyer *et al.* (1984) [25], Jones and Seymour (1986) [17], Sloan *et al.* (1996) [41] and Johnson *et al.* (1998). The muscle relaxation and depth of anesthesia were excellent in Group II and Group III as compare to Group I animals. This was in accordance with the observations made by Gurmita (2010) [11] and Arunkumar (2017) [3] and this could be due to premedicants which provided mild to moderate sedation, increases the muscle relaxation and analgesia before surgery as reported by Lukasik (1999) [24]. Mild drop in rectal temperature within the group of different intervals from five minute to 60th minute of anesthetic period and later returned back to normal level by 90th minute but there is no statistically significant difference within the group and between the groups. Non-significant decrease in rectal temperature in the present study might be attributed to the activation of α 2-receptors and direct effect of the sedatives/anesthetics drugs on thermoregulatory center in hypothalamus as earlier reported by Ponder and Clarke (1980) [33], Virtanen, (1988) [47] and Kuusela *et al*. (2001a) [20]. There was a significant decrease in respiratory rate from 5th minute to 60th minute of anesthetic period in all three groups. However, values returned back to normal physiological level by end of 90th minute and there was no significant difference between the groups during different intervals of anesthesia. Similar observations were earlier recorded by Parikh *et al.* (1995a) [31], Kuusela *et al.* (2001a) [20], Chonde (2002) [6], Granholm *et al.* (2007) [10], Gurmita (2010) [11] and Santosh *et al.* (2013) [37] in their studies. The decrease in respiration rate might be attributed to direct depressant action on central nervous system in general and respiratory center in particular (Parikh *et al.*, 1995a) [31] and activation of the alpha-2 adrenergic pathway, leading to inhibition of locus coeruleus neurons as stated by Oyamada *et al*. (1998) [29]. There was non-significant difference in heart rate within the group and between the groups during different intervals of anesthesia in all the three groups but in Group I there was significant decrease at 5th minute was recorded and the values returned to normal physiological range by end of 90th minute. Similar findings were recorded earlier by Granholm *et al.* (2007) [10], Arunkumar (2017) [3] and Rachel *et al.* (2017) [34] in their respective studies. Decrease in heart rate as observed in Group I might be due to Propofol induced vasodilatation leading to a fall in systemic vascular resistance as well as dose related depression of myocardial contractibility as reported by Duke, (1995) [9] and Mukati *et al.* (2006) [28] after administration of Propofol alone in dogs. Decreased heart rate in Group II and Group III due to direct action of alpha 2-agonist on the post synaptic receptors of the vascular smooth muscles leading to vasoconstriction and an initial transient hypertension followed by pronounced hypotension (Bufalari, 1998). Inhibition of sympathetic tone due to reduction in norepinephrine release from the CNS, vagal activity in response to Alpha-2-agonists induced vasoconstriction and direct increase in the release of acetylcholine from parasympathetic nerves have been reported as the possible mechanisms by which alpha-2-agonists induce bradycardia (MacDonald and Virtanen, 1992). There was no significant difference in pulse rate within the group and between the groups during different intervals from five minute to 60thminute of anaesthetic period in all the three groups but in Group I there was significant decrease at 5th minute was recorded later the values return to the normal level by 90th minute. The results were in concurrence with Bufalari *et al.* (1995) [5], Hofmeister *et al*. (2009) [13] and Rakesh (2019). This could be attributed to synchronization of pulse rate with reduced heart rate after premedication as stated by MacDonald and Virtanen (1992). During the maintenance period decrease in mean pulse rate was mainly because of dose dependent cardiac depression during deep plane of Isoflurane anesthesia in synchronization with heart rate, as

stated by Dobrinski *et al*. (1994) and Yadav *et al.* (2008).

Conclusion

In conclusion, the anesthetic protocol carried out in Group II and Group III given satisfactory results with respect to sedation, analgesia, muscle relaxation, smooth induction and recovery without any untoward events or the complications as compare to directly induced Propofol Group. Therefore, both the drugs produced potent sedative effect.

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