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RESEARCH ARTICLE

COMPARATIVE EVALUATION OF CLINICOPHYSIOLOGICAL CHANGES AFTER INTRAVENOUS ADMINISTRATION OF DEXMEDETOMIDINE-BUTORPHANOL AND DEXMEDETOMIDINE-MIDAZOLAM AS PREANAESTHETIC WITH PROPOFOL ANAESTHESIA IN DOG

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ABSTRACT

The present study was conducted to compare and evaluate the intravenous dexmedetomidine-butorphanol and dexmedetomidine-midazolam as preanaesthetic with propofol anaesthesia in dog. The study was conducted on 14 (fourteen) clinical cases of canine of either sex, irrespective of age presented to the T.V.C.C., COVAS, Parbhani for various surgical interventions randomly divided into two groups each consisting of seven dogs. All the dogs in study were administered with inj. Atropine sulphate @ 0.04 mg/kg body weight subcutaneously. In group A, after administration of inj. Atropine sulphate, 10 min later combination of Inj. Dexmedetomidine HCL (10 µg/kg body weight) and Inj. Butorphanol tartarate (0.2 mg/kg body weight) mixed in single syringe was administered intravenously whereas in group B, combination of Inj. Dexmedetomidine HCL (10 µg/kg body weight) and Inj. Midazolam maleate (0.2 mg/kg body weight) mixed in single syringe was administered intravenously. Quality of sedation was assessed followed by inj. Propofol was administered till the effect to get the surgical stage of anaesthesia and required amount was calculated as induction dose. Intermittent doses of propofol were given for maintenance of anaesthesia when required. The study was comparatively evaluated on the basis of clinical parameter, evaluation of reflexes and physiological parameters. It was found that all the dogs resumes lateral recumbency immediately after administration of drug combination (DB/DM) in both groups. Evaluation of various reflex revealed profound sedation with excellent jaw relaxation, moderate to completely abolished palpebral and pedal reflex and rostroventral eyeball position making pupil invisible during sedation and anaesthesia. From the present study it was concluded that intravenous administration of dexmedetomidine-butorphanol (DB) and dexmedetomidine-midazolam (DM) as preanaesthetic combinations produced profound sedation, rapid onset of action and excellent degree and depth of analgesia along with muscle relaxation extent of which is comparatively more in group DM than DB. Dexmedetomidine-butorphanol and dexmedetomidine-midazolam with propofol produced better quality and degree of basal an aesthesia for the minor and major surgeries in canine patients.

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INTRODUCTION

Anaesthesia is an indispensable pre-requisite for many surgical interventions with maximum technical efficiency and accuracy, so that surgeon can perform surgeries at ease. Surgical management of canine patients always necessitate an ideal anaesthetic which produces sleep, amnesia, analgesia and muscle relaxation to facilitate well-being of the surgical patient. Propofol (2, 6-diisopropylphenol) infusion as 1% emulsion may be used as a part of TIVA regime and has established itself as a qualified maintenance anaesthetic with a good quality recovery.

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Propofol as sole agent for TIVA is generally unsatisfactory, since its poor analgesic property. Consequently, it is necessary to supplement propofol with an analgesic and muscle relaxant. An appropriate selection of premedication drugs can significantly improve intraoperative cardiovascular stability, perioperative analgesia and the quality of recovery. The α_2-adrenergic receptor agonists are useful adjuncts to anaesthesia because of their sedative, anxiolytic and analgesic effects and their anaesthetic-sparing properties. Anticholinergic premedication has been recommended with α_2-agonists to prevent bradyarrhythmias and potential reduction in cardiac output produced by these agents and this recommendation has been widely adopted within most veterinary practices. Dexmedetomidine, an active optical isomer of Medetomidine, is a potent and highly selective α_2-adrenoceptor agonist with sympatholytic, sedative, amnestic and analgesic properties

which has been described as a useful and safe adjunct in many clinical applications. It provides a unique "conscious sedation" (patients appear to be asleep, but are readily aroused), analgesia, without respiratory depression. Hence, opioids and benzodiazepines are combined with α_2-adrenoceptor agonist to have synergistic action which provide profound sedation and potent analgesia prior to propofol anaesthesia in dog (Salmenpera *et al.,* 1994; Amarpal *et al.,* 1996; Bol *et al.,* 2000). Butorphanol is an opioid agonist-antagonist with sedative and analgesic properties. It is known to induce mild sedation accompanied by small decreases in arterial blood pressure, heart rate and arterial oxygen tension in dogs (Trim, 1983). Midazolam, is a short-acting water-soluble benzodiazepine having hypnotic-sedative effect with anxiolytic and marked amnestic properties. Keeping in view the above, the present study was planned with objective of comparative evaluation of clinicophysiological changes after intravenous administration of dexmedetomidine-butorphanol and dexmedetomidine-midazolam as preanaesthetic with propofol anaesthesia in dog.

MATERIALS AND METHODS

Selection and preparation of Animals: The present clinical study was conducted on 14 (fourteen) clinical cases of canine of either sex, irrespective of age presented to the Teaching Veterinary Clinical Complex, College of Veterinary and Animal Sciences, Parbhani for various surgical interventions. In all the dogs under study food was withheld for twelve hours and water withheld for eight hours prior to surgery. Weighing of each dog was done for calculating the exact dose of the anaesthetic agent prior to administration. All the dogs were subjected to clinical examination prior to surgery and physiological parameters were recorded as reference.

Anaesthetic protocol: All the 14 clinical cases were randomly divided into two groups each consisting of seven dogs. All the dogs in study administered with inj. Atropine sulphate @ 0.04 mg/kg body weight subcutaneously.

Group A: After administration of Atropine sulphate, 10 min later combination of Inj. Dexmedetomidine HCL (10 µg/kg body weight) and Inj. Butorphanol tartarate (0.2 mg/kg body weight) mixed in single syringe was administered intravenously.

Group B: After administration of Atropine sulphate, 10 min later combination of Inj. Dexmedetomidine HCL (10 µg/kg body weight) and Inj. Midazolam maleate (0.2 mg/kg body weight) mixed in single syringe was administered intravenously.

Assessment of sedation: The sedation was assessed after the administration of drug combination (dexmedetomidine-butorphanol/dexmedetomidine-midazolam) in both the groups. The level and grading of sedation was done depending upon the quality as described by Rauser and Lexmaulova, (2002). Good(level 1) - A state when the animal resumed lateral recumbence and it was easy to handle without any defence reactions, Moderately good (level 2) - A state when the animal took up lateral or sternal recumbence, handling, however, resulted in defence responses, Poor (level 3) - animal not resuming either lateral or sternal recumbence, reacting by defence responses and being able to walk (with a various degree of ataxia).

Induction and maintenance of anaesthesia: After the onset of sedation, inj. Propofol was given till the effect to get the surgical stage of anaesthesia and required amount was calculated as induction dose. Intermittent dosage for the maintenance of anaesthesia were given when required.

Clinical parameter: Induction time (time taken from intravenous administration of propofol till the loss of pedal reflex with animal entering in the surgical stage of anaesthesia), duration of anaesthesia (time elapsed from the abolition of pedal reflex to the time of appearance of pedal reflex), recovery time (time elapsed from intravenous administration of propofol to the appearance of pedal reflex), complete recovery time (time elapsed from the injection of drugs until the animal stood and walked unassisted) were recorded during the study.

Evaluation of reflexes: The various reflexes were evaluated clinically before preanesthetic (BP), during sedation (DS), during anaesthesia (DA-immediately, 15min, 30 min, 45 min, 60 min, 75 min) and during recovery (DR) in both the groups and scoring was done as per system described by Amarpal *et al.,* 1996. The other reflexes such as salivation, yawning, neck movement, gait, defecation, urination were recorded. Jaw tone-(score-0) not allowing to open the jaws, (score-1) resistance to opening the jaws and closed quickly, (score-2) less resistance to opening the jaws and closed quickly, (score-3) no resistance and jaws remain open. Palpebral reflexes-(score-0) intact and strong (quick blink), (score-1) intact but weak (slow response), (score-2) very weak (very slow and occasional response), (score-3) abolished (no response). Pedal reflexes-(score-0) intact and strong (strong withdrawal), (score-1) intact but weak (animal responding slowly), (score-3) intact but very light (slow and occasional response), (score-4) abolished completely.

Physiological parameter: The physiological parameters viz. heart rate (beats/min), respiration rate (breaths/min), and rectal temperature (^{0}F) were recorded before anaesthesia (BA), after atropine (AA-Immediately and0 10 min), after dexmedetomidine-butorphanol / dexmedetomidine-midazolam (ADB/ADM- Immediately and 10 min), after propofol during anaesthesia (DA- Immediately, 15 min, 30 min, 45 min, 60 min, 75 min), during recovery (DR) from anaesthesia in both the groups.

Statistical analysis: The data collected in the present study of different parameters were analyzed by conventional tools for data analysis (two-way ANOVA and 't' test) using WASP (Anonymus, 2018 WASP version 2.0 http://www.ccari.res.in/ wasp2.0/index.php Last assessed on 4 August 2018).

RESULTS

The surgeries carried out in group A were ovariohysterectomy, cyst excision, external fixation of intramedullary pinning correspondingly mammary tumor excision, surgical excision of Venereal granuloma, amputation of tail, surgical correction of Cherry eye, surgical excision of Capped elbow surgical excision of tumor over neck region and ovariohysterectomy were carried out in group B, respectively.

Assessment of sedation: All the dogs resumes lateral recumbence immediately after administration of drug combination (DB/DM) in both the groups.

Table 1. Mean ± SE values of various clinical parameters in Group A and Group B

Clinical parameter	Group A	Group B
Induction dose (mg/kg)	1.22 ± 0.23	0.57 ± 0.11
Induction time of premedicants(sec.)	55.71 ± 1.23	44.57 ± 1.29
Induction time of propofol (sec.)	25.29 ± 0.97	45.29 ± 1.29
Duration of anaesthesia (min.)	20.14 ± 4.20	25.71 ± 5.05
Recovery time (min.)	27 ± 5.42	22.29 ± 6.92
Complete recovery time (min.)	56.00 ± 13.41	38.71 ± 8.57

Table 2. Mean ± SE jaw tone in group A and group B

Time	Group A	Group B
BA	$^{a}0.00^{m}$	$^{a}0.00^{m}$
DS	$^{c}3.00\pm0.18^{m}$	$^{c}3.00\pm0.18^{m}$
Immediately DA	$^{c}3.00^{m}$	$^{c}3.00\pm0.14^{m}$
DA 15 min	$^{c}3.00^{m}$	$^{c}3.00\pm0.14^{m}$
DA 30 min	$^{c}3.00^{m}$	$^{c}3.00\pm0.14^{m}$
DA 45 min	$^{c}3.00^{m}$	$^{c}3.00\pm0.14^{m}$
DA 60 min	$^{c}3.00^{m}$	$^{c}2.43\pm0.37^{o}$
DA 75 min	$^{c}2.43\pm0.37^{m}$	$^{c}1.85\pm0.55^{o}$
DR	$^{b}0.43\pm0.20^{m}$	$^{c}0.71\pm0.18^{o}$
Mean ± SE	2.32 ± 0.06^{m}	2.22 ± 0.12^{m}
CD value Factor A. 0.170(5%), 0.224(1%); Factor B. 0.364(5%), 0.484(1%)		

{a, b, c superscript shows significant difference at regular interval during course of anaesthesia in a specific group only (within column); m, n, o superscript shows significant difference between two groups at specific interval of observation only (within row)}

Table 2. Mean ± SE palpebral reflex in group A and group B

Time	Group A	Group B
BA	$^{a}0.00^{m}$	$^{a}0.00^{m}$
DS	$^{c}2.14\pm0.14^{m}$	$^{c}2.57\pm0.20^{o}$
Immediately DA	$^{c}2.43\pm0.20^{m}$	$^{c}2.57\pm0.20^{m}$
DA 15 min	$^{c}2.29\pm0.18^{m}$	$^{c}2.57\pm0.20^{o}$
DA 30 min	$^{c}2.29\pm0.18^{m}$	$^{c}2.57\pm0.20^{o}$
DA 45 min	$^{c}2.29\pm0.18^{m}$	$^{c}2.00\pm0.31^{o}$
DA 60 min	$^{c}2.00\pm0.31^{m}$	$^{c}1.43\pm0.48^{o}$
DA 75 min	$^{c}0.71\pm0.18^{m}$	$^{\backslash b}0.43\pm0.20^{o}$
DR	$^{a}0.00^{m}$	$^{a}0.00^{m}$
Mean ± SE	1.57 ± 0.15^{m}	1.57 ± 0.20^{m}
CD value Factor A. 0.184(5%), 0.243(1%); Factor B. 0.395(5%), 0.525(1%)		

{a, b, c superscript shows significant difference at regular interval during course of anaesthesia in a specific group only (within column); m, n, o superscript shows significant difference between two groups at specific interval of observation only (within row)}

Table 3. Mean ± SE pedal reflex in group A and group B

Time	Group A	Group B
BA	$^{a}0.00^{m}$	$^{a}0.00^{m}$
DS	$^{b}2.43\pm0.20^{m}$	$^{b}2.86\pm0.14^{o}$
Immediately DA	$^{b}2.86\pm0.14^{m}$	$^{b}3.00^{o}$
DA 15 min	$^{b}2.86\pm0.14^{m}$	$^{b}3.00^{o}$
DA 30 min	$^{b}2.86\pm0.14^{m}$	$^{b}3.00^{o}$
DA 45 min	$^{b}2.86\pm0.14^{m}$	$^{b}2.71\pm0.29^{n}$
DA 60 min	$^{b}2.86\pm0.14^{m}$	$^{b}2.00\pm0.49^{o}$
DA 75 min	$^{b}1.00^{m}$	$^{b}0.57\pm0.20^{o}$
DR	$^{a}0.00^{m}$	$^{a}0.00^{m}$
Mean ± SE	1.97 ± 0.10^{m}	1.90 ± 0.12^{m}
CD value Factor A. 0.146(5%), 0.191(1%); Factor B. 0.309(5%), 0.403(1%)		

{a, b, c superscript shows significant difference at regular interval during course of anaesthesia in a specific group only (within column); m, n, o superscript shows significant difference between two groups at specific interval of observation only (within row)}

Table 4. Mean ± SE heart rate (beats/min) in group A and group B

Time	Group A	Group B
Before anaesthesia	$^{a}115.00 \pm 7.36^{m}$	$^{a}94.29 \pm 8.04^{o}$
Immediately after atropine	$^{a}128.00 \pm 7.35^{m}$	$^{b}112.00 \pm 7.12^{o}$
After atropine 10 min	$^{a}129.86 \pm 13.25^{m}$	$^{a}96.14 \pm 9.94^{o}$
Immediately after DB/DM	$^{a}99.14 \pm 8.47^{m}$	$^{a}92.00 \pm 7.66^{n}$
After DB/DM 10 min	$^{b}95.86 \pm 9.10^{m}$	$^{a}86.85 \pm 11.60^{o}$
Immediately after propofol	$^{a}101.43 \pm 13.77^{m}$	$^{b}115.00 \pm 12.70^{o}$
After propofol 15 min	$^{a}105.43 \pm 14.90^{m}$	$^{a}108.29 \pm 9.18^{m}$
After propofol 30 min	$^{a}111.57 \pm 14.33^{m}$	$^{a}107.00 \pm 9.48^{m}$
After propofol 45 min	$^{a}110.71 \pm 13.87^{m}$	$^{a}98.43 \pm 6.07^{o}$
After propofol 60 min	$^{a}112.43 \pm 13.42^{m}$	$^{a}95.71 \pm 6.10^{o}$
After propofol 75 min	$^{a}114.1 \pm 13.48^{m}$	$^{\backslash a}92.71 \pm 6.17^{o}$
After recovery from anaesthesia	$^{a}126.57 \pm 17.20^{m}$	$^{a}95.00 \pm 6.54^{o}$
Mean ± SE	112.51 ± 12.21^{m}	99.45 ± 8.38^{o}
Factor A (Between groups). 6.45 (5%), 8.48 (1%)		
Factor B (Within groups). 15.80 (5%), 20.77 (1%)		

{a, b, c superscript shows significant difference at regular interval during course of anaesthesia in a specific group only (within column); m, n, o superscript shows significant difference between two groups at specific interval of observation only (within row)}

Table 5. Mean ± SE respiration rate (breaths/min) in group A and group B

Time	Group A	Group B
Before anaesthesia	$^{a}72.00 \pm 13.29^{m}$	$^{a}89.00 \pm 17.27^{n}$
Immediately after atropine	$^{a}73.15 \pm 15.65^{m}$	$^{a}89.15 \pm 16.42^{n}$
After atropine 10 min	$^{b}56.15 \pm 13.01^{m}$	$^{b}59.15 \pm 23.65^{m}$
Immediately after DB/DM	$^{b}37.15 \pm 5.24^{m}$	$^{b}33.85 \pm 8.99^{m}$
After DB/DM 10 min	$^{b}35.43 \pm 5.31^{m}$	$^{b}35.15 \pm 10.32^{m}$
Immediately after propofol	$^{b}38.29 \pm 6.15^{m}$	$^{b}39.00 \pm 9.05^{m}$
After propofol 15 min	$^{b}40.71 \pm 7.10^{m}$	$^{b}33.85 \pm 8.19^{m}$
After propofol 30 min	$^{b}41.85 \pm 6.49^{m}$	$^{b}37.00 \pm 8.80^{m}$
After propofol 45 min	$^{b}44.43 \pm 6.07^{m}$	$^{b}40.85 \pm 9.59^{m}$
After propofol 60 min	$^{b}40.15 \pm 7.34^{m}$	$^{b}41.29 \pm 8.35^{m}$
After propofol 75 min	$^{b}42.43 \pm 8.34^{m}$	$^{b}43.43 \pm 8.55^{m}$
After recovery from anaesthesia	$^{b}41.71 \pm 6.69^{m}$	$^{b}37.85 \pm 6.18^{m}$
Mean ± SE	46.64 ± 8.39^{m}	48.30 ± 11.28^{m}
Factor A (Between groups). 6.88 (5%), 9.04 (1%)		
Factor B (Within groups). 16.87 (5%), 22.17 (1%)		

{a, b, c superscript shows significant difference at regular interval during course of anaesthesia in a specific group only (within column); m, n, o superscript shows significant difference between two groups at specific interval of observation only (within row)}

Table 6. Mean ± SE values of rectal temperature (^{0}F) in group A and group B

Time	Group A	Group B
Before anaesthesia	$^{a}101.40 \pm 0.68^{m}$	$^{a}102.11 \pm 0.26^{n}$
Immediately after atropine	$^{a}101.49 \pm 0.63^{m}$	$^{a}101.69 \pm 0.26^{m}$
After atropine 10 min	$^{a}101.39 \pm 0.49^{m}$	$^{a}102.01 \pm 0.2^{n}$
Immediately after DB/DM	$^{a}101.80 \pm 0.56^{m}$	$^{a}102.00 \pm 0.22^{m}$
After DB/DM 10 min	$^{a}101.53 \pm 0.56^{m}$	$^{a}101.77 \pm 0.30^{m}$
Immediately after propofol	$^{a}101.10 \pm 0.71^{m}$	$^{a}101.79 \pm 0.35^{n}$
After propofol 15 min	$^{a}100.89 \pm 0.75^{m}$	$^{a}101.64 \pm 0.3^{n}$
After propofol 30 min	$^{a}100.81 \pm 0.71^{m}$	$^{a}101.59 \pm 0.3^{n}$
After propofol 45 min	$^{a}100.53 \pm 0.72^{m}$	$^{b}101.46 \pm 0.32^{n}$
After propofol 60 min	$^{c}100.59 \pm 0.72^{m}$	$^{a}101.57 \pm 0.39^{n}$
After propofol 75 min	$^{b}100.53 \pm 0.61^{m}$	$^{a}101.57 \pm 0.52^{n}$
After recovery from anaesthesia	$^{b}100.19 \pm 0.54^{m}$	$^{c}100.84 \pm 0.38^{n}$
Mean ± SE	101.02 ± 0.64^{m}	101.67 ± 0.32^{n}
Factor A (Between groups). 0.28 (5%), 0.35 (1%)		
Factor B (Within groups). 0.66 (5%), 0.87 (1%)		

{a, b, c superscript shows significant difference at regular interval during course of anaesthesia in a specific group only (within column); m, n, o superscript shows significant difference between two groups at specific interval of observation only (within row)}

There was excellent jaw tone along with moderate to completely abolished palpebral and pedal reflexes observed in both the groups but the intensity was more marked in group B than group A. The position of eyeball was mostly rostroventral making pupil invisible in dogs of both the groups. The jaw was remained open and tongue was exposed manually without any difficulty in both groups upon DB/DM administration. There was no case of poor sedation in any group recorded. Comparision between two groups revealed rapid onset of action and profound sedation after administration of drug combination (DB/DM) in both the groups.

Induction and maintenance of anaesthesia: The mean ± SE dose of propofol required for induction of anesthesia for group A and group B was found to be 1.22 ± 0.23 mg/kg BW and 0.57 ± 0.11 mg/kg BW, respectively depicted in Table 1. Comparision among both groups revealed statistical significant difference ($P<0.05$) in induction dose. There was no propofol required for induction in solitary case (Case No. B_1).

Induction time (sec.): In present study, mean ± SE value of induction time of premedication and propofol was 55.71 ± 1.23 seconds and 44.57 ± 1.29 seconds and 25.29 ± 0.97 seconds and 45.29 ± 1.29 seconds in group A and group B, respectively depicted in Table 1. Statistically non-significant difference ($P<0.01$) was observed for induction time of premedicants and propofol in both the groups.

Duration of anaesthesia (min.): In present study, mean ± SE value of duration of anaesthesia was 20.14 ± 4.20 min and 25.71 ± 5.05 min in group A and group B, respectively depicted in Table 1. Comparision among both groups did not reveal any statistical difference in duration of anaesthesia.

Recovery time (min.): The mean ± SE value of recovery time was 27 ± 5.42 min and 22.29 ± 6.92 min in group A and group B, respectively depicted in Table 1. Comparision among both groups did not reveal any statistical difference in recovery time. All the animals in both groups observed calm and quite except in solitary case (B_2) where animal cried during recovery from anaesthesia.

Complete recovery time (min.): The mean ± SE value of complete recovery time was 56.00 ± 13.41 min and 38.71 ± 8.57 min, respectively depicted in Table 1. Comparision among both groups did not reveal any statistical difference in complete recovery time. The animals of both groups were observed quiet, calm, breathed normally and good analgesia (no response when the incision was palpated) except in solitary case (B_2) where animal cried during complete recovery from anaesthesia.

Evaluation of reflexes

Jaw tone: The mean ± SE values of jaw tone score in group A and group B are 2.32±0.06and 2.22±0.12, respectively. As shown in the Table 2, jaw tone was increased significantly ($P<0.01$) and started to abolished immediately after the administration of DB/DM in both the groups. It completely abolished at 10 min during sedation followed by complete abolishment after propofol till 45 min in both groups thereafter

decreased significantly (P<0.01) in group A while decreased nonsignificantly in group B till the recovery. Statistically significance increase (P<0.01) was observed in jaw tone at various intervals of both groups after administration of DB/DM from baseline till completion of surgery. Comparison among the both groups in jaw tone score revealed that there was no significant difference between groups except at the interval of during anaesthesia 60 min, 75 min and during recovery which might be due to irregular interval among the completion of surgery. Overall no statistically significance difference was observed between the groups.

Palpebral reflex: The mean ± SE values of palpebral reflex score in group A and group B are 1.57±0.15 and 1.57±0.20, respectively. As shown in the Table 2, palpebral reflex score was increased significantly (P<0.01) and abolished immediately after the administration of DB/DM and during sedation thereafter remained abolished till 75 min in group A and 60 min in group B after propofol administration in both* the groups. A significantly decrease (P<0.05) was observed at 75 min after propofol administration in group B. Thereafter, it was decreased nonsignificantly in both groups during recovery.

Comparison among the both groups in palpebral reflex score revealed that there was significant difference was observed between groups at the interval of during sedation, during anaesthesia at 60 min and 75 min and during recovery which might be due to irregular interval among the completion of surgery. Overall no statistically significance difference was observed between the groups.

Pedal reflex: The mean ± SE values of pedal reflex score in group A and group B are 1.57±0.15 and 1.57±0.20, respectively. As shown in the Table 3, pedal reflex score was increased significantly (P<0.01) and completely abolished immediately after the administration of DB/DM and during sedation thereafter remained completely abolished till 75 min after propofol administration in both the groups. Thereafter, it was decreased nonsignificantly in both groups during recovery. Comparison among the both groups in pedal reflex score revealed that there was significant difference was observed between the groups at the interval of during sedation, during anaesthesia till 75 min whereas nonsignificantly difference was observed during recovery which might be due to irregular interval among the completion of surgery. Overall no statistically significance difference was observed between the groups.

Other reflexes: The other parameters such as salivation, yawning, neck movement, gait, defecation, urination were recorded during sedation. There was normal salivation, no yawning or neck movement and absence of defecation observed among both group of animals during sedation and overall anaesthetic study whereas urination was observed in only one dog (A_2).

Physiological parameter

Heart rate: The mean ± SE values of heart rate in group A and group B are 112.51 ± 12.21 and 99.45 ± 8.38, respectively. As shown in Table 4, the comparision within the groups revealed that the HR increased non-significantly in group A at 10 min after atropine administration whereas increased significantly (P<0.05) in group B. A non-significant decreased was observed immediately upon administration of DB/DM in both groups whereas it was decreased significantly (P<0.05) at 10 min in group A upon DB administration and decreased nonsignificantly in group B upon DM administration. Immediately after propofol administration a non-significant increase was observed in group A till 30 min, whereas it was decreased non-significantly at 45 min, thereafter it was increased non-significantly till recovery at which the value return near to the baseline. In group B it was increased significantly (P<0.05) immediately after propofol administration, thereafter decreased nonsignificantly till recovery from anaesthesia. Comparison between both groups revealed a significant difference (p<0.01) among HR till 10 min after atropine administration from the baseline. Then a significant difference (P<0.05) was observed at immediately and (P<0.01) at 10 min upon DB/DM administration. A significant difference (P<0.01) was observed immediately and at 10 min after propofol administration, thereafter it was differed non-significantly at 15 min and 45 min interval. A significant difference (P<0.01) was observed at 60 min, 75 min and till recovery at which the values return to baseline. Overall significant difference (P<0.01) was observed between the groups.

Respiration rate: The mean ± SE values of respiration rate in group A and group B are 46.64 ± 8.39 and 48.30 ± 11.28, respectively. As shown in Table 5, the comparision within the groups revealed that the values of RR decreased significantly (P<0.05) in group A at 10 min after atropine administration whereas decreased significantly (P<0.01) in group B. A significant decrease (P<0.01) was observed immediately upon administration of DB in group A till 10 min whereas in group B it was decreased significantly (P<0.01) immediately and thereafter increased significantly at 10 min upon DM administration. A significant increase (P<0.01) was observed after propofol administration in both groups, whereas at 15 min significant increase (P<0.01) was observed in group A and significant decrease (P<0.01) in group B.

A significant increase (P<0.01) was observed from 30 min till 45 min after propofol administration in group A thereafter it was decreased significantly at 60 min, whereas it was increased at 75 min. In group B, a significant increase (P<0.01) was observed from 30 min till 75 min after propofol administration thereafter a significant decrease was observed during recovery in both the groups during recovery. Comparison between both groups suggested a significant difference (p<0.01) among RR up to 10 min from baseline to immediately after atropine administration, thereafter a non-significant difference was observed till recovery. Overall no significant difference was observed between the groups.

Rectal temperature: The mean ± SE values of rectal temperature in group A and group B are 101.02 ± 0.64 and 101.67 ± 0.32, respectively. As shown in Table 6, the comparision within the groups revealed that the values of RT increased non-significantly in group A from baseline to immediately after administration of atropine, whereas it was decreased at 10 min. A non-significant increase was observed immediately after DB administration till 45 min after propofol administration. A significant decrease (P<0.01) was observed at 60 min after propofol thereafter significantly decrease (P<0.05) till recovery whereas in group B, the values of RT was decreased non-significantly from baseline till the administration of atropine, whereas it was increased at 10 min. Thereafter, it was decreased non-significantly immediately

after DM administration till 30 min of after propofol administration. A significant decrease ($P<0.05$) was observed at 45 min after propofol, thereafter it was decreased non-significantly up to 75 min again it decreased significantly ($P<0.01$) at recovery. Comparison between both groups suggested a significant difference ($p<0.05$) among RT at baseline and at 10 min after atropine administration, thereafter significant difference ($P<0.05$) was observed at immediately after propofol administration till recovery in both groups. Overall significant difference ($P<0.05$) was observed between the groups.

DISCUSSION

The rapid onset of action of drug combination (dexmedetomidine-butorphanol and dexmedetomidine-midazolam) might be attributed to synergistic interaction between α_2-agonist,opioids and benzodiazepines and lipophilic property of dexmedetomidine (Salmenpera *et al.,* 1994; Amarpal *et al.,* 1996; Bol *et al.,* 2000). Similar findings were observed by Ko *et al*. (2000). The decrease in induction dosein dexmedetomidine-midazolam group than dexmedetomidine-butorphanol group might be due to synergistic interaction and additive analgesic effect of midazolam than butorphanol with dexmedetomidine which having poor analgesic properties (Salmenpera *et al.,* 1994; Amarpal *et al.,* 1996; Bol *et al.,* 2000). Similar findings were observed by Fabio *et al.* (2007). As the dose of propofol increased, the mean induction time decreased was reported by Salunke (2001) in xylazine (0.5 mg/kg)-propofol (2 mg/kg) anaesthetic study in dogs and concluded that the induction time was found to be dose related. This might be attributed to synergistic interaction of butorphanol and midazolam with dexmedetomidine which reduced time required for induction to the loss of reflexes and high lipid solubility of propofol followed by its rapid distribution phase responsible for quick induction. Similar findings were noted by Rolly and Versichelen (1985), Mathews *et al.* (1995).

The duration of anaesthesia was found prolonged in group B than group A. Salunke (2001) reported the duration of anaesthesia was directly proportional to the dose rate of propofol. Schutler *et al.* (1985) mentioned that high lipid solubility of the drugs enables it to cross cell membrane during the initial distribution phase as well as in the redistribution phase leading to longer duration of anaesthesia. The prolonged recovery and complete recovery time in group A was due to additive effect of butorphanol and its reduced metabolic activity to delay redistribution and metabolism as compared to midazolam in group B with dexmedetomidine. Similar findings were observed by Rafee *et al.* (2015). They recorded the increased standing recovery time might be attributed to increase in the number of drugs used correlated with the increased sedation and decreased metabolic rate in their study of effect of dexmedetomidine with or without butorphanol in dogs undergoing ovariohysterectomy in midazolam and ketamine anaesthesia. Jaw tone signifies the extent of muscle relaxation. In animal of all the groups excellent muscle relaxation was observed due to addition of butorphanol and midazolam having synergistic interaction with dexmedetomidine (Amarpal *et al.,* 1996, Bol *et al.,* 2000). All the α_2-agonists, including dexmedetomidine are well known to produce good muscle relaxation (Lemke, 2004) which is attributed to inhibition of intraneuronal transmission of impulses by α_2-agonists at the level of CNS (Marjorie, 2001). The intensity of jaw tone was more marked in group B than group A might be additive muscle relaxant effect of midazolam. Status of palpebral was taken as a measure of sedation. In animal of all the groups excellent sedation was observed due to addition of opioids and benzodiazepines having synergistic interaction with α_2-agonist (Amarpal *et al*., 1996, Bol *et al*., 2000). Similar findings observed by Leppanen *et al.*,(2006) indexmedetomidine-diazepam, dexmedetomidine-butorphanol, dexmedetomidine-buprenorphine in dogs. Status of pedal reflex was taken as depth of analgesia. In both group moderate to complete abolished pedal reflex after sedation and during anaesthesia attributed to the synergistic interaction of opioid and benzodiazepines with α_2-agonists (Amarpal *et al.*, 1996; Bol *et al.*, 2000). The significant difference at the baseline in heart rate could be due to the individual variations. Initial increase in heart rate even after the administration of dexmedetomidine with opioid might be attributed to the effect of atropine (Innes and Nickerson, 1975). Decrease in respiration rate might be attributed to combined effect of systemic administration of dexmedetomidine, butorphanol and midazolam (Sabbe *et al.,* 1994, Butola and Singh, 2007 and Wright, 1982). Similar findings observed by Jena *et al.* (2014) noted that in group dexmedetomidine, RR was decreased non-significantly ($P>0.05$) from 5 min but the decrease was significant ($P<0.01$) at 10 min and values remained significantly ($P<0.01$) lower than the base value during dexmedetomidine-propofol anaesthesia in dogs. Decrease in rectal temperature is attributed to the activation of α_2-receptors by dexmedetomidine, which mediate hypothermia (Lemke, 2004) in combination with a reduction in muscular activity and basal metabolic rate (Ponder and Clarke, 1989; MacDonald *et al*., 1988).

Conclusion

From the present study it was concluded that intravenous administration of dexmedetomidine-butorphanol and dexmedetomidine-midazolam both as preanaesthetic combinations produced profound sedation, rapid onset of action and excellent degree and depth of analgesia along with muscle relaxation extent of which is comparatively more in group DM than DB. Dexmedetomidine-butorphanol and dexmedetomidine-midazolam with propofol produced better quality and degree of basal anaesthesia for the minor and major surgeries in canine patients.

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