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Effects of pre-medication with acepromazine/midazolam/ dexmedetomidine and butorphanol on induction dose of propofol and incidence of apnoea during induction in canines

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ABSTRACT

The objective of the study was to evaluate the effect of ACE, MID, DEX (IM) and DEX (IV) with butorphanol on quality of induction, induction dose of propofol and incidence of apnoea during anaesthesia in client-owned dogs. Animals were randomly divided into four groups. After pre-medication with atropine sulphate, animals were administered with ACE @ 0.05 mg/kg b.wt IV in group A, MID @ 0.5 mg/kg IV b.wt in group B, DEX @ 15 µg/kg IM b.wt in group C and DEX @ 15 µg/kg IV b.wt in group D along with butorphanol @ 0.2 mg/kg b. wt. I/V. All animals were induced with propofol and maintained with isoflurane till the end of closing last skin suture. Adequate sedation and depth of analgesia was observed in the animals of the all four group and this sedation made handling of the animals proper and safe before induction. Significantly lower dose of propofol was needed for induction in the groups C and D as compared to groups A and B. Incidence of temporary apnoea in groups A and B was 10%, whereas in groups C and D was 30%, but they were managed by assisted ventilation and smoothly maintained with isoflurane without complication. It was found that ACE/MID/DEX with butorphanol has dose-sparing effect and provides adequate sedation and analgesia in the canines. Chances of apnoea may be more with DEX pre-medication, but they can be managed by assisted ventilation without any complication.

Keywords: Acepromazine, Apnoea, Dexmedetomidine, Induction, Midazolam, Propofol

Induction of anaesthesia with intravenous anaesthetic agent is extensively used for rapid and smooth induction in comparison to other anaesthetic technique. In the present time, a large number of induction agents are available, in which propofol is most often used as an anaesthetic induction agent in canines. Incidence of apnoea following induction with propofol is a common adverse effect and related with dose and speed of propofol administration (Sahinovic *et al.* 2015). Plasma level of propofol more than 6 mg/ml was associated with apnoea in canines. Duration of apnoea varied between individual canines but increased as the dose increased.

Proper pre-anaesthetic medication reduces the induction and maintenance dose of anaesthetic agents and improves respiratory and cardiovascular function (Murrell 2016). It also reduces muscle tone and undesirable autonomic reflexes of the nervous system (Dugdale 2010). Pre-anaesthetic medication includes administration of sedative, narcotics, tranquiliser with a view to minimize excitement and struggle during induction and recovery from anaesthesia. Acepromazine (ACE) is a long acting phenothiazine tranquilizer, routinely used as pre-anaesthetic agent in canines, felines and equines. Combinations of ACE and opioid reduce the requirement of both injectable and inhalant anaesthesia in canines (Monteiro *et al.* 2009). Pre-medication with midazolam reduces the induction dose of propofol (Robinson and Borer-Weir 2015).

Alpha-2 adrenoreceptor agonists are most commonly used sedatives in both small and large animal patients for sedation, muscle relaxation and analgesia. Dexmedetomidine (DEX) is a latest alpha-2 agonist; produces good muscle relaxation and pronounced cardiovascular effects including decreased heart rate and cardiac index, increased systemic vascular resistance and central venous pressure. Butorphanol (BUT) is a potent opioid analgesic for treating acute nociceptive pain like injury, peri-operative pain, post-operative pain, visceral and chronic pain (Ahsan *et al.* 2020). Combining an opioid with α-2 agonist or phenothiazine tranquilizer enhances sedation and analgesia and inhibits the side effects caused by opioid like central nervous system excitation and decreased gastrointestinal tract motility (Carregaro *et al.* 2020). The purpose of the study was to compare and evaluate the effect of ACE-BUT, midazolam-BUT, DEX (IM)-BUT and DEX (IV)-BUT on induction dose of propofol and incidence of apnoea during anaesthesia.

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MATERIALS AND METHODS

The study was conducted in Teaching Veterinary Clinical Complex and Referral Veterinary Polyclinic, IVRI, Izatnagar from 2018-20. Cinically healthy client owned canines (32), irrespective of breed, weighing more than 5 kg and 16 weeks age or more, were subjected for ovariohysterectomy in their physical status I according to the American Society of Anaesthesiologists Classification (Daabiss 2011). The dogs were randomly divided into four groups with different combination of pre-anaesthetic drugs. Groups A and B with 10 animals, whereas groups C and D had 6 animals. Induction and maintenance were carried out with propofol and isoflurane, respectively. The owner's consent was obtained for each dog to take part in the study.

All animals were subjected to pre-operative check-up for evaluating the physical status. The dogs were kept off-fed for 16 hrs before the trial of anaesthesia. After preparation of the animal, atropine sulphate was administered @ 0.04 mg/kg IV b.wt intramuscularly. Immediately animal was placed on an operation table and canulated with the intravenous catheter of suitable diameter attached to normal saline infusion line. After 10 min of atropine injection midazolam (MID) @ 0.05 mg/kg b. wt. IV in group A, ACE @ 0.5 mg/kg IV b. wt. in group B, DEX @ 15 µg/kg b. wt. IM in group C and DEX @15 µg/kg b. wt. IV in group D along with butorphanol 0.2 mg/kg b. wt. IV were administered using separate syringes. After 15 min of premedication, anaesthesia was induced with propofol till effect in all the four groups. Immediately after induction, the animals were intubated and anaesthesia was maintained with isoflurane until the last skin suture was closed.

Dose of drug for induction was assessed by calculating total dose (mg/kg) required for induction of anaesthesia. The quality of induction was recorded as excellent, rapid disappearance of laryngeal reflex with smooth induction; good, intubation with depressed laryngeal reflex or mild body movement; fair, if it was necessary to use lidocaine spray to control a laryngeal reflex; and poor, when intubation was difficult and propofol was added to control a laryngeal reflex (Sano *et al.* 2003b). Incidence of apnoea was recorded during or after induction with propofol. Extent of salivation in canines was recorded at various intervals and all recordings were made before administration of the pre-anaesthetic agents, 5 min after administration of the pre-anaesthetic agents, just after induction with propofol and at 20 and 40 min during maintenance of general anaesthesia with isoflurane and just after extubation. The subjective observations of salivation were graded from 0 to 3 according to the scales reported by Rafee (2013).

Statistical analysis: ANOVA (Analysis of variance) and Duncan's multiple range test (DMRT) were used to compare the means at different time intervals between different groups. Repeated measure ANOVA were used to compare the mean values at different intervals with their base values in each group. The subjective data generated from the scoring was analyzed by Tukey HSD testing among groups and within each group.

RESULTS AND DISCUSSION

On the clinical examination, adequate sedation and depth of analgesia was observed in the animals of all four groups and this sedation made handling of the animals proper and safe before induction. Respiratory rate, heart rate and rectal temperature remained in the normal physiological range throughout the observation period. Mean±Sd values for doses of propofol for induction in groups A, B, C and D were recorded as 3.60±0.85 mg/kg, 3.45±0.97 mg/kg, 1.06 ±.39 mg/kg and 0.69±0.67 mg/kg, respectively.

Comparison among groups showed that groups A and B required significantly ($p<0.05$) higher intravenous dose of propofol for induction in compared to groups C and D. In between comparison of group C and D, group C required non-significantly higher dose of propofol for induction than group D. However difference in the dose of induction between groups A and B was very slight. Quality of induction was excellent in the all four groups except good in one animal of group A and group B. However in one animal of group A, quality of induction was poor (Table 1).

Table 1. Quality of induction in all the four groups

Quality of Induction	Group			
	A	B	C	D
Excellent	8	9	6	6
Good	1	1	0	0
Fair	0	0	0	0
Poor	1	0	0	0

Incidence of apnoea recorded in groups A, B, C and D was 10%, 10%, 30% and 30% respectively (Fig. 1). Salivation was not observed in animals after induction and maintenance of anaesthesia except mild salivation in one animal in group A, however a mild degree of salivation was observed in some animals in groups A, B and D after

Table 2. Mean ± SD values of salivation scores recorded in all the four groups at different intervals

Parameter	Group-1	Before pre-anaesthetic	After 5 min. pre – anaesthetic	At induction	T20	T40	At extubation
Salivation	A	$0.00^{cb}\pm0.00^{B}$	$0.2^{a}\pm0.4^{B}$	$0.1^{b}\pm0.3^{A}$	$00^{c}\pm0.00^{A}$	$00^{c}\pm0.00^{A}$	$0.1^{b}\pm0.31^{C}$
	B	$0.0^{cb}\pm0.00^{B}$	$0.1^{b}\pm0.32^{C}$	$00^{c}\pm0.00^{A}$	$00^{c}\pm0.00^{A}$	$00^{c}\pm0.00^{A}$	$0.5^{a}\pm 0.85^{A}$
	C	$0.00^{a}\pm0.00^{B}$	$0.00^{a}\pm0.00^{D}$	$0.00^{a}\pm0.00^{A}$	$0.00^{a}\pm0.00^{A}$	$0.00^{a}\pm0.00^{A}$	$0.00^{a}\pm0.00^{D}$
	D	$0.5^{a}\pm0.55^{A}$	$0.33^{b}\pm0.52^{A}$	$0.00^{c}\pm0.00^{A}$	$0.00^{c}\pm0.00A$	$0.00^{c}\pm0.00^{A}$	$0.33^{c}\pm0.52^{B}$

Note: Means with a different lower case superscript in a row differ significantly and the means with a different upper case superscript in a column differ significantly ($p<0.05$).

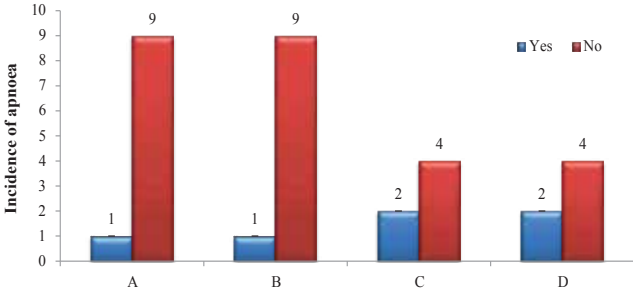

Fig. 1. Incidence of apnoea after induction in all the four groups.

pre-medication and extubation (Table 2).

Pre-anaesthetic medications induced adequate sedation and depth of analgesia before induction with propofol in all four groups. After that, the animal was maintained with isoflurane without any apparent problems. Induction was smooth and dose of induction with propofol was significantly decreased as compared to without pre-anaesthetic medication in all groups (Sano *et al.* 2003a). There is a wide range of induction dose of propofol in unpremeditated canines. The minimum dose of induction with propofol is 2 mg/kg (Robinson and Borer-Weir 2013) whereas average dose for induction is 6 mg/kg body weight in canine (Doebeli *et al.* 2013). In earlier study, a significant difference in mean dose of propofol for induction was observed after premedication with buprenorphine (20 µgm/kg)-acepromazine (0.03 mg/kg) combination and buprenorphine (20 µgm/kg)-dexmedetomidine (10 µgm/kg) combination (Hunt *et al.* 2013). However, Grasso *et al.* (2015) reported induction dose of propofol in canine as 3.0±0.1 mg/kg and 2.3±0.9 mg/kg, respectively, after premedication with acepromazine (0.05 mg/kg) and dexmedetomidine (15 gm/kg) without significant difference between the groups. Bigby *et al.* (2017) also reported decline in induction dose with propofol was non-significant between acepromazine (0.05 mg/kg) and dexmedetomidine (5 µg/kg) groups, which might be due to a lower dose of dexmedetomidine in comparison to present study. In the present study, difference in dose of propofol was significant in between acepromazine and dexmedetomidine groups. Kuusela *et al.* (2001) reported dose of propofol for induction was 0.8 ± 0.2 mg/kg after pre-medication with intravenous dexmedetomidine (20 µg/kg) whereas without pre-medication it was 6.0 ±1.1 mg/kg. Similar observations were observed in group D which were also reported by Kushwaha *et al.* (2012) in canines.

The degree of dose reduction for induction with propofol is related to the depth of sedation induced by each pre-anaesthetic medication (Kojima *et al.* 2002). Administration of dexmedetomidine induces deep sedation along with analgesia and relaxation of muscle in the animals by the activation of alpha-2-adrenoceptors in CNS and markedly reduces the induction dosage of anaesthetic agents. A marked synergistic effect between alpha-2 agonists, butorphanol and propofol was also reported. This synergistic effect is also responsible for the reduction of induction dosage of propofol in this study.

Acepromazine is a phenothiazine compound which induces moderate sedation, weak muscle relaxation and does not produce analgesia. However, butorphanol and acepromazine act synergistically and induce moderate depression of CNS resulting in a moderate decline in dose of propofol. Sano *et al.* (2003a) also reported the highest reduction of dose with alpha-2 agonist group compared to midazolam and acepromazine groups, whereas reduction in dose of induction in acepromazine and midazolam groups was nearly equal as recorded in the present study. Similarly, Munoz *et al.* (2017) reported a combination of hydromorphone and acepromazine which significantly reduced the dose of alfaxalone for induction by approximately 75% in comparison to unpremedicated dogs and Italiano and Robinson (2018) reported that induction dose of alfaxalone declined by approximately 35% when alfaxalone was combined with a benzodiazepine in healthy canines.

Quality of induction was excellent to good except one animal in acepromazine group. Laryngeal reflex in that case returned during intubation and other dose of propofol was required for intubation. Recovery was also smooth from anaesthesia, regardless of the pre-anaesthetic medication or duration of anaesthesia except one animal in group A and one animal in group C. Animals remained lightly to moderately sedated after recovery from anaesthesia. In group A, one animal was crying during recovery, whereas in group C one animal did not recover up to 4 hrs and alpha-2 antagonist was used to neutralise the effect of dexmedetomidine. After systemic administration of alpha-2 antagonist (atipamezole), the animal recovered within 10 min. Incidence of temporary apnoea recorded in groups A, B, C, and D was 10%, 10%, 30%, and 30% respectively, but they were managed by assisted ventilation and smoothly maintained with isoflurane without complication. Incidence of apnoea is a frequent and most common complication with induction by propofol and it depends on dose and speed of propofol administration (Sano *et al.* 2003b). Kuusela *et al.* (2001) reported the incidence of apnoea in 15% canines after pre-medication with dexmedetomidine (20 µgm/kg) accompanied by induction with propofol that lasted for 1 to 2 min. Kropf and Hughes (2019) observed apnoea in 4 dogs out of 38 dogs after pre-medication with ACE (0.03 mg/kg) and pethidine (3 mg/kg) followed by induction with propofol. Similarly, Kojma *et al.* (2002) reported apnoea in 2 dogs out of 7 dogs after pre-medication with medetomidine- midazolam followed by propofol that lasted for a period of < 60 sec.

Contrary to the present study, Sano *et al.* (2003a) reported temporary apnoea in 82.5% (33 in 40 dogs), 90% (27 in 30 dogs), and 20% (2 in 10 dogs) after pre-medication with midazolam-butorphanol, ACE-butorphanol, and medetomidine-butorphanol, respectively, followed by induction with propofol. Canfran *et al.* (2016) reported DEX potentiates apnoea during induction with propofol and observed apnoea in 4 animals out of 7 animals after pre-medication with dexmedetomidine–methadone

combination followed by induction with propofol. Apnoea can be avoided by administering propofol slowly for induction. If the propofol is injected too fast, it can cause apnoea. However, if the propofol is injected too slowly, it may not provide adequate induction of anesthesia in the animal due to rapid redistribution and metabolism. Proper administration of propofol effectively prevents apnoea and induces adequate general anaesthesia. In the present study, propofol was administered slowly (nearly 60 sec) in most of the dogs until the pedal reflex disappeared, which might have contributed to stable respiratory function in the animals. Use of comparatively low dose of propofol for induction after pre-medication is also the reason for the significant reduction in the occurrence of apnoea in the present study.

Absence of salivation in most of the animals could be attributed to antimuscarinic effects of atropine, but mild salivation in some animals after pre-medication and recovery may be due to decreased response of atropine or pronounced effect of pre-medication. One known side effect of benzodiazepines in canines is hyper-salivation, sometime vomition and salivation were observed even after administration of propofol in canines. In present study, clear view of the larynx was observed without the presence of saliva during intubation in all animals, which might be due to pre-medication with atropine (Lemke 2007). Results of the present study were in accordance with the study of Rafee *et al.* (2017) who observed the absence of salivation in animals after pre-medication with atropine-DEX and butorphanol combination. It was attributed to antimuscarinic effects of atropine, proper fasting, and withholding of water of the canines for a minimum of 12 hrs and the effect of DEX on the alpha-2 adrenergic receptor which causes a decrease of gastric secretions and intestinal motility. However, in the present study a mild salivation was observed in two animals after recovery in group D. This hyper-salivation in dogs might be due to abdominal pain related to ovariohysterectomy and nausea. Postoperative vomiting and nausea is an important complication in humans and canines (Swallow *et al.* 2017).

It can be concluded that all pre-anaesthetic protocols provide adequate sedation and depth of analgesia before induction with propofol and reduce the induction dose of propofol considerably. Intravenous DEX group induced deepest sedation as well as has most potent dose-sparing effect. Quality of induction was excellent to good and clear view of the larynx was observed without presence of saliva during intubation in the animals. Chances of apnoea may be more with DEX pre-medication as compared to ACE and midazolam, when used with butorphanol, before induction with propofol but they can be managed by assisted ventilation without any complications.

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