Indian Journal of Animal Sciences **92** (11): 1285–1288, November 2022/Short communication
https://doi.org/10.56093/ijans.v92i11.127068

Comparison of the sedative and analgesic effects of butorphanol with acepromazine, midazolam, or dexmedetomidine following propofol induction and isoflurane maintenance in canines

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Received: 19 August 2022; Accepted: 19 September 2022

Keywords: Acepromazine, Analgesia, Dexmedetomidine, Midazolam, Pain Score, Sedation

Sedation and analgesia are essential components of pre-anaesthetic medication. It is necessary to emphasize that with pre-medication, we tend to achieve all these effects. The most common pre- anaesthetic medication used in veterinary practice is anticholinergics, sedatives and analgesic agents (Bednarski *et al.* 2011). Acepromazine (ACE) is a common component of neuroleptanalgesia. Neuroleptanalgesia is used to provide a calming effect and analgesia, and facilitates the handling of animals before induction of anaesthesia (Costa *et al.* 2020).

Midazolam (MID) has anticonvulsant, anxiolytic, sedative, hypnotic, amnesic and muscle relaxant properties (Wang *et al.* 2020). Its affinity for benzodiazepines receptors in central nervous system is approximately twice as compared to diazepam. Midazolam produces reliable sedation in young, old and debilitated canines and has limited effects on cardiorespiratory function (Tranquilli *et al.* 2013). Dexmedetomidine (DEX) is the most potent and selective alpha-2 adrenergic agonist (Shirasaka *et al.* 2007). It produces deep sedation, muscle relaxation and analgesia, and allows a reduction in the dose of general anaesthetic agents (Kumar *et al.* 2020).

Butorphanol (BUT) is an opiate partial agonist (Commiskey *et al.* 2005) commonly used as pre-anaesthetic medication or for post-operative analgesia. It is more effective against visceral rather than somatic pain. Combination of opioid with α-2 agonist or tranquilizer enhances sedation and analgesia and inhibits the side effects caused by opioid like central nervous system excitation (Carregaro *et al.* 2020).

Induction of anaesthesia with intravenous anaesthetic agent is extensively used for comparatively rapid and smooth induction in comparison to other anaesthetic technique. Propofol is widely used in canine (Hopkin *et al.* 2014), as intravenous anaesthetic agents, it provides rapid and smooth induction along with fast and smooth recovery. Propofol also has hypnotic and anti-convulsant properties, however lower dose sometimes promotes seizure activity. Isoflurane and sevoflurane is extensively used anaesthetic agent in animal surgery for maintenance of anaesthesia. This study aims to evaluate and compare the sedative and analgesic effect of ACE-BUT, midazolam-BUT, DEX (IM)-BUT and DEX (IV)-BUT pre-medication following induction with propofol and maintenance with isoflurane for elective ovariohysterectomy of client-owned dogs.

The study was conducted in Teaching Veterinary Clinical Complex and Referral Veterinary Polyclinic, IVRI, Izatnagar from 2018-20. Clinically healthy client owned canines (32), irrespective of breed, weighing more than 5 kg and 16 weeks age or older were subjected for ovariohysterectomy in their physical status I according to the American Society of Anaesthesiologists Classification (Daabiss 2011). The animals were randomly divided into four groups. The groups A and B had 10 animals each, and groups C and D had 6 animals each. The group A was pre-medicated with acepromazine 0.05 mg/kg IV b.wt , group B with midazolam 0.2 mg/kg IV b.wt, group C with dexmedetomidine 15 µg/kg b.wt IM and group D with dexmedetomidine 15 µg/kg b.wt IV along with butorphanol 0.2 mg/kg body weight IV after 10 min of atropine injection. Pre-medication was followed by induction with propofol and maintenance with isoflurane. The owner's consent was obtained for each dog to take part in the study.

Subjective evaluation of composite sedation score and analgesia were made before administration of drug, 5 min after administration of pre-anaesthetic, immediately after induction and at 20, 40, 60 min during maintenance and after extubation. The subjective evaluation of sedation score was graded on 0 to 16 and then these scores were added for composite sedation score (Honkavaara *et al.* 2008). Similarly, subjective evaluation of analgesia was graded on 0 to 3 by observing animal reaction after the pinching of animal's hind foot interdigital skin (Ahmad *et al.* 2013).

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Table 1. Mean ± SD of composite sedation score recorded in all the four groups at different intervals

Parameter/ Groups	Before pre-anaesthetic	After 5 min. pre-anaesthetic	At induction	T20	T40	At extubation
Sedation Score						
A	$0.00^{d}\pm0.00^{A}$	$7.7^{c}\pm1.57^{D}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$11.1^{b}\pm0.88^{B}$
B	$0.10^{d}\pm.0.31^{A}$	$9.7^{b}\pm3.27^{C}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$8.3^{c}\pm2.67^{C}$
C	$0.00^{c}\pm0.00^{A}$	$12.67^{b}\pm1.37^{B}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$12.83^{b}\pm1.17^{A}$
D	$0.00^{d}\pm0.00^{A}$	$14.00^{b}\pm1.41^{A}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$16.0^{a}\pm0.00^{A}$	$12.67^{c}\pm1.37^{A}$

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 ($p<0.05$).

The values of composite sedation score (CSS) in the all groups were elevated significantly ($p<0.05$) at 5 min after pre-medication from respective base values (Table 1 and Fig. 1). Composite sedation score further increased to reach at maximum after induction and remained throughout the maintenance of anaesthesia. However at extubation, composite sedation score values in all group significantly decreased in comparison to the maintenance period. The comparison between the groups at different intervals showed that the composite sedation score ($p<0.05$) significantly lowered considerably in group A than in groups B, C, and D at 5 min after pre-medication. Comparison among groups also revealed composite sedation score (CSS) was significantly elevated in group D with respect to the others groups after pre-medication. However during maintenance of anaesthesia composite sedation score remained same in the all groups.

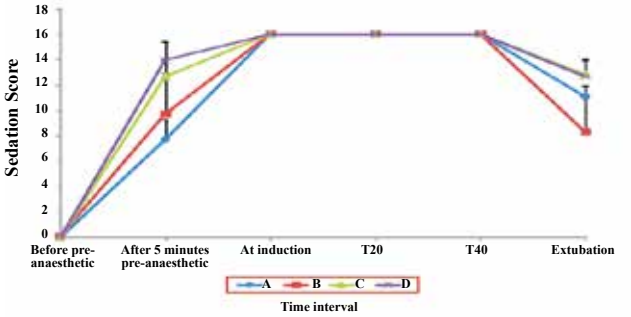

Fig. 1. Mean ± SD of composite sedation score recorded in all four groups at different intervals.

Similarly, depth of analgesia score (Fig. 2) in all four groups was elevated significantly ($p<0.05$) from the base values at 5 min after pre-medication. Depth of analgesia further increased to reach a maximum after induction and remained throughout maintenance period. However, at extubation, depth of analgesia score in all four groups was significantly lowered than maintenance of anaesthesia, but was still ($p<0.05$) higher than the values at after pre-medication in group A and significantly lower in other groups.

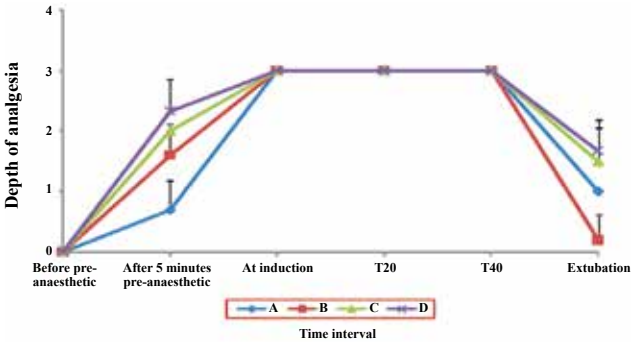

Fig. 2. Mean ± SD of depth of analgesia scores recorded in all the four groups at different intervals.

Comparison between the groups at different interval showed that the depth of analgesia score was significantly ($p<0.05$) lower in group A, in comparison to groups B, C and D.

In all groups, pre-anaesthetic medications induced a moderate to excellent sedation before induction with propofol. 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.* 2003). The sedation score in the intravenous dexmedetomidine group was significantly higher than others group. Higher sedation score with dexmedetomidine could be due to central attributed alpha-2 agonists induced deep sedation along with analgesia and relaxation of muscle (Correa-Sales *et al.* 1992). Marked synergistic effect was also observed between alpha-2 agonists, and butorphanol. This synergistic effect between dexmedetomidine and butorphanol caused deep sedation (Pypendop *et al.* 2017). A comparatively weak sedation in canine was observed when midazolam was administered alone but midazolam has highly synergistic effect with opioid and combination of MID and BUT produced light to moderate sedative effect with mild changes in cardiovascular and pulmonary functions (Kojima *et al.* 1999). Acepromazine is a phenothiazine compound with anti-dopaminergic effects in the CNS and that effect produces sedation (Canfran *et al.* 2016). Acepromazine along with butorphanol produces a neuroleptanalgesia (Bufalari *et al.* 1997). The difference in sedation score in groups C and D might be due to peak levels of analgesia and sedation occurred earlier in the animals after intravenous administration of dexmedetomidine due to difference in pharmacokinetics of the two different routes (Granholm *et al.* 2007). Bigby *et al.* (2017) also reported significant difference in sedation score between dexmedetomidine (5 µg/kg)-methadone (0.5 mg/kg), and acepromazine (0.05 mg/kg)-methadone (0.5 mg/kg).

Complete analgesia was observed in all groups after induction with propofol and continued during maintenance with isoflurane. Significantly higher depth of analgesia after pre-medication and at extubation in DEX (I/M) and DEX (IV) groups might be anti-nociceptive effect of dexmedetomidine (Murrell and Hellebrekers 2005) which are more than that of acepromazine and midazolam. Comparatively higher analgesic score in groups C and D could also be due to the synergistic interaction among alpha- 2 agonists and opioids. Benzodiazepines have no intrinsic analgesic properties, so they are frequently used with opioids to enhance sedation and analgesia. Midazolam has a highly synergistic effect with opioids and produces moderate analgesia. Like other phenothiazine derivatives, acepromazine also has mild analgesic properties (Murrel 2007). Butorphanol produces analgesia by the activation of kappa receptors (Monteiro *et al.* 2009), but the analgesic properties of butorphanol are not potent (Murrell 2007). However, combination of butorphanol and acepromazine has neurolept-analgesic properties and produce moderate analgesia (National Office of Animal Health 2010).

SUMMARY

Adequate sedation and excellent depth of analgesia were recorded in all the four groups after induction to the end of surgical procedure, however, significantly higher sedation score and depth of analgesia were observed in group D and significantly lower was observed in group A in comparison to other groups. Butorphanol with acepromazine, midazolam, or dexmedetomidine provides adequate sedation and analgesia in the dogs, before induction with propofol, so it made handling of the animals proper and safe before induction. Dexmedetomidine produces most profound sedation and analgesia followed by midazolam and acepromazine along with butorphanol.

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