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Effects of intraperitoneal bupivacaine and bupivacaine-dexmedetomidine for intra-operative and post-operative pain management in dogs

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Abstract
Pain management is difficult in animals due to their inability to verbalize the discomfort and adequacy of treatment. The study was aimed to evaluate the use intraperitoneal bupivacaine and bupivacaine-dexmedetomidine for intra-operative and post-operative pain management in dogs. Eighteen clinical cases of dogs requiring laparotomy were randomly divided into three groups *viz*. Group-B, BD and N comprising of six dogs in each. The animals were premedicated with glycopyrrolate, meloxicam and diazepam. Anaesthetic induction and maintenance was done by using propofol. Intraperitoneally bupivacaine, bupivacaine-dexmedetomidine and normal saline were infused in the three groups. Time for sedation, quality of sedation, time for induction, quality of induction, depth of anaesthesia, recovery time, quality of recovery and intra-operative analgesia, post-operative analgesia, heart rate, rectal temperature, respiratory rate and blood pressure were recorded. Intraperitoneal infusion of bupivacaine and bupivacaine-dexmedetomidine combination improved the intraoperative and postoperative analgesia. Clinical and cardiorespiratory changes following intraperitoneal bupivacaine and bupivacaine-dexmedetomidine combination were within physiological range.

Keywords: bupivacaine, dexmedetomidine, dogs, intraperitoneal

Introduction
Understanding as well as managing of pain in all animals is a challenging and often subjective task. It is important for animal health care professionals and researchers to consider different components that may affect the animal responses to pain, to assess any indication of pain in each of the components and tailor treatment simultaneously. Postoperative pain in animals is harmful to the patient as it can cause loss of appetite, behavioural changes, increase protein catabolism, cardiac dysrhythmias, depress respiratory function, central stimulation and may also leads to the chronic pain (Kim *et al.*, 2012) [8]. Accordingly it increases the period of hospitalization and postoperative treatment cost (Guerrero *et al.*, 2016) [5]. Systemic analgesics or local anaesthetics combinations are used for postoperative pain management (Hewson *et al.*, 2006) [6]. Economical, easily accessible and relevant local anaesthetics have been commonly used intraperitoneally in veterinary as well as human medicine to avoid or alleviate pain (Korkmaz *et al.*, 2019) [10]. Bupivacaine is a lipophilic long acting amino amide local anaesthetic commonly used for regional and infiltration anaesthesia of longer duration. Dexmedetomidine is an effective and well selective adrenoceptor α-2 agonist with analgesic and sedative properties (Sampaio *et al*., 2020) [16]. The present clinical study was conducted to evaluate the effectiveness the intraoperative and postoperative analgesia, clinical, cardiorespiratory changes following intraperitoneal bupivacaine and dexmedetomidine in dogs.

Materials and Methods
The study was conducted in the Teaching Veterinary Clinical Complex and Department of Veterinary Surgery and Radiology, College of Veterinary Sciences and Animal Husbandry, Central Agricultural University, Selesih, Aizawl, Mizoram in the year of 2020-2021. Eighteen clinical cases of dogs requiring laparotomy procedure were divided into 3 groups viz. Group-B, Group-BD and Group-N comprising of 6 dogs in each. All the animals were fasted for 12 hours for food and 4 hours for water. The animals were examined for physiological and haematobiochemical parameters prior to surgery and premedicated with glycopyrrolate @ 0.01 mg/kg b. wt and meloxicam @ 0.2 mg/kg b. wt through intramuscular route and after 10

minutes diazepam was administered @ 1 mg/kg b. wt intravenously. Induction was done by using propofol @ 5 mg/kg b. wt intravenously or till effect and the anaesthesia was maintained with incremental doses of propofol. After laparotomy incision intraperitoneally bupivacaine @ 2 mg/kg in Group B, bupivacine and dexmedetomidine combination @ 2 mg/kg and 1µg/kg in Group BD along with equal volume of normal saline and in Group N normal saline solution was administered.

Time for sedation was recorded from the administration of diazepam till the animal showed the first sign of sedation. Quality of sedation was determined according to the method described by Amengual *et al.* (2013) [2]. Time for induction was determined from the administration of the induction agent till the loses reflexes. The quality of induction was assessed according to the method described by Amengual *et al.* (2013) [2]. The quality of intra-operative analgesia was assessed by pricking the inter-digital space of the hind foot with a needle, as described by Jimenez *et al.* (2012) [7]. Anaesthetic depth was assessed according to the method described by Ahmad *et al.* (2013) [1]. Recovery time was calculated from the time of discontinuation of anaesthesia till the animal's ability to walk unassisted. The quality of recovery was determined as per the method described by Sams *et al.* (2008) [17]. The numerical pain scoring system Leibetseder *et al.*, 2006) [11] was used to assess postoperative pain in at 0 min, 6 hrs, 12 hrs and 24 hrs of post recovery. Heart rate (beats/ minute), Rectal temperature (°C), Respiration rate (breaths/minute), Blood pressure (mm Hg) were recorded before premedication at 0 min (baseline), 30 min (after induction), 2 hrs and 24 hrs. The statistical package for social sciences (SPSS) version 25 was used to analyse the data. The data was analysed by using one-way analysis of variance (ANOVA) and a post-hoc test using Duncan's multiple range tests. The data was displayed as Mean Standard Error and differences were considered statistically significant when $P<0.05$.

Table 1: Mean ± SE values of clinical parameters in Group B, BD and N.

Parameters	Group-B	Group-BD	Group-N	P value
Time for sedation(min)	1.66±0.33	1.83±0.30	1.50±0.22	0.721^{NS}
Quality of sedation	1.33±0.21	1.33±0.21	1.50±0.22	0.821^{NS}
Time for induction(sec)	36.00±2.39	31.16±1.70	34.33±1.66	0.237^{NS}
Quality of induction	0.50±0.22	0.33±0.21	0.50±0.22	0.827^{NS}
Intra-operative analgesia	0.33±0.21	0.33±0.21	0.50±0.22	0.821^{NS}
Depth of anaesthesia	2.66±0.21	2.83±0.16	2.16±0.16	0.052^{NS}
Time for recovery(min)	$20.50±0.84^{a}$	$25.50±1.11^{b}$	$20.83±1.16^{a}$	0.007^{**}
Quality of recovery	$0.83±0.16^{ab}$	$0.33±0.21^{a}$	$1.50±0.22^{b}$	0.004**

**: $P\leq0.01$, ^{NS}: non-significant (NS) Values in the same row with different superscripts (small font) differ significantly

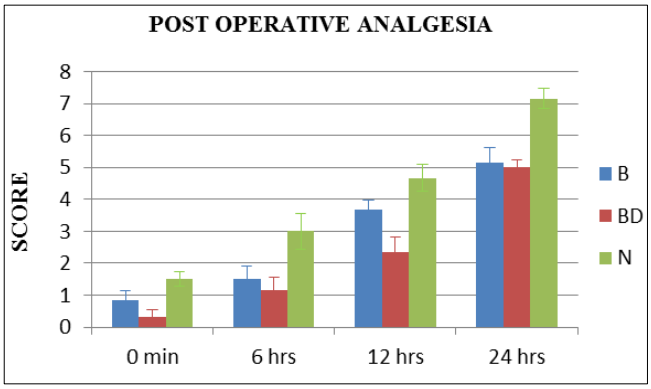

Fig 1: Post operative analgesia in Group B, BD and N

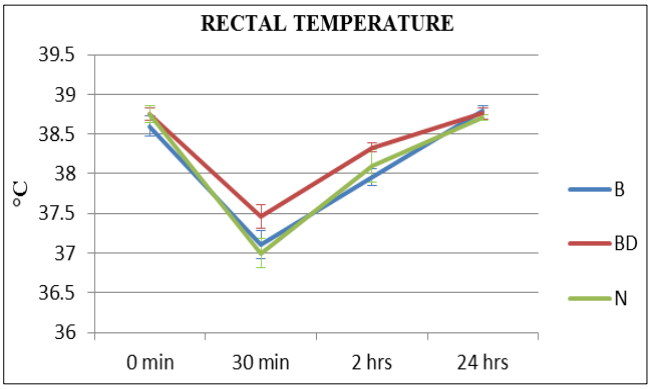

Fig 3: Rectal temperature in Group B, BD and

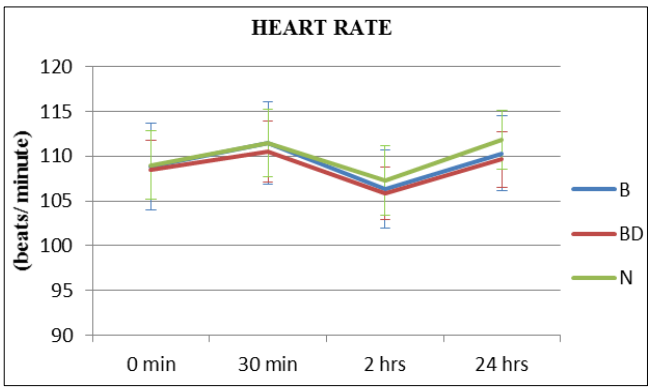

Fig 2: Heart rate in Group B, BD and N

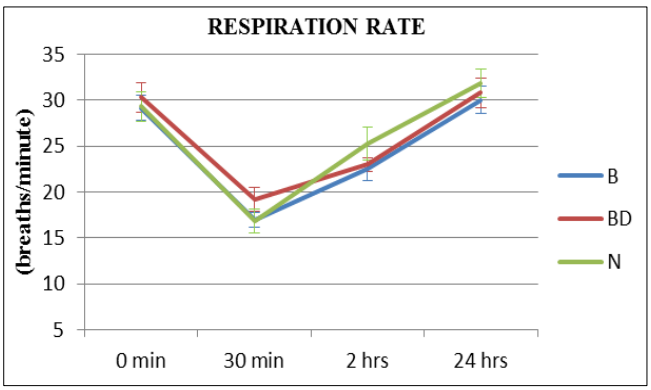

Fig 4: Respiration rate in Group B, BD and N

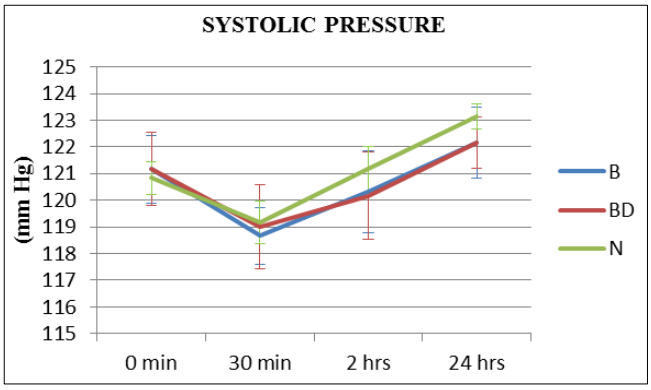

Fig 5: Systolic pressure in Group B, BD and N

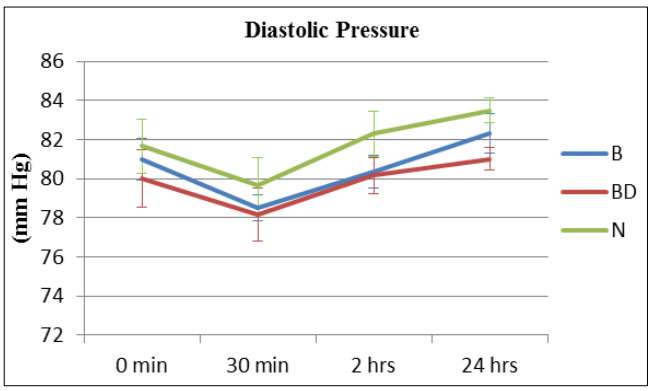

Fig 6: Diastolic pressure in Group B, BD and N

Results and Discussion

The mean body weight of the dogs included in the present study was 10.5±0.23 kg ranging from 9-12 kg and the mean age was 12.4±0.29 months ranging from 11-15 months. Dogs of different breeds and either sex were covered in this study. The sedation time and sedation quality (Table 1) recorded in all the three groups were similar and did not vary significantly. Mild sedation was observed in 4 animals in Group B, 5 animals in Group BD and 4 animals in Group N and rest of the animals showed moderate level of sedation. The induction was fast in all the groups and the induction time did not differ significantly among the groups. The faster induction might be due to the sedative effect of diazepam as a preanaesthetic. The level of sedation might reduce the induction time and anaesthetic dose as observed by Amengual *et al*. (2013) [2]. Glowaski and Wetmore (1999) [4] and Ko *et al*. (2006) [9] also reported shorter induction time and reduction in induction dose of propofol after intravenous administration of diazepam as preanaesthetic in dogs. Induction quality (Table 1) did not differ significantly among all the three groups. All the animals in Group B, BD and N showed smooth transition with no paddling to intermittent slow paddling movements during induction. All the animals in Group B, BD and N showed no pain to mild pain and values did not show any statistically significant variation among the Group B, BD and N (Table 1). The lower pain response in all the groups might be due to the premedication with meloxicam and adequate anaesthetic depth during the surgical procedure. But in Group B and BD the lower intraoperative pain score was observed than the Group N. Local anaesthetics produces total sensory nerve fibres blockade and prevents central sensitization (Lemke and Dawson, 2000) [12]. The combination of local anaesthesia with α-2 adrenergic agonist like dexmedetomidine might enhance the duration and quality of analgesia through direct inhibition on the peripheral nerve endings, reserve of insulin secretion along with vasoconstriction caused by dexmedetomidine might delay the absorption of local anaesthetic and prolong the elimination period (Sampaio *et al*., 2020) [16]. There was no significant variation noticed among Group B, BD and N for depth of anaesthesia (Table 1). Animals in all the three groups showed no response to very slow and occasional palpebral reflex. Recovery time (Table 1) was significantly higher in Group BD than Group B and N. The longer recovery time in the animals of Group BD might be due to residual sedative action of dexmedetomidine. Similar findings were also reported by Nicacio *et al.* (2020) [14] after intraperitoneal administration of ropivacaine and dexmedetomidine in cats. The score for recovery quality (Table 1) was significantly higher in Group N followed by Group B and BD. In Group B and BD, all the animals exhibited a smooth-easy to uncomplicated recovery whereas the animals in Group N showed uncomplicated to difficult recovery. A significantly higher scoring observed in Group N might be due to more surgical stress or pain as compared to other two groups. Improved quality of recovery was also observed by Nicacio *et al.* (2020) [14] after intraperitoneal administration of ropivacaine and dexmedetomidine in cats.

The postoperative analgesia score differed significantly ($P<0.01$) among the groups at different observation period with a highest value in Group N and a lowest value in Group BD. Within the group, the mean postoperative analgesia score was lower at 0 min (after recovery) in all the groups followed by significant ($P<0.01$) increase at subsequent observation period with a highest value in Group N. The animals in Group BD exhibited a better postoperative analgesia as compared to Group B and Group N (Fig 1). Similar findings were also observed by Rapolu *et al*. (2016) [15] after intraperitoneal administration of bupivacaine and dexmedetomidine combination in human patients following laparoscopic cholecystectomy. The heart rate (Fig 2) increased non-significantly at 30 min followed by a non-significant decrease at 2 hrs and at 24 hrs in all the groups. At 2 hrs and 24 hrs of observation period the Group BD showed a slightly lower heart rate than Group B and N after intraperitoneal administration of drugs. Guerrero *et al.* (2016) [5] observed a decreased heart rate after intraperitoneal administration of bupivacaine in dogs and with bupivacaine and tramadol combination by Memis *et al.* (2005) [13]. The rectal temperature (Fig 3) decreased significantly at 30 min followed by significant increase at 2 hrs and 24 hrs interval in all the groups. The respiratory rate (Fig 4) decreased significantly at 30 min followed by significant increase at 2 hrs and 24 hrs. A slightly higher in respiratory rate was observed in Group N at 2 hrs and 24 hrs interval than the other two groups which might be indicative of more pain in Group N animals. The changes in the respiratory rate in the present study in support with the findings observed by Guerrero *et al*. (2016) [5]. The mean systolic pressure (Fig 5) decreased non-significantly at 30 min and thereafter increased non-significantly until the end of the observation period in Group B and BD but in Group N the subsequent increase in systolic pressure was significant. A slightly lower systolic pressure was observed after intraperitoneal administration in Group B and BD than Group N. A significantly lower blood pressure was observed by Guerrero *et al*. (2016) [5] following administration of bupivacaine intraperitoneally in dogs. Nicacio *et al.* (2020) [14] also noticed lower systolic pressure

in cats after intraperitoneal administration of ropivacaine and dexmedetomidine combination. Dexmedetomidine decreases in mean arterial pressure due to stimulation of α-2A and α-2B adrenergic receptors (Ahmad *et al*., 2013) [1]. The intraperitoneal administration of bupivacaine might have lead to stable haemodynamics owing to enhanced analgesia (Das and Deshpande, 2017) [3]. The mean diastolic pressure (Fig 6) decreased non-significantly at 30 min from baseline value and thereafter increased slowly until the end of the study period in all the groups. At 2 hrs and 24 hrs interval diastolic pressure was found to be lowest in Group BD and highest in Group N. Nicacio *et al.* (2020) [14] noticed lower diastolic pressure in cats after intraperitoneal administration of ropivacaine and dexmedetomidine combination.

Conclusion

Intraperitoneal infusion of bupivacaine and bupivacaine-dexmedetomidine combination improved the intraoperative and postoperative analgesia in dogs during laparotomy. The clinical, cardiorespiratory changes following intraperitoneal bupivacaine and bupivacaine-dexmedetomidine combination in dogs were within physiological range. Better analgesia was provided by bupivacaine-dexmedetomidine combination.

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