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Effect of epidural dexmedetomidine with or without local anesthetics on pain score and serum IL-6 levels in dogs undergoing elective ovariohysterectomy

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Abstract: To evaluate the postoperative analgesic effects of epidural dexmedetomidine with or without local anesthetics, prospective randomized double-blinded clinical trials were performed with 24 healthy client-owned mixed-breed adult dogs with an average weight of 18.1 ± 2.4 kg allotted equally (n = 6) to four groups: A, B, C, and D. All animals were premedicated intramuscularly with atropine (0.04 mg/kg) and after 5 min by intravenous midazolam (0.7 mg/kg). After 10 min of premedication, in group A dexmedetomidine (7 µg/kg) and in groups B, C, and D, in addition to dexmedetomidine (7 µg/kg), lidocaine (4.4 mg/kg), bupivacaine (2 mg/kg), and ropivacaine (2 mg/kg), respectively, were administered to the lumbosacral epidural space, respectively. Anesthesia was maintained with 1% propofol as and when needed. Postoperative analgesia was assessed subjectively using the University of Melbourne Pain Scale (UMPS) at 1, 2, 4, and 24 h postoperatively and objectively by measuring the circulating levels of interleukin-6 (IL-6) at 0 (baseline), 1, 2, 4, and 24 h postoperatively. Overall, UMPS scores were lower in groups B, C, and D at all time points compared to group A. Serum IL-6 levels showed a nonsignificant decrease in groups B and C with a nonsignificant increase in group D at different intervals as compared to baseline. However, a significantly higher serum IL-6 level was recorded at 4 h in group A as compared to the other three groups. It was concluded that epidural dexmedetomidine in combination with lidocaine, bupivacaine, or ropivacaine at the doses studied provides better postoperative analgesia than dexmedetomidine alone in dogs undergoing elective ovariohysterectomy. However, the dexmedetomidine/ropivacaine combination revealed comparatively lower postoperative analgesia than dexmedetomidine/lidocaine and dexmedetomidine/bupivacaine combinations.

Key words: Elective ovariohysterectomy, dexmedetomidine, local anesthetics, serum interleukin-6, University of Melbourne Pain Scale, dogs

1. Introduction

The control of pain in the perioperative period is important to hasten recovery and maintain comfort during surgery (1,2). Among different anesthetic techniques, epidural and intrathecal anesthesia is an efficient analgesic procedure for retro-umbilical surgeries. The epidural administration of local anesthetic drugs with opioids or α2-adrenergic agonists provides excellent intra- and postoperative analgesia (3,4). Spinal and epidural anesthesia techniques produce analgesic effects by blocking nerves in the subarachnoid space. Furthermore, due to the accumulation and systemic absorption of drugs in the epidural adipose tissue, the epidural dose remains higher than the intrathecal dose (5). Dexmedetomidine activates α2-receptors in the brain and spinal cord and inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia (6). The synergism between local anesthetics and α2-adrenoceptor agonists has been found to produce effective analgesia (7).

Assessment of postoperative pain in dogs is difficult owing to the lack of verbal communication with humans. Therefore, the assessment of pain relies mostly on subjective indicators, for which different scales like visual analog scales, simple descriptive scales, and numerical rating scales have been developed. These scales rely on subjective evaluation of behaviors without any correlation to physiological indicators of pain. In an effort to improve this situation, the University of Melbourne Pain Scale (UMPS) (8), with six broad categories consisting of physiological and behavioral observations, each of which is divided into three or more levels and assigned a different numerical weight, was introduced. During surgery neuropathic pain causes central and peripheral sensitization through excitatory amino acids, nitrous oxide, and free radicals (9), thus providing a basis for objective evaluation of pain. Interleukin-6 (IL-6) appears during initial stages of the surgical process (10,11) and has

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been detected after 60 min with peak blood concentration between 4 and 6 h (10,12).

Keeping in view the use of α2-agonists and local anesthetics for different analgesic studies, the present study was carried out to evaluate the postoperative analgesic effects of epidural dexmedetomidine with or without local anesthetics in dogs undergoing elective ovariohysterectomy.

2. Materials and methods

2.1. Animals

Twenty-four healthy client-owned adult mixed-breed dogs with an average body weight of 18.1 ± 2.4 kg were presented for elective ovariohysterectomy surgeries. Food and water were withheld for 12 h and 6 h respectively before surgery. Written consent was obtained from the owners before attempting surgery. The dogs were equally (n = 6) allotted to four groups: A, B, C, and D.

2.2. Anesthesia

A 20-G catheter was fixed in the cephalic vein for fluid and drug administrations. After proper restraint and recording of baseline data, all animals were premedicated with an intramuscular (IM) injection of atropine (atropine sulfate injection, 0.5 mg/mL, Bhavani Pharmaceuticals (P) Ltd., India) at 0.04 mg/kg. After 5 minutes, midazolam (Mezolam, 1 mg/mL, Neon Laboratories Limited, India) at 0.7 mg/kg was administered intravenously to induce sedation in all animals. Following proper sedation after 10 min of midazolam administration, animals were positioned in sternal recumbency with hindlimbs flexed cranially and the lumbosacral intervertebral space (L7–S1) was located. The area was shaved and aseptically prepared for epidural injection and a 20-G needle was correctly placed on the midline caudal to the L7 spinous process and inserted until a distinct popping sensation was felt as the needle penetrated the interarcuate ligament. Epidural anesthetic agent combinations were administered using a single syringe in each animal as follows: group A- dexmedetomidine, 7 µg/kg (Dextomid, 100 µg/mL, Neon Laboratories Limited); group B- dexmedetomidine, 7 µg/kg and lidocaine, 4.4 mg/kg (LOX 2%, Neon Laboratories Limited); group C- dexmedetomidine, 7 µg/kg and bupivacaine, 2 mg/kg (ANAWIN 0.5%, Neon Laboratories Limited); and group D- dexmedetomidine, 7 µg/kg and ropivacaine, 2 mg/kg (ROPIN 0.75%, Neon Laboratories Limited). In all the groups 1% propofol (Nirfol 1%, Nirlife Limited, India) was used intravenously as an intraoperative supplemental anesthetic agent, as and when needed.

2.3. Evaluation of postoperative analgesia

Postoperative analgesia was assessed subjectively by using the UMPS (in which 0 corresponds to no pain and 27 to the worst pain possible) at 1, 2, 4, and 24 h postoperatively and objectively by measuring the circulating levels of IL-6 (Canine IL-6 ELISA Kit, RayBiotech, Inc., USA) at 0 (baseline), 1, 2, 4, and 24 h postoperatively. Blood samples were collected in heparin tubes at the same corresponding intervals for serum separation. The serum samples were stored at –80 °C until analysis.

2.4. Statistical analysis

SPSS 16.0 was used for testing the statistical significance of data (SPSS Inc., USA). One-way analysis of variance and Duncan's multiple range test were applied for objective data to compare the means at different time intervals between groups. The paired t-test was used to compare the mean values at different intervals with their base values in each group. The Kruskal–Wallis test was applied for the analysis of subjective data (13). The differences were considered significant at a value of $P < 0.05$ in each analysis.

3. Results

3.1. UMPS score

A continuous increase in UMPS score (Figure 1) from 1 h to 24 h postoperatively with the highest score of 10 at 24 h was recorded in animals of group A. The scores showed a decrease up to 4 h followed by an increase with scores of 6 and 7 at 24 h in groups B and C, respectively. A slight increase in UMPS score initially, followed by a score of 0 at 4 h and score of 6 at 24 h, was observed in group D. Pain scores were never higher than 7 out of 27 in any animals in groups B, C, and D and no need for additional analgesia was felt for a period of 24 h. However, in group A, the highest pain score of 10 was recorded at 24 h. Comparison among groups revealed a significant ($P < 0.05$) increase in UMPS score in animals of group A at 4 h postoperatively as compared to groups B, C, and D.

3.2. Serum IL-6 level

Serum IL-6 (Figure 2) level revealed a significant ($P < 0.05$) increase in group A at 4 h with a nonsignificant ($P > 0.05$) increase at other times as compared to the baseline value. In groups B, C, and D nonsignificant ($P > 0.05$) changes in serum IL-6 levels were recorded at different

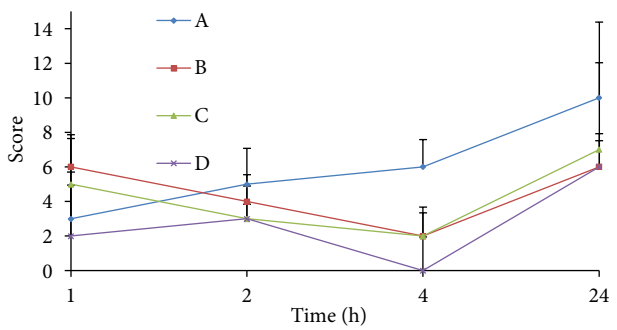

Figure 1. Median ± SD values of UMPS scores in different groups at different times.

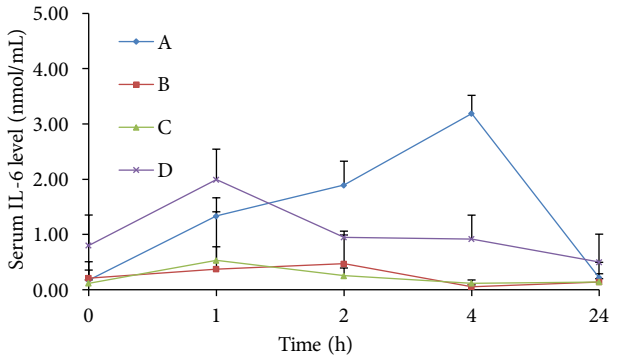

Figure 2. Mean ± SD values of serum IL-6 levels (nmol/mL) in different groups at different times.

times as compared to baseline. A significantly ($P < 0.05$) higher serum IL-6 level was recorded at 4 h in group A as compared to other groups. No significant ($P > 0.05$) difference was observed among groups B, C, and D in this study.

4. Discussion

In the present study, increase in UMPS scores in parallel with rising serum IL-6 levels until 24 h postoperatively was observed in Group A. Furthermore, the increases in UMPS score and serum IL-6 level were significant at 4 h as compared to groups B, C, and D. Dexmedetomidine, when given epidurally, has been shown to produce strong analgesic effects in awake rats (14) as well as in dogs (15). Caudal dexmedetomidine has been proven to be an attractive adjunct to provide excellent analgesia without side effects over a 24-h period (16). Previous studies revealed reduced intraoperative and postoperative secretion of cytokines like tumor necrosis factor-α, IL-1β, IL-6, IL-4, and IL-10 when dexmedetomidine was administered epidurally to dogs (17,18). However, in our study, high postoperative pain in animals of group A in contrast to other groups, as reflected by increased levels of IL-6 and UMPS scores, may be related to the use of dexmedetomidine alone. Furthermore, the higher doses of intraoperative propofol consumed by animals of group A compared to the three other groups confirmed its weak analgesic properties. It has been reported that dexmedetomidine together with local anesthetics augments their effects by hyperpolarizing nerve tissues at presynaptic C-fibers and postsynaptic dorsal horn neurons (19). The local vasoconstrictive effects of dexmedetomidine allowed the local anesthetics to remain in the epidural space for a prolonged period, thus comparatively reducing sensory stimulation in groups B, C, and D more than in group A. Significantly lower UMPS scores were reported when epidural dexmedetomidine/bupivacaine was given to dogs (18). It has been estimated that clonidine (1 μg/kg), when added to 0.25% bupivacaine for caudal analgesia in subumbilical surgeries, significantly prolongs the duration of postoperative analgesia when compared to 0.25% bupivacaine in normal saline (20). Nonsignificant increases in UMPS score and serum IL-6 levels in group D compared to groups B and C may be related to the lower sensory blockade potential of ropivacaine (21). The potency of a local anesthetic depends on its lipid solubility; thus, bupivacaine, being more potent, produces a longer duration of anesthetic action than the less lipid-soluble ropivacaine. Significantly longer duration of intrathecal anesthesia has been observed with bupivacaine as compared to ropivacaine (22). A significantly shorter duration of sensory and motor blockade has also been reported for ropivacaine than bupivacaine (23), thus confirming the findings of our study. However, no contrasts have been observed in depth and duration of sensory block produced by spinal administration of ropivacaine and bupivacaine (24).

As a limitation of this study, the recording of UMPS scores and measurement of serum IL-6 levels was restricted to a period of 24 h only, keeping in mind owner compliance, because the study included clinical cases. Thus, studies with prolonged recording periods need to be carried out. Furthermore, to effectively assess and monitor postoperative pain, other inflammatory indicators like acute-phase proteins, C-reactive proteins, and fibrinogen need to be evaluated.

In conclusion, dexmedetomidine used together with lidocaine, bupivacaine, or ropivacaine at the doses used in this study provides better postoperative analgesia than dexmedetomidine alone, as evidenced by reduced overall UMPS scores and serum IL-6 levels in dogs subjected to elective ovariohysterectomy. Furthermore, dexmedetomidine/ropivacaine produced less postoperative analgesia as compared to dexmedetomidine/lidocaine and dexmedetomidine/bupivacaine combinations.

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