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Comparison of Lidocaine, and Lidocaine–Neostigmine for Epidural Analgesia in Dogs

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ABSTRACT

The Objectives or the current study was to evaluate and compare the analgesic effect of epidural lidocaine and lidocaine- neostigmine combination in dogs. Six healthy dogs of mixed breed weighing 12–15 kg was selected for this study. All dogs received all treatments in a cross-over design with at least two-week interval. Dogs were premeditated with Xylazine (0.5 mg/kg) and general anesthesia was induced with thiopental sodium (12.5 mg/kg) to perform the lumbosacral puncture. Epidural analgesia was done using either 6 mg/kg of lidocaine 2% or a combination of 6 mg/kg of lidocaine 2%, with 10 µg/kg neostigmine. The degree of analgesia was evaluated using a numerical rating scale. Analgesia was defined as absence of a reaction to pin prick test and pressure from hemostat clamp and was performed after one hour of epidural injection, and thereafter every 10 min until complete recovery. Heart rate (HR), respiratory rate (RR), and rectal temperature (RT) were recorded before (baseline, 0) and at every 10 min, until a complete recovery was observed. HR, RR and RT did not differ between treatments at any time point. The lidocaine–neostigmine combination produced a significant ($P < 0.05$) longer duration of analgesia than lidocaine alone. Adding neostigmine to epidural administered lidocaine in dogs increases the analgesic effect on both hind limbs and perineal region. Co administration of epidural neostigmine and lidocaine appears to be a useful technique for postoperative analgesia as it increases the duration of analgesia.

1. INTRODUCTION

Epidural analgesia is one of the most efficient alternatives for alleviating post-operative pain in veterinary medicine (Garcia, 2018). Epidural administration of local anesthetics and analgesics is nowadays broadly utilized in orthopedic methodology, including the rear limb in dogs (Pascoe, 1992; Hendrix et al., 1996; Hoelzler et al., 2005; Kona et al., 2006; Steagall et al., 2017). Close to its clinical application, in the most recent decade, epidural anesthesia has been the focus of a countless of experimental researches (Jones, 2001; Campagnol et al., 2011; Son et al., 2011; Zhang et al., 2011; Steagall et al., 2017).

Lidocaine is the most utilized answer for epidural analgesia (Skarda, 2007). The exemplary mode of action of local anesthetics is a reversible hindrance of nerve function. This promote to desensitization, analgesia, and immobilization in the anaesthetized area (Jones, 2001). It is effective with a rapid onset of action, after 10–15 min in dogs, at a dose of 6 mg/kg of 2% lidocaine that produce anesthesia of the body caudal to the first lumbar vertebra with a motor and analgesic effect (Day and Skarda, 1991; Almedia et al., 2010; Derossi, 2013). In spite of, it is a cheap nearby analgesic medication, yet its impact for a brief term and this is a restriction of utilizing a solitary epidural infusion (Jones, 2001; Campagnol et al., 2011). Several combinations and adjuvant medications have been studied to prolong the duration of action (Natalini, and Robinson, 2000; Walker et al., 2002). Xylazine (Campagnol et al., 2011), detomidine (Zhang et al.,

2011), morphine (Jones, 2001; Skarda, 2007), tramadol (Almedia et al., 2010; Derossi et al., 2013) and ketamine (Derossi, 2013) can be co-administered with epidural lidocaine to augment and broaden the analgesia.

Lately, epidural injection of neostigmine as adjuvant has been proposed to create analgesia in human and animals (Yaksh, 1995; Lauretti, 200; Lauretti, 1999; Omais, 2002; Memis et al., 2003; Kumar et al., 2005; Marucio, 2008; Derossi, 2012; Derossi et al., 2013; Derossi, 2013; Ibrahim, 2013; Ghazy et al, 2015; Lauretti, 2015). Neostigmine is a cholinomimetic agent in anesthesia for offending the activity of non-depolarizing neuromuscular blocking agents. This medication is without neurotoxic impacts when administered intrathecally to dogs and rats (Yaksh, 1995). In human, there has been renewed enthusiasm in this drug as it improves the postoperative analgesia when administered epiduraly in conjunction with other drugs like lidocaine, bupivacaine, and morphine significantly (Lauretti, 1999; Omais, 2002). In human, Epidural neostigmine in three different doses combined with lidocaine produced a dose-independent analgesic effect (approximate 8 h) compared to the control group (approximate 3.5 h), and a reduction in postoperative analgesic consumption without increasing the occurrence of unfavorable impacts (Lauretti, 1999).

There are relatively few studies on epidural neostigmine, in veterinary medicine. Neostigmine was separately found to prolong the duration of analgesia in dogs (Almeida, 2010; Lauretti, 2015) and cows (Bigham, 2010; Ismail, 2018) compared with morphine or lidocaine alone. In horses and buffalo, neostigmine co-administered with lidocaine improved and extended the duration of analgesia in the perineal region (Derossi, 2012; Derossi, 2013; Ghazy et al., 2015). The analgesic impacts of epidural lidocaine joined with neostigmine have not been explored at this point in dogs. So, the point of this work is to assess and compare the span of analgesia gave by, a lidocaine-neostigmine combination with that gave by lidocaine administration in the epidural lumbosacral space of dogs.

2. MATERIALS AND METHODS

2.1. Animals:

The Faculty of Veterinary Medicine, Kafrelsheikh University Ethical Committee, approved this study. Six apparently healthy (after clinical and hematological evaluations), mixed breed dogs (3 males and 3 females), had a mean body weight of 13 ± 3.6 kg, a mean age of 2 ± 0.5 years.

2.2. Anesthesia:

After withdrawal of food but not water for 12 hours, dogs were premedicated intramuscularly (i.m.) with 0.5 mg/kg Xylazine HCl (*Xyla*-Ject, ADWIA Pharmaceuticals Co. Cairo, Egypt). The skin was aseptically prepared and an intravenous (iv) 20-gauge cannula was placed in the cephalic vein. Five minutes after premedication, general anesthesia was induced with 12.5 mg/kg iv Thiopental Sodium (Thiopental 500mg, Eipico, Egypt). After a stable anesthesia level was achieved, the epidural injection was performed in the lumbosacral space by the technique described by Jones (2001) and the right situating of the needle was affirmed by the lack of cerebrospinal fluid or blood at the needle hub or by the hanging drop technique. Epidural anesthesia was produced in all dogs by 6 mg/kg of lidocaine 2% (Xylocaine®, AstraZeneca, Paris, France) and NaCl 0.9% up to 5 ml. And 2 weeks later an epidural anesthesia was induced in all dogs by combination of 6 mg/kg of lidocaine 2%, 10µg/kg of neostigmine (Neostigmine, Amriya Pharm. Ind. Alex. Egypt) (Marucio, 2008), and NaCl 0.9% up to 5 ml. In this manner, all dogs got a fixed all out volume of 5 mL of anesthetic solution. The infusion of solution into the epidural space should be ought to be done over a time of around 30 to 60 seconds and solutions should be at body temperature (Jones, 2001; Skarda and Tranquilli, 2007). Following the epidural injection, the animals were maintained in sternal recumbency for 20 minutes, to insure the uniform distribution of the drugs in the epidural space and due to the latency period of lidocaine (Almeida et al., 2010).

2.3. Evaluation:

At least one hour slipped by between the anesthetic induction (thiopental) and the time that the principal assessment was performed (Almeida et al., 2010). Analgesia was defined as absence of a reaction to pressure from hemostat clamp applied first in the perineal area and afterword moved caudally toward the rear limb until a reaction (movement associated with pin prick test or hemostat pressure) was observed. The score used to assess analgesia and motor block made according to Ismail, 2018 (table 1)

Table 1: Scoring the degree of analgesia and motor block according to (Ismail, 2018)

	Degree of analgesia	Degree of motor block
0	strong reaction to pinprick stimuli	walk normally
1	moderate response to pinprick stimuli	stand and walk with ataxia
2	mild response to pinprick stimuli	positive pedal reflexes but unable to stand
3	non-responsive to pinprick stimuli	unable to move his rear limb

Duration, anatomic distribution of the analgesia and time to standing were recorded. Analgesic testing using a hemostat was played out each 10 min until a total recovery was observed. Duration of analgesia [time interval between time of injection and reappearance of pain response inflicted by a hemostat] was calculated. Time to standing [time interval between reappearance of the pedal withdrawal reflex and the dog's ability to retain its hind limbs and walk around] were calculated. To keep away from any bias or potential manipulation of data, the same investigator assessed the anesthesia in all cases and was unaware of the treatment given.

Heart rate (HR), respiratory rate (RR) and rectal temperature (RT) were measured before epidural drug administration (time 0) and at 5 min, 10 min, 15 min, 20 min, 30 min, 40 min, 50 min, and 60 min after the drug injection and, thereafter, every 15 min until a complete recovery was observed.

2.4. Statistical analysis

Data were recorded as mean±SD. Differences between treatments at each time point, differences in time for each treatment were compared using analysis of variance (ANOVA) for repeated-measures, with time and group as factors, followed by Duncan's test. Statistical analysis was undertaken using SPSS Version 20 for Windows) SPSS, MicroMaster, Richboro, PA, USA) and $p \leq 0.05$ was considered significant.

3. RESULTS

All treatments were effective in producing analgesia in the tail, perineum, hind limbs and abdominal region in all dogs. We considered satisfactory analgesia to have been obtained when dogs did not respond to pin prick or hemostat clamping. The duration of analgesia was significantly ($P<0.05$) prolonged with lidocaine plus neostigmine (135 ± 5.2 min) compared with treatment with lidocaine alone (90 ± 4.1 min) (Fig. 1). Time to standing was significantly ($P<0.05$) prolonged with lidocaine plus neostigmine (95 ± 6.8 min) compared with treatment with lidocaine alone (70 ± 4.3 min) (Fig No 2). Dogs injected with lidocaine plus neostigmine retain their feet significantly ($P<0.05$) later than those injected with lidocaine alone (140 ± 3.8 and 95 ± 4.3 respectively) (Fig. 2).

There were no significant differences between the lidocaine and lidocaine plus neostigmine in HR, RR and rectal temperature during the anesthetic period. After the recovery period, RR was significantly ($P<0.05$) decreased with lidocaine plus neostigmine in the period between 50 to 110 min after epidural injection. Rectal temperature remained consistent in the lidocaine and lidocaine plus neostigmine. Neither lidocaine nor lidocaine-neostigmine treatments produce adverse behavioral changes in tested dogs.

4. DISCUSSION

The goal when combining analgesic drugs administered into epidural space is to achieve a synergistic analgesic effect via inhibition of nociception through various pathways (Wetmore and Glowaski, 2000; Walker et al., 2002). Epidural use of neostigmine, along with its analgesic effect, has been reported in man, horses, cows and dogs (Lauretti et al., 1999; Natalini, and Robinson, 2000; Marucio, 2008; Ismail, 2018). Enhancement of the analgesic action of epidural neostigmine when used in combination with tramadol, morphine or lidocaine has been used in animals and human (Marucio, 2008; Lauretti et al., 1999; Natalini, and Robinson, 2000; Almeida et al., 2010; Bigham et al., 2010; Ghazy et al., 2015) resulting in post-operative analgesia with low incidence of adverse effects. The dose of neostigmine (10 µg/kg) in the study reported here was determined on the basis of the dose recommended for ovariohysterectomy in dogs (Marucio et al., 2008).

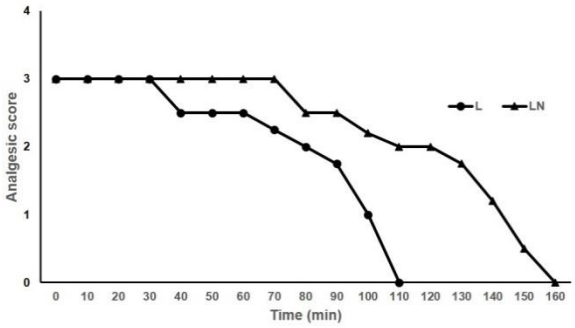

Fig. 1: Line graph illustrating the analgesic score (duration of analgesia) of epidural injection of Lidocaine alone (L) and Lidocaine plus Neostigmine (LN) in dogs.

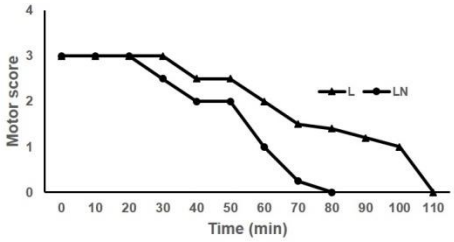

Fig. 2. Line graph illustrating the degree of motor block of epidural injection of Lidocaine alone (L) and Lidocaine plus Neostigmine (LN) in dogs

No investigation to date has assessed the pharmacokinetics of epidural neostigmine. The analgesic effect coming about because of epidural admistration of neostigmine might be because of hindrance the breakdown of endogenous acetylcholine (Achl) and successively increasing Achl levels to work on both muscarinic and nicotinic receptors in the spinal cord gives analgesia (Lauretti et al., 1999; Memis et al., 2003; and Kumar et al., 2005).

Blockage of Na+ and K+ flows in the anterior horn neurons of the spinal cord of rats are the main cause of analgesic effect of neostigmine (Olschewski et al., 1998). Neostigmine is a cholinesterase inhibitor. Neostigmine is a hydrophilic molecule as morphine, and when injected epidurally, takes a time to diffuse in dura mater and reach the sub-arachnoid space (Lauretti et al. 2000; Marucio et al 2008).

Epidural neostigmine in human and animals has also produced inconsistent results about its efficacy. The duration of post-operative analgesia did not differ between bupivacaine and bupivacaine plus neostigmine treatments in children (Memis et al., *2003)* or between morphine and morphine plus neostigmine treatments in dogs (Marucio et al 2008). In contrast, other studies in children concluded that the combination of bupivacaine and neostigmine epiduraly provide superior analgesia and lessen the requirement for supplementary analgesics compared with bupivacaine or neostigmine alone (Kumar et al., 2005). In the current study, adding neostigmine to lidocaine 2% epiduraly extended the period of analgesia and motor block in dogs. This observation is consistent with the findings of a previous study reported by (Derossi, 2013). Lidocaine-neostigmine or xylazine-neostigmine can be injected epiduraly in standing surgical procedures in adult dairy cows to increase sedation but not analgesia (Ismail, 2018), in contrast in the current study epidural neostigmine and lidocaine in dogs increases both sensory and motor block than lidocaine alone, and these results agreed with Ibrahim, 2013.

Motor block is normal after lidocaine administration as it initiate analgesia as well as motor block; it is related to an acetylcholine effect on the motor neuron that can potentiate the axonal conduction block caused by local anesthetics (Day and Skarda, 1991). Lidocaine alone

gives a motor block for the same duration as the analgesia. While lidocaine-neostigmine increases the duration of motor block and decreases the analgesia in these animals. Epidural neostigmine may enhance the lidocaine motor block (Derossi, 2013).

HR and RT were not significantly different compared with baseline values all through the experiment. Similar results were obtained after epidural administration of tramadol in horses (Natalini and Robinson, 2000) or epidural neostigmine in man (Lauretti et al., 1999). But RR was significantly ($P<0.05$) decreased with lidocaine plus neostigmine, and this may be due to the sedative effect of neostigmine as mentioned in a study on human done by (Kaya et al., 2004), they stated that epidural neostigmine produce gentle sedation for few hours in ladies after Cesarean Delivery.

Unfriendly reactions with epidural tramadol or neostigmine in human patients incorporate sickness, vomiting and loose bowels; the most genuine is early or postponed respiratory depression after epidural admiration of narcotics (Wilder-Smith, 1998; Lauretti et al., 1999). Such adverse effects were not observed in the present study.

It concludes that adding neostigmine to lidocaine epiduraly, are safe and improve the duration of analgesia just as motor block in tail, perineum and rear limb if compared with administration of lidocaine alone, in dogs.

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