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Original Article

Cardiorespiratory effects of epidurally administered ketamine or lidocaine in dogs undergoing ovariohysterectomy surgery: a comparative study

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Abstract

Background: Analgesic and hemodynamic effects of ketamine in subanesthetic doses during surgical anesthesia and postoperative, are due to the action on the N-methyl-D-aspartate receptors (NMDAR). **Aims:** To evaluate the intraoperative cardiorespiratory effects provided by ketamine compared to lidocaine, both administered epidurally, in bitches submitted to ovariohysterectomy. **Methods:** Thirty-six dogs of different breeds were used in a randomized, prospective, and blinded clinical trial. Two groups were formed: G_{KET} (ketamine 3 mg/kg, n=18) and G_{LIDO} (lidocaine 4 mg/kg, n=18). Animals were premedicated with acepromazine 0.05 mg/kg intravenous. Anesthesia was induced with propofol 5 mg/kg intravenous. Anesthetic maintenance was performed with isoflurane in 100% oxygen. Every 5 min during surgery, heart rate (HR), respiratory rate (RR), esophageal temperature (°C), oxygen saturation (SPO_2), end tidal carbon dioxide ($ETCO_2$) and mean arterial pressure (MAP) were monitored. **Results:** Cardiorespiratory variables during anesthesia were within normal ranges. Heart rate was significantly higher at 5 (108 ± 12 *vs* 95 ± 11) and 10 (110 ± 11 *vs* 97 ± 11) min in G_{KET} compared to G_{LIDO} after the start of surgery (P=0.03 and P=0.01, respectively). Mean arterial pressure was higher in G_{KET}, (100 ± 23, 105 ± 35, and 103 ± 35 mmHg) in comparison with G_{LIDO} (66 ± 7, 74 ± 10, and 67 ± 9 mmHg) at 20, 25 and 30 min (P=0.01, P=0.004, and P=0.002, respectively). Mild hypothermia at 25 (36.5 ± 1.3°C) and 30 (36.5 ± 1.4°C) min in the G_{KET} was recorded. **Conclusion:** Epidural administration of ketamine provides better hemodynamic stability, compared to the use of epidural lidocaine.

Key words: Analgesia, Dog, Epidural, Ketamine, Lidocaine

Introduction

Ketamine is well known for its analgesic and anesthetic properties; it has a central and peripheral effect when acting in the N-methyl-D-aspartate receptors (NMDAR), alpha amino-3-hydroxy-5-methyl-4-isoxazo propionic acid (AMPA), kainate and gamma-aminobutyric acid (GABA) (Chizh *et al*., 2001; Pozzi *et al*., 2006). It also inhibits the reuptake of serotonin and dopamine, nitric oxide pathways and μ opioid receptors (Niesters *et al*., 2014). As a result of these multiple actions, it has been proved to effectively reduce allodynia, hyperalgesia, and tolerance to opioids (Wagner *et al*., 2002; Kaka *et al*., 2016). The documented effects of ketamine on NMDARs include those related to neuronal plasticity, induction and control of central and peripheral sensitization, as well as the reduction of visceral pain (Annetta *et al*., 2005).

In veterinary anesthesiology, the analgesic and hemodynamic effects of ketamine during surgical anesthesia and postoperative periods have been studied by various authors. For example, the analgesic action on the NMDAR has been demonstrated with the use of subanesthetic doses of ketamine, where a deep analgesia can be observed especially in situations of somatic pain (Klepstad *et al*., 1990; Annetta *et al*., 2005). Therefore, administration of ketamine before a painful stimulus controls the central sensitization and prevents the development of hyperalgesia or chronic pain when it is included in various analgesic protocols (Aida *et al*., 2000).

Ketamine has also been shown to bind to opioid receptors μ, ∂ and κ. Since these effects are not reversed by naloxone, some authors consider the interaction of

ketamine with opioid receptors and its analgesia as still unknown or found in study (Prommer, 2012; Mion and Villevieille, 2013). This drug has been used in various protocols as an adjuvant in perioperative analgesia, such as continuous intraoperative infusions (Fajardo *et al*., 2012; Gutiérrez *et al*., 2015), to control acute perioperative pain in bitches subjected to ovariohysterectomy. Analgesia provided by ketamine administered epidurally has also been evaluated in dogs with chemically induced synovitis (Hamilton *et al*., 2005). It has been reported that this drug generates sympathetic stimulation by increasing the serum concentration of catecholamines resulting in a direct positive chronotropic and inotropic effect, as well as improving ventilation, oxygenation and transoperative hemodynamics effects (Martin *et al*., 1997; Boscan *et al*., 2005). The aim of this study was to evaluate the intraoperative cardiorespiratory effects provided by ketamine compared to lidocaine, both administered epidural route in dogs undergoing ovariohysterectomy.

Materials and Methods

The study was a prospective, randomized, blinded clinical trial.

Animals

Thirty-six bitches (weight 9.27 ± 1.60 kg; 5.28 ± 3.33 years old) of different breeds (16 mixed-breed, 8 poodles, 5 schnauzers, 3 cocker spaniels, 2 beagles, and 2 dachshunds) were used with the previous owner informed consent, fasting for 8 h before surgery. All the animals included in the study received no medication and were clinically healthy according to the criteria of the American Society of Anesthesiologists (ASA1) determined by physical examination and preoperative laboratory tests (blood count, urinalysis, and blood chemistry). The study was reviewed and approved by the Internal Committee for the Care and Use of Animals in Experimentation of the Faculty of Higher Studies Cuautitlan, National Autonomous University of Mexico.

Anesthesia and surgical procedure

All anesthetic procedures were performed by the same anesthetist. All animals were aseptically catheterized in the cephalic vein. An isotonic fluid solution (0.9% sodium chloride Solution, Pisa, Mexico) was administered at a flow rate of 10 ml/kg/h through the catheter. Subsequently, premedication with acepromazine maleate at 0.05 mg/kg intravenous (IV) (Calmivet, Vetoquinol, Mexico) was done. Fifteen min later, induction of anesthesia was performed with propofol at 5 mg/kg IV (Recofol, Pisa, Mexico) to allow endotracheal intubation with a cuffed tube, then connecting the patient to an anesthetic rebreathing circuit with an oxygen flow of 45 ml/kg/min. The maintenance of anesthesia was carried out through the administration of isoflurane (Sofloran, Pisa, Mexico) vaporized in 100% oxygen (WATO EX-20 VET, Mindray, Germany), with an initial end tidal isoflurane concentration (ET_{ISO}) of 1.7%. This concentration was increased or decreased based on the depth of anaesthesia required for surgery. The isoflurane vaporizer dial was adjusted to deliver sufficient concentration based on clinical signs, including absence of palpebral reflex, absence of jaw tone, and mean arterial pressure (MAP) between 60 and 100 mmHg (Kalchofner *et al*., 2016). Patients were ventilated in a controlled manner by means of a presometric ventilation mode [airway pressure (Paw) of 12-15 cm H_2O].

Experimental design

The animals were randomly assigned into two study groups: G_{KET} (ketamine 3 mg/kg, n=18) and G_{LIDO} (lidocaine 4 mg/kg, n=18). Once the anesthetic plane was established, epidural analgesia was performed with dogs in sternal recumbency with the pelvic limbs pulled forward through a median approach at the lumbosacral intervertebral space (L7-S1) with a Tuohy needle (caliber Perican 22, B. Braun, Mexico) (Jones, 2001). Patients assigned to G_{KET} were medicated with ketamine at 3 mg/kg (Anesket, Pisa, Mexico) while those of G_{LIDO} received lidocaine at 4 mg/kg (Pisacaina, Pisa, Mexico), both epidurally using the low resistance syringe technique. The ovariohysterectomy started 20 min after the epidural injection, performed by the same surgeon through a midline surgical approach.

Anesthesia monitoring

During the anesthesia and surgical procedure, heart rate (HR), respiratory rate (RR), esophageal temperature (°C), oxygen saturation (SPO_2), and non-invasive mean blood pressure (MAP) by oscillometry using a Model VS2000V U veterinary multi-parameter monitor (Chongqing, China), through a blood pressure cuff (size #3, model SunTech VetBP, Mexico) placed proximal to the carpus over the radial artery were monitored every 5 min. End tidal carbon dioxide ($ETCO_2$) was monitored through the EMMA portable capnography monitor (Masimo, USA) every 5 min.

Intraoperative rescue analgesia

Intraoperative pain and nociception in anesthetised animals can be conventionally assessed by detection of haemodynamic reactivity, defined as tachycardia and increased blood pressure, as well as changes in respiratory patterns or movement (Firth and Haldane, 1999; Katoh *et al*., 1999). Therefore, at each moment of evaluation, when an increase in the sympathetic tone in the registered values of HR, RR, and MAP of 20% was observed from the baseline parameter (Odette and Smith, 2013; Saritas *et al*., 2015), the administration of fentanyl (Fenodid, Pisa, Mexico) in a dose of 5 µg/kg in a single bolus was postulated as intraoperative rescue analgesia (Gutiérrez *et al*., 2015).

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 8.1.1. The Shapiro-Wilk test was used for the assessment of data normality. A two-way ANOVA

Table 1: Cardiorespiratory variables monitored (mean±SD) of G_{KET} and G_{LIDO} groups during 30 min of surgery

Parameters	Period (min)							
	Study group	Baseline	5	10	15	20	25	30
HR (beats per min)	G_{KET}	130 ± 11	108 ± 12*†	110 ± 11*†	105 ± 11*	109 ± 11*	106 ± 11*	105 ± 11*
	G_{LIDO}	124 ± 11	95 ± 11*	97 ± 11*	99 ± 11*	100 ± 10*	99 ± 11*	97 ± 11*
RR (breaths per min)	G_{KET}	28 ± 8	10 ± 1	10 ± 1	10 ± 1	10 ± 1	10 ± 1	10 ± 1
	G_{LIDO}	29 ± 9	9 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 1	9 ± 1
MAP (mmHg)	G_{KET}	93 ± 16	102 ± 37	101 ± 31	97 ± 27	100 ± 23†	105 ± 35†	103 ± 35†
	G_{LIDO}	95 ± 17	85 ± 18	82 ± 13	73 ± 10	66 ± 7*	74 ± 10	67 ± 9*
Temperature (°C)	G_{KET}	38.2 ± 0.3	37.4 ± 1.0	37.0 ± 1.0	36.8 ± 1.1	36.7 ± 1.0	36.5 ± 1.3*	36.5 ± 1.4*
	G_{LIDO}	38.2 ± 0.9	37.8 ± 1.0	36.9 ± 2.3	37.4 ± 1.0	37.2 ± 1.2	37.0 ± 1.0	36.7 ± 1.5
SPO_2 (%)	G_{KET}	94 ± 2	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1
	G_{LIDO}	93 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1	99 ± 1
$ETCO_2$ (mmHg)	G_{KET}	35 ± 4	36 ± 6	37 ± 5	39 ± 6	37 ± 4	37 ± 4	34 ± 5
	G_{LIDO}	35 ± 5	36 ± 6	36 ± 5	37 ± 6	34 ± 5	36 ± 6	34 ± 8

G_{KET}: Ketamine 3 mg/kg (n=18), G_{LIDO}: Lidocaine 4 mg/kg (n=18), HR: Heart rate, RR: Respiratory rate, MAP: Mean arterial pressure, SPO_2: Oxygen saturation, $ETCO_2$: End tidal carbon dioxide. * Statistically significant differences from baseline values ($P<0.05$), and † Statistically significant differences between treatments ($P<0.01$)

for repetitive samples test followed by a Tukey post-hoc test was used to analyze the HR, RR, esophageal temperature, $ETCO_2$, and MAP. Data is reported as mean ± standard deviation (SD). The Kruskall-Wallis test was performed to analyze the values of SPO_2. This non-parametric data is reported as median (min, max). Values were considered statistically different when $P<0.05$.

Results

Anesthesia and surgery were uneventful in all dogs. The duration of anesthesia in G_{KET} was 49.44 ± 6.15 min and in G_{LIDO} 50.55 ± 8.20 min ($P>0.05$). The duration of surgery in G_{KET} was 29.4 ± 6.1 min and in G_{LIDO} 30.5 ± 8.2 min ($P>0.05$). No patient required rescue analgesia. Cardiorespiratory values during anesthesia were within acceptable normal ranges for anesthetized patients. The monitored variables are presented in Table 1.

Heart rate at 5 and 10 min after the start of surgery showed a statistically significant difference ($P=0.03$ and $P=0.01$, respectively) in G_{KET} in comparison with G_{LIDO}. Subsequently, after 15 min and until the monitoring was completed, no statistical differences were reported between the groups ($P>0.05$). With respect to MAP, this was higher in G_{KET} (100 ± 23, 105 ± 35, and 103 ± 35 mmHg) in comparison with G_{LIDO} (66 ± 7, 74 ± 10, and 67 ± 9 mmHg) at 20, 25, and 30 min ($P=0.01$, $P=0.004$, and $P=0.002$, respectively).

The esophageal temperature shows a statistically significant difference in the G_{KET} at 25 and 30 min, decreasing to 36.5 ± 1.3 and 36.5 ± 1.4°C, respectively, compared to baseline values (Table 1).

Discussion

The correct management of analgesia during a surgical procedure is a fundamental part of anesthesia because a nociceptive stimulus triggers hemodynamic, respiratory, digestive, urinary, neurological, and neuroendocrine changes in patients who, if not identified and corrected, compromise their health, welfare and recovery (Hellyer *et al*., 2007). The physiological manifestations that indicate hemodynamic reactivity associated with pain are generated by sympathetic-adrenergic and motor activation (Pérez and Castañeda, 2012). In the present study, the analgesia in both groups provided by general anesthesia with isoflurane and epidural anesthesia with either lidocaine or ketamine, was adequate to perform ovariohysterectomy in bitches, so no patient required rescue analgesic. With the results obtained, it can be inferred that epidural ketamine provides a significant increase in HR and MAP compared to the use of lidocaine, however, the cardiorespiratory parameters monitored during the anesthetic-surgical procedure reflect intraoperative respiratory and cardiovascular stability, such as mentioned by Duque *et al*. (2004) and Dalla-Porta *et al*. (2005) in bitches subject to ovariohysterectomy. These changes are beneficial during anesthesia because ketamine improves respiratory and cardiovascular function during anesthetic-surgical procedures with isoflurane. In addition to the temperature, urine production and gastrointestinal integrity are preserved during the combination of ketamine with isoflurane (Boscan *et al*., 2005).

The most frequently used epidural anesthetic is lidocaine which is known to have excellent diffusion and penetrability, as well as a rapid onset and establishment of surgical anesthesia, however it does produce a sensory and motor blockade causing proprioceptive deficits in the immediate postoperative period of 60-120 min on average. Local anesthetics such as lidocaine block voltage-gated sodium channels in the nociceptive fibers A-∂ and C, which produces a sympathetic block that in turn generates vasodilation (hypotension) (Jones, 2001; Valverde, 2008). This last effect was perceptible in this investigation in the G_{LIDO} at 20, 25, and 30 min of evaluation, where a progressive decrease of MAP was observed with significant difference.

Although local anesthetics and opioids have traditionally been administered for balanced anesthesia, ketamine may represent an alternative because it conserves or increases cardiac output, blood pressure, oxygen transport and body temperature in healthy dogs (Pozzi *et al*., 2006). Ketamine has been used as an adjuvant to local anesthetics for epidural block, making possible to extend the analgesia up to 22 h approximately, reducing the need for additional analgesics (DeRossi *et al*., 2011). Epidural and intrathecal administration of ketamine produces analgesia in dogs, provides perineal analgesia without generating cardiorespiratory changes associated with

hemodynamic reactivity (Ram *et al*., 2014; Sarotti *et al*., 2015), condition that was observed in the present study using epidural ketamine in bitches undergoing elective ovariohysterectomy.

In the present study, the HR recorded in G_{KET} after epidural administration, manifested higher values at the beginning of the evaluation (108 ± 12 and 110 ± 11 beats per min), being significantly higher in the group compared to G_{LIDO}. This increase in HR could be a consequence of a rapid absorption and systemic distribution of drugs from epidural space. Some authors have reported a significant increase in HR after epidural administration of ketamine (Ram *et al*., 2014). This also coincides with other studies where ketamine generates an increase in HR (Ahmad *et al*., 2013; Romagnoli *et al*., 2017), this cardiovascular effect is attributed to stimulation of the sympathetic nervous system through a central mechanism resulting in the increase of plasma concentrations of norepinephrine and epinephrine, as well as an increase in cardiac output, vagus nerve inhibition and increased myocardial oxygen consumption (Niesters *et al*., 2014; Bressan *et al*., 2017; Franco *et al*., 2018).

With regard to the MAP, it is reported that it tends to increase from low doses (2-5 mg/kg) and high (10-20 mg/kg), observed from 5 to 90 min after the epidural administration of ketamine, while only the 23 to 30% of patients developed hypotension and bradycardia (Ahmad *et al*., 2013; Bressan *et al*., 2017). Similarly, there are reports with increases of 61% from 5 min using doses of 2.5 mg/kg, which were maintained in normal ranges (80/120 mmHg) (Amarpall *et al*., 2003; Gutiérrez *et al*., 2015), as observed in the patients of the present study. Brown *et al*. (2007) mentioned the normal values in dogs as 103 ± 15 with an acceptable increase of 15 mmHg for medium-sized dog breeds. On the other hand, the indications for moderate hypertension are 160/95 and severe superior to 180 mmHg, which were not observed in the studied dogs. As already indicated, the MAP had a greater record in G_{KET} compared to G_{LIDO}, where an opposite effect was observed when there was a gradual decrease in the values measured. These effects are attributable to the increase of plasma concentrations of norepinephrine and epinephrine, as well as an increase in cardiac output, vagus nerve inhibition and increased myocardial oxygen consumption (Ram *et al*., 2014; Bressan *et al*., 2017). Epidural administration of ketamine at 2 mg/kg in dogs anesthetized with isoflurane has been shown to provide deep analgesia, without respiratory or hemodynamic depression (Martin *et al*., 1997). In that study, the researchers recorded baseline HR data of 108 ± 6 and during the anesthetic period of 113 ± 3.6 beats per min; MAP baseline values of 85 ± 10 and during the anesthetic procedure of 95 ± 10 mmHg, found increases in HR and MAP. These observations were similar to those recorded in the present study with the administration of 3 mg/kg.

Results from this study provide evidence that hypothermia can occur in dogs following epidural administration of ketamine. The values indicate that there was statistically difference between G_{KET} to 25 (36.5 ± 1.3°C) and 30 min (36.5 ± 1.4°C) compared to baseline (38.2 ± 0.3°C). Regarding this, it has been described that the decrease with use of ketamine or alpha-2 agonists is due to the low metabolic rate, muscle relaxation, central nervous system (CNS) depression and thermoregulatory centers of the hypothalamus (Amarpall *et al*., 2003; Mwangi *et al*., 2014). In this study, dogs in G_{KET} suffered mild hypothermia between 10 and 30 min post-administration. The effects of hypothermia include prolonged recovery time, acute renal tubular necrosis, increased hemorrhage, decreased of MAP, delayed oxygen-hemoglobin dissociation, mental derangements ranging from depression to coma and diminished resistance to infection (Armstrong *et al*., 2005; Bornkamp *et al*., 2016).

In conclusion, epidural administration of ketamine provides better hemodynamic stability, compared to the use of epidural lidocaine. The incorporation of ketamine and lidocaine might be considered in combination with other first-line analgesics (eg, opioids and nonsteroidal anti-inflammatory drugs [NSAIDs]) as part of a comprehensive multimodal approach to the treatment of pain in animals (Pozzi *et al*., 2006).

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Conflicts of interest

The authors declare no conflict of interest.

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