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Effects of lidocaine constant rate infusion on sevoflurane requirement, autonomic responses, and postoperative analgesia in dogs undergoing ovariectomy under opioid-based balanced anesthesia

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ABSTRACT

The effects of constant rate infusion (CRI) of lidocaine on sevoflurane (SEVO) requirements, autonomic responses to noxious stimulation, and postoperative pain relief were evaluated in dogs undergoing opioid-based balanced anesthesia. Twenty-four dogs scheduled for elective ovariectomy were randomly assigned to one of four groups: BC, receiving buprenorphine without lidocaine; FC, receiving fentanyl without lidocaine; BL, receiving buprenorphine and lidocaine; FL, receiving fentanyl and lidocaine. Dogs were anesthetized with intravenous (IV) diazepam and ketamine and anesthesia maintained with SEVO in oxygen/air. Lidocaine (2 mg/kg plus 50 μg/kg/min) or saline were infused in groups BL/FL and BC/FC, respectively. After initiation of lidocaine or saline CRI IV buprenorphine (0.02 mg/kg) or fentanyl (4 μg/kg plus 8 μg/kg/h CRI) were administered IV in BC/BL and FC/FL, respectively. Respiratory and hemodynamic variables, drug plasma concentrations, and end-tidal SEVO concentrations (E'SEVO) were measured. Behaviors and pain scores were subjectively assessed 1 and 2 h post-extubation.

Lidocaine CRI produced median drug plasma concentrations <0.4 μg/mL during peak surgical stimulation. Lidocaine produced a 14% decrease in E'SEVO in the BL ($P < 0.01$) but none in the FL group and no change in cardio-pulmonary responses to surgery or postoperative behaviors and pain scores in any group. Thus, depending on the opioid used, supplementing opioid-based balanced anesthesia with lidocaine (50 μg/kg/min) may not have any or only a minor impact on anesthetic outcome in terms of total anesthetic dose, autonomic responses to visceral nociception, and postoperative analgesia.

Introduction

In small animal practice sevoflurane (SEVO) enjoys popularity because of a number of favorable properties such as low blood solubility, a non-irritating and non-pungent odor, more rapid induction and emergence from anesthesia, and somewhat less respiratory depressant effects compared to traditional inhalant anesthetics (Haitjema and Cullen, 2001; Steffey and Mama, 2007). However, SEVO also causes dose-dependent cardiovascular depression (Steffey and Mama, 2007). A balanced anesthetic approach using a combination of anesthetic agent and a potent analgesic has therefore been widely advocated to allow for a reduction of inhalant anesthetic dose and resultant alleviation of cardiovascular and respiratory depression (Ilkiw, 1999).

Currently, opioids are the primary analgesics used in balanced anesthesia in the dog because of their potent antinociceptive action (Lemmens, 1995). Among them, buprenorphine is used frequently for perioperative analgesia (Brodbelt et al., 1997; Joubert, 2001; Roughan and Flecknell, 2002) as it is 25–50 times more potent than morphine (Jaffe and Martin, 1990) and produces prolonged analgesia of 6–8 h (Bowdle, 1993; Brodbelt et al., 1997). It is further characterized by slow (40–60 min) onset of action (Slingsby et al., 2006) and has only minor side effects (Martinez et al., 1997). Fentanyl is a fast yet short-acting highly lipid soluble synthetic μ-opioid approximately 100 times more potent than morphine (Pascoe, 2000). It is frequently administered as constant rate infusion (CRI) to reduce inhalant anesthetic requirements (Ilkiw, 1999).

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Lidocaine administered intravenously (IV) seems to act as an analgesic (Lauretti, 2008) and when infused IV in dogs decreases the dose requirements for isoflurane (Muir et al., 2003; Valverde et al., 2004) and SEVO (Wilson et al., 2008; Matsubara et al., 2009). The SEVO minimum alveolar concentration (MAC)-sparing effect of lidocaine is dose-dependent and not associated with marked changes in hemodynamic function (Matsubara et al., 2009). Muir et al. (2003), however, did not detect such an effect in dogs when comparing the impact of an infusion of morphine alone on isoflurane MAC with that of a CRI of morphine, lidocaine plus ketamine. In contrast, Schubert et al. (1992) observed a significant reduction in amplitude of median nerve somatosensory evoked potentials (SSEPs) and a slightly prolonged latency in patients receiving an IV infusion of lidocaine in addition to a sufentanil–nitrous oxide–isoflurane regimen for anesthesia.

No current balanced anesthesia protocol for dogs stands out as the single superior regimen with regard to side effects (hemodynamic and respiratory), profile and analgesic efficacy. Pharmacodynamic data of lidocaine suggest that lidocaine combined with an opioid provides qualitatively better anesthetic conditions and improves postoperative analgesia compared to the use of an opioid alone with SEVO. We therefore hypothesized that in previously pain-free dogs undergoing ovariectomy the addition of a lidocaine CRI to two different opioid-based balanced anesthesia protocols with quantitatively different MAC-sparing properties would further reduce SEVO requirements and autonomic responses to noxious stimulation, thereby helping maintain a better hemodynamic status intraoperatively and improve pain relief post-operatively.

Materials and methods

Study design

A randomized prospective, single blinded one-center clinical trial was carried out in female dogs undergoing elective ovariectomy. The study was approved by the Institutional Animal Care and Use Committee in compliance with Italian law (D.L. 116/1992) and European Community directive CEE n.86/609. For each animal a written consent was obtained from the owners.

Dogs

Twenty-four systemically healthy, mixed-breed bitches with a mean (±SD) age and bodyweight of 2.4 ± 1.8 years and 17.3 ± 6.8 kg, respectively, were enrolled. None was pregnant or showed any ovarian pathology. Dogs were kept off food for 12–18 h and off water for 3–4 h prior to surgery. They were randomly assigned to four groups (n = 6 dogs each): group BC received buprenorphine without lidocaine CRI (buprenorphine control); group FC a CRI of fentanyl without lidocaine CRI (fentanyl control); group BL buprenorphine and a lidocaine CRI, and group FL a CRI of both fentanyl and lidocaine.

Pre-medication, induction and maintenance of anesthesia

Dogs in each group received initially IV ketoprofen 1.0 mg/kg (Vet-Ketofen 1%, Merial) and IV diazepam 0.3 mg/kg (Diazepam 0.5%, Intervet). Anesthesia was induced with IV diazepam 0.5 mg/kg and IV ketamine 5–6 mg/kg (Ketavet; Intervet) followed by orotracheal intubation. Following intubation the endotracheal tube was connected to a small animal semi-closed anesthetic circle system (Fabius GS, Dräger).

SEVO (Sevoflo; Abbott) in oxygen (O_2)/air was delivered through an agent-specific calibrated vaporizer (Blease Sevo, Blease Datum). The O_2 and air flow rates were set to 20 mL/kg/min each for the initial 10 min and then reduced to 1.77 ± 0.39 mL/kg/min each for the remainder of the anesthetic period, but could be intermittently increased should a rapid increase in SEVO delivery be necessary to deepen anesthesia. The inspired O_2 concentration (FiO_2) was held above 0.4. The end-tidal concentration of SEVO (E′SEVO) was maintained at a level sufficient to ensure a surgical plane of anesthesia, verified by an absence of palpebral reflexes, jaw tone and abdominal straining, and mean arterial blood pressures of 60–100 mm Hg (Steagall et al., 2006). If necessary, the anesthetist had the option to administer IV ketamine (0.5–1.0 mg/kg) should the animal respond with movement or otherwise to surgical stimulation ('break through' anesthetic). Saline solution (NaCl 0.9%, Acme Drugs) was infused at a rate of 5–10 mL/kg/h.

Approximately 15 min after induction of anesthesia, IV lidocaine (2 mg/kg over 5 min followed by 50 μg/kg/min; Lidocaine 2%, Fort Dodge) or saline in equivalent volume were administered in groups BL/FL and BC/FC, respectively following a dose regimen previously described in dogs (Valverde et al., 2004; Wilson et al., 2008; Egger, 2009). Lidocaine CRI was discontinued before skin closure. After initiation (10 min) of lidocaine or saline infusion, IV buprenorphine (0.02 mg/kg; Temgesic, Schering-Plough) was administered in groups BC and BL, and IV fentanyl (4 μg/kg over 5 min followed by 8 μg/kg/h; Fentanest, Actavis) was administered in groups FC and FL.

Instrumentation and monitoring

In each dog, both cephalic veins were catheterized for IV drug and fluid administration, using 18 or 20 Ga catheters (Delta Ven 1, Delta Med). The dorsal pedal or auricular artery was percutaneously catheterized with a 20–22 Ga catheter (Delta Ven 1, Delta Med) using an aseptic technique and para-arterial infiltration of subcutaneous tissue with mepivacaine 2% (Mepibil, Hospira).

The electrocardiogram (ECG), invasive systolic (SAP), diastolic (DAP) and mean arterial blood pressures (MAP, mm Hg), respiratory rate (f_R per min), tidal volume (V_T, mL), fresh gas (O_2/air) flow (L/min), arterial oxygen saturation (SpO_2), esophageal body temperature (°C), E′SEVO (vol.%), end-tidal partial pressure of CO_2 (P'_ECO_2, mm Hg, kPa), and FiO_2 were continuously recorded using the Infinity Delta vital parameter monitor and its Scio four Oxi Plus gas module (Dräger). The E′ gas module was calibrated daily using gas standards (1% SEVO, 5% CO_2; Calibration Gas, Air Liquide Healthcare America).

Traction of about 2-min duration was exerted on first the left and then the right ovarian ligament, sufficient for ovarian pedicle ligation. Traction was measured at least four times in kg load using a handheld scaling device (Kop 24382, Keen Optics) calibrated with Ohaus hook weights (Ohaus International); average values were then converted into N. The total volume of saline (mL/kg) infused during anesthesia was recorded at the end of the anesthetic procedure. Respiratory minute ventilation (V, mL/kg/min) was calculated as $f_R \times V_T$ and total inhalation anesthesia time (h) averaged for each dog. In addition, the area under the E'SEVO over time curves (AUC, vol.%/min; Fig. 1) was determined and E'SEVO concentrations transformed

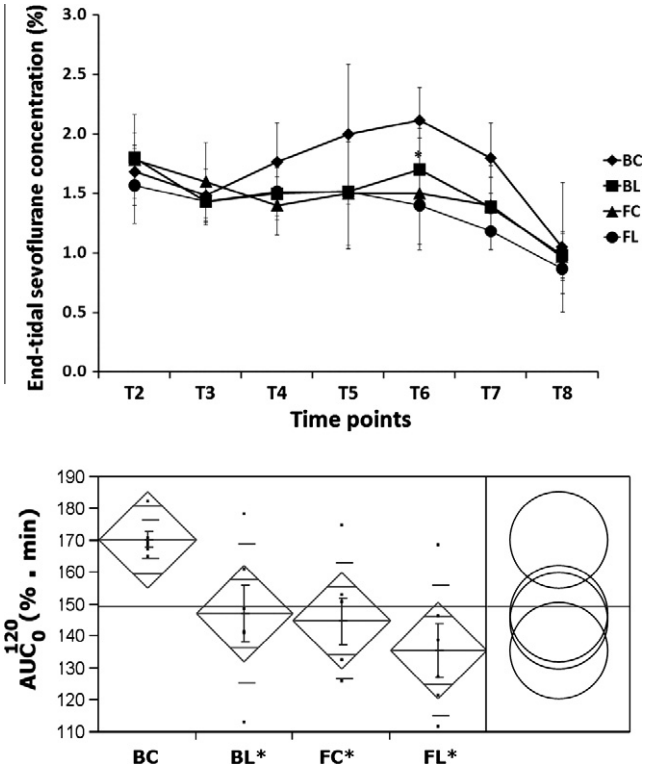

Fig. 1. End-tidal sevoflurane concentrations (upper panel) and area under the end-tidal sevoflurane over time curves (in AUC; lower panel) in dogs undergoing ovariectomy under an opioid-based balanced anesthesia protocol with sevoflurane and supplemented or not by a lidocaine constant rate infusion (CRI). Four groups (n = 6/group) were used: group BC receiving buprenorphine without lidocaine CRI (buprenorphine control); group FC receiving a CRI of fentanyl without lidocaine CRI (fentanyl control); group BL receiving buprenorphine and a lidocaine CRI; and group FL receiving a CRI of both fentanyl and lidocaine. Data represent means ± SD. *P < 0.01, significant differences between groups based on one-way ANOVA with post hoc paired Student's t test.