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Original Article

The clinical effects of a low dose dexmedetomidine constant rate infusion in isoflurane anesthetized cats

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ABSTRACT

The aim of this study was to evaluate the effects of a low dose dexmedetomidine constant rate infusion (CRI) on cardiopulmonary function, inhalant anesthetic concentration and recovery in isoflurane anesthetized cats. In a prospective, randomized, blinded, controlled design, 12 cats undergoing anesthesia for ovariohysterectomy were administered hydromorphone (0.1 mg/kg) intramuscularly, propofol (4.3–7.8 mg/kg) intravenously and maintained with isoflurane. During isoflurane anesthesia, the cats were administered either a dexmedetomidine loading dose (0.5 μg/kg) followed by a dexmedetomidine CRI (0.5 μg/kg/h) (group LDD), or a saline loading dose followed by a saline CRI (group SAL). Heart rate (HR), respiratory rate, blood pressure, temperature, oxygen saturation (SpO_2), end tidal carbon dioxide concentration (ET_{CO_2}), end tidal isoflurane concentration (ET_{ISO}) and anesthetic depth were recorded at nine time points (T0–T8). Overall effects (T1–8) and individual time point results were compared between groups. There were no significant differences in baseline variables (T0), age, weight, propofol dose, anesthesia and surgery time, time to extubation or recovery score between groups. Among the physiological variables measured, significant differences were observed in respiratory rate, ET_{CO_2}, and mean and diastolic blood pressure, between groups at individual time points. Systolic blood pressure, HR, SpO_2, ET_{ISO} and temperature were not significantly different between groups at individual time points. Overall, ET_{CO_2} and ET_{ISO} were significantly lower and respiratory rate was significantly higher for LDD compared to SAL. At the doses administered, a CRI of dexmedetomidine reduced isoflurane requirements in anesthetized cats undergoing ovariohysterectomy. The utility of a low dose dexmedetomidine CRI in the perioperative setting requires further investigation, since intraoperative cardiopulmonary values during dexmedetomidine infusion were not different from those receiving saline.

Introduction

The technique using anesthetic or analgesic intravenous infusions in conjunction with inhalant anesthetic agents is termed partial intravenous anesthesia (PIVA). Utilizing PIVA may reduce volatile anesthetic requirements potentially maintaining cardiopulmonary function, enhance perioperative pain management and improve recovery quality (Uilenreef et al., 2008; Souza et al., 2010; Gutierrez-Blanco et al., 2013; Steagall et al., 2015). The benefits of constant rate infusions (CRIs) during elective surgeries have been evaluated in dogs (Steagall et al., 2006; Gutierrez-Blanco et al., 2013) and cats (Steagall et al., 2015; Machado et al., 2017).

Perioperatively, α_2-adrenoreceptor agonists are administered as intermittent parenteral injections or as CRIs during PIVA in small animal clinical practice (Ko et al., 2000; Lemke, 2004; Rioja et al., 2013). Binding to α_2 receptors located in the cerebral cortex, brain stem and spinal cord results in dose-dependent sedation, muscle relaxation, spinal and supraspinal analgesia and reduction in the minimum alveolar concentration (MAC) of inhalants (Leppänen et al., 2006; Slingsby and Taylor 2008; Wegner et al., 2008; Acevedo-Arcique et al., 2014; Pypendop and Ilkiw, 2014; Hector et al., 2017). Despite these benefits, CRIs of α_2-adrenoreceptor agonists decrease heart rate, cardiac output, cardiac index and oxygen delivery in a dose-dependent fashion in dogs and cats (Pascoe et al., 2006; Kaartinen et al., 2010; Pypendop et al., 2011).

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These adverse effects are due to their direct effects on vascular smooth muscle (vasoconstriction) and centrally mediated effects on heart rate (bradycardia) in dogs (Kaartinen et al., 2010; Moran-Munoz et al., 2017) and cats (Pypendop et al., 2011; Honkavaara et al., 2017).

The use of low dose dexmedetomidine CRIs has been studied in anesthetized dogs to identify a dose required to reduce inhalant requirements, while minimizing the negative cardiovascular effects (bradycardia, vasoconstriction, decreased cardiac output) that accompany the drug (Pascoe, 2015). Anesthetized dogs receiving medetomidine (Kaartinen et al., 2010) or dexmedetomidine (Pascoe et al., 2006; Pascoe, 2015) CRIs of 1 μg/kg/h or less had reduced inhalant requirements, with limited adverse effects on cardiopulmonary function. In isoflurane anesthetized cats receiving a dexmedetomidine target-controlled infusion, MAC decreased in a plasma concentration-dependent manner (Escobar et al., 2012), with minimal effects on heart rate, systemic vascular resistance, cardiac index and mean arterial blood pressure at the lowest plasma dexmedetomidine concentrations (0.16 ng/mL) (Pypendop et al., 2011). To the authors' knowledge, the perioperative effects of low dose dexmedetomidine CRIs have not been studied in cats.

The aim of the study was to evaluate the effects of a low dose dexmedetomidine CRI on intraoperative physiological variables, inhalant anesthetic requirements and recovery quality in healthy cats undergoing routine elective ovariohysterectomy. Our primary hypothesis was that the use of a low dose dexmedetomidine CRI would provide a reduction in inhalant anesthetic requirements when compared to a CRI of saline. Our secondary hypothesis was that a low dose dexmedetomidine CRI would result in improved cardiopulmonary stability during surgery when compared to a CRI of saline.

Materials and methods

Subjects

The study was approved by the Texas A&M University College of Veterinary Medicine and Biomedical Sciences Institutional Animal Care and Use Committee (IACUC approval number 2016-0018; date of approval 25 March 2016). Twelve healthy female domestic short hair research cats, with a mean ± standard deviation (SD) age of 14.2 ± 0.3 months and weight of 3.86 ± 0.8 kg, were included in the study. Cats were deemed to be systemically healthy on the basis of pertinent medical history, physical examination, complete blood count and serum biochemistry analysis. All cats were considered to have an American Society of Anesthesiologists Physical Status[1] of I. All cats were under the care of the principal investigator and lived in a temperature and humidity regulated environment. Cats were fed dry food ad libitum, wet food on occasion and had free access to water. Food but not water was withheld 12 h prior to induction of anesthesia.

Experimental design

In a prospective, randomized, controlled design, 12 cats were randomly allocated via an online software program[2] to either a dexmedetomidine or a saline group. Cats were premedicated with hydromorphone (0.1 mg/kg; Hydromorphone HCl, West-ward) administered into the semimembranosus muscle with minimal restraint. Fifteen minutes post-premedication, an antebrachium was aseptically prepared and a 22 G catheter was introduced and secured into a cephalic vein.

Propofol (Propoflo, Zoetis) was administered slowly intravenously through the catheter at a median (range) dose of 5.5 (4.3–7.8) mg/kg by one investigator (CDC) blinded to treatments until ventral medial rotation of the eyes, loss of palpebral reflex and loss of jaw tone were appreciated. Lidocaine (2 mg) was sprayed on the larynx and the cats were intubated with an appropriate sized cuffed-endotracheal tube so the bevel of the endotracheal tube was at the level of the thoracic inlet.

Cats were attached to a non-rebreathing system (Modified Jackson Rees Circuit, Smiths Medical ASD) and immediately placed on inhaled oxygen at a flow rate of 300 mL/kg/min, with a minimum flow rate of 1 L/min, if necessary. Cats were then moved from sternal to dorsal recumbency on a heating pad (Hotdog, Augustine Temperature Management) and an endotracheal tube leak test was performed. The anesthesiologist auscultated for air at the level of the pharynx during positive pressure ventilation to a peak inspiratory pressure of 20 cm H_2O on the anesthesia delivery system pressure manometer; if air was not auscultated bypassing the cuff and endotracheal tube, then the cuff was considered to be leak-free.

Once it was determined that the endotracheal tube cuff was leak-free, the isoflurane vaporizer was turned on to a standard setting of 2% and anesthesia was maintained with isoflurane (Isoflurane, Piramal Enterprises) with oxygen as the sole carrier gas through a calibrated, precision, out-of-circuit vaporizer (Ohmeda Isotec 3, BOC Health Care). To avoid excessive apparatus dead space, the endotracheal tube was cut so that the machine end was at the level of the mouth.

A side stream adapter was placed between the endotracheal tube connecter and the non-rebreathing circuit to continuously measure the end-tidal isoflurane concentration (ET_{ISO}), respiratory rate (f_r), and end-tidal carbon dioxide concentration (ET_{CO_2}) via a gas analyzer (CritiCare POET IQ2 Gas Monitor 8500Q, CSI CritiCare Systems) which was calibrated on the morning of each day of experimentation with a standard gas mixture provided by the manufacturer using standard calibration procedures. Cats were permitted to breathe spontaneously throughout the procedure. If apnea occurred for a duration longer than 30 s, manual positive pressure ventilation was provided with a peak airway pressure of 15 cm H_2O once every 30 s until spontaneous ventilation restarted.

A continuous lead II electrocardiogram tracing was performed to monitor heart rate (HR) and rhythm. Systolic (SBP), mean (MBP) and diastolic (DBP) indirect blood pressure measurements were determined with an oscillometric device (DRE Waveline EZ Patient Monitor, DRE Veterinary) using a blood pressure cuff with a width approximately 40% of the circumference of the antebrachium. Core body temperature was monitored via an esophageal temperature probe placed at the level of the heart base. A pulse oximeter with a transmission probe to measure percent arterial hemoglobin oxygen saturation (SpO_2) was placed on the tongue. Lactated Ringer's solution was administered intravenously at a rate of 7.5 mL/kg/h throughout surgery.

A single board certified veterinary anesthesiologist (BTS) adjusted the anesthetic depth by increasing or decreasing the vaporizer based on jaw tone, palpebral reflex, eye position and movement in response to surgical stimulation. Anesthetic depth was categorized using a numerical score for plane of anesthesia: (1) light: eyes centrally located, brisk palpebral reflex and moderate jaw tone; (2) appropriate: eyes with ventral medial rotation, minimal to absent palpebral reflex and minimal to absent jaw tone; and (3) deep: eyes centrally located, absent palpebral reflex and absent jaw tone, and was verbally relayed to another investigator (EMS or EJM) for recording at each time point. The anesthesiologist (BTS) was blinded to the inhalant concentrations delivered to each cat, via opaque tape which covered the concentration control dial, and the gas analyzer measurements (ET_{ISO}, f_r, ET_{CO_2}), throughout the procedure. After surgical draping and appropriate depth for surgical stimulus was confirmed by the investigator (BTS) and relayed to the co-investigator (EMS), baseline (T0) physiological measurements (HR, SBP, MBP, DBP, f_r, ET_{CO_2}, temperature, SpO_2), anesthetic depth and ET_{ISO} were recorded by a co-investigator (EMS or EJM).

Following T0 measurements, a CRI of low dose dexmedetomidine (Dexdomitor 0.5 mg/mL, Zoetis) or 0.9% saline (0.9% Sodium Chloride, Hospira) was initiated. Cats randomly selected in the low dose dexmedetomidine (LDD) group were administered a loading dose of 0.5 μg/kg dexmedetomidine through the intravenous catheter over 5 s, immediately followed by a dexmedetomidine CRI (0.5 μg/kg/h) in saline. For the dexmedetomidine CRI, dexmedetomidine was added to saline, which was administered at a rate of 2.5 mL/kg/h via syringe pump (Medfusion 3010a, Medex). The dilution in saline was to ensure accurate dexmedetomidine delivery based on the syringe pump minimum delivery rate specifications. Cats randomly selected in the saline (SAL) group were administered a loading dose of 0.05 mL/kg of saline (0.9%) through the intravenous catheter over 5 s, immediately followed by a saline CRI (2.5 mL/kg/h). The loading dose and CRI volumes used were identical (on a mL/kg basis) amongst treatments. All infusions were administered directly into the catheter port via a 22 G needle. The anesthesiologist (BTS), who was blinded to inhalant concentrations, was also blinded to the treatment groups.

Three minutes following the start of the CRI and immediately before the initial skin incision (T1), physiological variables, ET_{ISO} and anesthetic depth were recorded in a similar fashion as performed at T0. Data were recorded at specific time points as previously reported for similar studies (Steagall et al., 2015): immediately post-celiotomy (T2), during traction and following ligation of the right ovarian pedicle (T3), during traction and following ligation of the left ovarian pedicle (T4), during hysterectomy (T5), mid-point of the linea alba closure (T6), mid-point of the subcutaneous layer closure (T7) and mid-point of the intradermal closure (T8). The ovariohysterectomy procedure was performed by a single surgeon (WMK).

CRIs were discontinued immediately following the T7 measurement. Duration of surgery (time from initial incision to placement of last suture), duration of anesthesia (time from turning on to turning off the vaporizer dial) and time to extubation (time from turning off the vaporizer until extubation) were recorded for all cats. Following extubation, subcutaneous meloxicam (Loxicam, Norbrook Laboratories; 0.2 mg/kg) and high concentration buprenorphine (Simbadol, Zoetis; 0.24 mg/kg) were administered. All cats received a second dose of meloxicam (0.05 mg/kg) orally at 24 and 72 h following the initial dose.

[1] See: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system (accessed 13 November 2017).
[2] See: www.randomizer.org (accessed 13 November 2017).