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*Original article*

# Comparison of the cardiovascular and respiratory effects and sevoflurane requirement in dogs premedicated with two doses of medetomidine and butorphanol undergoing surgical sterilization

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## Abstract

The aim of this study was to compare the cardiovascular and respiratory effects and sevoflurane requirement in dogs premedicated with two doses of medetomidine and butorphanol undergoing surgical sterilization. The dogs were randomly assigned to two different groups: group 1 received a lower dose of medetomidine (0.014 mg/kg) and butorphanol (0.14 mg/kg) and group 2 received a higher dose of medetomidine (0.024 mg/kg) and butorphanol (0.24 mg/kg). Anesthesia was induced with intravenous propofol and maintained with sevoflurane 2% in pure oxygen. Heart rate, $SpO_2$, respiratory rate, $EtCO_2$, esophageal temperature, systolic and diastolic arterial blood pressures, capillary refill time, reflexes (palpebral, pedal), jaw tone, and eye position (straight, down) were assessed. Anesthesia was monitored continuously by an anesthesiologist, and variables were recorded every 5 min. During general anesthesia, the median sevoflurane (SVO) concentrations and the median HR were significantly lower in group 2 than group 1 ($p<0.05$). The median HR was 96.3 (85.8-100.8) in group 1, whereas in group 2 it was 77.0 (67.5-84.6) ($p<0.05$). It might be concluded that the higher dose of medetomidine and butorphanol allows the use of a lower sevoflurane concentration during routine surgical treatments and ensures stable work of the cardiovascular and respiratory systems.

**Key words**: Medetomidine, butorphanol, sevoflurane, sedation, canine.

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## Introduction

The maintenance of general anesthesia with more than one medication is common (Hall et al. 2001), and although this has traditionally involved the administration of analgetics, such as opioids, the use of an inhalant anesthetic in combination with drugs possessing anesthetic properties, such as propofol, has also been reported (Luo et al. 2010, Dzikiti et al. 2011). By using multidrug regimens, clinicians employ different characteristics of drugs and the additive action between or among drugs in order to potentially improve patient safety by decreasing the dose of a volatile anesthetic, thereby lessening its negative cardiovascular effects.

Alpha-2 adrenoceptor agonists are widely used to produce sedation and analgesia in veterinary medicine for minor surgical treatments and diagnostic procedures, or to provide preanesthetic medication before the induction of anesthesia (Gleed 1987, Muir and Hubbell 1995, Hall et al. 2001).

Medetomidine is a highly selective alpha-2 adrenoceptor agonist, which induces cardiovascular effects and stimulates receptors centrally to produce dose-dependent sedation and analgesia (Sinclair 2003, Puighibet et al. 2015). It is frequently used alone or in combination with opioids for minor procedures or as a premedication agent before general anesthesia (Pypendop and Verstegen 1998). The recommended dose of medetomidine, administered intravenously (IV), intramuscularly (IM), or subcutaneously (SC), in dogs ranges from 10 to 80 µg/kg (Pfizer Ltd, Domitor summary of product characteristics [SPC] 09/2007). In dogs, the dose of 30 µg/kg IV produces deep sedation concomitantly with bradycardia. The cardiovascular effects of medetomidine are maximal at a dose of 0.005 mg/kg in dogs, but below this dose the effects are dose-dependent (Girard et al. 2010).

Pypendop and Verstegen in 1998 showed that the two lowest doses of medetomidine produced lower cardiovascular depression (1 and 2 µg/kg) than higher doses (5, 10 or 20 µg/kg).

Butorphanol is a synthetic kappa opioid agonist and a mu opioid antagonist (Lamont and Mathews 2007). The dose of butorphanol administered IV, IM, or SC in dogs ranges from 0.1 to 0.8 mg/kg ( Hosgood 1990, Lamont and Mathews 2007). The onset time of this drug is about 16 min when administered IM (Kojima et al. 1999), and its analgesic duration ranges from 1 to 3 h (Hosgood 1990). According to Lamont and Mathews (2007), the recommended dose of butorphanol in dogs is 0.1-0.4 mg/kg. When using IV, these doses produce dose-dependent analgesic (Houghton 1991) and sedative (Trim 1983) effects.

It has been reported that premedication with alpha-2 adrenoceptor agonists and opioids can improve the quality of anesthesia and can reduce the required dose of volatile anesthetic agents for induction and inhalation anesthesia (Murphy and Hug 1982, Trim 1983, Karas 1999).

Sevoflurane is a volatile anesthetic with a low blood-gas partition coefficient, and it produces a rapid induction of and recovery from anesthesia (Haitjema and Cullen 2001). It causes dose-dependent hypotension, hypoventilation, impaired cardiac contractility, and hypothermia (Mutoh et al. 1997). Due to these side effects, sevoflurane must be carefully titrated, and vigilant monitoring should be employed to avoid excessive anesthetic depth (Pypendop and Verstegen 1998).

Scientific information about the influence of different doses of medetomidine and butorphanol on sevoflurane requirement and heart rate (HR) during general anesthesia is scarce. Therefore, the aim of this study was to compare cardiovascular and respiratory effects and sevoflurane requirement in dogs undergoing surgical sterilization and premedicated with two doses of medetomidine and butorphanol.

## Materials and Methods

A total of 30 client-owned dogs scheduled for ovariohysterectomy or orchiectomy surgery were used in this study. There were 16 males and 14 females (age range 15 to 18 months) weighing 12.4 ± 3.3 kg. All the dogs were judged to be in ASA I group according to the classification by the American Society of Anesthesiologists, based on a physical examination, complete blood cell count, analysis of serum biochemistry, and thoracic radiographs. The dogs were fasted for 12 h before anesthesia with free access to water. All the animals were weighed on calibrated scales (Kruuse PS250, Langeskov, Denmark), and an intravenous catheter (Bio-Flon, Haryana, India) was placed in the left cephalic vein before surgery.

By using 30 envelopes with cards, the dogs were randomly assigned to two different groups: group 1 (n=15) received a lower dose of medetomidine (0.014 mg/kg) and butorphanol (0.14 mg/kg) and group 2 (n=15) received a higher dose of medetomidine (0.024 mg/kg) and butorphanol (0.24 mg/kg) (Cepetor® 1 mg/mL, CP Pharma Handelsgesellschaft mbH, Burgdorf, Germany and Butomidor®, 10 mg/mL, Richter Pharma AG., Wels, Austria). The doses were selected according to the summary of sedative characteristics. Ketoprofen at a dose of 2 mg/kg (Ketofen 1%, Merial, Toulouse, Cedex, France) was administered IV to all dogs

before surgery. Medetomidine and butorphanol were administered IM in both groups. After injection, the dogs were kept in the same quiet dark room for 15 min under the direct supervision of an anesthesiologist. Anesthesia was induced 20 min later with propofol IV (propofol 10 mg/mL, 20 mL amp, Fresenius Kabi, Sweden) in order to allow tracheal intubation. Propofol (2-3 mg/kg) was administered IV by hand within 60 s until clinical signs showed the onset of anesthesia. Anesthesia was assessed by an anesthesiologist. The onset of anesthesia was achieved when eye position was down (eyeball rotates down) and there were no palpebral (tested by lightly tapping the medial or lateral canthus of the eye and observing whether the animal blinks in response) and pedal (elicited by pinching a digit and observing whether the animal flexes the leg, withdrawing the paw) reflexes and no jaw tone (assessed by attempting to open the jaws wide and estimating the amount of passive resistance). All the dogs were preoxygenated before tracheal intubation. After tracheal intubation, an endotracheal tube was attached to an anesthesia machine (Mindray WATO EX-35) with a calibrated sevoflurane vaporizer (Penlon Sigma Delta, Abingdon, Great Britain). Anesthesia was maintained with sevoflurane (SVO) 2% (SevoFlo 100%, 250 mL, Zoetis, Belgium) in pure oxygen (2 L/min), 25 min after sedation. After the patient was connected to the anesthesia machine, the sevoflurane vaporizer setting was adjusted from 1.6% to 2.2% according to the depth of patient anesthesia. All the dogs were administered 0.9% sodium chloride solution at a flow rate of 10 mL/kg/h through a 22-gauge catheter placed in the left cephalic vein by the use of an infusion pump (Infusomat® fmS Braun, Melsungen, Germany).

HR, saturation of hemoglobin with oxygen ($SpO_2$), respiratory rate (RR), end-tidal $CO_2$ ($EtCO_2$), esophageal temperature, noninvasive systolic (SAP), and diastolic arterial blood pressures (DAP) were monitored using a veterinary patient monitoring system (iM8 VET, Edan, Germany). Capillary refill time (CRT), reflexes (palpebral, pedal), jaw tone, and eye position (straight, down) were also assessed. Esophageal temperature was measured using an electric thermometer probe placed orally into the thoracic esophagus. HR was monitored by placing the electrodes at the level of the right and left elbows and the left patella. Systolic and diastolic arterial blood pressures were monitored by using standard oscillometry blood pressure measurement. The numeric cuff size was 40% of the circumference of the cuff site. The cuff was placed on the right antebrachium. $SpO_2$ and $EtCO_2$ were measured by a pulse oximeter (infrared sensor attached to the dog's tongue) and a capnograph, respectively, which were installed into the anesthesia machine (WATO EX-35, Mindray, China). A circulating warm heating pad (FIR Therapeutic Pad, MHP-E1220, Mainland, China) was used to maintain temperature between 37.5°C and 38.5°C. Anesthesia management, depth, and animal status was monitored continuously by an anesthesiologist who was blinded to the treatment used, and variables were recorded every 5 min.

The dogs were extubated when the swallowing reflex appeared, and they were considered as awake from anesthesia.

## Statistical analysis

Statistical analysis was performed using the SPSS 22 computer software program (Statistical Package for Social Sciences 22 for Windows). Data were processed using a nonparametric statistical method between groups 1 and 2 using the Mann-Whitney test. Nonnormally distributed data are presented as median and range. The level of significance was set at $p<0.05$.

The study was performed in compliance with the Lithuanian animal welfare regulations (No. B1-866, 2012; No. XI-2271, 2012) and was approved by the Lithuanian Committee of Veterinary Medicine and Zootechnic Sciences (Protocol No. 07/2010).

## Results

Initially, the requirement of SVO % was the same in both the groups (Table 1). Based on the depth of the anesthesia, the requirement of SVO % remained the same in group 1; however, in group 2 it decreased from the 10th minute to 1.8 or more. A significant difference in the requirement of SVO % between the groups was recorded from the 10th minute, and lasted until the end of surgery ($p<0.05$). During general anesthesia, the median values of SVO concentrations were significantly lower in group 1 than group 2 ($p<0.05$) (Table 1).

During general anesthesia, the median values of HR were significantly lower in group 2 than group 1 ($p<0.05$) (Table 2). A significant difference was documented at the beginning of surgery when general anesthesia was maintained with SVO ($p<0.05$).

No significant differences in $SpO_2$ (Table 3), RR (Table 4), $EtCO_2$ (Table 5), esophageal temperature (Table 6), SAP (Table 7), and DAP (Table 8) between the groups were recorded. Moreover, there were no significant changes in CRT, palpebral reflex, jaw tone, and eye position between the groups.

Table 1. Changes in sevoflurane requirement during general anesthesia by dose of sedative.

| SVO by 5-min intervals, % | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| SVO 0 | 2.0 (2.0-2.0) | 2.0 (2.0-2.0) | 1.0 |
| SVO 5 | 2.0 (2.0-2.0) | 2.0 (1.8-2.0) | 0.775 |
| SVO 10 | 2.0 (1.8-2.0) | 1.8 (1.8-2.0) | 0.050 |
| SVO 15 | 2.0 (1.8-2.2) | 1.8 (1.8-1.8) | 0.026 |
| SVO 20 | 2.0 (1.8-2.2) | 1.8 (1.8-1.8) | 0.014 |
| SVO 25 | 2.0 (1.8-2.2) | 1.8 (1.8-1.8) | 0.016 |
| SVO 30 | 2.0 (1.8-2.2) | 1.8 (1.6-1.8) | 0.010 |
| SVO 35 | 2.0 (1.8-2.2) | 1.8 (1.6-1.8) | 0.006 |
| SVO 40 | 2.0 (1.8-2.2) | 1.8 (1.6-1.8) | 0.006 |
| SVO 45 | 2.0 (1.8-2.2) | 1.6 (1.6-1.8) | 0.006 |
| SVO 50 | 2.0 (1.8-2.2) | 1.8 (1.6-1.8) | 0.019 |
| SVO 55 | 2.0 (1.8-2.2) | 1.8 (1.6-1.8) | 0.013 |

Values are median (range). * Mann-Whitney criterion was applied.

Table 2. Changes in heart rate (HR) during general anesthesia the dose of sedative.

| HR by 5-min intervals, bpm | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| HR 0 | 96.0 (84.0-104.0) | 76.0 (68.0-80.0) | 0.000 |
| HR 5 | 96.0 (84.0-104.0) | 80.0 (68.0-80.0) | 0.000 |
| HR 10 | 96.0 (84.0-100.0) | 80.0 (68.0-80.0) | 0.000 |
| HR 15 | 96.0 (80.0-104.0) | 76.0 (68.0-84.0) | 0.001 |
| HR 20 | 96.0 (84.0-104.0) | 76.0 (68.0-84.0) | 0.002 |
| HR 25 | 96.0 (84.0-108.0) | 76.0 (68.0-88.0) | 0.002 |
| HR 30 | 92.0 (84.0-104.0) | 76.0 (68.0-88.0) | 0.003 |
| HR 35 | 96.0 (84.0-104.0) | 76.0 (68.0-88.0) | 0.002 |
| HR 40 | 96.0 (84.0-100.0) | 76.0 (64.0-88.0) | 0.003 |
| HR 45 | 96.0 (84.0-100.0) | 76.0 (68.0-92.0) | 0.003 |
| HR 50 | 96.0 (84.0-100.0) | 76.0 (68.0-88.0) | 0.002 |
| HR 55 | 96.0 (83.0-101.0) | 76.0 (68.0-88.0) | 0.002 |

Values are median (range). * Mann-Whitney criterion was applied.

Table 3. Changes in saturation of hemoglobin with oxygen ($SpO_2$) by dose of sedative.

| $SpO_2$ by 5-min intervals, % | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| $SpO_2$ 0 | 99.0 (98.0-99.0) | 99.0 (98.0-99.0) | 0.486 |
| $SpO_2$ 5 | 99.0 (99.0-99.0) | 99.0 (98.0-99.0) | 0.045 |
| $SpO_2$ 10 | 99.0 (99.0-99.0) | 99.0 (99.0-99.0) | 0.967 |
| $SpO_2$ 15 | 99.0 (98.0-99.0) | 99.0 (98.0-99.0) | 0.512 |
| $SpO_2$ 20 | 99.0 (98.0-99.0) | 99.0 (98.0-99.0) | 0.838 |
| $SpO_2$ 25 | 99.0 (99.0-99.0) | 99.0 (98.0-99.0) | 0.174 |
| $SpO_2$ 30 | 99.0 (98.0-99.0) | 99.0 (99.0-99.0) | 0.305 |
| $SpO_2$ 35 | 99.0 (98.0-99.0) | 99.0 (98.0-99.0) | 0.683 |
| $SpO_2$ 40 | 99.0 (99.0-99.0) | 99.0 (98.0-99.0) | 0.174 |
| $SpO_2$ 45 | 99.0 (99.0-99.0) | 99.0 (98.0-99.0) | 0.041 |
| $SpO_2$ 50 | 99.0 (98.0-99.0) | 99.0 (98.0-99.0) | 0.412 |
| $SpO_2$ 55 | 99.0 (99.0-99.0) | 99.0 (98.0-99.0) | 0.880 |

Values are median (range). * Mann-Whitney criterion was applied.

Table 4. Changes in respiratory rate (RR) depending on dose of sedative.

| RR by 5-min intervals, breaths/min | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| RR 0 | 12.0 (8.0-12.0) | 10.0 (8.0-12.0) | 0.567 |
| RR 5 | 10.0 (8.0-12.0) | 12.0 (8.0-12.0) | 0.653 |
| RR 10 | 12.0 (8.0-12.0) | 12.0 (8.0-12.0) | 0.412 |
| RR 15 | 12.0 (8.0-12.0) | 12.0 (8.0-12.0) | 0.624 |
| RR 20 | 10.0 (8.0-12.0) | 12.0 (8.0-12.0) | 0.935 |
| RR 25 | 10.0 (10.0-12.0) | 12.0 (8.0-12.0) | 0.653 |
| RR 30 | 12.0 (10.0-12.0) | 12.0 (8.0-12.0) | 0.806 |
| RR 35 | 12.0 (10.0-12.0) | 12.0 (10.0-12.0) | 0.775 |
| RR 40 | 12.0 (10.0-12.0) | 12.0 (10.0-12.0) | 0.595 |
| RR 45 | 12.0 (10.0-12.0) | 12.0 (10.0-12.0) | 0.806 |
| RR 50 | 10.0 (10.0-12.0) | 12.0 (10.0-12.0) | 0.806 |
| RR 55 | 12.0 (10.0-12.0) | 12.0 (10.0-12.0) | 0.935 |

Values are median (range). * Mann-Whitney criterion was applied.

Table 5. Changes in end-tidal $CO_2$ ($EtCO_2$) by dose of sedative.

| $EtCO_2$ by 5-min intervals, mmHg | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| $EtCO_2$ 0 | 49.0 (48.0-52.0) | 49.0 (48.0-51.0) | 0.870 |
| $EtCO_2$ 5 | 48.0 (48.0-49.0) | 48.0 (48.0-50.0) | 1.000 |
| $EtCO_2$ 10 | 48.0 (48.0-49.0) | 48.0 (48.0-49.0) | 1.000 |
| $EtCO_2$ 15 | 48.0 (48.0-50.0) | 48.0 (48.0-49.0) | 0.325 |
| $EtCO_2$ 20 | 48.0 (48.0-48.0) | 49.0 (48.0-50.0) | 0.041 |
| $EtCO_2$ 25 | 48.0 (48.0-49.0) | 48.0 (48.0-50.0) | 0.539 |
| $EtCO_2$ 30 | 48.0 (48.0-49.0) | 48.0 (48.0-50.0) | 0.539 |
| $EtCO_2$ 35 | 48.0 (47.0-49.0) | 48.0 (48.0-49.0) | 0.367 |
| $EtCO_2$ 40 | 47.0 (47.0-48.0) | 48.0 (47.0-49.0) | 0.325 |
| $EtCO_2$ 45 | 48.0 (47.0-48.0) | 48.0 (47.0-50.0) | 0.412 |
| $EtCO_2$ 50 | 48.0 (47.0-48.0) | 48.0 (47.0-49.0) | 0.436 |
| $EtCO_2$ 55 | 48.0 (47.0-48.0) | 48.0 (47.0-49.0) | 0.653 |

Values are median (range). * Mann-Whitney criterion was applied.

Table 6. Changes in esophageal temperature by dose of sedative.

| Temperature by 5-min intervals, °C | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| Temperature 0 | 38.5 (38.5-38.6) | 38.5 (38.5-38.6) | 0.935 |
| Temperature 5 | 38.4 (38.4-38.5) | 38.5 (38.4-38.5) | 0.267 |
| Temperature 10 | 38.4 (38.4-38.4) | 38.4 (38.4-38.5) | 0.870 |
| Temperature 15 | 38.3 (38.3-38.4) | 38.3 (38.3-38.4) | 0.967 |
| Temperature 20 | 38.3 (38.2-38.3) | 38.3 (38.2-38.4) | 0.935 |
| Temperature 25 | 38.2 (38.2-38.3) | 38.2 (38.1-38.2) | 0.935 |
| Temperature 30 | 38.1 (38.1-38.2) | 38.1 (38.0-38.2) | 0.935 |
| Temperature 35 | 38.1 (38.0-38.1) | 38.1 (37.9-38.1) | 0.713 |
| Temperature 40 | 38.0 (37.9-38.1) | 38.0 (37.9-38.0) | 0.775 |
| Temperature 45 | 38.0 (37.9-38.0) | 37.9 (37.9-38.0) | 0.744 |
| Temperature 50 | 37.9 (37.9-38.0) | 37.9 (37.8-38.0) | 0.838 |
| Temperature 55 | 37.8 (37.8-37.9) | 37.8 (37.8-37.9) | 0.838 |

Values are median (range). * Mann-Whitney criterion was applied.

Table 7. Changes in systolic arterial blood pressure (SAP) by dose of sedative.

| SAP by 5-min intervals, mmHg | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| SAP 0 | 119.0 (115.5-126.0) | 116.0 (113.5-120.0) | 0.126 |
| SAP 5 | 117.0 (114.0-121.0) | 116.0 (114.5-119.0) | 0.744 |
| SAP 10 | 121.0 (114.0-123.0) | 115.0 (111.0-122.0) | 0.242 |
| SAP 15 | 121.0 (114.0-124.0) | 115.0 (110.5-123.5) | 0.202 |
| SAP 20 | 122.0 (115.0-124.0) | 115.0 (113.0-120.5) | 0.174 |
| SAP 25 | 115.0 (114.0-120.0) | 116.0 (112.0-120.0) | 1.000 |
| SAP 30 | 118.0 (116.0-122.0) | 119.0 (113.5-122.0) | 0.461 |
| SAP 35 | 119.0 (114.0-122.0) | 115.0 (111.0-116.0) | 0.056 |
| SAP 40 | 120.0 (111.0-122.0) | 121.0 (115.0-125.0) | 0.345 |
| SAP 45 | 120.0 (114.0-123.0) | 115.0 (112.0-123.5) | 0.325 |
| SAP 50 | 119.0 (117.0-124.0) | 115.0 (113.5-118.0) | 0.053 |
| SAP 55 | 121.0 (116.5-124.0) | 117.0 (113.5-120.0) | 0.074 |

Values are median (range). * Mann-Whitney criterion was applied.

Table 8. Changes in diastolic arterial blood pressure (DAP) by dose of sedative.

| DAP by 5-min intervals, mmHg | Group 1 (medetomidine 0.014 mg/kg + butorphanol 0.14 mg/kg) | Group 2 (medetomidine 0.024 mg/kg + butorphanol 0.24 mg/kg) | p* |
|---|---|---|---|
| DAP 0 | 79.0 (75.0-81.0) | 78.0 (72.5-82.5) | 0.653 |
| DAP 5 | 79.0 (76.5-81.5) | 75.0 (73.0-77.0) | 0.190 |
| DAP 10 | 75.0 (67.5-80.0) | 74.0 (68.0-78.0) | 0.461 |
| DAP 15 | 75.0 (75.0-78.5) | 75.0 (71.5-81.5) | 0.713 |
| DAP 20 | 75.0 (72.0-78.5) | 74.0 (72.0-78.5) | 0.870 |
| DAP 25 | 75.0 (68.5-76.0) | 77.0 (70.5-83.5) | 0.233 |
| DAP 30 | 75.0 (72.0-79.5) | 78.0 (73.5-82.5) | 0.267 |
| DAP 35 | 78.0 (73.5-81.0) | 72.0 (71.0-81.0) | 0.512 |
| DAP 40 | 77.0 (72.5-80.5) | 77.0 (70.0-80.0) | 0.806 |
| DAP 45 | 77.0 (75.0-80.0) | 78.0 (69.5-82.5) | 0.624 |
| DAP 50 | 75.0 (72.0-79.0) | 72.0 (69.5-76.5) | 0.325 |
| DAP 55 | 72.0 (71.0-76.5) | 72.0 (71.5-76.5) | 1.000 |

Values are median (range). * Mann-Whitney criterion was applied.

The time to awakening was significantly longer in group 1 than group 2 (9.6 (8.5-10.5) vs. (5.6 (5-6.5) min, $p<0.05$).

## Discussion

Experimental studies have shown many differences in cardiovascular and respiratory parameters and emergence times comparing different volatile anesthetics used during general anesthesia (Bernard et al. 1990, Merin et al. 1991, Pagel et al. 1991, Ebert et al. 1998). The dogs in this study were premedicated IM, and induction was done with an anesthetic agent IV. Premedication with medetomidine and butorphanol certainly has an influence on cardiovascular, respiratory, and recovery parameters. Propofol, as an induction agent, is short acting, with rapid metabolism, and it has been reported to have a minimal influence on emergence time and SVO % (Shafer et al. 1988, Smith et al. 1994).

The results of our study have demonstrated that a higher dose of premedication agents (medetomidine and butorphanol) had an impact on sevoflurane requirement during general anesthesia. The higher the dose of the premedication agent was, the lower the amount of inhalant anesthetic was required. SVO concentrations were significantly lower in group 2 than group 1. Due to the fact that we used a lower dose of SVO for the maintenance of anesthesia, it helped us keep the dogs' HR within the reference limits (Smith 2016). This helps the organism obtain a proper amount of oxygen and nutrition, and it could prevent oxidative stress (Parks and Granger 1986). According to the literature, one of the purposes of anesthetic premedication is to decrease volatile anesthetic requirement for the surgical procedure (White 1986). It has been reported that premedication with alpha-2 adrenoceptor agonists and opioids can improve quality of anesthesia and can reduce the required dose of volatile anesthetic agents for induction and inhalation anesthesia (Trim 1983,Murphy and Hug 1982, Glass et al. 1997, Karas 1999).

According to Girard et al. (2010), the combination of medetomidine (1 μg/kg) and butorphanol (0.1 mg/kg) IV produced a significant sedative effect compared with normal saline or medetomidine alone. In our study, the combination of medetomidine (0.024 mg/kg) and butorphanol (0.24 mg/kg) was easily applied and allowed deep sedation after the administration of drugs.

However, it has been reported that SVO causes dose-dependent hypotension, hypoventilation, impaired cardiac contractility, and hypothermia (Mutoh et al. 1997). Another study, where SVO was used for the induction and maintenance of anesthesia, has shown that MAC of SVO in younger dogs was higher (2.25% ± 0.15%) as compared with older dogs (1.86% ± 0.29%) (Yamashita et al. 2009).

In our study, we also used young dogs (age range 15 to 18 months), and because we applied sedation with medetomidine and butorphanol, the requirement of SVO was significantly lower in group 2. This means that the higher dose of premedication agents not only allowed us to use a lower amount of SVO % and to maintain HR within the reference limits, but also the dogs in this group (group 2) woke up and reacted more quickly compared with the dogs from group 1. Furthermore, the higher dose of premedication agents used in group 2 helped us control pain and anesthesia more effectively, because we could maintain general anesthesia with a significantly lower requirement of SVO % as compared with group 1. Yamashita et al. (2009) during their study did not apply sedation, and therefore they had to use a higher MAC of SVO, which resulted in mild-to-moderate cardiovascular and respiratory depressions.

For premedication, we used a lower dose of medetomidine and butorphanol in group 1, and sedation was mild as compared to group 2. As a result, the dose of propofol and requirement of SVO% was significantly greater in group 1 than group 2 during general anesthesia.

In our study, the median HR was significantly lower in group 2 compared to group 1 (77.0 vs. 96.3 bpm, $p<0.05$), but was still within the reference limits. In nonpremedicated dogs, SVO used at a MAC of 1.2 induces an increase in HR (Bernard et al. 1990, Mutoh et al. 1997). Activation of the baroreceptor-reflex, induced by decreased arterial blood pressure, has been reported to be mainly responsible for this rise in HR (Merin et al. 1991).

Under general anesthesia, a HR of <55-60 bpm in most dogs would be considered too slow. Normal resting physiologic reference limits for HR in dogs is 60-120 bpm. Normally, dogs that received alpha-2 agonists and opioids are expected to be bradycardic due to the effects of these agents (Smith 2016). In our study, we managed to maintain HR within the reference limits during general anesthesia. Most opioids have minimal effects on cardiac output, cardiac rhythm, and arterial blood pressure when clinically relevant analgesic doses are administered. Bradycardia may be caused by opioid-induced medullary vagal stimulation (Grim et al. 2011). The doses administered in our study were lower than analgesic doses and we can speculate that if HR is within the reference limits, it means that the organism gets a proper amount of oxygen and it helps minimize oxidative stress after anesthesia. It is well

known that under hypoxic conditions the organism undergoes greater oxidative stress after general anesthesia and this can affect wound healing (El-Bassiouni et al. 1998).

All volatile anesthetic agents cause a dose-related respiratory depression in dogs. This decrease in the RR results in hypoventilation with increasing $EtCO_2$ mmHg (Doi et al. 1987, Mutoh et al. 1997). In our study, the RR decreased and $EtCO_2$ mmHg increased in both groups, but it was not significant between the groups probably because of the fact that the difference in the requirement of SVO % between the groups was not high.

Volatile anesthetic agents induce a dose-related decrease in arterial blood pressure (Steffey and Howland 1977, Frink et al. 1992). This decrease in blood pressure is partly caused by decreased peripheral vascular resistance and partly by a decrease in stroke volume (Malan et al. 1995, Lowe et al. 1996, Mutoh et al. 1997). In our study, SAP and DAP were within the reference limits, probably because we used intravenous fluids according to the protocol.

Inhalation anesthetic recovery is mostly influenced by the blood-gas partition coefficient of the anesthetic agent (Strum and Eger 1987, Steffey 1996). Other factors such as alveolar ventilation, cardiac output, and duration of anesthesia also have an influence on recovery from inhalation anesthesia (Stoelting and Eger 1969, Carpenter et al. 1987).

One of the possible parameters for evaluation of anesthesia recovery in dogs is the swallowing reflex. In our study, the dogs restored the swallowing reflex more quickly in group 2 compared to group 1, probably because the SVO % used in group 2 was lower than in group 1. It has been reported in rodents that the differences in times to recovery endpoints between anesthetics are smaller when low concentrations of anesthetics are used (Eger and Johnson 1987).

## Conclusions

The higher dose of medetomidine and butorphanol allows the use of a lower sevoflurane concentration during routine surgical treatments and ensures stable work of the cardiovascular and respiratory systems.

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