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Comparison of Isoflurane and Sevoflurane Anesthesia in Holstein Calves for Placement of Portal and Jugular Vein Cannulas

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ABSTRACT

Isoflurane and sevoflurane are the two most commonly used inhalation anesthetics in veterinary medicine today. This study compared the anesthetic effects between isoflurane and sevoflurane in 17 calves undergoing surgery for placement of portal and jugular vein cannulas. Using a randomized control trial, calves were assigned to receive sevoflurane or isoflurane. Anesthesia was induced with xylazine and ketamine then maintained with the assigned inhalation anesthetic. Parameters for heart rate, respiratory rate, indirect blood pressures, oxygen hemoglobin saturation and end-tidal carbon dioxide were monitored and recorded during surgery. The anesthetic concentrations of the vaporizers were adjusted according to the calves' responses, e.g., blood pressure, eye position, respiratory and heart rate, to surgical stimulation. Upon discontinuation of the inhalation anesthetic, calves were placed in sternal recumbency and recovery variables including time to extubation, time to first movement, attempts to stand and time to standing were observed and recorded. Statistical analysis was performed using a two-sample t-test on the recorded variables. There were no statistical differences between isoflurane and sevoflurane for any of the parameters recorded during anesthetic maintenance or recovery. The results of this study showed a faster time to first movement and extubation, 3.38±1.85 min and 11.75±3.73 min for sevoflurane compared to 7.56±5.34 min and 15.56±8.69 min for isoflurane, respectively. Attempts to stand were 3.00±2.14 for sevoflurane and 3.22±1.79 for isoflurane. Though the time to standing during recovery was not statistically different between anesthetics, the values did indicate a quicker trend of recovery from sevoflurane. Both inhalation anesthetics produced comparable anesthetic qualities and there were no statistical differences between the parameters recorded during maintenance of anesthesia. On the basis of the reported results, sevoflurane and isoflurane are suitable inhalation anesthetics for use in calves. However, present cost of sevoflurane is a limiting factor for its use in food animals.

Keywords: Anesthesia, Sevoflurane, Isoflurane, Inhalation, Cattle

1. INTRODUCTION

Isoflurane and sevoflurane are the two most commonly used inhalation anesthetics in veterinary medicine today. Isoflurane exists as a clear nonflammable, halogenated methyl ethyl ether with a blood-gas partition coefficient of 1.46 (Steffey and Mama, 2007; Stoelting, 1999). Sevoflurane is nonflammable, fluorinated methyl isopropyl ether with a lower blood-gas partition coefficient of 0.68 (Steffey and Mama, 2007; Stoelting, 1999). The blood-gas partition coefficient represents the partial pressure or solubility of an anesthetic between blood and gas at equilibrium. The higher the value of blood-gas partition coefficient, the

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greater the solubility of an anesthetic in the blood and vice versa, the lower the value, the lower the blood solubility of the anesthetic. The substitution of a fluorine for chlorine in sevoflurane decreases its blood solubility and hence a lower blood-gas partition coefficient which allows a more rapid increase in alveolar anesthetic concentration during induction and a faster decrease during recovery, thus shorter anesthetic induction and recovery times (Johnson *et al*., 1998; Kazama and Ikeda, 1988; Mutoh *et al*., 1995; Steffey and Mama, 2007; Stoelting, 1999). In addition, a lower partition coefficient allows for a faster change of the anesthetic depth which greatly increases the safety of anesthesia.

The cardiovascular effects of sevoflurane are reportedly similar to isoflurane where both anesthetics cause dose dependent decreases in blood pressure, cardiac output and systemic vascular resistance in humans, dogs, horses, goats and sheep (Aida *et al*., 1996; Ebert *et al*., 1995; Hikasa *et al*., 1998; 2000; Mutoh *et al*., 1997). An increase in heart rate has been reported in dogs (Bernard *et al*., 1990; Ebert *et al*., 1995; Mutoh *et al*., 1997) whereas it remained unchanged in humans, sheep and goats (Ebert *et al*., 1995; Hikasa *et al*., 1998; 2000) during sevoflurane anesthesia. At 1 Minimum Alveolar Concentration (MAC), both sevoflurane and isoflurane cause a dose dependent decrease in respiratory rate and an increase in end-tidal partial pressures of carbon dioxide (PETCO2) in dogs, sheep and goats (Galloway *et al*., 2004; Hikasa *et al*., 1998; 2000; Johnson *et al*., 1998; Mutoh *et al*., 1997). Sevoflurane has the advantage of causing less airway mucosa irritation than isoflurane in humans, particularly during mask induction (Doi and Ikeda, 1993).

Sevoflurane has been reported to be a safe and effective inhalation anesthetic in adult cattle with a rapid and smooth recovery (Hikasa *et al*., 1994). However, because the high cost of sevoflurane, isoflurane is more frequently used in farm animal practice. The purpose of this study was to compare the anesthetic effects of isoflurane and sevoflurane in calves undergoing surgery for placement of portal and jugular vein cannulas.

2. MATERIALS AND METHODS

2.1. Calves

Seventeen healthy Holstein steer calves with a mean body weight of 279.94 ± 36.06 kg were utilized in this study. The project was approved by the Auburn University Institutional Animal Care and Use Committee. The calves were anesthetized for surgical placement of portal and jugular vein cannulas for research purposes. Feed and water were withheld for 24 and 12 h, respectively, prior to anesthesia to minimize the potential for bloat, regurgitation and aspiration pneumonia. All calves received 2.2 mg/kg of ceftiofur sodium (Naxcel®, Pharmacia and Upjohn Co., Pfizer Inc., New York, NY) intravenously, prior to surgery. For induction of anesthesia and administration of fluid therapy during surgery, a 14 gauge, 140 mm catheter (Abbocath, Hospira, Inc., Lake Forest, IL) was placed aseptically in the right jugular vein before surgery.

2.2. Induction and Anesthetic Equipment

Anesthesia was induced with a bolus administration of 0.11 mg/kg of xylazine (AnaSed®, Lloyd Laboratories, Shenandoah, IA) and 2.2 mg/kg of ketamine (Ketaset®, Fort Dodge Labs, Inc, Ft. Dodge, IA) intravenously via the jugular catheter. The calves were maintained in sternal recumbency for tracheal intubation and then placed in left lateral recumbency for the surgical procedure. Anesthesia was maintained with either isoflurane or sevoflurane in oxygen via a semi-closed circle breathing system. Calves were maintained on spontaneous ventilation, although a manual breath (sigh) by compressing the rebreathing bag was provided every 3 to 5 min at a pressure of 20 cm of H2O to ensure appropriate ventilation. The anesthetic concentrations of the vaporizers were adjusted according to the calves' responses, e.g., blood pressure, eye position, respiratory and heart rate, to surgical stimulation. A balanced electrolyte solution (Veterinary Plasma-lyte A, Abbott Laboratories, North Chicago, IL) was administered continuously through the jugular catheter at a rate of 10 mL/kg/ h for the duration of the anesthesia.

2.3. Experimental Design and Surgical Procedure

Calves were assigned at random to either isoflurane (Attane™, Piramal Critical Care, Bethlehem, PA) or sevoflurane (SevoFlo™, Abbott Laboratories, Chicago, IL) groups. Portal vein cannulation was performed in all calves. Aseptic techniques were used during the laparotomy and placement of the portal vein cannulas. A 30-cm abdominal incision was made at a location approximately 4 cm caudal to the 13th rib and 5 cm ventral to the first lumbar vertebra. The skin incision followed the costal arch and the underlying muscle layers and peritoneum were incised individually to access the peritoneal cavity. The portal vein was identified in the omasal impression region between the left and quadrate lobes of the liver. Using blunt dissection, the hepatic lymph node was displaced in order to visualize and gain access to the portal vein. Using a 3 cm, 16-gauge peel-away introducer needle, a

16-gauge, 120 cm polyurethane catheter (Mila International, Inc., Erlanger, KY) was placed in the hepatic portal vein at the level of the porta hepatis. The tip of the catheter was positioned in close proximity to where the portal vein enters the liver permitting blood sampling from the entire splanchnic circulation. The portal catheter was maintained in place with adjustable sutures and suture wings placed along the lateral surface of the portal vein and the omentum surrounding the pancreas and duodenum. The catheter was exteriorized in the dorsolumbar region between the transverse processes of the 2nd and 3rd lumbar vertebra. A nylon purse-string suture secured the catheter at the exit site. The laparotomy incision was closed in routine fashion: with the peritoneum and transverse abdominal muscle closed together using #2 chromic gut in a continuous pattern; internal and external abdominal oblique muscles closed using #2 chromic gut in a continuous pattern; and skin closed using #2 Nylon in a Ford interlocking pattern.

2.4. Data Collection and Measurements

All parameters were collected using a Surgivet Advisor Monitor (Smiths Medical PM, Inc., Waukesha, WI). Heart Rate (HR), Respiratory Rate (RR), systolic, mean and diastolic arterial blood pressures (SAP, MAP and DAP, respectively), end-tidal partial pressure carbon dioxide (PETCO2) and oxygen hemoglobin Saturation (SpO2) were monitored continuously and the values recorded at time 0 (baseline), which was immediately following induction with xylazine and ketamine and 10, 20, 40, 60 and 80 min during maintenance with isoflurane or sevoflurane. HR and Electrocardiogram (ECG) were monitored using a multi-functional electrocardiograph via hookup to Einthoven's triangle. SAP, MAP and DAP were measured by a non-invasive oscillometric cuff placed over the coccygeal artery at the base of the tail. RR was determined by movement of rebreathing bag and/or chest movement. The PETCO2 was measured by an infrared gas analysis with as ample line placed at the tip of the Y piece. The PETCO2 monitor is calibrated monthly. SpO2 was measured by means of a pulse oximetry placed on the lingual artery. The time to extubation, time to first movement, attempts to stand and time to standing were observed and recorded after discontinuation of the anesthetic.

2.5. Statistical Analysis

All data was analyzed for normality using a normality probability plot test using Minitab® (Minitab®, Minitab Inc., State College, PA). A paired T test was then performed on the data using Minitab®. Values of $P < 0.05$ were considered significant.

3. RESULTS

All the parameters in this study were expressed as mean ± SD. All data analyzed fit the trend lines on the probability plot therefore it was considered normal. There were no significant differences for HR, RR, SpO2, PETCO2, SAP, MAP and DAP between isoflurane and sevoflurane during surgery (**Table 1**).

Table 1. Maintenance/monitored variables comparing isoflurane (Iso) vs. sevoflurane (Sevo) in Holstein calves undergoing surgery for portal cannula placement

	ISO					
Minutes of anesthesia	0	10	20	40	60	80
Variable						
Heart rate (beats/min)	60.10± 10.10	71.22± 4.87	72.00 ± 8.77	68.33 ± 9.01	69.40 ± 10.80	72.00 ± 13.70
Respiratory rate (breaths/min)	48.20 ± 14.00	46.10 ± 13.40	40.60 ± 17.70	37.70 ± 18.20	39.30 ± 12.60	40.00 ± 7.94
Oxygen hemoglobin saturation (%HbSat)	96.60 ± 2.46	95.60 ± 3.95	95.90 ± 3.51	94.80 ± 6.41	94.50 ± 6.84	95.63 ± 4.44
End-tidal CO^2 (mm Hg)	22.38 ± 8.30	30.00 ± 7.45	31.75 ± 8.53	35.80 ± 13.00	34.10 ± 10.10	35.30 ± 12.50
Systolic blood pressure (mm Hg)	116.40 ± 11.40	104.30 ± 13.10	97.80 ± 11.10	103.30 ± 15.50	106.10 ± 13.80	112.10 ± 10.40
Mean blood pressure (mm Hg)	91.80 ± 20.10	77.80 ± 17.20	69.56 ± 8.00	86.20 ± 19.20	91.90 ± 16.70	95.30 ± 17.80
Diastolic blood pressure (mm Hg)	82.70 ± 14.80	68.30 ± 16.40	55.33 ± 4.80	67.20 ± 16.00	75.80 ± 11.60	75.11 ± 8.68
Sevo						
Variable						
Heart rate (beats/min)	63.1± 16.30	72.38 ± 8.98	70.75 ± 7.57	69.75 ± 07.55	67.00 ± 8.00	67.70 ± 10.00
Respiratory rate (breaths/min)	34.60 ± 21.20	35.00 ± 18.90	46.71 ± 7.95	39.30 ± 10.80	42.86 ± 8.05	44.33 ± 6.43
Oxygen hemoglobin saturation (%HbSat)	94.88 ± 4.45	97.00 ± 2.07	96.13 ± 3.60	98.38 ± 1.19	96.38 ± 2.39	98.00 ± 1.00
End-tidal CO^2 (mm Hg)	31.10 ± 13.00	37.38 ± 9.35	30.90 ± 11.80	38.50 ± 10.10	43.25 ± 7.67	43.33 ± 7.57
Systolic blood pressure (mm Hg)	113.40 ± 12.10	96.50 ± 18.40	93.30 ± 16.70	106.10 ± 14.00	117.40 ± 15.10	120.60 ± 14.40
Mean blood pressure (mm Hg)	89.00 ± 10.30	75.90 ± 19.10	73.90 ± 14.90	85.10 ± 13.40	98.60 ± 18.50	96.00 ± 8.76
Diastolic blood pressure (mm Hg)	81.40 ± 15.10	64.50 ± 19.80	58.40 ± 12.90	69.30 ± 10.90	80.60 ± 20.50	82.50 ± 16.80

Table 2. Anesthesia recovery data comparing isoflurane (Iso) vs. Sevoflurane (Sevo) in Holstein calves undergoing surgery for portal cannula placement

	ISO	SEVO	*SEVO minus calf 70
Time to first movement (minutes)	7.56 ± 5.34	3.38 ± 1.85	3.57 ± 1.90
Time to extubation (minutes)	15.56 ± 8.69	11.75 ± 3.73	12.57 ± 3.15
Time to standing (minutes)	47.20 ± 29.00	53.90 ± 61.90	32.70 ± 17.30
Attempts to stand (number of attempts)	3.22 ± 1.79	3.00 ± 2.14	2.29 ± 0.75

* Corrected sevoflurane data minus calf #70. Calf 70 removed from data for post-surgical hemorrhage complication.

There was no statistical difference for the time to standing during recovery between isoflurane and sevoflurane (**Table 2**). The results of this study showed a faster time to first movement (3.38±1.85 min for sevoflurane vs. 7.56±5.34 min for isoflurane) (**Table 2**) and time to extubation (11.75±3.73 min for sevoflurane vs. 15.56±8.69 min for isoflurane) (**Table 2**). Once the anesthetic was discontinued, the number of attempts to stand was 3.00±2.14 for sevoflurane and 3.22±1.79 for isoflurane (**Table 2**). Though the time to standing during recovery was not statistically different between isoflurane and sevoflurane (47.20±29.00 min for isoflurane vs. 53.90±61.90 min for sevoflurane) (**Table** 2), with sevoflurane having a longer time to standing. These values are misleading due to an abnormally long recovery in one calf (calf #70) due to a post-surgical hemorrhage complication. Removal of calf 70 improved the standing time to 32.70±17.30 min for sevoflurane (**Table 2**). These values did indicate a trend that recovery from sevoflurane was faster than isoflurane as supported by the faster time to first movement, time to extubation and standing time (**Table 2**).

4. DISCUSSION

Isoflurane is the most widely used inhalation anesthetic in veterinary practice today, with sevoflurane gaining popularity especially in small animals. Clinically, the lower blood-gas partition coefficient of sevoflurane has been shown in dogs to result in a more rapid increase in alveolar anesthetic concentration during induction and decrease during recovery, as reflected in a faster induction and quicker recovery (Johnson *et al*., 1998; Kazama and Ikeda, 1988; Mutoh *et al*., 1995). Sevoflurane has been reported to be an effective inhalation anesthetic in adult cattle with a rapid and smooth recovery (Hikasa *et al*., 1994).

The cardiovascular effects of sevoflurane are reportedly similar to isoflurane where both anesthetics cause dose dependent decreases in blood pressure, cardiac output and systemic vascular resistance in humans, dogs, horses, sheep and goats (Aida *et al*., 1996; Ebert *et al*., 1995; Hikasa *et al*., 1998; 2000; Mutoh *et al*., 1997; Steffey and Mama, 2007; Stoelting, 1999). In awake cattle, normal HR and MAP have been reported to range from 60-80 beats per min with a pressure range of 90-140 mm Hg, respectively (Muir *et al*., 2007). Results from this study showed no statistical differences in SAP, MAP or DAP between the two anesthetics. Between 0 and 20 min, following the administration of isoflurane and sevoflurane anesthetics, the SAP, MAP and DAP all decreased. This is thought to be due to absence of surgical stimulation and the wearing off of the induction drugs, xylazine and ketamine. The surgical procedure started at approximately 30 min following the induction drugs. At 40 min, post induction, both anesthetics showed similar increases in SAP, MAP and DAP, which is believed to be a response to the surgical stimulation. Close analysis of the data in this study shows that the values of blood pressures for both anesthetics were similar throughout the surgery. A decrease in blood pressure, cardiac output and systemic vascular resistance can cause an increase in HR due to baroreceptor reflex (Stoelting, 1999). Several studies indicated an increase in heart rate in dogs (Bernard *et al*., 1990; Ebert *et al*., 1995; Mutoh *et al*., 1997) whereas heart rate remained unchanged in humans, sheep and goats (Ebert *et al*., 1995; Hikasa *et al*., 1998; 2000) during sevoflurane anesthesia. In dogs, it has been suggested that the differences in vagolytic activity of the inhalation anesthetics is responsible for the increase in HR observed (Steffey and Mama, 2007). In horses HR increased as the concentration of sevoflurane increased above 1 MAC, but the differences were not significant (Aida *et al*., 1996). In the present study, heart rate remained steady throughout the surgery and there was no statistical differences noted between sevoflurane and isoflurane. No hematological or serum chemistry profile analysis were performed in this study. However, no significant differences were observed in the blood work of sheep (Hikasa *et al*., 2000) receiving isoflurane or sevoflurane.

Sevoflurane and isoflurane have been reported to cause similar dose-dependent respiratory effects

characterized by a decrease in RR and an increase in PETCO2 in dogs, horses and goats when maintained at 1 MAC (Aida *et al*., 1996; Galloway *et al*., 2004; Hikasa *et al*., 1998; Johnson *et al*., 1998; Mutoh *et al*., 1997). In ruminants, positioning in lateral recumbency (Fujimoto and Lenehan, 1985) and bloating due to continuous ruminal fermentation during anesthesia has been shown to impair ventilation (Lin and Pugh, 2012). These factors may contribute to higher levels of PETCO2, respiratory acidosis and lower SpO2. In the present study, neither isoflurane nor sevoflurane caused significant effects on RR nor was there a significant difference on RR between the two anesthetics. Although an increase in PETCO2 levels were observed during surgery with sevoflurane and isoflurane calves with the values for sevoflurane being slightly higher than that for isoflurane, these values were not statistically significant. These findings in calves are similar to those reported in sheep (Hikasa *et al*., 2000). The SpO2 concentration was slightly higher for sevoflurane than isoflurane but both were within normal reference ranges.

In previous studies, the duration of recovery to standing has always been shorter with sevoflurane than with isoflurane in horses, sheep and dogs (Hikasa *et al*., 2000; Johnson *et al*., 1998; Matthews *et al*., 1998). Recovery quality of sevoflurane has been reported as comparable to or better than isoflurane in dogs and horses (Johnson *et al*., 1998; Matthews *et al*., 1998). Although this study found no statistical difference in the time to first movement, time to extubation, time to standing or attempts to stand between the two anesthetics, sevoflurane anesthetized calves appeared to awaken from anesthesia faster as indicated by the less time to first movement and extubation.

Calf #70, anesthetized with sevoflurane, had an abnormally prolonged recovery time as a result of a dislodged portal vein cannula, which led to excess blood loss and muscle weakness. A balanced electrolyte solution (Veterinary Plasma-lyte A, Abbott Laboratories, North Chicago, IL) was administered to offset the blood loss and the calf recovered and stood in 197 min after removal of the endotracheal tube. When calf #70 is excluded from the data, time to standing and attempts to stand drastically improved over isoflurane. Treating calf #70 as an outlier and removing it from the sevoflurane group and statistical analyzed data, sevoflurane calves had faster recovery time to standing and less attempts to stand (32.70±17.30 min and 2.29±0.75 attempts) than isoflurane calves (47.20±29.00 min and 3.22±1.79 attempts), though the differences were not statistically significant (**Table 2**).

Sevoflurane has a number of advantages over isoflurane. Sevoflurane has a lower blood-gas partition coefficient of 0.68 compared to 1.46 for isoflurane (Steffey and Mama, 2007; Stoelting, 1999). This lower blood solubility allows for a rapid induction of and recovery from anesthesia and rapid anesthetic depth changes, which greatly increases the safety of anesthesia for large animal patients. Possible disadvantages of sevoflurane over isoflurane include the possibility of nephrotoxicity and higher cost. Sevoflurane has also been reported to cause less airway mucosa irritation than isoflurane in humans, particularly if mask induction is used (Doi and Ikeda, 1993).

Dry CO2 absorbents can degrade isoflurane to carbon monoxide (CO) and sevoflurane to a vinyl ether (fluoromethyl-2,2-difluoro-1-9trifluoromethyl) also known as compound A (Higuchi *et al*., 2000; Kenna and Jones, 1995; Stoelting, 1999). Potassium hydroxide (KOH) and sodium hydroxide (NaOH), primary components of CO2 absorbents, have been identified as major determinants in the production of CO and compound A (Higuchi *et al*., 2000). Rats appear to be especially sensitive to the nephrotoxic effects of compound A, while humans are at relatively low risk (Kenna and Jones, 1995). Dogs anesthetized with 4% to 5% sevoflurane in 500 mL per min oxygen (O2) flow for 3 h sessions did not produce concentrations of compound A associated with renal toxicity, as evidenced by changes in serum biochemistry and urinalysis (Wallin *et al*., 1975). When using a rebreathing system, the risk of compound A induced nephrotoxicity can be reduced by using an O2 flow rate higher than the animal's metabolic requirement in order to dilute and flush out compound A from the breathing system (Muir and Gadawski, 1998; Stoelting, 1999). The calves in this study were maintained on a semi-closed rebreathing system using an O2 flow rate that is three times the O2 metabolic requirement. Other options include using newer CO2 absorbents, Amsorb® (Armstrong Medical, Coleraine, Northern Ireland), which contains neither KOH nor NaOH, Drägersorb 800 plus® (Dräger, Luebeck, Germany) and Medisorb® (Datex-Ohmeda, Bromma, Sweden) which contain minimal amounts of NaOH (1-2%) and trace amounts of KOH (0.003%) (Higuchi *et al*., 2000).

The higher cost of Sevoflurane is also a disadvantage, especially in production animals. At present, sevoflurane cost seven times that of isoflurane per mL. Sevoflurane also has a lower potency when

compared to isoflurane. The MAC reported for sevoflurane is 2.25% compared to 1.5% for isoflurane in sheep and goats (Antognini and Eisele, 1993; Mohamadnia *et al*., 2008), which is 0.75% or 1.67 times higher MAC requirement for sevoflurane than isoflurane. This higher MAC, for anesthetic maintenance plus the higher cost per mL for the anesthetic obviously lead to a higher overall anesthesia cost. In production animals, added costs affect producer profitability, which are already small on a per animal basis.

5. CONCLUSION

This study indicates that sevoflurane and isoflurane are both suitable inhalation anesthetics for the maintenance of general anesthesia in Holstein calves undergoing elective surgery. The results of the study showed no statistically significant differences in cardiovascular or respiratory effects when comparing sevoflurane to isoflurane, which are consistent with previous reports in dogs, sheep, goats, humans and horses (Aida *et al*., 1996; Ebert *et al*., 1995; Hikasa *et al*., 1998; 2000; Matthews *et al*., 1998; Mutoh *et al*., 1997). Attempts to stand and recovery times appeared to occur faster for sevoflurane upon review of the data, although not statistically significant. Sevoflurane appears to have a slight advantage over isoflurane in the recovery phase of anesthesia but, at present, that advantage may be overcome by the higher cost of the drug in production animals.

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