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## Effects of the morphine-lidocaine-ketamine combination on cardiopulmonary function and isoflurane sparing in sheep

### Efeito da associação de morfina-lidocaína-ketamina sobre a função cardiopulmonar e concentração expirada de Isoflurano em ovelhas

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#### Abstract

The aims of this study were to evaluate the isoflurane sparing and clinical effects of a constant rate infusion of morphine – lidocaine – ketamine (MLK) in healthy sheep undergoing experimental gastrointestinal surgery. Twelve adult female sheep (Texel breed) were used, weighing  $36.5 \pm 8.1$  kg. The sheep were anesthetized for the implantation of duodenal cannulas. The sheep were premedicated with  $0.3 \text{ mg kg}^{-1}$  intramuscular (IM) morphine and  $20 \text{ } \mu\text{g kg}^{-1}$  intravenous (IV) detomidine. After premedication, anesthesia was induced using  $5 \text{ mg kg}^{-1}$  ketamine and  $0.5 \text{ mg kg}^{-1}$  diazepam IV and maintained using isoflurane in 100% oxygen. After the induction of anesthesia, the animals were allocated into two groups (each  $n=6$ ); the GMLK (MLK group –  $10 \text{ mg}$  morphine,  $150 \text{ mg}$  lidocaine,  $30 \text{ mg}$  de ketamine were added in  $500 \text{ mL}$  saline) received a  $10 \text{ mL kg}^{-1}\text{h}^{-1}$  MLK infusion during the maintenance of anesthesia, and GCON (control group) received  $10 \text{ mL kg}^{-1}\text{h}^{-1}$  of  $0.9\%$  sodium chloride. The animals were mechanically ventilated. Cardiopulmonary variables and end-tidal isoflurane concentration (FE'Iso) were measured at baseline (immediately before the surgery) and 15, 30 and 45 minutes after initiation of surgery. In GMLK, there was a decrease in the FE'Iso at 15, 30 and 45 minutes, a reduction of up to  $75.6\%$  during the surgery. The HR was lower in GMLK compared with GCON at 30 minutes, and the MAP was at during baseline in GCON compared with GMLK. The standing time was less in GMLK than in GCON. The use of intravenous MLK was demonstrated to offer great efficiency as part of a balanced anesthesia protocol in sheep, with a  $75.6\%$  reduction in the need for isoflurane, providing stability of the cardiovascular parameters and blood gases with a shortened recovery period.

**Key words:** Sheep, morphine, lidocaine, ketamine, isoflurane

#### Resumo

Os objetivos deste estudo foram avaliar a redução na concentração expirada de isoflurano, bem como os efeitos clínicos de uma infusão constante de morfina – lidocaína – cetamina (MLK) em ovinos saudáveis submetidos a cirurgia gastrointestinal experimental. Foram utilizados doze ovinos adultos da raça Texel, fêmeas, pesando  $36,5 \pm 8,1$  kg. Os animais foram anestesiados para implantação de cânulas no duodeno, sendo pré-medicados com morfina  $0,3 \text{ mg kg}^{-1}$ , pela via intramuscular (IM), e detomidina  $20 \text{ } \mu\text{g kg}^{-1}$  pela via intravenosa (IV). Após a pré-medicação, a anestesia foi induzida com cetamina  $5 \text{ mg kg}^{-1}$  e diazepam  $0,5 \text{ mg kg}^{-1}$  IV, sendo mantidos com isoflurano em oxigênio a  $100\%$ . Após a indução da

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anestesia os animais foram divididos em dois grupos (n = 6): GMLK (grupo MLK – 10 mg de morfina, 150 mg de lidocaína e 30 mg de cetamina foram adicionados em 500 ml de solução salina) que recebeu infusão contínua de MLK na taxa de 10 mL kg<sup>-1</sup>h<sup>-1</sup> durante a manutenção da anestesia; e o GCON (grupo de controle) que recebeu infusão contínua de cloreto de sódio a 0,9% na taxa de 10 mL kg<sup>-1</sup>h<sup>-1</sup> durante a manutenção da anestesia. Os animais foram submetidos à ventilação mecânica. As variáveis cardiopulmonares e concentração de isoflurano ao final da expiração (FE'Iso) foram avaliados durante o momento basal (imediatamente antes da cirurgia), e 15, 30 e 45 minutos após o início da cirurgia. Em GMLK ocorreu uma redução na FE'Iso aos 15, 30 e 45 minutos, sendo observada redução de até 75,6 % durante a cirurgia. A FC foi menor no GMLK em comparação ao GCON aos 30 minutos, e a PAM foi menor no momento basal no GCON em relação ao GMLK. O tempo de recuperação total foi menor no GMLK. O uso da infusão contínua intravenosa da solução MLK mostrou ser eficiente como parte de um protocolo de anestesia balanceada em ovinos, com uma redução de 75,6 % na concentração expirada de isoflurano, proporcionando estabilidade cardiovascular e com um período de recuperação reduzido.

**Palavras-chave:** Ovino, morfina, lidocaína, cetamina, isoflurano

## Introduction

The use of continuous rate infusions for analgesia and for the reduction of other anesthetics in a balanced anesthesia protocol for ruminants has not been explored fully. The combination of anesthetic drugs for continuous rate infusion is advantageous because it reduces the need for inhaled anesthetics for analgesia while promoting transoperative, postoperative and synergistic effects through various mechanisms of action, all without causing significant hemodynamic changes (MUIR; WIESE; MARCH, 2003).

The use of morphine by continuous infusion at a rate of 3.3 µg kg<sup>-1</sup>minute<sup>-1</sup> can reduce the isoflurane MAC in dogs by up to 48% (MUIR; WIESE; MARCH, 2003). Intravenous lidocaine has been used to supplement general anesthesia and to decrease postoperative pain when administered during the preoperative period (KOPPERT et al., 2004). In calves, the end-tidal concentration of isoflurane was significantly lower in groups treated with 50 µg kg<sup>-1</sup> minute<sup>-1</sup> lidocaine, representing a 16.7% reduction in anesthetic requirement during lidocaine CRI (VESAL et al., 2011).

According to Valverde et al. (2004), dogs anesthetized with isoflurane while receiving a continuous infusion of lidocaine at rates of 50 and 200 µg kg<sup>-1</sup> minute<sup>-1</sup> required 18.7 and 43.3% less halogenated agent, respectively. Another study in calves reported that lidocaine causes a decrease

in heart rate that is unlikely to be of clinical significance in healthy animals but could be a concern in compromised animals (ARAÚJO et al., 2014).

Ketamine possesses analgesic and anesthetic properties at subanesthetic doses via its antagonism of N-methyl-D-aspartate (NMDA) receptors. Ketamine administered at a rate of 50 µg kg<sup>-1</sup> minute<sup>-1</sup> reduces the MAC of isoflurane by 49.6% in goats (DOHERTY et al., 2007). In sheep, another study observed that administering 10 µg kg<sup>-1</sup> minute<sup>-1</sup> ketamine and 20 µg kg<sup>-1</sup> minute<sup>-1</sup> lidocaine in IV fluids to sheep during orthopedic surgery decreased the required concentration of isoflurane by 23% while still providing sufficient anesthesia (RASKE et al., 2010). The combination of lidocaine (100 µg kg<sup>-1</sup> minute<sup>-1</sup>) and ketamine (50 µg kg<sup>-1</sup> minute<sup>-1</sup>) reduced the MAC of sevoflurane by 62.8% in dogs (WILSON et al., 2008), whereas administering a similar course of drugs in goats led to a 69.4% decrease (DOHERTY et al., 2007). However, there are no reports or studies that have examined the association of morphine-lidocaine-ketamine (MLK) in ruminants. The objective of this study was to evaluate the isoflurane-sparing and cardiovascular and respiratory effects of a constant rate infusion of morphine, ketamine and lidocaine in sheep undergoing gastrointestinal surgery.

We hypothesized that a constant rate infusion of morphine, ketamine and lidocaine would decrease

the amount of required isoflurane when compared with the control group.

## Material and Methods

This study was approved by the Ethics and Animal Care (CETEA/CAV) committee with protocol number 1.24/10. A total of 12 adult Texel breed sheep, with an average weight of  $36.5 \pm 8.1$  kg, were included. The health status of the sheep was assessed by physical examination and laboratory screening (complete blood cell count). All of the laboratory values were within reference ranges. The animals were acclimated (during one week before the experimental procedure) and maintained in individual pens with access to water and commercial feed *ad libitum*. Before each experimental procedure, food and water were withheld for 24 and 6 hours, respectively.

### Experimental design

For each sheep, the experiment was conducted during a single anesthetic procedure. The premedication was performed with  $0.3 \text{ mg kg}^{-1}$  morphine (Dimorf®;  $10 \text{ mg mL}^{-1}$ , Cristália, BR) intramuscularly (IM), and after 20 minutes,  $20 \mu\text{g kg}^{-1}$  detomidine (Dormiun®;  $5 \text{ mg mL}^{-1}$ , Agener, BR) was administered intravenously (IV). After the detomidine, a 16-G catheter (Angiocath®; BD Medical Ltd., BR) was placed percutaneously at the jugular, and the animals were induced using ketamine (Vetaset®;  $100 \text{ mg mL}^{-1}$ , Fort Dodge Animal Healthy,  $5 \text{ mg kg}^{-1}$ ) in combination with diazepam (Valium®;  $5 \text{ mg mL}^{-1}$ , Roche, BR,  $0.5 \text{ mg kg}^{-1}$ ) administered intravenously over a period of 1 minute. Following the induction of anesthesia, each sheep was intubated, and the endotracheal tube was connected to a circle system with 100% oxygen during the first 15 minutes at a rate of  $40 \text{ mL kg}^{-1} \text{ minute}^{-1}$  and subsequently at a rate of  $20 \text{ mL kg}^{-1} \text{ minute}^{-1}$  for the remainder of anesthesia. Anesthesia was maintained with isoflurane (Isoforine®;

Cristália São Paulo, BR) using a calibrated vaporizer (Forane; Yorkshire, UK). The vaporizer setting was adjusted to maintain a moderate depth of anesthesia, including the absence of palpebral reflexes, the absence of jaw tone and the absence of movement in response to surgical stimulation as well as an appropriate blood pressure (MAP from 60 to 90 mmHg) and heart rate (from 60 to 90 bpm). Each animal was mechanically ventilated to a peak inspiratory pressure and respiratory rate between 10 to 15 cm H<sub>2</sub>O and 8 to 15 breaths min<sup>-1</sup>, respectively, while the inspiration-to-expiration ratio was held constant (1:2) to maintain a PE'CO<sub>2</sub> concentration at 35 to 45 mm Hg. The sheep was positioned in dorsal recumbency. Samples of the airway gases were collected continuously by a monitor (DX2010, Dixtal Medical, Manaus, BR) at a constant rate ( $200 \text{ mL min}^{-1}$ ), and an infrared gas analyzer was used to monitor the FE'Iso and PE'CO<sub>2</sub> concentrations.

A 22-G catheter (BD Medical, BR) was placed in the medial branch of the rostral auricular artery, and the direct arterial blood pressure was measured to determine the mean arterial pressure (MAP) and to collect blood samples to determine the arterial blood gas. The blood pressure monitoring system consisted of non-complacent tubing (20 cm) filled with heparin solution, a three-way stopcock and non-complacent tubing (20 cm) connected to the calibrated aneroid manometer (Manometer BD Medical, BR), which collects measurements in mmHg. The heart was considered the zero reference point.

Arterial blood samples were collected in previously heparinized syringes and immediately analyzed in a gas analyzer (Model 348 Blood Gas Analyzer, Chiron Diagnostics, Halstead, UK). The determined blood gas values were corrected for the body temperature recorded at each sampling time point.

The monitor (DX2010, Dixtal Medical, Manaus, BR) was used during the surgery to monitor the heart rate; the electrodes were placed on the skin

for a lead II ECG. The body temperature (BT) was monitored via a rectal digital thermometer (G-Tech, Accumed-Glicomed, Duque de Caxias, RJ), and the temperature was maintained at  $> 37.0^{\circ}\text{C}$  using an electric heating pad.

After performing the instrumentation and before the surgery, the baseline parameters were measured, including HR, respiratory rate ( $f_R$ ), end-tidal isoflurane concentration (FE'Iso), end-tidal carbon dioxide (PE'CO<sub>2</sub>), body temperature (BT), and a first sampling of the arterial blood gases. The evaluated arterial blood gases parameters included the hydrogen potential (pH), the partial pressure of carbon dioxide in the arterial blood (PaCO<sub>2</sub>), the partial pressure of oxygen in the arterial blood (PaO<sub>2</sub>), the levels of bicarbonate (HCO<sub>3</sub>), the base excess (BE) and the oxyhemoglobin saturation (SaO<sub>2</sub>). The value of FE'Iso was corrected using the following formula:  $\text{FE'Iso} \times 660 \text{ mmHg} / 760 \text{ mmHg}$ , which corresponds to a 660 mmHg mean atmospheric pressure at the location of the study and a 760 mmHg atmospheric pressure at sea level.

The animals were allocated in two treatments of 6 animals each, with the treatment varying according to the maintenance of anesthesia. Treatment by morphine, lidocaine and ketamine (GMLK) included a bolus of lidocaine (Xylestesin® 20 mg mL<sup>-1</sup> Cristália BR, 1.5 mg kg<sup>-1</sup>), followed by an infusion of 10 mL kg<sup>-1</sup> h<sup>-1</sup> of MLK to maintain anesthesia (10 mg morphine + 150 mg of lidocaine + 30 mg of ketamine added to 500 mL of saline solution (saline solution® 0.9% 500 mL, Baxter BR) correspond to an infusion of morphine 0.2 mg kg<sup>-1</sup> h<sup>-1</sup>, lidocaine 3 mg kg<sup>-1</sup> h<sup>-1</sup> and ketamine 0.6 mg kg<sup>-1</sup> h<sup>-1</sup>). The maintenance medication was administered immediately after the induction of anesthesia using a morphine- (pre-anesthesia) and ketamine-like (induction) bolus. For the control treatment (GCON), the animals received a bolus of saline corresponding to the volume of lidocaine followed by an infusion of saline solution at a rate of 10 mL kg<sup>-1</sup> h<sup>-1</sup>. The infusions were administered using a peristaltic infusion pump (Digipump, Digicare Animal Health, Florida, USA).

The baseline was considered immediately before the surgery; data were collected 30 minutes after starting the infusions, and surgery commenced immediately after baseline data collection.

The evaluation was performed by an experienced anesthesiologist who was blind to the treatment and increased or decreased the concentration of isoflurane using criteria based on physiological parameters. If jaw tone increased too much (e.g., if the anesthesiologist could not open the jaw), then the anesthesiologist would increase the isoflurane concentration by 0.5%. Conversely, if jaw tone was completely absent, the anesthesiologist would decrease the isoflurane concentration by 0.5%. The anesthesiologist maintained MAP between 60 and 90 mmHg. If MAP increased or decreased by 10 mmHg, the anesthesiologist would increase or decrease the isoflurane by 0.5%, respectively. The anesthesiologist maintained the heart rate between 60 and 120 beats per min. If the heart rate increased or decreased by 10 beats per min, the anesthesiologist would increase or decrease isoflurane concentration by 0.5%. This method was based on the study of Raske et al. (2010).

The physiological parameters and blood gas sampling were collected for the following time points: baseline (30 minutes after the start the infusion and immediately before surgery) and 15, 30 and 45 minutes after the start of surgery.

At the end of surgery, additional postoperative analgesia was administered to all of the animals for pain control (Flunixin Meglumine – Schering-Plough, Rio de Janeiro, BR): 1.1 mg kg<sup>-1</sup> IM and 0.3 mg kg<sup>-1</sup> IM morphine. The infusion solution was stopped, the vaporizer was turned off, IPPV was discontinued, and the oxygen flow rate was increased (40 mL kg<sup>-1</sup> minute<sup>-1</sup>). Ventilation was supported manually until spontaneous ventilation returned. When spontaneous breathing began, the endotracheal tube was disconnected from the circular breathing circuit, and the sheep were positioned in lateral recumbency to be evaluated for their recovery from the anesthesia.



The following parameters were evaluated: infusion total time (IT); duration of surgery; and recovery period [time in minutes to sternal recumbency (time at lateral recumbency until the sheep could obtain sternal); and the time in minutes in lateral recumbency until they could reach a standing quadrupedal position)].

#### *Statistical analysis*

Normal distribution of the data was verified by using the Shapiro-Wilk test. Data are reported as the mean  $\pm$  SD. The time points per group were analyzed using one-way analysis of variance with multiple repetitions (ANOVA-RM), followed by

the Student-Newman-Keuls method. For analysis between groups, the T test was used. A significance level of 5% ( $P \leq 0.05$ ) was considered. Statistical analyses were performed using a commercial software program (SigmaStat, BR).

#### **Results**

There were no significant differences between treatments with respect to the infusion time, the duration of surgery, or the time to regain sternal recumbency (Table 1). The GCON animals took longer to stand ( $66.6 \pm 14.6$  minutes) compared with the GMLK animals ( $42.0 \pm 13.4$  minutes); this difference was significant (Table 1).

**Table 1.** Mean values and standard deviation (mean $\pm$ SD) of infusion time (IT), surgery duration (SD), time for sternal recumbency (SR) and time for standing (ST) of GMLK and GCON sheep in minutes.

Group	Infusion time (IT)	Surgery duration (SD)	Sternal recumbency (SR)	Standing time (ST)
<b>GCON</b>	65.2 $\pm$ 6.3	59.5 $\pm$ 11.1	38.8 $\pm$ 9.1	66.6 $\pm$ 14.6a
<b>GMLK</b>	64.3 $\pm$ 9.2	56.8 $\pm$ 9.3	34.1 $\pm$ 9.8	42.0 $\pm$ 13.4b

Different subscripts (a,b) in the same row indicate significant differences between groups by t test ( $P \leq 0.05$ ).

**Source:** Elaboration of the authors.

The cardiopulmonary data are presented in Table 2. Compared with baseline, there was no significant difference in the HR values in both treatments. When compared between treatments, the HR values at time point 30 minutes were significantly lower

in the GMLK treatment compared with that of the GCON treatment. The MAP exhibited a significant difference at baseline (before the start of the surgery); the values of the GMLK treatment were higher than those of the GCON treatment.

**Table 2.** Mean and standard deviation (mean±SD) of heart rate (HR), respiratory rate ( $f_R$ ), end-tidal isoflurane concentration (FE'Iso), end-tidal carbon dioxide CO<sub>2</sub> (PE'CO<sub>2</sub>), mean arterial blood pressure (MAP), hydrogenionic potential (pH), partial pressure of carbon dioxide (PaCO<sub>2</sub>), partial pressure of oxygen (PaO<sub>2</sub>), standard bicarbonate (HCO<sub>3</sub>), base excess (BE), oxyhemoglobin saturation (SaO<sub>2</sub>) and body temperature (T °C) in sheep submitted to surgery with or without infusion of morphine-lidocaine and ketamine (MLK).

Variable	Group	Before premedication	Before surgery	Time after initiation of surgery (minute)		
			Baseline	15	30	45
<b>HR</b> (beats minute <sup>-1</sup> )	<b>GCON</b>	91 ± 23	77 ± 20	72 ± 11	81 ± 12 <sup>a</sup>	82 ± 15
	<b>GMLK</b>	77 ± 3	64 ± 5	67 ± 17	65 ± 11 <sup>b</sup>	71 ± 14
<b><math>f_R</math></b> (breaths minute <sup>-1</sup> )	<b>GCON</b>	30 ± 6	10 ± 1 <sup>A</sup>	8 ± 2 <sup>A</sup>	9 ± 3 <sup>A</sup>	9 ± 3 <sup>a</sup>
	<b>GMLK</b>	24 ± 4.9	12.3 ± 4.1 <sup>A</sup>	9.8 ± 2.6 <sup>A</sup>	9.5 ± 2.6 <sup>A</sup>	9.2 ± 2.8 <sup>a</sup>
<b>FE'Iso</b> (%)	<b>GCON</b>		0.85 ± 0.38	1.23 ± 0.34 <sup>a</sup>	1.15 ± 0.12 <sup>a</sup>	1.15 ± 0.2 <sup>a</sup>
	<b>GMLK</b>		0.72 ± 0.21	0.37 ± 0.16 <sup>A b</sup>	0.35 ± 0.19 <sup>A b</sup>	0.28 ± 0.19 <sup>A b</sup>
<b>PE'CO<sub>2</sub></b> (mmHg)	<b>GCON</b>		40.8 ± 8.2	40.8 ± 6.5	41.2 ± 5.5 <sup>a</sup>	41.3 ± 5.4 <sup>a</sup>
	<b>GMLK</b>		39.2 ± 3.9	39.3 ± 5.2	34.7 ± 4 <sup>b</sup>	34.3 ± 4 <sup>b</sup>
<b>MAP</b> (mmHg)	<b>GCON</b>		103 ± 6 <sup>a</sup>	114 ± 9	105 ± 10	103 ± 9
	<b>GMLK</b>		113 ± 8 <sup>b</sup>	111 ± 11	104 ± 10	99 ± 12
<b>pH</b>	<b>GCON</b>		7.45 ± 0.1	7.48 ± 0.05	7.47 ± 0.04	7.47±0.03
	<b>GMLK</b>		7.44 ± 0.05	7.46 ± 0.04	7.48 ± 0.07	7.48±0.06
<b>PaCO<sub>2</sub></b> (mmHg)	<b>GCON</b>		42.6 ± 2.9 <sup>a</sup>	43.3 ± 5.8 <sup>a</sup>	45.6 ± 6.6 <sup>a</sup>	45.8 ± 5.3 <sup>a</sup>
	<b>GMLK</b>		39 ± 4.7 <sup>b</sup>	38.5 ± 3.6 <sup>b</sup>	36.5 ± 7 <sup>b</sup>	37.3 ± 4.3 <sup>b</sup>
<b>PaO<sub>2</sub></b> (mmHg)	<b>GCON</b>		309.7 ± 53.7	346.8 ± 43.7	346.7 ± 32.6	345.5 ± 22
	<b>GMLK</b>		346.5 ± 36.5	342.9 ± 45.9	352.3 ± 51.9	349.1 ± 34.3
<b>HCO<sub>3</sub></b> (mmol/L)	<b>GCON</b>		31.4 ± 2.5 <sup>a</sup>	31.7 ± 1.4 <sup>a</sup>	32.1 ± 2.1 <sup>a</sup>	31.9 ± 1.9 <sup>a</sup>
	<b>GMLK</b>		25.9 ± 4.1 <sup>b</sup>	26.5 ± 3.4 <sup>b</sup>	25.7 ± 4.1 <sup>b</sup>	26.4 ± 4.2 <sup>b</sup>
<b>BE</b>	<b>GCON</b>		5.3 ± 2.5	7.4 ± 1.5 <sup>A a</sup>	7.3 ± 1.3 <sup>A a</sup>	7.0 ± 1.6 <sup>A a</sup>
	<b>GMLK</b>		2.8 ± 2.9	3.4 ± 2 <sup>b</sup>	3.5 ± 2.6 <sup>b</sup>	4.1 ± 3 <sup>b</sup>
<b>SaO<sub>2</sub></b>	<b>GCON</b>		99.9 ± 0.07	99.9 ± 0.05	99.9 ± 0.05	99.9 ± 0.05
	<b>GMLK</b>		99.9 ± 0.06	99.9 ± 0.08	99.9 ± 0.1	99.9 ± 0.1
<b>BT</b> (°C)	<b>GCON</b>	37.9 ± 0.9	37.2 ± 0.9 <sup>A</sup>	36.8 ± 1.0 <sup>A</sup>	36.3 ± 1.0 <sup>A a</sup>	36.1 ± 1.1 <sup>a</sup>
	<b>GMLK</b>	38.7 ± 0.6	38.2 ± 0.7 <sup>A</sup>	37.8 ± 0.6 <sup>A</sup>	37.6 ± 0.6 <sup>A b</sup>	37.3 ± 0.7 <sup>b</sup>

Different subscripts (a,b) in the same column indicate significant differences between the groups by t test ( $p \leq 0.05$ ); uppercase A in the row indicates significant differences between the M-15 (for HR,  $f_R$  and BT) and baseline in the same group by ANOVA-RM test, followed by Student-Newman-Keuls correction ( $P \leq 0.05$ ).

**Source:** Elaboration of the authors.

The  $PE'CO_2$  remained higher during the procedure in the GCON treatment group compared with the GMLK treatment group (Table 2), with significant differences 30 and 45 minutes after surgery began. The  $PaCO_2$  remained higher during the procedure in the GCON treatment compared with the GMLK treatment (Table 2), with significant differences at all time points.

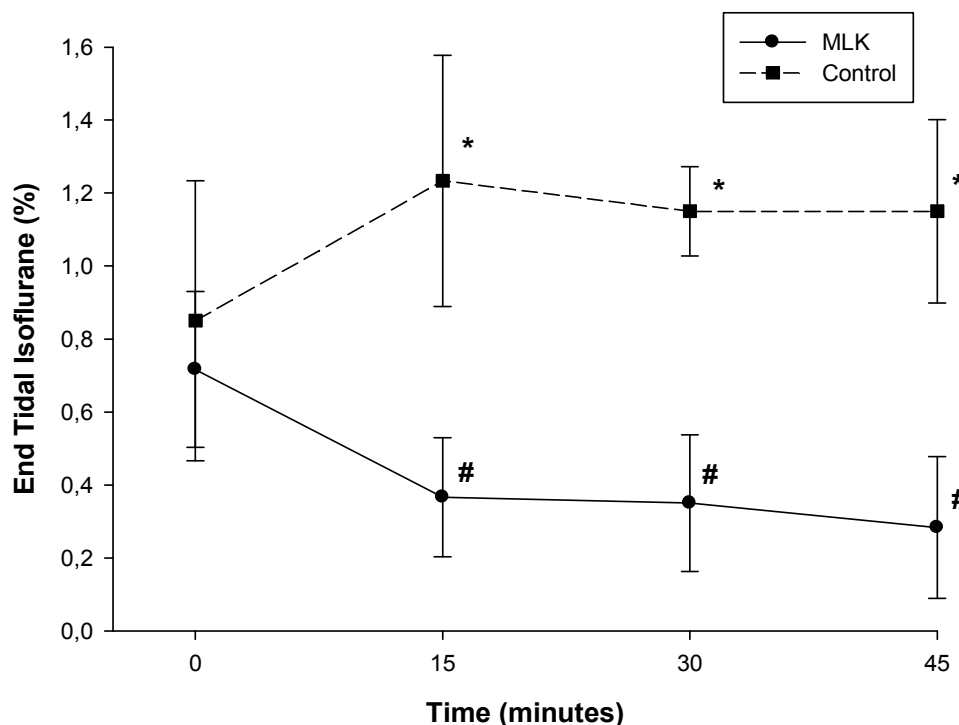
The BE remained higher during the procedure in GCON, and there were significant differences at 15, 30 and 45 minutes after the surgery when compared with baseline (Table 2); the GCON treatment values differed significantly from those of the GMLK treatment at times 15, 30 and 45 minutes after the surgery began.

The  $HCO_3$  remained higher during the procedure in the GCON treatment compared with the GMLK treatment (Table 2). The  $PaO_2$ ,  $SaO_2$  and pH did not

differ between treatments or at baseline (Table 2). The respiratory rate was reduced across all time points compared with time before the premedication.

The end-tidal isoflurane concentrations were determined (Figure 1). Prior to the initiation of surgery (baseline), there were no significant differences in the  $FE'Iso$  concentrations among the groups. At baseline, the mean  $\pm$  SD  $FE'Iso$  % values were  $0.85 \pm 0.38$  and  $0.72 \pm 0.21$  for the GCON and GMLK animals, respectively. After surgery began, the mean  $\pm$  SD  $FE'Iso$  % values ranged from  $1.15 \pm 0.12$  to  $1.23 \pm 0.34$  in the control group. In the GMLK treatment group, the mean  $\pm$  SD  $FE'Iso$  % values ranged from  $0.28 \pm 0.19$  to  $0.37 \pm 0.16$ . The requirements for maintaining a surgical level of anesthesia were lower in the GMLK treatment group, with mean  $FE'Iso$  values approximately 70% lower than those in the control group after surgery began.

**Figure 1.** End-tidal isoflurane in the GMLK and GCON. The # indicates differences of the baseline in the same group; and \* difference between groups.



Source: Elaboration of the authors.



In GMLK, sheep exhibited a faster return to spontaneous respiration ( $4.5 \pm 2.3$  min) when compared with the control group ( $5.3 \pm 1.6$  min) as well as a shorter time remaining in lateral recumbency and standing time (Table 1).

## Discussion

Many surgical procedures in small ruminants can be performed using local anesthesia and physical or chemical restraints (EWING, 1990; TAYLOR, 1991). In certain circumstances, general anesthesia is required, and it becomes necessary to evaluate the protocols for balanced anesthesia.

The combination of a morphine, lidocaine and ketamine infusion has been used as a balanced anesthesia technique in veterinary medicine in many species, although it has not previously been applied to sheep. Our results confirm the results of others studies (MUIR; WIESE; MARCH, 2003; AGUADO; BENITO; SEGURA, 2011) in which MLK was shown to reduce the required concentration of inhalant anesthetic needed to maintain anesthesia.

The range of the MAC of isoflurane in sheep is 1.58% (PALAHNIUK; SHNIDER; EGER, 1974) to 1.53% (BERNARDS; KERN; CULLEN, 1996). In the present study, prior to the initiation of surgery (baseline), there was no significant difference in the FE'Iso concentrations between the groups, but the FE'Iso was lower than the range of the MAC of isoflurane in sheep. This difference relative to the MAC determined in other studies can be explained due to the premedication with the alpha 2 agonist, detomidine, which might have contributed to the FE'Iso reduction. Kästner et al. (2006) observed a 30% reduction in the FE'Iso concentration after premedication with medetomidine in sheep. Dose-dependent anesthetic sparing effects of medetomidine have been demonstrated in a variety of species (VICKERY et al., 1988; SEGAL; VICKERY; MAZE, 1989). A reduction of up to 90% of the minimum alveolar concentration (MAC)

of halothane was observed in dogs after  $10 \mu\text{g kg}^{-1}$  of medetomidine IV (VICKERY et al., 1988).

This is a clinical study, and we used animals that were submitted to gastrointestinal surgery for duodenal cannula implantation. These surgeries were all performed by the same surgeon, and the depth of anesthesia was controlled by the same anesthesiologist, which reduced variability, especially regarding intraoperative isoflurane requirements because different anesthesiologists and surgeons might have introduced variability into the evaluation of the anesthesia depth.

Detomidine contributed to the reduction of FE'Iso; however, the addition of lidocaine, morphine and ketamine helped to augment this reduction. Although this is not an MAC study, the observed reduction in the FE'Iso was greater than the reductions observed by other authors who used single infusions of morphine, lidocaine or ketamine or a combination of lidocaine and ketamine in dogs and goats (MUIR; WIESE; MARCH, 2003; VALVERDE et al., 2004; DOHERTY et al., 2007; WILSON et al., 2008). Muir, Wiese and March (2003) observed a 45% reduction of the MAC of isoflurane in dogs using the same solution (MLK) as the present study. In another study using morphine intravenously ( $2 \text{ mg kg}^{-1}$ ) in goats, Doherty et al. (2004) observed a 29.7% reduction of the MAC of isoflurane. In calves, the end-tidal concentration of isoflurane was significantly lower in the group treated with  $50 \mu\text{g kg}^{-1} \text{ minute}^{-1}$  lidocaine, indicating a 16.7% reduction in anesthetic requirement during lidocaine CRI (VESAL et al., 2011).

In sheep, another study observed that administering  $10 \mu\text{g kg}^{-1} \text{ minute}^{-1}$  ketamine and  $20 \mu\text{g kg}^{-1} \text{ minute}^{-1}$  lidocaine in IV fluids to sheep during orthopedic surgery decreased the required concentration of isoflurane by 23% while still providing sufficient anesthesia (RASKE et al., 2010). However, the animals in the aforementioned study received a lower dose of ketamine (loading dose  $3.3 \text{ mg per kg body weight IV ketamine}$  during

anesthesia induction) and did not received a loading dose of lidocaine. These two differences between these studies (dose of ketamine and loading dose of lidocaine) and the addition of morphine might explain why in our study we observed a greater reduction in the requirement of isoflurane.

In a study on dogs, the sevoflurane requirement was reduced by 62.8% when augmented by IV infusions of ketamine and lidocaine, both 100  $\mu\text{g kg}^{-1} \text{ minute}^{-1}$ . These dogs also received loading doses of IV lidocaine and IV ketamine, 2 mg per kg body weight and 3 mg per kg body weight, respectively, demonstrating that increasing the dose of lidocaine and ketamine can explain the low requirement of anesthetic (WILSON et al., 2008).

The results of these same studies (MURPHY; HUG, 1982; STEFFEY et al., 1994; WAGNER et al., 2002) suggest that a reduction in the inhalant anesthetic requirements should improve cardiopulmonary function, thereby improving the safety of general anesthesia. The IV combination of morphine and lidocaine or morphine and ketamine has been found to be synergistic and to prevent CNS hypersensitivity when administered to humans with inflammatory or neuropathic pain (WU et al., 2002). The combination of these drugs induces analgesia by various pharmacologic mechanisms and is known as multimodal or balanced analgesia (KEHLET; DAHL, 1993).

It should also be noted that the reduction in required isoflurane in this study was followed by cardiovascular stability. The HR was reduced during the entire procedure; however, the values were normal for sheep (between 60-90 bpm) and did not reflect bradycardia (MUIR et al., 2008). Although the alpha 2 agonist reduced the HR in both groups, a significant difference was found at the 30-minute timepoint in the GMLK treatment group compared with the control group. This effect may be caused by a surgical stimulus, which was more pronounced at this time due to the implantation of the duodenal cannula.

Despite the HR reduction, the arterial blood pressure (MAP) remained stable. These results corroborate the finding by Muir, Wiese and March (2003) that using MLK (at the same rate as the present study) leads to a decrease in HR but that the arterial blood pressure was stable in dogs maintained with isoflurane.

Intravenous administration of morphine can induce mild respiratory depression that is responsive to naloxone (STEFFEY et al., 1994). We could not assess the effects on ventilation because our sheep were mechanically ventilated.

Local anesthetics cause local analgesia by blocking individual sodium channels in sensory nerve fibers, thereby inhibiting the production or conduction of electrical impulses. An IV bolus administration or infusion of lidocaine is known to reduce the requirement for injectable and inhalant anesthetics (BUTTERWORTH; STRICHARTZ, 1990; HAHNENKAMP et al., 2002). In dogs, the administration of lidocaine reduced the FE'Iso and did not cause changes in heart rate or mean arterial blood pressure, indicating that it has little or no effect on cardiovascular function (MUIR; WIESE; MARCH, 2003).

The potential adverse effects of IV administration of lidocaine include disorientation, signs of anxiety, vocalization, mild sedation, seizures, vomiting, defecation, muscle twitching, and, rarely, respiratory depression and hypotension (WILCKE; DAVIS; NEFF-DAVIS, 1983). Alterations in behavior, which include visual dysfunction, anxiety and ataxia, were observed after overdosing with lidocaine at plasma concentrations of 1850-4530 ng/mL in horses (MEYER et al., 2001). Tremors and signs similar to visual dysfunction, including staring and inspecting the walls and floor were observed in some of the horses that received the same dose of lidocaine used in the present study (VALVERDE et al., 2005). We did not observe any neurologic behavior or cardiovascular effects during the infusion of lidocaine in any sheep during the study.

The institution of controlled ventilation maintained respiratory stability as well as adequate levels of  $PE'CO_2$  and  $SaO_2$ , in both groups. These parameters, in combination with the values of  $PaCO_2$ , demonstrate that the ventilation was performed efficiently and properly. The  $PaCO_2$  was within normal limits in both groups. As a rule, the  $PaO_2$  value is approximately five times the  $FiO_2$  (HARSTFIELD, 2007). In this study,  $FiO_2$  was between 0.8 and 1, and the  $PaO_2$  values reduced after the premedication. The major disadvantage in the use alpha 2 agonists in sheep is the possible development of severe hypoxemia and pulmonary edema (CELLY et al., 1997). The pathogenesis of these phenomena is uncertain (CELLY et al., 1999). A peripheral effect has been established (CELLY; McDONELL; BLACK, 1999) that involves the stimulation of intravascular pulmonary macrophages, platelet aggregation and pulmonary hypertension after the vasoconstriction of postcapillary venules (RAPTOPOULOS et al., 1995; CELLY et al., 1999).

With regard to the blood gas parameters, pH, and base excess (BE), animals in both groups exhibited mild metabolic alkalosis, but this state was not detrimental to their homeostasis. Compensatory metabolic alkalosis occurs with hypoventilation and occurred in some GCON individuals at baseline as observed in the  $PaCO_2$  values. At other timepoints, it was not possible to observe any of the changes described above nor any respiratory depression because the institution of mechanical ventilation masked these effects.

The levels of  $HCO_3$  and BE were higher in the GCON treatment group compared with the GMLK treatment group, which exhibited normal levels for this species. This effect may be a compensatory mechanism for the increase in  $PaCO_2$  levels.

In both groups, BT decreased relative to the premedication values, which can be explained by a reduction in the basal metabolism and a depression

of the thermoregulatory center by the anesthetic drugs used in various protocols (BUSH et al., 1977).

Although the evaluation of side effects was not one of the goals of this study, a prolonged morphine infusion could lead to a decrease in gastrointestinal motility and ruminal atony postoperatively; however, no complications were observed post-surgery.

In the GMLK group, although the animals did not exhibit a significantly briefer recovery relative to the control group, they exhibited a faster return to spontaneous respiration, remaining in lateral recumbency for less time, and a significant difference in the time to standing (42 minutes versus 66.6 minutes for the GCON group). A faster recovery is advantageous in sheep because a faster recovery means a faster return to homeostasis and, in the case of larger animals, a smaller hardship caused by the prolonged recumbency during recovery.

## Conclusion

The use of intravenous MLK was shown to offer great efficiency as part of a balanced anesthesia protocol in sheep, with a 75.6% reduction in the need for isoflurane, providing stability of the cardiovascular parameters and blood gases with a shortened recovery period.

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