Journal MVZ Cordoba
2023; january-april. 28(1):e2854.
https://doi.org/10.21897/rmvz.2854

Original

Effect of retrobulbar block on heart rate variability during exenteration in cows

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Received: June 2022; Accepted: December 2022; Published: January 2023.

ABSTRACT

Objective. To evaluate the effect of retrobulbar block during orbital exenteration on heart rate variability (HRV). **Materials and methods**. Fourteen adult cows with ocular squamous cell carcinoma were used. Ocular exenteration is performed under multimodal anesthesia. The cows were sedated (xylazine 2%) and the auriculopalpebral nerve was blocked (lidocaine 2%). They were randomly assigned to two groups, one with a four-point block (n=7) and the second with a retrobulbar block (n=7). Electrocardiograms were recorded during two hours of the surgery in six moments by means of a Holter monitor (Cardio Trak Digital Holter Recorder, Model CT-085, BENEWARE). The data obtained were analyzed using linear methods in the frequency and time domain. Mean heart rate (HR) and mean beat-to-beat interval (RR) duration were evaluated in the time domain. The frequency domain included low frequency (LF), high frequency (HF) and sympathovagal balance (LF/HF) of HRV. **Results.** In both groups there was a significant increase in heart rate during ocular traction. There were no significant changes in HRV between the different moments of the procedure. **Conclusions**. During manipulation and exenteration of the eyeball, no decrease in HR associated with the oculocardiac reflex was detected, but sympathetic activation was detected as a result of painful surgical stimuli. No central nervous system (CNS) toxicity from local anesthetics occurred in the animals.

Keywords: Anesthesia; reflex; autonomic nervous system (*Source: MeSH*).

RESUMEN

Objetivo. Evaluar en vacas el efecto del bloqueo retrobulbar durante la exenteración sobre la variabilidad de la frecuencia cardiaca (VFC). **Materiales y métodos.** Catorce vacas con carcinoma ocular de células escamosas se les realizó exenteración ocular bajo anestesia multimodal. Las vacas fueron sedadas con xilacina 2% y se bloqueó el nervio auriculopalpebral con lidocaína al 2%. Fueron asignadas al azar a dos grupos, uno con un bloqueo de cuatro puntos, (n = 7) y el segundo con bloqueo retrobulbar (n=7). Los electrocardiogramas (ECG) se registraron durante dos horas del procedimiento quirúrgico en seis momentos por medio de un Holter (Cardio Trak Digital Holter Recorder, Model CT-085). Los datos se analizaron por medio de métodos lineales en el dominio de

How to cite (Vancouver).
Cedeño QDA, Botina JM, Enriquez RC. Effect of retrobulbar block on heart rate variability during exenteration in cows. Rev MVZ Cordoba. 2023; 27(1):e2854. https://doi.org/10.21897/rmvz.2854

frecuencia y tiempo. En el dominio del tiempo se evaluó la media de la frecuencia cardíaca (FC) y la duración media del intervalo latido a latido (RR). En el de frecuencia, incluyó baja (LF), alta frecuencia (HF) y el equilibrio simpatovagal (LF/HF) de la VFC. **Resultados.** En ambos grupos se presentó un aumento significativo de la frecuencia cardíaca durante la tracción del globo ocular. No hubo cambios significativos en cuanto a la VFC entre los distintos momentos del procedimiento. **Conclusiones.** Durante la manipulación del globo ocular y la exenteración no se detectó disminución de la FC asociada al reflejo óculo-cardiaco, pero si una activación simpática, como resultado de estímulos quirúrgicos dolorosos.

Palabras clave: Anestesia; reflejo; sistema nervioso autónomo (*Fuentes: CAB*).

INTRODUCTION

Orbital exenteration is a surgical procedure performed on dairy cows in Nariño, Colombia (1). It is a simple surgery to perform, relieves a painful ophthalmic pathology, and stops the progression of neoplasms such as ocular squamous cell carcinoma (2). Mitigating stress during surgery and improving the function of the cardiovascular system are critical factors in the quality of anesthesia and the animal's well-being during the procedure and recovery. A deep plane of anesthesia with the animal in decubitus is recommended. However, as the surgical intervention is performed in the field, general anesthesia in cattle is not recommended due to the potential risk of hypoventilation, hypotension, tympanism, myopathies, or traumatic recovery, as well as the cost involved (3). For this reason, surgery is performed in the field with the animal standing, with multimodal anesthesia (sedation and local or regional blockade), to avoid cardiopulmonary and digestive complications (4).

Local anesthesia complications include orbital hemorrhage, ocular globe perforation, optic nerve injury, cardiac arrhythmias (bradyarrhythmias), and death after injection into the optic nerve meninges (5). There are also inconveniences associated with eye surgery such as hypertension or cardiac arrest caused by stimulation of the vagus nerve during surgery. This phenomenon can be explained by the oculocardiac reflex, a known complication in ophthalmologic surgery (6). This reflex is caused by intense manipulation and is mediated by a trigeminal-vago-vagal reflex through fibers originating from the ophthalmic nerve. There seem to be significant differences between species for the oculocardiac reflex (dogs, cats, horses, and birds), whether it is a cardiac component, a respiratory component or a combination of both (7). In addition to induced bradycardia, concurrent respiratory depression may be deeper. The reflex can be initiated by several ophthalmic manipulations, including eye pressure massage for glaucoma, intraorbital injections of local anesthetics (also used to block this reflex), surgical traction of the extraocular muscles, and eyelids muscle manipulations (8).

There is a risk of injury to the central nervous system in these anesthetic procedures. Central nervous system (CNS) toxicity can arise from local anesthetic injection into the nasopharyngeal and optic nerve meninges (9). Clinical signs of CNS toxicity from local anesthetics include hyperexcitability, decubitus, opisthotonus, tonic-clonic seizures, and cardiorespiratory arrest (10).

The non-invasive technique widely used to assess the activity of the autonomic nervous system is performed by monitoring heart rate (HR) and heart rate variability (HRV) (11). HRV is a sensitive factor for obtaining sympathovagal stimulation during multimodal anesthesia (12). The heart rate variability analysis includes the mean heart rate (HR) and the mean duration of the beat-to-beat interval (RR) in the time domain. In the frequency domain, it includes low frequency (LF), high frequency (HF), and sympathovagal balance (LF/HF) of HRV. The high-frequency spectral pattern is associated with parasympathetic activity, and a low-frequency range is associated with sympathetic and parasympathetic activity (13). Studies with horses (14) and cattle (15,16) showed that heart rate variability varies significantly between baseline conditions and situations of psychological stress and pain.

This study hypothesized that nociceptive surgery and vagal stimulation during orbital exenteration would affect heart rate variability, and that these would be attenuated or prevented with a retrobulbar anesthetic block. The study aimed to analyze and compare heart rate variability in sedated and anesthetized cows before and during surgical nociceptive stimulation with or without the presence of retrobulbar block.

MATERIALS AND METHODS

Type of study. A randomized experimental study was carried out on dairy cows with ocular squamous cell carcinoma. The project has the approval of the Bioethical Committee of Universidad de Nariño and the farm owners' consent.

Location. The study was conducted on dairy farms in the municipalities of Pasto, Pupiales, and Tuquerres in Nariño, Colombia. The farms are located 2,500 to 3,000 meters above sea level, with average temperatures of 14°C, 82% relative humidity, a rainfall of 800 mm per year, a minimum of 80 sunshine hours/month, and a maximum of 107 sunshine hours /month, a minimum UV index of 12.8 and a maximum of 15.3.

Animals. Fourteen Holstein (n=11) and Creole (n=3) female bovines ages 6 to 12 were used. The cows had no medical history of heart or lung problems. They presented ocular and periorbital lesions of invasive squamous cell carcinoma with a cracked cauliflower appearance, necrosis, covered with blood, mucus, fibrin, and/or pus with a broad base that burst into adjacent tissues, according to the histopathological study. The animals were immobilized in cattle chutes, which were introduced 10 to 20 minutes before starting sedation. A detailed clinical examination was performed in the cattle chute, and the baseline data of heart rate, respiratory rate, and body temperature were recorded in a table. After ten minutes, the electrodes and the Holter were placed on the body.

Multimodal anesthesia. As the farmer requested the veterinary service, the surgical technique was performed randomly until each group completed the number of surgeries. The animals were sedated, and the auriculopalpebral nerve was blocked. Group 1 also received a retrobulbar block, and group 2 a four-point block.

Protocol 1.
Sedation. A dose of 2% xylazine sedation was administered at a 0.015-0.03 mg/kg IV rate in the coccygeal vein to ensure that the cow remained upright.

Auriculopalpebral nerve block. Lidocaine blockade of the auriculopalpebral nerve removes the functionality of the eyelid (motor blockade of the orbicularis oculi muscle). A line is drawn from the base of the ear to the medial canthus of the eye. In the middle of this line, below the zygomatic arch, 5 to 10 mL of lidocaine are injected two centimeters deep (Figure 1A).

Retrobulbar block. A $3^{1/2}$-inch 19-gauge spinal needle was used. It was curved to form an arc with a radius of approximately 10 cm. The needle was inserted directly above the eyeball to a point beyond the globe and then turned inward to penetrate the conus muscle, where the nerves emerge from the orbital foramen rotundum (Figure 1B). 20 ml of lidocaine solution were injected.

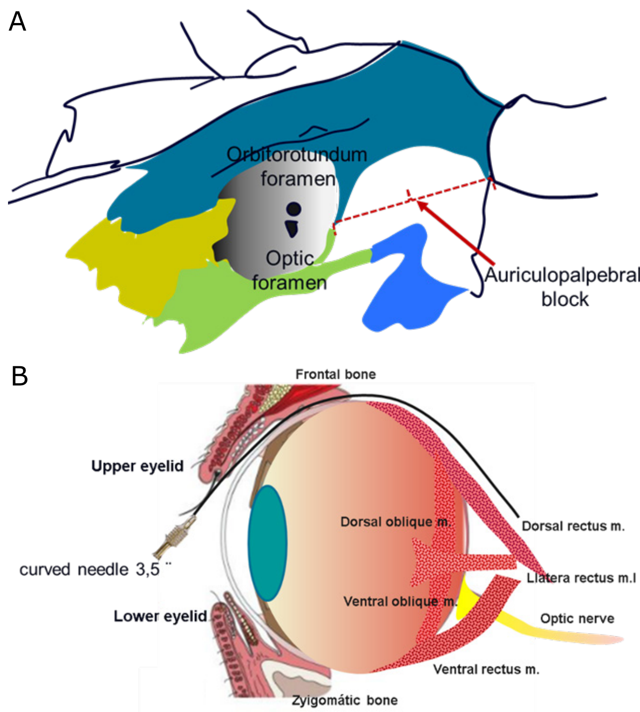

Figure 1. A. Auriculopalpebral block **B**. retrobulbar block

Protocol 2.
Sedation. The cows were administered a sedative dose of 2% xylazine at a 0.015-0.03 mg/kg IV rate in the coccygeal vein.

Auriculopalpebral nerve block. The infiltration of the auriculopalpebral nerve is performed to remove the functionality of the eyelid, since it is a motor block in the orbicularis oculi muscle. A line is drawn from the base of the ear to the medial canthus of the eye. At the middle of this line, below the zygomatic arch, 5 to 10 mL of lidocaine is injected two centimeters deep.

Four-point block. The four-point block is injected through the eyelids, both dorsally and ventrally (at 6 and 12 o'clock) and at the lateral and medial canticles (at 3 and 9 o'clock) (Figure 2A). The objective is to deposit about 60 ml (distributed among the four points) of local anesthetic at the apex of the orbit with straight 18-gauge inch-and-a-half needles (Figure 2B).

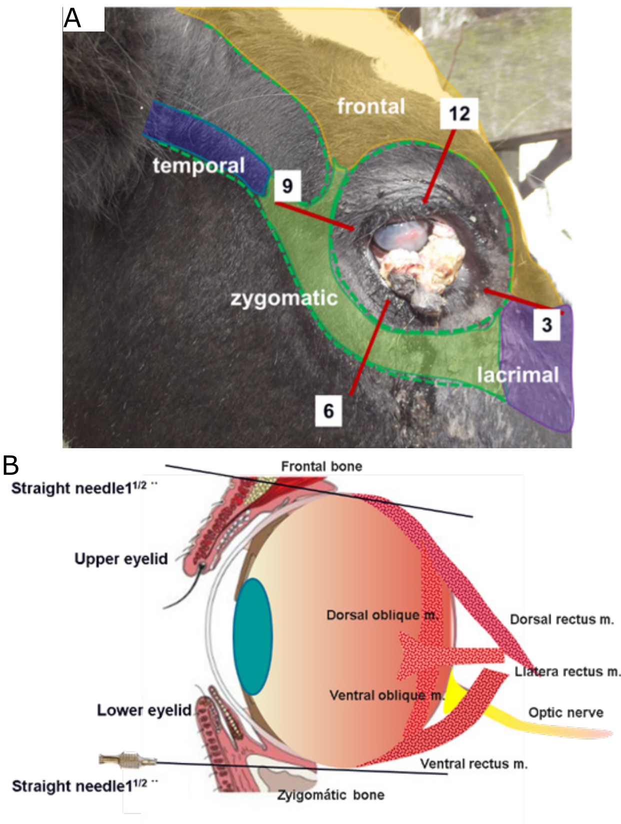

Figure 2. A. Four-point blockade, distribution of a 60 ml lidocaine solution spread over each point (12,3,6,9). **B.** Insertion of a straight needle between the eyeball and the frontal (point 12) and zygomatic (point 6) bones.

Surgery. All animals underwent exenteration using a transpalpebral approach after tarsorrhaphy and blunt dissection to remove the conjunctiva, periorbita, extraocular muscles, eyeball, and tumor.

Postoperative. Analgesia. All animals undergoing a surgical procedure were administered a 3 mg/kg dose of ketoprofen intramuscularly for three days.

Antibiotherapy. An antibiotic protocol based on procaine, benzathine and potassium penicillin was formulated intramuscularly at a dose of 20.000 IU/kg.

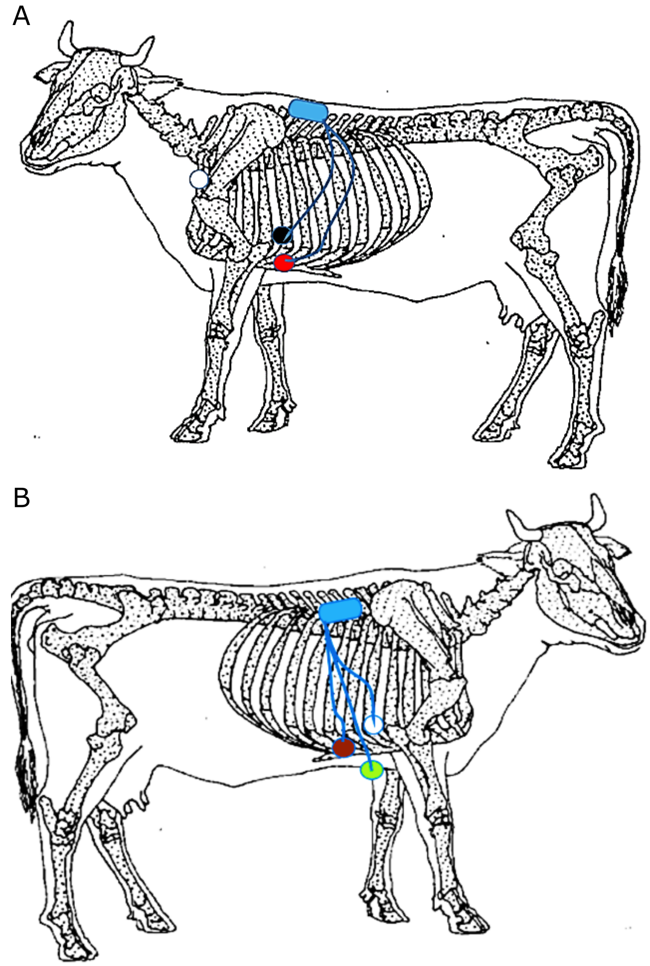

Figure 3. Electrode placement. **A.** Left side: two electrodes (black and red) **B.** Right side: three electrodes (white, brown, and green)

Electrocardiogram. The monitor used has 2 channels and 5 electrodes. Electrode leads were placed on the extremities (17). The electrodes are placed slightly caudal (5-10 cm) to the forelimbs in a slightly ventral (precordial) position. Figure 3 shows where the electrodes were placed on the left (Figure 3A) and right (Figure 3B). The site was shaved and degreased with alcohol, and self-adherent pads were attached to connect the electrodes (Figure 4A). Finally, the electrodes, cables, and monitor were wrapped around the cow's chest with a 10-15 cm-wide elastic bandage. An extra band was used for the monitor (Figure 4C).

Heart rate variability analysis. The times before the surgical procedure, during the surgical procedure, and during recovery were recorded in an Excel table. The electrocardiograms were recorded before, during, and after the surgical procedure using the Cardio Trak Digital Holter Recorder, Model CT-085 (Suzhou Beneware

Medical Equipment Co. Ltd, Suzhou, China) (Figure 4B). HRV indicator data were analyzed using linear methods in the frequency and time domains. HRV was analyzed in the time domain, expressed as mean heart rate (HR) and beat-to-beat interval (RR). The variability in the frequency domain was examined by power spectral analysis using the Fast Fourier Transform and calculated as the activity in HF, LF ranges, and the LF/HF ratio (18). Frequency component thresholds were set at 0.01–0.07 Hz for low frequency and 0.07–0.6 Hz for high frequency (19). The LF and HF were calculated in normalized units, which allows the comparison of different measurements.

Figure 4. A. Shaved sites and self-adhesive pads for electrode placement. **B.** Verification of Holter electrocardiogram recordings. **C.** Bandage placement over the leads and electrodes and the Holter band.

The monitoring time before, during and after the surgical procedure added up to 2 hours approximately. ECG sequences lasting 5 minutes (300 s) without artifacts were analyzed each time. The process was divided into 6 moments: (T1) basal condition (pre-surgical in the cattle chute); (T2) during sedation; (T3) in a blockade in the absence of nociceptive stimulation; (T4) during surgical stimulation; (T5) intense traction on the globe and ocular muscles, (orbital excenteration) and (T6) one hour after surgery (recovery). Values from cows without retrobulbar block were compared with those from patients with retrobulbar block. Beat-to-beat interval recordings were imported into the Beneware HRV analysis software.

Statistical analysis. It was performed with SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were performed to calculate the means and standard deviation (mean, SD). The normal distribution of the data was checked using the Kolmogorov-Smirnov test. Repetitive measurements were performed with ANOVA, in the case of normal distribution (at each moment and in both groups). The groups (multimodal anesthesia with retrobulbar block versus without retrobulbar block) were compared at each time point. A parametric test calculated the correlation for normal distribution (two-sample t-test). Non-parametric tests were chosen for non-normal distribution (Mann-Whitney U test). The minimum number of animals was calculated using the following formula, $N = (10 / k) + 1$, where k is the number of groups (20). A statistical power calculation for the ANOVA and the comparison between groups were also performed to verify the appropriate size of the study group. The group size obtained 1.1 power with a significant level. The level of significance was set as $p \leq 0.05$.

RESULTS

The average age of cows in protocol 1 (retrobulbar block) was 8.3 years, with a 602.3 kg average body weight. Two cows were three months pregnant. In protocol 2 (four-point block), the average age was 9.4 years old, and their body weight was 590.7 kg.

The mean and standard deviation (SD) of the heart rate (HR) values and heart rate variability (HRV) indicators of the two multimodal anesthesia protocols are summarized in Table 1. The behavior of heart rate in protocol-1 anesthetized cows (retrobulbar block) increases from the basal moment (T1) to the time when the eyeball is manipulated, and eyeball traction begins (T5). It then drops to base values in the recovery stage (T6). Normalized low-frequency units remain similar to baseline values until T4 when they begin to decline. In contrast, high-frequency power and the LF/HF ratio remain the same for the first four stages up to surgical pacing and decline at the moment of traction of the eyeball (T5). However, there are no statistically significant differences between the low, high frequency, and low-frequency/high-frequency ratio values during the different moments.

Table 1. Parameters (mean ± SD) of heart rate variability (HRV) in different surgical stages in cows with protocol 1 retrobulbar (n=7) and protocol 2 four points (n=7)

Parameter	PR	(T1)	(T2)	(T3)	(T4)	(T5)	(T6)
HR(l/m)	1	62.4 ±2.4	59.8 ±2.7	62.8 ±1.8	71.6 ±4.8	79.2 ±5.5*	62.2 ±2.5
	2	62.2 ±2.3	61.2 ±2.4	64.4 ±2.6	73.2 ±5.1	99.6 ±7.7	65.8 ±4.1
RR (ms)	1	984 ±61.2	942 ±96.2	917 ±15	837 ±25.6	740 ±122.3	951.2 ±42.8
	2	959.2 ±43.9	950.8 ±63.6	942 ±31.3	846 ±34.5	662.8 ±96.5	913.4 ±36.5
LF (un)	1	77.7 ±5.3	77.1 ±10.1	83.06 ±7.15	89.32 ±7.27*	89.95 ±1.39*	71.74 ±2.91*
	2	79.3 ±43.9	73.5 ±11.9	84.6 ±10.8	75.8 ±8.6	66.8 ±3.2	84.08 ±4.4
HF (un)	1	13.5 ±0.6	14 ±0.38	14.14 ±0.9	14.38 ±1.44	12.92 ±1.28	14.96 ±0.46*
	2	13.4 ±0.8	13.8 ±1.07	14.34 ±0.82	14.24 ±1.04	13.98 ±2.63	16.8 ±1.82
LF/HF	1	2.41 ±0.44	2.5 ±0.15	2.4 ±0.34	2.2 ±0.15	3.8 ±0.28*	2.4 ±0.35
	2	2.4 ±0.16	2.4 ±0.25	2.5 ±0.25	2.4 ±0.64	2.7 ±0.71	2.3 ±0.37

*(p<0.05) between cows with/without retrobulbar block; PR: Protocol; HR- heart rate; RR- mean beat-to-beat interval; LF- low frequency; HF- high frequency; LF/HF- ratio between low and high frequency: un- normalized units: ms- milliseconds; l/m- beats per minute.

T1- In the cattle chute (pre-surgical); T2- Sedation; T3- Blockade; T4- Surgical stimulation; T5- Eyeball traction; T6- Recovery (post-surgery).

The behavior of the heart rate among protocol-2 cows (four-point block) showed a significant increase (p=0.04) at the moment of eyeball traction (T5) compared to the pre-surgical (T1), sedation, and block moments (T3 and 4). Low-frequency power normalized units decreased at T5. The high frequency increased slightly without statistical significance until the moment of traction, where it decreased as a sign of vagal stimulation. The mean beat-to-beat interval duration was significantly shorter at T5 compared to earlier stages (p=0.03).

There was a significant heart-rate difference (p=0.05) between both groups at the time of manipulation and traction of the eyeball (T5). Cows from protocol 2 showed a significantly higher heart rate during manipulation and traction of the eyeball (T5) compared to T1 (p<0.001), T2 (p=0.002), T3 (p<0.001), and T4 (p< 001). However, the high and low-frequency power was similar to the baseline (pre-surgical) conditions. No statistically significant differences between cows with and without retrobulbar block were observed during surgical stimulation and global traction when comparing mean power spectral values (high frequency, low frequency, and high-frequency/low-frequency ratio).

Mean heart rate values for all cows were 59.8 ± 2.7 l/min (lowest) and 99.6 ± 7.7 l/min (highest). Values below 50 l/min were not detected (Figure 5).

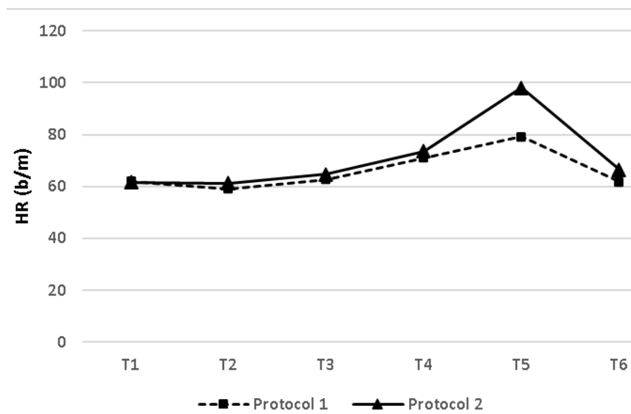

Figure 5. Heart rate behavior before, during, and after the surgical procedure expressed in beats per minute.

DISCUSSION

Ocular squamous cell carcinoma (OSCC) is considered one of the primary neoplastic diseases with the highest rates of cattle morbidity and mortality in Nariño, commonly observed in the Holstein breed, the most used breed (2).

This study was designed to evaluate the effect of an ophthalmic surgical procedure under multimodal anesthesia on the spectral components of HRV. HRV can be used during anesthesia to assess and characterize ANS activity (11,12). Many factors influence anesthesia since it results from the complex interaction between surgical stimulation, analgesia, and the direct cardiovascular effects of drugs (14).

When comparing the anesthetic stability stage with the surgical stimulation stage, a heart-rate increase was observed in both protocols. However, it can be inferred that the HR change was significant in group 1 due to the sympathetic stimulation during severe traction of the eyeball since orbital exenteration involves removal with aggressive debridement of the periorbital structures. The HR increase in both groups can be explained by sympathetic activation, shown by an increase in normalized units of low-frequency (LF) power due to surgical trauma in ocular tissues during orbital exenteration. This sympathetic activation caused by painful surgical stimuli probably overlaps with the vagal drive (21).

The oculocardiac reflex is defined as a heart rate decrease by at least twenty percent of the baseline value. The reflex can be initiated by applying traction to the external ocular muscles, applying pressure to the globe, or applying iatrogenic pressure to the orbital fat pad (as an aid to homeostasis after exenteration). The reflex can also be initiated by the presence of an intra-orbital hematoma or by injecting a substance, such as a retrobulbar block (22). However, neither group exhibited a significant heart rate decrease (bradycardia). Thus, we cannot conclude that retrobulbar block can prevent heart disease by slowing the rate and bradyarrhythmias caused by vagal stimulation, which occurs during exenteration of the eye as in canines and horses (6.7). No apparent complications occurred in this study with retrobulbar injection (Protocol 2). However, a slight decrease in normalized high-frequency power units was observed when the block was performed as a sign of mild parasympathetic stimulation (23).

Since there is a high risk of hypoventilation, hypotension, tympanic membrane, myopathy and prolonged or traumatic recovery from anesthesia when cattle are in a deep plane of anesthesia, it is best to opt for sedation while the animal is standing. The effects of xylazine, such as bradycardia, decreased cardiac output, and first or second-degree atrioventricular blocks, were not detected. These situations are normally induced by increased vagal tone (24). This may be due to the low dose administered via the coccygeal vein to keep the animal on its feet. However, two animals with the four-point block and one with the retrobulbar block showed restlessness with pain-sign movements during the surgical procedure. This may be because the animals presented with an aggressive and invasive tumor in the adjacent peri-orbital tissues. The effects of local anesthetics are lowered by inflammation and tumors. Inflammation causes metabolic acidosis that lowers the pH of affected tissues, altering the pharmacokinetics and pharmacodynamics of local anesthetics by reducing their interactions with lipid bilayers and/or membrane lipids (25).

No CNS toxicity due to local anesthetics, hyperexcitability, decubitus, opisthotonus, tonic-clonic seizures, or cardiorespiratory arrest –which are extremely rare in the author's experience (4)– were observed in the animals.

There was a HR increase in both cow groups, which can be explained by sympathetic activation resulting from painful surgical stimuli, probably superimposed on the vagal impulse. However, we can conclude that the heart rate behavior was stable in protocol 2 since the increase was not significant at the time of exenteration. This surgery can be performed in the field with multimodal anesthesia, sedating the animal with a dose to keep it on its feet. At the time of manipulation and traction of the eyeball, no HR decrease or bradyarrhythmias associated with the oculocardiac reflex were detected, contrary to reports by other authors in other species (6.7).

Conflict of interests

The authors hereby state they have no conflict of interest.

Acknowledgments

The authors thank the Vice-Rector of Postgraduate Research and International Relations at Universidad de Nariño for project funding support. Likewise, we thank the ranchers who trusted us and facilitated the work with the animals.

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