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Glyceryl guaiacol ether for sedation of horses undergoing orchiectomy when standing

[*Éter gliceril-guaiacol para sedação de equinos submetidos à orquiectomia em pé*]

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ABSTRACT

A study was designed to compare two sedation protocols to be used in horses undergoing orchiectomy when standing. In both protocols, the induction to the sedative state was performed with bolus detomidine at a dose of 10 µg/kg, intravenously (IV). In the first protocol (eight horses), the sedative state was maintained with 1% glyceryl guaiacol ether (GGE) in continuous infusion, at a dose of 1ml/kg/hour IV. In the second protocol (eight horses) this sedative effect was maintained with detomidine in continuous infusion at the same dose and induction route. Orchiectomy was performed on all animals. The two protocols allowed the surgeries to be performed when standing. However, horses kept under sedation by the GGE showed greater relaxation and a more intense degree of sedation. It should be noted that the use of GGE to maintain the sedative state in horses is unprecedented in the literature. The drug is used in anesthetic protocols in the species, but only in pre-anesthetic medication in general anesthesia. It was concluded that the two sedation protocols allowed the performance of orchiectomy with the horses when standing. However, the protocol in which 1% GGE was used showed more profound sedation, without adverse effects.

Keywords**:** horse, detomidine, guaifenesin, infusion continues, sedation

RESUMO

Foi realizado um estudo para comparar dois protocolos de sedação a serem utilizados em equinos submetidos à orquiectomia em estação. Em ambos os protocolos, a indução ao estado sedativo foi realizada com bolus *de detomidina, na dose de 10µg/kg, por via intravenosa (IV). No primeiro protocolo (oito cavalos), o estado sedativo foi mantido com 1% de éter gliceril guaiacol (GGE) em infusão contínua, na dose de 1mL/kg/hora IV. No segundo protocolo (oito cavalos), esse efeito sedativo foi mantido com detomidina, em infusão contínua, na mesma dose e via de indução. Foi realizada orquiectomia em todos os animais. Os dois protocolos permitiram que as cirurgias fossem realizadas em estação No entanto, os cavalos mantidos sob sedação pelo GGE apresentaram maior relaxamento e grau de sedação mais intenso. Ressalta-se que o uso de GGE para manutenção do estado sedativo em equinos é inédito na literatura. O fármaco é utilizado em protocolos anestésicos na espécie, mas apenas na medicação pré-anestésica em anestesia geral. Concluiu-se que os dois protocolos de sedação permitiram a realização da orquiectomia com os cavalos em estação. No entanto, o protocolo em que foi utilizado GGE 1% apresentou sedação mais profunda, sem efeitos adversos*.

Palavras-chave: cavalo, detomidina, guaifenesina, infusão contínua, sedação

INTRODUCTION

In horses, the performance of general anesthesia should be restricted to vulnerable horses that are debilitated, without the possibility of undergoing procedures when standing (Pearce, 2020). Thus, in this species anesthetic protocols are indicated that allow the performance of procedures when standing. Several complications can occur when general anesthesia is used in horses, including injuries to various body systems (digestive, locomotor, respiratory, cardiovascular, and nervous system) (Valverde, 2021). On the other hand, procedures with the horse when standing have several advantages such as cost reduction

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for the professional and owner and reduction of hospitalization time with a consequent decrease in morbidity and mortality (Valverde, 2021).

Guaiacol glyceryl ether (GGE), also called guaifenesin, is a centrally acting muscle relaxant drug (Pratt *et al.*, 2019), extracted from trees of the genus Guaiacum (Pang, 2013). The mechanism of action of this drug occurs in the spinal cord through inhibition of polysynaptic reflexes, resulting in sedation and muscle relaxation (Pang, 2013). Due to this effect, the drug is used in various anesthetic protocols in horses, providing quiet and gentle anesthetic induction (Pratt *et al.*, 2019). This is due to the intense muscle relaxation produced by the drug (Pratt *et al.*, 2019). An important aspect of the drug is that it produces myorelaxation without affecting the diaphragmatic muscle (Pratt *et al.*, 2019). However, GGE should not be used as a single agent in anesthetic protocols for surgical procedures. This is because very high doses are required to induce immobility with the drug (Pratt *et al.*, 2019).

Alpha2 agonists are mainly used for their sedative properties, but they are also analgesic drugs (Gozalo-Marcilla *et al.*, 2019). Among the alpha2 agonists, detomidine has good results in equine sedation (Hollis *et al.*, 2020).

The aim of this study was to compare the sedative effect of 1% GGE when used by continuous infusion by the intravenous route in horses with the continuous infusion of detomidine for performing orchiectomy when standing horses.

MATERIAL AND METHODS

Sixteen male horses were selected, classified as ASA I (healthy animal) (ASA…, 2019), weighing between 180 and 470kg, of different breeds. The age of the animals ranged from one year and six months to ten years. These horses underwent elective orchiectomy when standing.

On the day before the surgical procedure, benzathine penicillin at a single dose of 40,000 international units (IU)/kg was administered intramuscularly and tetanus serum at a dose of 5,000 IU per animal intravenously.

In all horses, blood counts and analysis of renal function (urea and creatinine) were performed.

The animals were submitted to a 12-hour solid fast for the sedation protocol. Water fasting was not performed.

On the day of the surgical procedure, immediately before the institution of the sedation protocol, the following baseline parameters were measured: heart rate, respiratory rate, and body temperature. Body temperature was assessed using a rectal digital thermometer. The respiratory rate was assessed by counting costal movements for one minute. Heart rate was assessed using a Mindray® MEC12 multiparameter monitor. For this, four electrodes were placed in the chest region. The same monitor was used to perform the electrocardiogram and to measure systolic, mean, and diastolic pressures. Pressures were measured using a cuff fitted at the base of the tail (Fig. 1A). All these parameters were evaluated every five minutes during all procedures until the animal showed absence of sedation (head, lip and eyelids in normal position and normal ambulation).

The animals were evaluated for mental status (basal; moment zero) using the following criteria: response to the sound stimulus (clapping behind the animal), response to the tactile stimulus (touching the ear with the finger), degree of ataxia (position of the animal in the restraint trunk), height (in centimeters) from the head to the ground in a normal mental state (Ringer *et al.*, 2012) (Fig. 1B), presence or absence of eyelid ptosis, presence or absence of lip ptosis.

Mental status was interpreted in numbers: 0 - no sedation, 1 - mild sedation, 2 - moderate sedation, 3 - intense sedation (Table 1). A summation of the criteria evaluated in the degree of sedation was performed. It was considered: 1) absence of sedation: animals presented a sum of zero to three; 2) mild sedation: animals presented a sum of four to nine points; 3) moderate sedation: animals presented a sum of ten to fifteen points; and 4) intense sedation: animals had a sum of more than fifteen points (Table 1).

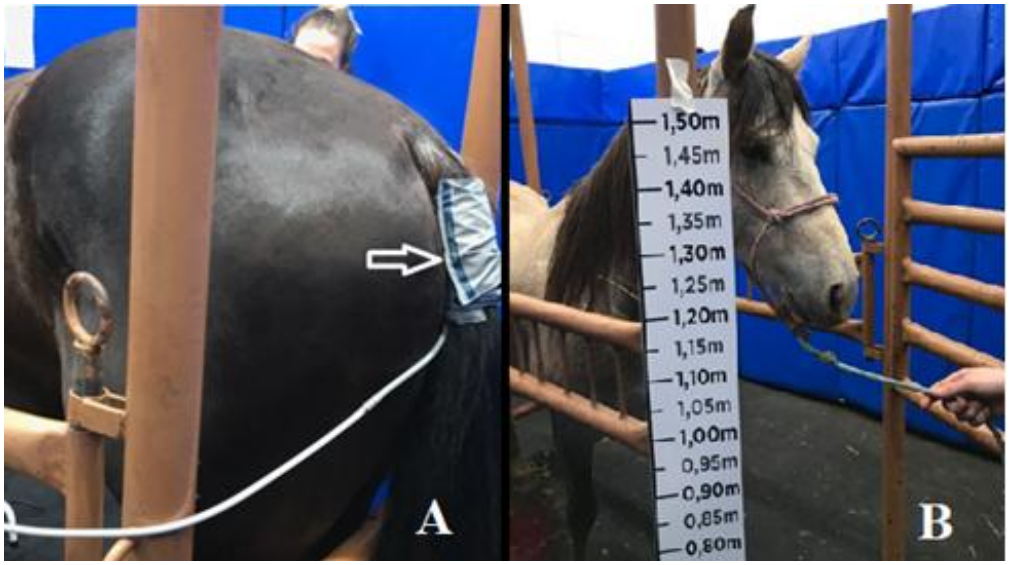

Figure 1. A Male horse, monitored for standing orchiectomy. Cuff adjusted at the base of the tail to measure blood pressure (arrow). In B, Horse, male, two years old, 330kg, in normal mental state, before being submitted to sedation for orchiectomy. Note the numerical scale in centimeters used to measure the distance from the head to the ground.

Table 1. Descriptive numerical scale to assess the degree of sedation in horses. 0-3: no sedation; 4-9: mild sedation; 10-15: moderate sedation; 15-18: intense sedation

Parameter	Criterion	Degree
Palpebral ptosis	Absent	0
	Discreet	1
	Moderate	2
	Intense	3
Labial ptosis	Absent	0
	Discreet	1
	Moderate	2
	Intense	3
Response to the sound stimulus (dapping behind the animal)	Absent	3
	Discreet	2
	Moderate	1
	Intense	0
Response to the tactile stimulus (touching the ear with the finger)	Absent	3
	Discreet	2
	Moderate	1
	Intense	0
Degree of ataxia (position of the animal in the restraint trunk)	Normal position (no abduction)	0
	Discreet abduction	1
	Moderate abduction	2
	Intense abduction	3
Measure from head to ground in centimeters	Basal	0
	Slight (reduction of 10% up to 29% from basal measure)	1
	Moderate (reduction of 30% up to 49% from basal measure)	2
	Intensive (reduction below 50% of basal measure)	3
Total		18

In all animals, at moment zero (baseline), venous access was performed in the jugular vein through catheterization with a 14g catheter and a three-way stopcock was attached. In both protocols evaluated, detomidine was used in bolus at a dose of 10 micrograms per kg intravenously to initiate the sedation protocol. Animals were considered sedated when they showed signs of sedation including head lowering, positioning of the limbs in abduction, presence of eyelid and lip ptosis and other signs of sedation. Such signs were observed in all animals approximately five minutes after administration of detomidine (Fig. 2).

Figure 2. Male horses, sedated for standing orchiectomy. Note eyelid and lip ptosis. A: Sedation protocol with 1% glyceryl-guaiacol-ether in continuous infusion (1ml/kg/hour). B: protocol of sedation with detomidine in continuous infusion (10mcg/kg/hour).

The animals were randomly divided into two equal groups, with the animals in the first group (eight horses) submitted to the protocol with detomidine in continuous infusion, called the detomidine group (DG). In the animals of the second group (eight horses) GGE was used in continuous infusion, being called group GGE (GEEG).

For the first protocol to be analyzed (DG), five minutes after administration of the bolus detomidine, an equipment with 0.9% sodium chloride solution (0.9% NaCl) was inserted for 6+continuous administration of detomidine. The continued administration of detomidine occurred at a dose of 10 micrograms/kg/hour (Wilson *et al.*, 2002) in 40mL of 0.9% NaCl solution, for 90 minutes. During this period, the degree of sedation was assessed at the following times: T0 (baseline), T1 administration of detomidine bolus, T2 five minutes after administration of the bolus of detomidine and initiation of continuous infusion of detomidine; T3 after 10 minutes of the sedative drug and application of the local block; T4 15 minutes after administration of the sedative drug; T5 start of surgery (20 minutes after sedation); T6 25 minutes after the sedative; T7 30 minutes after the sedative; T8 at 35 minutes of sedation; T9 at 40 minutes; T10 at 45 minutes; T11 at 50 minutes, T12, 55 minutes, T13, 60 minutes, T14, 65 minutes, T15, 70 minutes, T16, 75 minutes, T17, 80 minutes, T18, 85 minutes, T19, 90 minutes.

In the second protocol to be evaluated (GEEG), consisting of continuous infusion of GGE, a 5% glucose solution was used to dilute the drug. This solution was heated for three minutes at maximum power in a common microwave. After this heating, 400 ml of the solution was withdrawn from the flask and placed in a sterilized one liter becker. In this solution, 10 grams of GGE powder were diluted, being homogenized by means of gentle circular

movements. The 5% glucose solution associated with GGE was again inserted into the original vial using a sterile equipment, by means of a siphoning process.

Thirty minutes after this dilution, the continuous infusion of the solution was started. Five minutes after administration of bolus detomidine, at a dose of 10 micrograms per kg intravenously, the device with 5% glucose solution associated with GGE was inserted. Such administration was performed by means of an infusion pump adjusted to a dose of 20 mg/kg of GGE/kg/hour (2 ml/kg/hour). The continuous infusion lasted for 90 minutes. During this period, the degree of sedation was assessed at the following times: T0 baseline, T1 administration of detomidine bolus, T2 five minutes after administration of the bolus of detomidine and initiation of continuous infusion of GGE; T3 after 10 minutes of the sedative drug and application of the local block; T4 15 minutes after administration of the sedative drug; T5 start of surgery (20 minutes after sedation); T6 25 minutes after the sedative; T7 30 minutes after the sedative; T8 at 35 minutes of sedation; T9 at 40 minutes; T10 at 45 minutes; T11 at 50 minutes, T12, 55 minutes, T13, 60 minutes, T14, 65 minutes, T15, 70 minutes, T16, 75 minutes, T17, 80 minutes, T18, 85 minutes, T19, 90 minutes.

To complement the protocols, all animals were submitted to local anesthesia with lidocaine. This drug was administered at time three (ten minutes after administration of the detomidine bolus). Lidocaine at 2% was used at a dose of 3 mg/kg (Massone *et al.*, 1990). Local anesthetic administration was performed by means of infiltration using a 30x8 needle attached to a syringe suitable for the volume. The final volume calculated for each animal was divided into four equal portions. A portion was injected into the right testicle and another portion into the left testicle. A fourth part was administered to the right spermatic cord and another fourth part to the left spermatic cord. The remaining two portions were administered at the right and left incision lines respectively.

The start of surgical procedures was standardized at 20 minutes (T5) after bolus administration of detomidine. This time was standardized because the drugs used are considered to have a maximum effect twenty minutes after intravenous administration.

Ten minutes after the administration of the last volume of local anesthetic at the incision line, orchiectomy was started, and all orchiectomies were performed by the same surgeon. This surgical procedure was performed according to the open orchiectomy technique described in the literature (Auer and Stick, 2018) with adaptations. An incision was made parallel to the median scrotal raphe and opening of the tunica vaginalis with exposure of the testis, followed by rupture of the testicular ligament, clamping of the spermatic cord and subsequent hemostasis with a nylon wire. The procedure was performed first on the right testicle, followed immediately by orchiectomy of the left testis. Tissues were not approximated, and the surgical time was carefully noted for each animal.

The effects of sedation were evaluated using the same tests as at time zero (Chart 1). The assessment of the degree of sedation in all animals was performed blindly, that is, the evaluator had no prior knowledge of the established protocol.

At the end of the surgical procedure, all animals were accompanied and monitored for 90 minutes. At the end of this time, continuous infusion was discontinued in both protocols and the animals were followed until the return of normal ambulation and the degree of sedation evaluated from zero to three (Chart 1). At this time, flunixin meglumine was administered at a dose of 1.1mg/kg intramuscularly. This drug was administered for two more days at the same dose and route.

After the surgical procedure and the return of sedation, the animals were housed in individualized stalls for seven days. The wound was cleaned, and its appearance was evaluated. All animals were taken for a walk twice a day for 15 minutes. After this period, the animals were discharged.

Descriptive statistics, normality test and t test were performed for comparison between groups. The significance level was 5% for all tests. Spearman's test was performed to observe the correlation between all clinical parameters evaluated (heart rate, respiratory rate, mean

blood pressure, systolic blood pressure, diastolic blood pressure and temperature).

RESULTS AND DISCUSSION

There were no deaths during the experiment and no postoperative infections or other complications were observed. The absence of deaths is expected in animals classified in ASA I (Deutsch and Taylor, 2021). The non-occurrence of postoperative infections is probably due to the antibiotic prophylaxis protocol used, as well as the fact that they are elective surgical procedures (Canola *et al.*, 2020).

The GGE dilution used in the animals of the GEEG protocol was simple, easy, and quick. The continuous infusion of GGE was facilitated by the dilution performed (1%). Therefore, the dilution of GGE to be used at 1% was considered fundamental for the success of the protocol in which this drug was used. The slight heating (Fig. 3 D) allowed the dilution in an adequate way (Fig. 3 E), allowing the use of the drug safely. Such dilution is unprecedented in the consulted literature. At higher concentrations (5 to 10%) GGE has serious adverse effects such as thrombophlebitis (Bettschart-Wolfensberger, 2015) and intravascular hemolysis (Pang, 2013). The occurrence of hemolysis in horses has been documented when the concentration exceeds a 15% solution. Intravascular thrombus formation is also dose related, and concentrations above 7% are associated with an increased risk of thrombosis. This effect is related to the concentration of the solution and not to the speed of its administration. Histological changes, including endothelial loss with fibrin clot formation, have been reported (Pang, 2013).

Clinical parameters evaluated at basal moment were normal for the species. All horses evaluated at baseline for the degree of sedation were classified as 0 (Chart 1).

The two protocols used allowed the procedures to be performed when standing (Fig. 2), and all horses presented sedation after administration of the drugs (detomidine and GGE) (Fig. 3). The patients did not show signs of pain or discomfort (Fig. 2), allowing the procedures to be performed uneventfully. The performance of surgical procedures when standing has several advantages in the equine species. For anesthesiologists and surgeons, such advantages refer to the reduction in the use of advanced technical support, resulting in lower operating costs. This reduction is also amplified by the decrease in the time spent in performing the procedures, compared to general anesthesia (Gilger and Davidson, 2002). Reducing the length of permanence in an inpatient regimen has benefits for the patient, who shows fewer pathological changes related to complications arising from general anesthesia in the recovery period (Valverde, 2021). The advantages mentioned in the literature were observed in the animals of the present study.

The sedation presented by all horses after administration of detomidine is due to the sedative effects of the drug. Detomidine has good results in equine sedation (Gozalo-Marcilla *et al.*, 2019; Hollis *et al.*, 2020) and has been used in other studies with standing horses (Gozalo-Marcilla *et al.*, 2019; Hollis *et al.*, 2020), including for performing complex surgeries such as laparotomies (Hollis *et al.*, 2020).

Statistically ($p<0.01$) it was observed that the sedation protocol using GGE promoted a higher degree of sedation than the detomidine protocol (Fig. 3). Besides, the recovery of the animals in which the GGE protocol was used was uneventful and smooth (Fig. 4).

It is important to note that the use of GGE in anesthetic protocols for horses described in the literature refers to general anesthesia (Pratt *et al.*, 2019). The use of the drug in sedation protocols for performing standing procedures in the equine species was not recorded in the consulted literature. Thus, the protocol proposed in the present study is unprecedented in literature.

The decrease in clinical parameters (heart rate, respiratory rate, mean arterial pressure, systolic arterial pressure, diastolic arterial pressure, and temperature) (Fig. 5, 6, 7, 8) in all animals is due to the sedative action of the drugs used in the protocol (detomidine and GGE) (Pang, 2013). In other studies, it was recorded that detomidine in horses produces reductions in the same clinical parameters observed in the present work (Yamashita *et al*., 2000; Carregaro *et al*., 2020). Regarding GGE, the same changes were also observed in the aforementioned clinical parameters (Massone *et al*., 1990; Mello *et al*.,

2000; Hellu *et al*., 2012). One of the most important parameters to evaluate the effect of drugs is blood pressure. Although there was a decrease in this clinical parameter in all animals, there were no clinically detectable deleterious effects in patients. Thus, it can be stated that the protocols used were safe from the point of view of blood pressure. Other studies using the same sedatives showed similar results (Yamashita *et al*., 2000; Carregaro *et al*., 2020; Mello *et al*., 2000; Hellu *et al*., 2012.

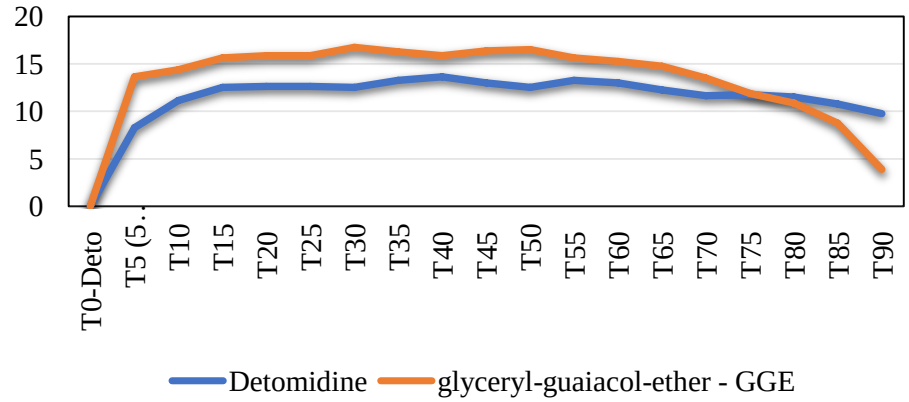

Figure 3. Mean degree of sedation (0 - 3: no sedation; 4 - 9: mild sedation; 10 - 15: moderate sedation; 15 - 18: intense sedation) of horses submitted to standing orchiectomy with two sedation protocols: detomidine in continuous infusion (n=8) and glyceryl-guaiacol–ether in continuous infusion (n=8). T: time in minutes; Deto: detomidine.

Figure 4. Male horse submitted to standing orchiectomy, sedated with continuous infusion of glyceryl-guaiacol–ether in the immediate recovery period after the surgical procedure.

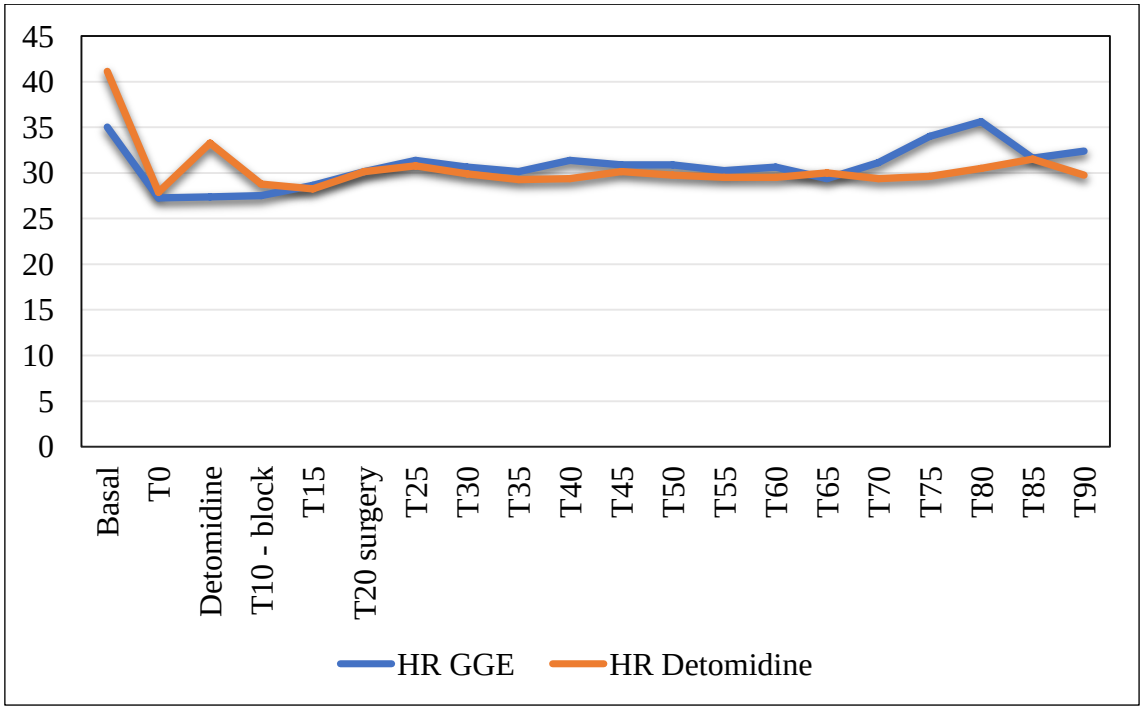

Figure 5. Mean Heart Rate (HR; beats per minute) of horses sedated with glyceryl-guaiacol-ether (GGE) (n=8) in continuous infusion and detomidine in continuous infusion (n=8) over time (90 minutes) to perform a standing orchiectomy. T: time in minutes; Block: administration of local anesthetic.

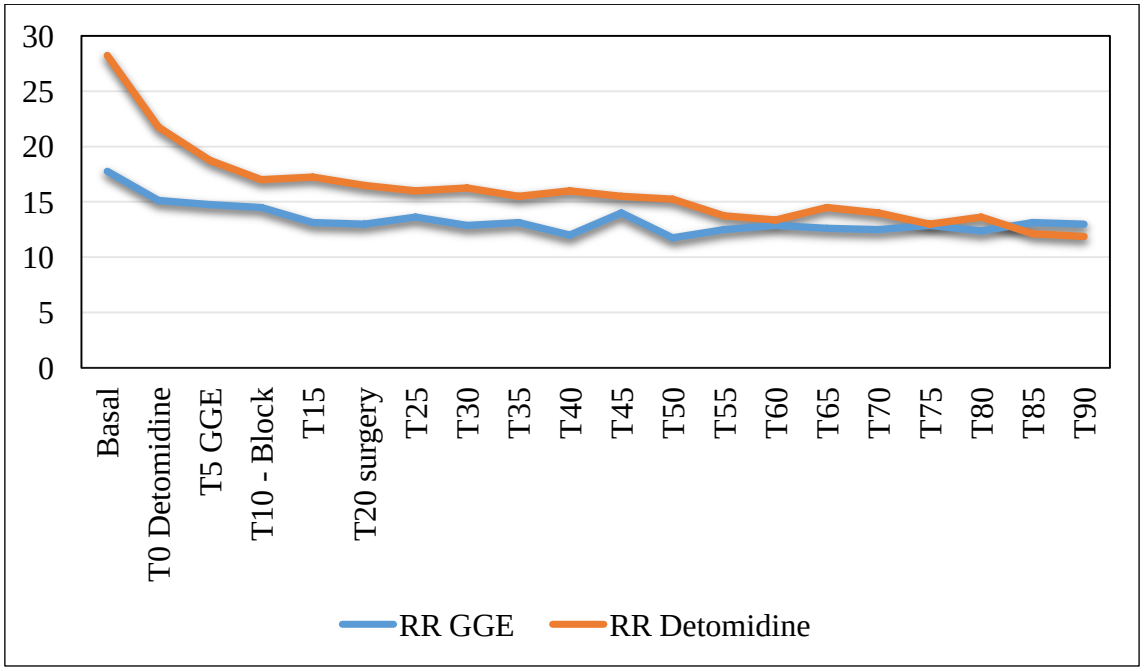

Figure 6. Mean Rate Respiratory (RR; movements per minute) of horses sedated with glyceryl-guaiacol-ether (GGE) (n=8) in continuous infusion and detomidine in continuous infusion (n=8) over time (90 minutes) to perform a standing orchiectomy. T: time in minutes; Block: administration of local anesthetic.

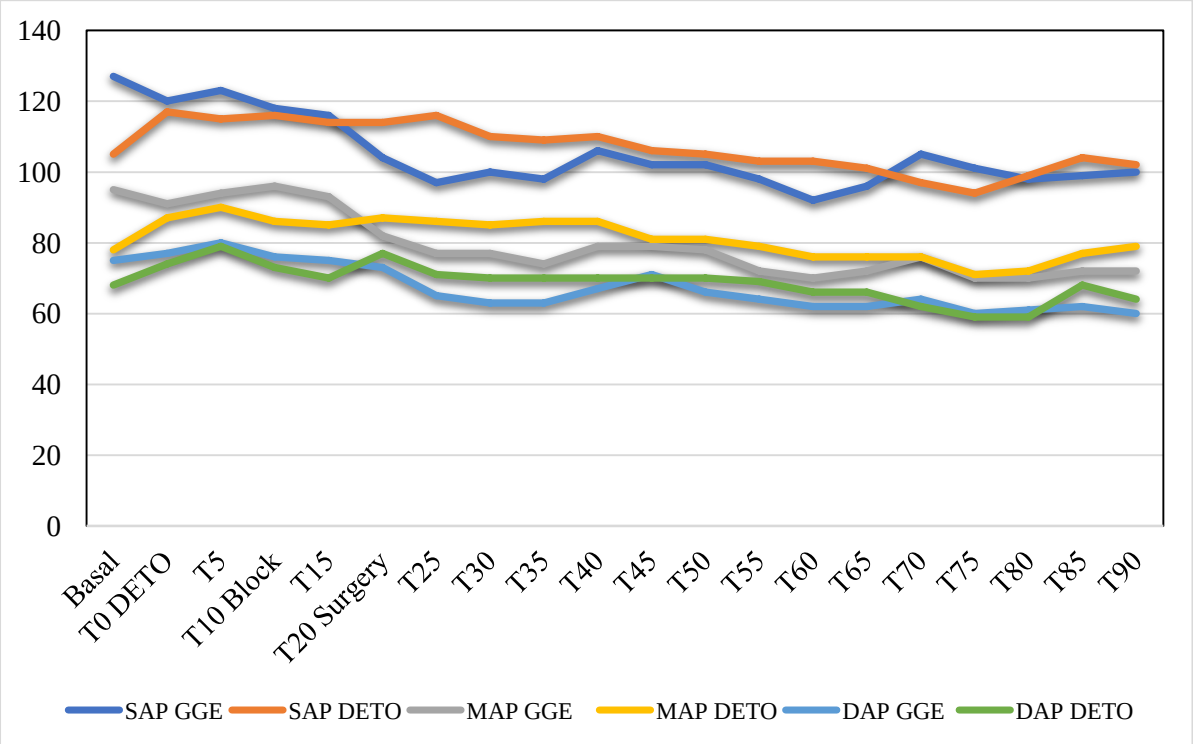

Figure 7. Systolic arterial pressure (SAP), Mean arterial pressure (MAP), Diastolic arterial pressure (DAP) (millimeters of mercury) of horses sedated with glyceryl-guaiacol -ether (GGE) (n=8) in continuous infusion and detomidine (DETO) in continuous infusion (n=8) over time (90 minutes) to perform a standing orchiectomy. T: time in minutes; Block: administration of local anesthetic.

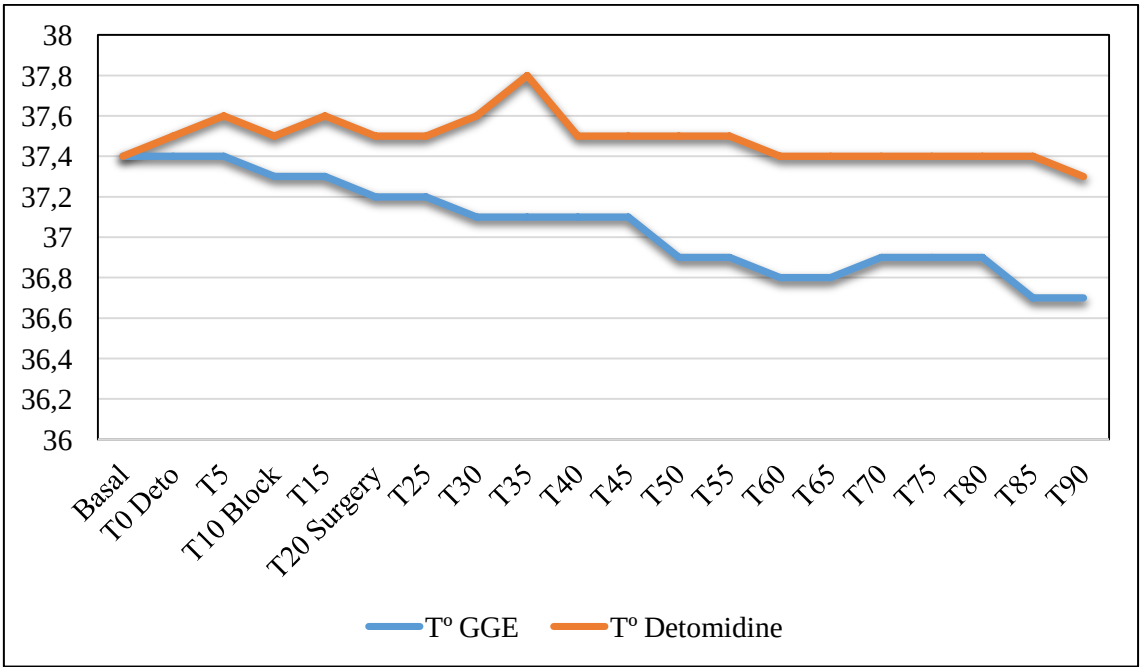

Figure 8. Mean temperature (Tº; degrees centigrade) of horses sedated with glyceryl-guaiacol-ether (GGE) (n=8) in continuous infusion and detomidine (Deto) in continuous infusion (n=8) over time (90 minutes) to perform a standing orchiectomy. T: time in minutes; Block: administration of local anesthetic.

The high degree of sedation promoted by GGE protocol is particularly advantageous for the surgeon and staff, as it allows surgical maneuvers to be performed without patient interference. In addition, it provides welfare to the horse, ensuring a smooth and uneventful recovery, as observed in the studied animals (Fig. 3).

CONCLUSION

The two sedation protocols tested in the present work made it possible to perform standing orchiectomies in the equine species. However, the protocol in which guaiacol glyceryl ether is used in a 1% solution presented a more profound sedative effect, deserving preferential indication for performing procedures when standing in the equine species. Additionally, the protocol proved to be safe and without adverse effects.

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