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# Preemptive effects of epidural s (+) - ketamine or ketamine in the horse's postincisional pain

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## Abstract

The aim of this study was to evaluate the pre-emptive effect of epidural ketamine S (+) (SK) or racemic ketamine (RK) administration, in post-incisional pain in horses. Were used in a blinded, randomized experimental study, sixteen mixed breed mares, 6±2 years old, weighting 273.2±42.0 kg. An epidural catheter was inserted 24 hours before the trials. The thigh region was shaved bilaterally, and mechanical cutaneous sensibility was measured using von Frey filaments (T-30). Using the left side as the control one, local anesthesia was performed at the right side. Twenty-five minutes later, SK was injected in G1 or RK in G2 through the epidural catheter. Five minutes after the ketamine injection, a 10 cm skin incision was made on the right side, and then sutured. Mechanical post-incisional pain was measured using von Frey filaments, at 1, 3 and 5 cm around the incision at 15 minutes intervals, for 2 hours, then 4, 6 and 8 hours after suturing. No changes were observed in the heart and respiratory rate and rectal temperature among groups or times of each group. Hind limb ataxia was observed in 62.5% and 12.5% of G1 and G2 respectively. SK and RK reduced cutaneous sensibility in the right and the left sides to mechanical postincisional pain during all time of experiment. Epidural SK and RK produce similar post-incisional analgesic effects, did not interfere in the cardio-respiratory parameters. The SK induces more intense ataxia in mares and presents a larger analgesic potency in the first 60 minutes after the administration.

**Key-words:**
S (+) – Ketamine.
Hyperalgesia.
Von Frey.
Horses.
Pain

## Introduction

The painful process begins in periphery of tissue damaged, after activation of specialized receptors in the nociceptive inputs that transmits the message to the spinal cord though sensitive fibers. The acute pain is transmitted by painful mielinated fibers type A and chronic pain is transmitted by stimulation of amielinated fibers type C. Eventually, the sensitive threshold is reduced by different factors, leading to a hyperalgesia due to increasing nociceptive sensitivity called primary hyperalgesia (PH), or by facilitated sensory transmission, called secondary hyperalgesia (SH)[1]. The PH is a variety in the sensitivity of the injuried area characterized by enhanced threshold to heat and mechanical stimuli due to central sensitivity (CS), and is induced by afferent nociceptor activation associated with central hyper excitability. SH is a variety in the area surrounding the injury characterized by an increasing of pain threshold to mechanical stimuli only, caused by an increased excitability of neurons of spinal cord[2].

The mechanism responsible to the transmission of spinal and supra spinal nociceptive information can be interrupted or minimized through anesthetics or analgesics spinally administered. Thus, low doses of analgesics infused by epidural route have been proposed like alternative blockade to CS to pain because it has negative regulatory effect of nociceptive information leading to analgesia. The pharmacological

effects of ketamine when injected by systemic routes are characterized by dissociative anesthesia state and emphasized simpatomimetic activity with important side effects like hallucination, excessive increased blood pressure and heart rate. However, the necessary dose for analgesia effects is lower than those necessary for surgery anesthesia[3,4]. The epidural racemic ketamine (RK) does not induce respiratory depression or other side effects[5,6]. Epidural low doses seem to affect the nociceptive information modulation and produces analgesia[7] preventing heat hyperalgesia, by selective sensorial blockade without motor control changes[8]. The epidural RK produced effective analgesia of tail, perineum and thigh, and, additionally, verified that duration of these effects were dose-dependent[9].

On the other hand, if only considered the SK effects, it enables to see that its pharmacological properties are very similar, when compared to RK. Nevertheless, SK has a high therapeutic index causing less locomotor activity and psicomimetic effects at hypnotic doses [10]. The effects of the two substances were compared and found that SK is two or three times more potent that RK. In the same research the authors observed that giving half dose of SK, patients recovered their activities faster than those treated with RK[11]. This fact demonstrated that administrating 50% of the initial RK dose is possible to obtain equipotent clinical effects with SK[12]. SK affinity to N-methyl-D-asparte (NMDA) receptors is 3-4 times higher than RK, with lower activity at the sigma receptors[13].

Observed, that Ketamine actives the monoaminergic descending system by stimulation of opioid receptors, and that NMDA receptors activation in the spinal cord has an important role in pathologic pain states like allodynia and hyperalgesia, observed after tissue or nervous injury[14]. The non-competitive NMDA receptor blockade has been considered the most important mechanism that explains the simpatomimetic, analgesic and anesthetic effects of ketamine[12]. The recovery period can be improved and reduced if the inflammatory response and the CS are minimized by preemptive use of different drugs[15]. The NMDA receptors antagonist, when administered before the surgical trauma, can inhibit the nociceptive inputs facilitating the postoperative pain control[16].

The von Frey filaments have been widely used to induce mechanical stimuli and determine mechanical threshold, mechanical pain threshold and wind up like pain in rat[17], dogs[18], horses[7] and humans[16]. The device is composed by twenty-one nylon filaments of different diameter, fixed in an acrylic bar. When applied around or over the injured area, determined force (grams force) is delivered to produce nociceptive stimuli[16].

The objective of this study was to evaluate the effects of pre-emptive epidural SK or RK injection on wound sensitivity in horses tested by using von Frey filaments.

## Materials and Method

Sixteen healthy mixed breed mares, 6?2 years old, weighting 273.2?42.0 kg were used, randomly into G1 (n=8) and G2 (n=8). The animals were weighted and clinically evaluated due to heart rate (HR), respiratory rate (RR) and rectal temperature (RT) and were sedated with 1.0 mg/kg of xylazine (Sedomin 10% König São Paulo, Brazil) intravenously. The sacrococciygeal region was shaved and local anesthesia was performed subcutaneously at the first intercoccygeal space with 3.0 mL of 2% lidocaine without vasoconstrictor (Xilestesin, Cristália, São Paulo, Brazil). A spinal needle (Tuohy 80x16F, Becton Dickinson Ind. Ltda, Curitiba, Brazil) was inserted into the epidural space and its correct placement determined by lack of resistance during injection of 5.0 mL of air or by the hanging-drop technique[9]. An epidural catheter (Portex Epidural Catheters 16G, Siems Portex Limited, UK) was inserted in this region and advanced 15 cm cranially.

Twenty-four hours later the thigh

region was shaved bilaterally and skin was drawn in white color (Helios Carbex, São Paulo Brazil) in a rectangular pattern around the incision side at distances of 1, 3 and 5 cm (Figure 1-A). Than the cutaneous sensibility of peri-incisional side was measured by mechanical stimuli with von frey filaments (von Frey Anesthesiometer, Model 1601, IITC Inc. Life Science - CA, USA), along the rectangle lines. This first evaluation was performed before any surgical procedure characterizing the T-30. There after, local anesthesia on intended incision side was performed subcutaneously on the right thigh with 6 mL of lidocaine 2% without vasoconstrictor (Xilestesin, Cristália, São Paulo, Brazil). Twenty-five minutes after lidocaine injection 1.0 mg/kg of SK (Ketamin S (+), 50 mg/ml, Cristália, São Paulo, Brazil) or 1.0 mg/kg of RK (Ketamin, 50 mg/ml, Cristália, São Paulo, Brazil) was administered through epidural catheter in groups 1 and 2, respectively. The final volume of ketamine dilution was standardized using the formula 3.4 mL + (body weigh in kg x 0.013 saline)[9].

After the epidural injection, a 10 cm skin incision was made in the local anesthetic infiltrated line and than closed with a simple interrupted monofilament nylon (Nylon 2.0 monofilament, 45 cm, Brasmedica, Brazil). The sensibility of peri-incisional region was measured with von Frey filaments at 1, 3 and 5 cm around the incision, called evaluation of T0 (Figure 1-B), and than at 15 minutes intervals until 120 minutes, and at 240, 360 and 480 minutes after sutured. At the same time were recorded heart rate, respiratory rate and rectal temperature. Heart rate was evaluated by electrocardiography (Miniscope Intramed Indústria Médico Hospitalar, Porto Alegre, Brazil) and respiratory rate was evaluated by observation of the chest movement. Additionally any clinical and behavior change was evaluated and recorded.

Using the Von Frey filaments made cutaneous peri-incisional sensibility evaluation. The filaments were applied in four different points around the incisional line all sides of the rectangles drawn at 1, 3 and 5 centimeters. Each filament, starting for the thinnest one, was placed on the skin and pressed to bow the nylon for 1.5 seconds, with no obtained response, the next filament was tested. Following, to record the analgesic effect, it was considered the thickest filament that elicited a response. If no response was obtained after the last filament the test was interrupted, inferring an analgesic effect

Peri-incisional sensibility threshold was established for the diameter of the filament that elicited a response, and this value was converted to kg/force by a conversion scale available for the manufacturer. For the statistic analysis the mean values obtained from the evaluations at 1, 3 and 5 centimeters were used.

The same procedure was repeated on the left side (non incised side) in the same time intervals The cumulative score was calculated by summation of force values obtained from the 1, 3 and 5 cm evaluations around the incision, for each time intervals.

The data of HR, RR and RT was submitted analyses to t-test ($p \leq 0.05$). The means between groups and between the times of each group were compared using the Student-Newman-Keuls test ($p \leq 0.05$), to detected significant differences. Data collected from von Frey filaments were recorded in grams and analyzed by non-parametrical Mann-Whitney Rank Sum test ($p \leq 0.05$) among groups and the times of each group by Kruskall Wallis test ($p \leq 0.05$). Incised and non-incised sides were analyzed by Wilcoxon Signed Rank test ($p \leq 0.05$).

## Results

The administration of SK produced behavior alterations as repeated movement of the tail and fore limb, and head ptosis in 3 animals (37.5%). It also produced hind limb ataxia in 5 animals (62.5%). The administration of RK did not produce behavior alterations, but produced hind limb ataxia in 1 animal (12.5%). No changes were

observed in the heart and respiratory rate and rectal temperature among groups or times of each group.

The nociceptive threshold was significantly lower on the incised side for the SK group at T75 until T480 when compared with non incised side (Figure 2). For the RK group the nociceptive threshold was significantly lower at T0 until T480 on the incised side, when compared with non-incised side (Figure 2).

After SK and RK injection the higher von Frey filaments was used, therefore a higher force was produced over cumulative distances (1+3+5 cm) of the incision line, since T0 until T45, and the nociceptive threshold was lower at T75 until T480, when compared the T-30 (Figure 3).

## Discussion

No changes were observed in the heart and respiratory rate and rectal temperature among groups or times of each group after epidural injection of SK or RK. These results, confirming previous study about the minimal cardiopulmonary effects produced by epidural administration of RK[9,7]. Although there are not studies about cardiopulmonary effects of SK in horses, the results obtained showed absence of significant alteration on HR and RR.

The behavior evaluation showed that SK produced sedation and stereotypy in 12.5% and 25% of the animals, respectively. If we assumed that the relationship of anesthetic potency between SK and RK is true in equine, it could be supposed that the sedative effect observed after epidural SK is related to the high administered dose (50% more when compared to RK), since it was verified that SK anesthetic potency is twice more than RK in human[12,11]. Stereotypy observed after epidural RK could be due to dopaminergic stimulation[19], inducing a state of high activity of the CNS, characterized by increase of motor activity, bizarre postures and hallucinatory behavior. Otherwise, epidural RK did not produce behavioral alterations according to[7].

The high incidence of ataxia (62.5%) observed until 35 minutes, could be related to the local anesthetic effect of the SK described for [20]. This effect is related to non-competitive NMDA receptor antagonism and its interference with sodium channels decreasing neuronal depolarization. The low percentage of ataxia (12.5%) observed in RK can support the hypothesis that SK could be responsible for this effect. Confirming this hypothesis it was observed that the RK dose used for[5], was not enough to produce motor blockaded in the human being. Additionally, were described a higher incidence and more prolonged ataxia of the hind limbs after epidural SK[18].

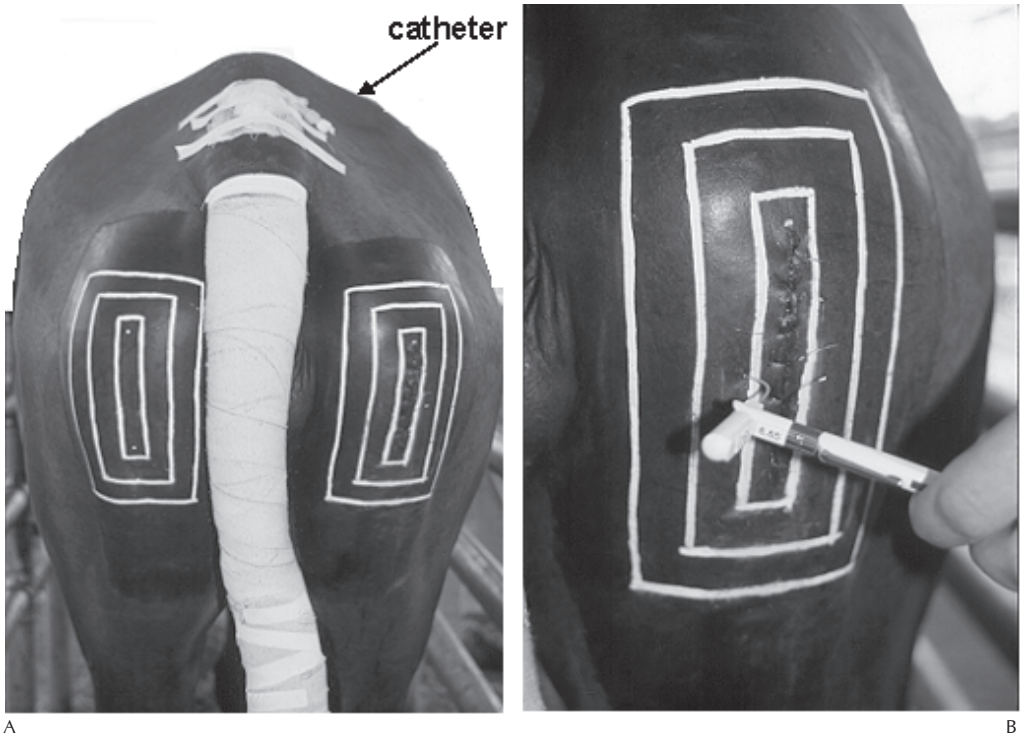
In a previous study the von Frey filaments were used to determine the mechanical pain threshold in areas of secondary hyperalgesia induced by burn. Mechanical force was applied by the filaments, to obtain a verbal response, and the mechanical pain threshold was defined by the lowest force able to produce discomfort[16]. However, in animal's models the verbal response is absent and pain or discomfort is characterized by aversive responses that can be interpreted like pain signs. The von Frey filaments were used to quantify hyperalgesia after epidural ketamine in man, and probed the efficiency of the model[21]. In the same way[22], measured mechanical hyperalgesia by using the von Frey filaments in different areas surrounding surgical wound, and verified that this model is a trustful method to quantify hyperalgesia in rats.

The post-operative increase of nocicepitve threshold after epidural injection of both drugs might be explained by two mechanisms, inhibitory effect of input produced by the non competitive antagonism of NMDA receptor[23], and the blockade of sodium input[24]. The nociceptive threshold between the three distances of the incision was not different within the several observation periods. The same results were observed in the opposite side. However there

were many differences between the incised and non incised rider which can be a result of the presence of SH. Therefore, the repetitive stimulation of the rectangle drew induced a wind-up phenomenon, which is the progressive raise of the spinal cord nociceptor neurons response. The wind-up, as well as, CS involve NMDA receptors [25] and could happen in animals [13]. Nevertheless, were reported that ketamine do not behave as a preventive analgesic because its preference on open ionic channels, situation only existent in the presence of nociceptive input. It could be, at least SH[26].

The differences of the responses to the mechanical stimuli could demonstrate that the local anesthetic did not avoid the wind-up. According, a manner to inhibit the wind-up could be blocking the afferent nociceptive inputs by infiltration of the surgical area with local anesthetic, avoiding the CS[27]. Nevertheless, several studies have used this model with controversial results, because the local blockade had a short effect and did not prevent the SH. Thus, considering that the first von Frey evaluation (T0) was carried out 60 minutes after the local blockade the local infiltrative anesthesia was applied 25 minutes before the epidural injection (and the time between the injection with latency of 10 minutes and 25.2 ? 3.3 minutes until the end of suture) and the low dose of lidocaine 2% (6 ml) showing a duration of effect about 45 to 60 minutes, approximately [28]. It was assumed that a local anesthetic effect could be occurring until the first evaluations of painful sensitivity. However, all force values obtained with SK and RK were lowest in T0 until T480 when compared to T-30. Additionally, there was no difference in response or analgesic duration effect between SK and RK groups during the study. Similar results were obtained showing no difference between the pain threshold after SK and RK[29].

Were described, that the analgesic effect of SK exceeded 273 minutes[20], and




A B

Figure 1– A Skin drawn in a rectangular pattern around the incision side and the line (non incised side) at distances of 1, 3 and 5 cm. B - Evaluation of cutaneous peri-incisional sensibility of incised side by mechanical stimuli with von Frey filaments.

observed analgesic effects of RK until 480 minutes[7]. Additionally, SK was more effective that RK in the first 70 minutes, similar findings were described[11,30,31]. In both SK and RK groups the force necessary to produce a painful stimulus at 0, 15, 30 and 45 minutes in the incised side, was higher than the force used to obtain a response before the epidural injection (T-30). When analyzed, the force necessary to produce a painful response since 75 to 480 minutes, in relationship to the force used at T-30, it could suppose that the pre-emptive epidural administration of SK or RK minimized but not avoided secondary hyperalgesia, according to previous studies [17,26]. These findings demonstrated that SK and RK have a similar anti-hyperalgesic activity.

Were observed that NMDA receptor blockade before or during the injury could prevent or reduce the CS development [21]. Indeed, ketamine can abolish a current CS state[15], by blocking of the nociceptive pathways in the spinal cord[30]. Similarly, were proved that ketamine administered in the pre or postoperative period inhibits SH[2,32]. The analgesic effects of epidural ketamine were described for many authors[16,22,33]. Low doses of ketamine had preventive analgesic effects in neuropathic and postoperative pain[34].

It was concluded that both presentations of ketamine reduced the intensity of SH for eight hours, and no differences were observed about the duration of the analgesic effect. However, SK showed a higher clinical analgesia at the first 70 minutes after its administration. Epidural SK and RK at the dose of 1 mg/kg did not interfere in the cardiopulmonary parameters of the equine.

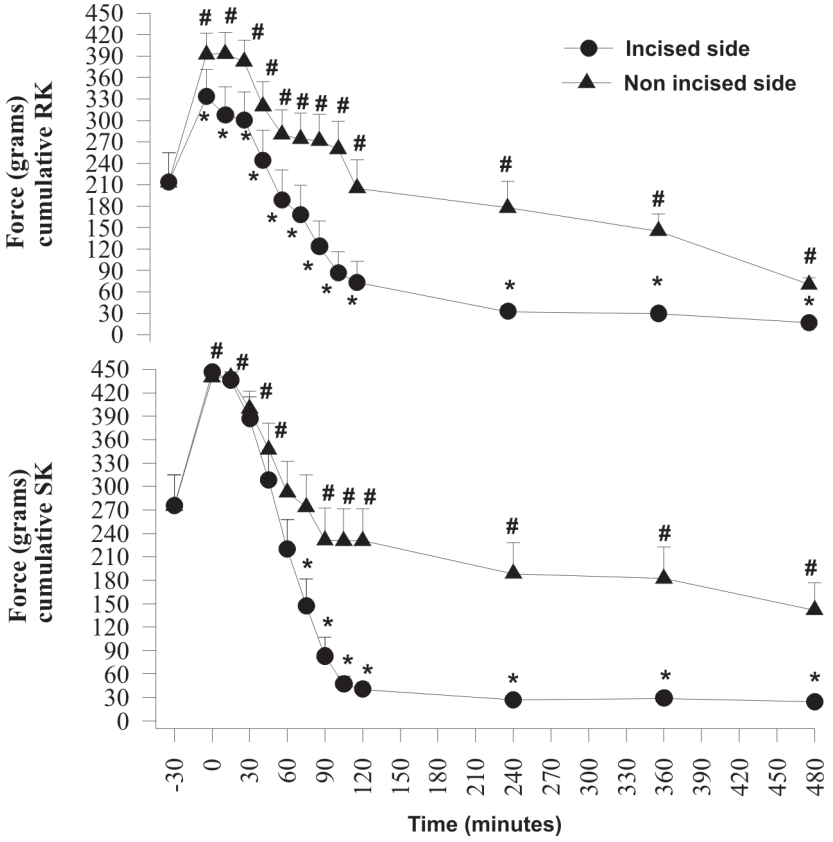



Figure 2 - Cumulative score (1 + 3 + 5 cm) of force in grams by von Frey filaments to incised and non-incised side, observed after epidural SK (1 mg/kg) or RK (1 mg/kg) in horses. *Different from the RK group (Mann-Whitney Rank Sum test, p≤0.05), #Different from the time –30 (Kruskall Wallis test, p ≤0.05).

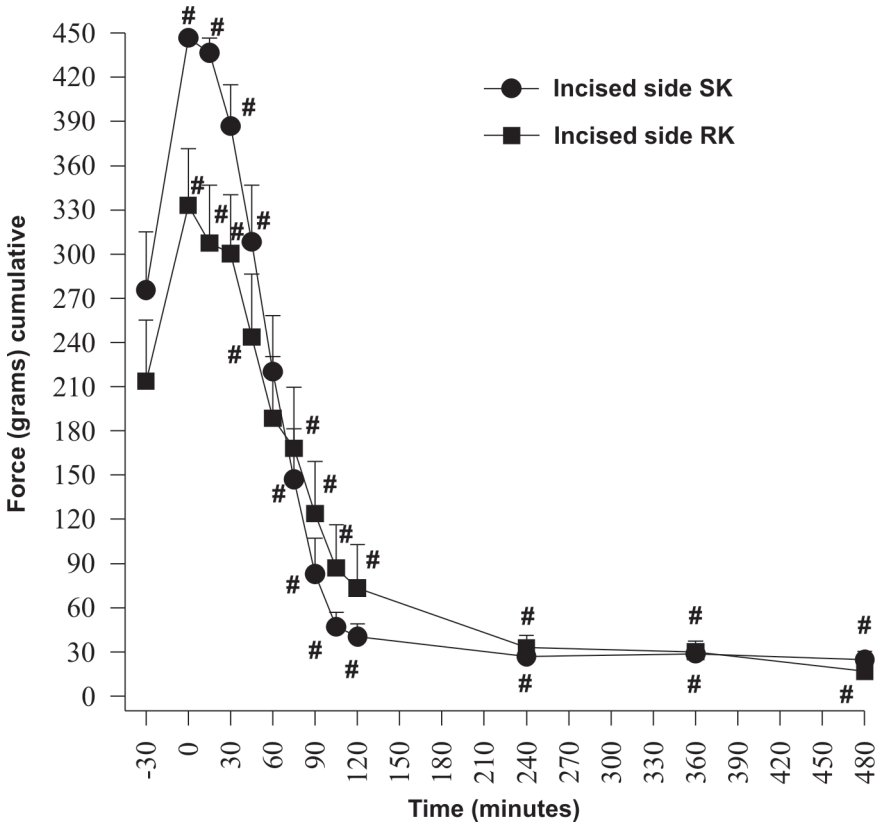



Figure 3 - Cumulative score (1 + 3 + 5 cm) of force in grams by von Frey filaments to incised side, observed after epidural SK (1 mg/kg) or RK (1 mg/ kg) in horses. #Different from the time –30 (Kruskall Wallis test, p≤0.05)

## Conclusion

Clinically the SK presents a larger analgesic potency in the first 70 minutes after the administration, additionally, the SK and RK at the dose of 1.0 mg/kg, for epidural route, reduced the secondary hyperalgesia intensity for, at least eight hours in equines and did not interfere in the cardio-respiratory parameters in equines.

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## Injeção epidural de cetamina ou cetamina levógira no controle da dor pós-incisional, em eqüinos

## Resumo

O objetivo deste estudo foi avaliar o efeito analgésico da administração prévia de cetamina S(+) ou cetamina, na dor pós-inciosal em eqüinos. Utilizaram-se, em um estudo duplo-cego ao acaso, 16 éguas com idade de 6±2 anos, pesando 273,2 ± 42,0 kg. 24 horas antes do início do experimento introduziu-se um cateter epidural. No dia seguinte, as regiões isquiáticas direita e esquerda foram tricotomizadas e, a sensibilidade cutânea aferida utilizando-se os filamentos de Von Frey,

**Palavras-chave:**
Cetamina S (+).
Hiperalgesia.
Von Frey.
Eqüinos.

tempo -30 (T-30). Realizou-se bloqueio anestésico em linha, no lado direito e, 25 minutos após administrou-se através do cateter epidural cetamina S(+) no G1 e cetamina no G2. Cinco minutos após a injeção de cetamina, realizou-se uma incisão de pele de 10 cm no lado direito, seguida de sutura. Avaliou-se a dor pós-incisional, utilizando-se os filamentos de Von Frey, a 1, 3 e 5 cm ao redor da incisão (lado incindido) e a sensibilidade cutânea (lado controle), em intervalos de 15 minutos, por 2 horas e então, 4, 6 e 8 horas após a sutura de pele. Não foram observadas alterações nas freqüências cardíaca ou respiratória e temperatura retal entre os grupos ou entre os tempos de cada grupo. Observou-se ataxia de membros pélvicos em 62,5% e 12,5% dos animais, para o G1 e G2, respectivamente. A cetamina S(+) e cetamina reduziram a sensibilidade cutânea no lado direito e esquerdo, para os estímulos mecânicos produzidos pelos filamentos de Von Frey, durante todo os período experimental. A cetamina S(+) e cetamina produziram duração de efeito analgésico similares e não interferiram nos parâmetros cardiorrespiratórios. Observou-se ataxia mais intensa e potência anestésica superior nos primeiros 60 minutos após a administração de cetamina S(+).

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