Epidural analgesia with morphine or buprenorphine in ponies with lipopolysaccharide (LPS)-induced carpal synovitis

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Abstract

This study evaluated the analgesia effects of the epidural administration of 0.1 mg/kg bodyweight (BW) of morphine or 5 μg/kg BW of buprenorphine in ponies with radiocarpal joint synovitis. Six ponies were submitted to 3 epidural treatments: the control group (C) received 0.15 mL/kg BW of a 0.9% sodium chloride (NaCl) solution; group M was administered 0.1 mg/kg BW of morphine; and group B was administered 5 μg/kg BW of buprenorphine, both diluted in 0.9% NaCl to a total volume of 0.15 mL/kg BW administered epidurally at 10 s/mL. The synovitis model was induced by injecting 0.5 ng of lipopolysaccharide (LPS) in the left or right radiocarpal joint. An epidural catheter was later introduced in the lumbosacral space and advanced up to the thoracolumbar level. The treatment started 6 h after synovitis induction. Lameness, maximum angle of carpal flexion, heart rate, systolic arterial pressure, respiratory rate, temperature, and intestinal motility were evaluated before LPS injection (baseline), 6 h after LPS injection (time 0), and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h after treatments. Although the model of synovitis produced clear clinical signs of inflammation, the lameness scores in group C were different from the baseline for only up to 12 h. Both morphine and buprenorphine showed a reduction in the degree of lameness starting at 0.5 and 6 h, respectively. Reduced intestinal motility was observed at 0.5 h in group M and at 0.5 to 1 h in group B. Epidural morphine was a more effective analgesic that lasted for more than 12 h and without side effects. It was concluded that morphine would be a valuable analgesic option to alleviate joint pain in the thoracic limbs in ponies.

Résumé

La présente étude visait à évaluer les effets analgésiques de l'administration épidurale de 0,1 mg/kg de poids corporel (BW) de morphine ou de 5 μg/kg de BW de buprenorphine chez des poneys avec une synovite de l'articulation radio-carpienne. Six poneys ont été soumis à 3 traitements par épidurale : le groupe témoin (C) a reçu 0,15 mL/kg de BW d'une solution de 0,9 % de chlorure de sodium (NaCl); le groupe M a reçu 0,1 mg/kg de BW de morphine; et le groupe B a reçu 5 μg/kg de BW de buprenorphine, les deux dilués dans une solution de 0,9 % de NaCl pour atteindre un volume total de 0,15 mL/kg de BW administré par voie épidurale au rythme de 10 s/mL. Le modèle de synovite était induit en injectant 0,5 ng de lipopolysaccharide (LPS) dans l'articulation radio-carpienne gauche ou droite. Un cathéter épidural était plus tard introduit dans l'espace lombo-sacré et avancé jusqu'au niveau thoraco-lombaire. Le traitement commença 6 h après l'induction de la synovite. La présence de boiterie, l'angle maximal de flexion carpienne, le rythme cardiaque, la pression artérielle systolique, le rythme respiratoire, la température et la motilité intestinale ont été évalués avant l'injection de LPS (niveau de base), 6 h après l'injection de LPS (temps 0), et 0,5, 1, 2, 4, 6, 8, 10, 12, 16, 20 et 24 h après les traitements. Bien que le modèle de synovite ait induit des signes cliniques évidents d'inflammation, les pointages de boiterie pour le groupe C étaient différents du niveau de base seulement jusqu'à 12 h. Autant la morphine que la buprenorphine ont induit une réduction du degré de boiterie débutant respectivement à 0,5 h et 6 h. Une réduction de la motilité intestinale a été observée après 0,5 h dans le groupe M et aux temps 0,5 et 1 h dans le groupe B. La morphine épidurale était un analgésique plus efficace qui dura plus longtemps que 12 h et ce sans effet secondaire. En conclusion, la morphine serait une option valable pour l'analgésie afin de diminuer la douleur articulaire dans les membres thoraciques chez les poneys.

(Traduit par Docteur Serge Messier)

Introduction

Joint disease is the major cause of decreased performance in horses (1), especially in cases of synovitis normally located at the carpal and metacarpal/metatarsophalangeal joints in young Thoroughbred horses during the early stages of training (2). The clinical signs of acute synovitis include effusion with joint capsule distension, an increase in skin temperature over the joint, hypertrophy and hyperplasia of the synovium, pain on palpation, reduction of joint movement, and lameness (3,4).

Pain control is crucial in treating this condition because it reduces the detrimental effects associated with inflammation and

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neuroendocrine response to pain as well as the discomfort of the animals. If not properly treated, it becomes a chronic condition that leads to irreversible changes in the synovial membrane and in the joint cartilage such as permanent osteoarthritis, lameness, (1) and laminitis in the collateral limb (5).

Although opioids stand out in pain control due to intense analgesia, there is some resistance to their use in horses due to excitability of the central nervous system (CNS) and intestinal hypomotility. The CNS excitation is related to the central dopaminergic activation and seems to be minimized or even not observed in animals with clinical signs of pain (6–8). The hypomotility, which is 1 of the major side effects associated with the use of opioids in horses, can lead to impaction of the large colon and adynamic ileus (9–12).

When administered in the epidural space, opioids give long-term analgesia with a low incidence of side effects (5,13,14). Analgesia can result from the interaction with opioid receptors located at the dorsal horn of the spinal cord or from the systemic absorption through blood vessels in the epidural space, depending on the physicochemical properties of each drug (15,16).

Epidural administration of morphine in horses produces 20 to 40 min of intense analgesia, which lasts up to 19 h (5,17,18), providing analgesia from the hind limbs (5,14,19) to the thoracic region (20). Studies have demonstrated, however, that morphine does not promote analgesia in the thoracic limb of ponies (21,22), unlike what has been observed in dogs (23). It is possible that in large animals the diameter of the epidural canal and the distance from the injection site to more cranial areas can affect the absorption and the cephalic distribution of the morphine through the cerebrospinal fluid (24). The volume administered in the epidural space might also interfere with the analgesic quality (21).

In humans, the analgesic effects of epidural buprenorphine are of supraspinal origin due to its high lipid solubility and consequent absorption in the veins at the epidural space (16). In horses that underwent arthroscopy, the epidural administration of this opioid promoted analgesia of a similar intensity and duration to that achieved using morphine (14), as well as that observed in dogs (25). Nevertheless, there are no studies about the epidural use of buprenorphine for a noxious stimulus at the equine thoracic region.

This study evaluated the analgesia and physiological effects of the epidural administration of 0.1 mg/kg bodyweight (BW) of morphine or 5 μg/kg BW of buprenorphine in ponies with synovitis induced by injecting 0.5 ng of lipopolysaccharide (LPS) from *Escherichia coli* in the radiocarpal joint.

Materials and methods

Six adult ponies were used in the experiment, 4 males and 2 females, aged 5.3 ± 2.7 y and weighing 131.3 ± 17.8 kg, all considered clinically healthy through physical examination and laboratory tests [complete blood (cell) count and liver and kidney screening]. This study was approved by the Institutional Animal Care Committee (number 26/2009).

The study consisted of 3 experimental treatments using all the animals and a Latin square model. Carpal synovitis was induced 3 times in each pony, 2 of them at 1 joint (left or right) and 1 at the contralateral side. The treatments were performed within an interval greater than 7 d and the minimum interval was 15 d for the second injection of the same joint.

The animals were sedated with 1 mg/kg BW of xylazine IV (Anasedan 20 mg/mL; Agribrands Purina do Brasil, Paulínia, SP, Brazil) before hair clipping and aseptic preparation of the left or right radiocarpal joint, according to the experimental design. The thoracic limb was flexed and arthrocentesis was performed using a 23-gauge needle. One mL of synovial fluid was aspirated and 0.5 ng of lipopolysaccharide (LPS) from *Escherichia coli* strain 055:B5 (*E. coli* 055:B5; Sigma Chemical, St. Louis, Missouri, USA), diluted in a saline solution buffered with phosphate (PBS, pH 7.4), was injected to a final volume of 1 mL. Right after the arthrocentesis, the same aseptic preparation was done in the lumbosacral region followed by subcutaneous injection of 2 mL of lidocaine to desensitize the skin (Xilestesin 2%; Cristália, Itapira, SP, Brazil). A 14-gauge Tuohy needle was introduced at a 90° angle and directed cranially into the epidural space. A 16-gauge epidural catheter (Perifix-Katheter; B. Braun, São Gonçalo, RJ, Brazil) was introduced through the Tuohy needle up to the thoracolumbar space that corresponded to the insertion of 21 cm of the catheter and then properly fixed to the skin. Placement of the needle into the epidural space was verified by palpable penetration of the ligamentum flavum, disappearance of a drop of sterile physiologic saline solution from the needle hub (hanging-drop technique), ease of injection of sterile physiologic saline solution, and ease of catheter advancement (14,19,20). Six hours after the synovitis induction, 1 mL of synovial fluid was aspirated from the affected joint to confirm the inflammatory reaction and then 1 of the 3 treatments was administered by epidural injection.

The treatments were separated into a control group (C) in which the animals received 0.15 mL/kg BW of 0.9% NaCl. In group M, 0.1 mg/kg BW of morphine (Dimorf 10 mg/mL; Cristália) and in group B, 5 μg/kg BW of buprenorphine (Temgesic; Schering-Plough, Rio de Janeiro, RJ, Brazil) were diluted in a 0.9% NaCl solution to a final volume of 0.15 mL/kg BW administered by epidural at a rate of 10 s/mL. The final volumes were standardized according to the literature (21) and to ensure that the observer could not recognize the treatment used.

Lameness, maximum angle of carpal flexion, heart rate (HR), systolic arterial pressure (SAP), respiratory rate (f_R), body temperature (T), and intestinal motility were evaluated before sedation (baseline), 6 h after injection of LPS (time 0), and 30 min and 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h after epidural administration.

To assess lameness, the ponies were recorded while being led at a walk and a trot on a hard surface. The images were randomly analyzed by an experienced observer (Dr. De La Côrte) who was completely unaware of the treatments used and the time of each measurement. The lameness was scored as: 0 — absence of visible lameness; 1 — discrete asymmetry, sometimes inconsistent; 2 — visible lameness, rarely inconsistent; 3 — visible lameness at all times; and 4 — severe lameness, rare or no weight-bearing (26). For statistical purposes, the highest score at the walk and trot was considered. The carpal maximum flexion angle was measured using a goniometer (27). The HR was evaluated by auscultation, in beats per min (bpm); the SAP with a Doppler transducer positioned on the coccygeal artery, in mmHg; the f_R by visualization of the thorax,

in breaths per min (brpm); and the T was measured in Celsius (°C) using a rectal thermometer.

Intestinal motility was evaluated by abdominal auscultation of the 4 abdominal quadrants in sequence (upper and lower on the left and right side) using a scoring system (12). A subjective score was assigned to each quadrant in accordance with a scoring system: 0 — no intestinal sounds; 1 — mild, low-pitched crepitation-like sounds audible once per min at both sites within a quadrant; 2 — low-pitched crepitation-like sounds audible more than once per min at both sites within a quadrant; 3 — long, loud gurgling sounds audible once per min at both sites within a quadrant; and 4 — long, loud gurgling sounds audible more than once per min at both sites within a quadrant. Scores from the 4 quadrants were added so that the score ranged from 0 to 16.

If any animal had behavioral or physiological abnormalities indicative of severe pain and stress, a rescue analgesia was administered with 0.1 mg/kg BW of morphine and 1 mg/kg BW of flunixin meglumine IV (Desflan 50 mg/mL; Ouro Fino, Cravinhos, SP, Brazil). All ponies received 1 mg/kg BW of flunixin meglumine IV once a d for 3 d after the end of the evaluation period.

Analysis of variance (ANOVA) for paired samples was used and the Dunnett test for mean comparisons inside each treatment related to time 0 (GraphPad Instat; GraphPad Software, San Diego, California, USA). Analysis of variance followed by the Tukey test was used for intertreatment comparisons in each limb for HR, f_R, SAP, T, and flexion angle. Intestinal motility and lameness were evaluated by ANOVA followed by the Friedman test for intertreatment and temporal comparisons. The parametric results were expressed as mean ± standard deviation (s). The scores corresponding to nonparametric data were expressed in median ± interquartile interval. The differences were considered significant when $P < 0.05$.

Results

All ponies were lame for 6 h after synovitis was induced (0 min). In group C, lameness was significantly different than the baseline for up to 12 h after epidural treatment. The difference from the baseline in group M was observed up to 30 min, while in group B, it was different for up to 4 h. Groups M and B differed from group C at 30 min and at 6 to 12 h, respectively (Figure 1). The maximum angle of carpal flexion increased significantly in both groups C and B 6 h after synovitis induction (Table I). After treatment was administered, ponies in groups C and B had increased flexion angle for up to 24 h, compared to their baseline values. The angle of flexion increased in group M from 4 to 24 h.

Physiological values are shown in Table I. No treatment showed variations in HR, compared with baseline values. Only group B had high HR at 0 min and 16 h compared to group C. The SAP increased only at 4 h in group C, but was within a physiological range for ponies. No changes were observed in f_R. There was an increase in T in group M between 30 min and 10 h and in group B, from 1 to 10 h with a peak in both groups (around 38.5°C) between 2 to 6 h. Hypomotility occurred in group M 1 h after epidural treatment and in group B 30 min to 1 h after treatment. However, none of the animals had abdominal discomfort during the study.

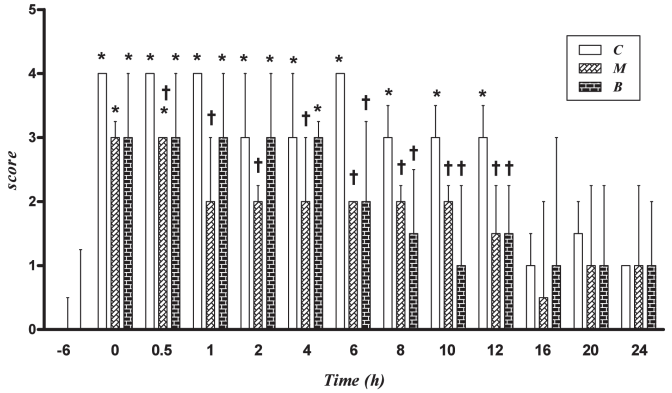

Figure 1. Lameness score in ponies with experimental synovitis treated with epidural 0.9% NaCl solution (C), 0.1 mg/kg BW of morphine (M), or 5 μg/kg BW of buprenorphine (B).
Values expressed as median ± interquartile interval.
*** — Different from baseline.**
† — Different from control treatment at that time.

One animal in group C had severe behavioral and clinical changes and was given rescue analgesia 4 h after epidural injection. The pony did not support weight on the affected limb, became recumbent, lost its appetite, did not drink, and vocalized at any touch of the punctured joint. Cardiorespiratory parameters returned to basal levels 15 min after the rescue analgesia and at 30 min, the pony got up, stood on the affected limb, and began to walk and drink water. These data were not considered for statistical analysis.

Discussion

The synovitis model (0.5 ng of LPS) used in this study was chosen because it is a well accepted model for inducing low to moderate acute synovitis (28–31). Some authors describe the use of higher doses of LPS than that used in the present study, but these doses are associated with the occurrence of intense hyperthermia (32), endotoxemia (33), and permanent changes in joint morphology (34), which limit its use as a model for acute synovitis and submits the subject to the undesirable risk of a permanent lesion or even death. As shown by the results obtained in the present study, the chosen joint synovitis model induced a clinical condition compatible with acute synovitis, according to the references that demonstrate that the inflammation associated with pain developed only after 6 h (30,31).

Although synovitis produced clinical lameness, the model was adequate for only 12 h of evaluation due to the fact that the lameness in group C did not differ from its baseline from 16 h on. There was therefore a time-limiting factor after 12 h of treatment, making it impossible to determine the analgesic efficiency of the drugs after this period.

Some studies report joint effusion and lameness for 36 h, with complete resolution in 48 h using the same dose of LPS (28,31) or even with higher doses of LPS (32). Other authors, however, report that the maximum degree of lameness occurred 12 h after synovitis was induced and that lameness resolved within 24 h (29). These differences may be due to the use of different *E. coli* strains and different breeds of ponies, as the models described above were applied to horses.

Table I. Physiological values of ponies with experimental synovitis treated with epidural 0.9% NaCl solution (C), 0.1 mg/kg BW of morphine (M), or 5 μg/kg BW of buprenorphine (B)

		Time (h)												
Parameter	Group	Baseline	0	0.5	1	2	4	6	8	10	12	16	20	24
Carpal	C	23 ± 3*	71 ± 20*	73 ± 18*	67 ± 31*	60 ± 25*	75 ± 16*	80 ± 10*	78 ± 18*	73 ± 19*	64 ± 13*	61 ± 21*	69 ± 25*	63 ± 19*
flexion	M	33 ± 6	64 ± 13	56 ± 19	69 ± 26	64 ± 24	78 ± 19*	74 ± 25*	79 ± 27*	75 ± 24*	73 ± 19*	72 ± 21*	72 ± 25*	64 ± 27
angle	B	30 ± 10	64 ± 18*	66 ± 18*	68 ± 21*	64 ± 13*	75 ± 21*	79 ± 21*	76 ± 20*	75 ± 25*	71 ± 16*	70 ± 18*	70 ± 18*	60 ± 18
HR	C	47 ± 12	53 ± 16	55 ± 17	55 ± 18	54 ± 17	57 ± 23	50 ± 6	51 ± 8	49 ± 8	46 ± 9	42 ± 8	47 ± 7	46 ± 7
	M	44 ± 11	46 ± 10	50 ± 13	50 ± 13	53 ± 12	53 ± 15	52 ± 11	51 ± 11	51 ± 12	47 ± 11	44 ± 8	47 ± 12	51 ± 9
	B	42 ± 12	57 ± 14†	52 ± 6	51 ± 5	52 ± 8	57 ± 8	55 ± 5	59 ± 12	59 ± 10	55 ± 11	53 ± 12†	51 ± 12	49 ± 9
SAP	C	103 ± 24	134 ± 15	150 ± 16	144 ± 22	144 ± 27	158 ± 74*	132 ± 17	141 ± 45	131 ± 21	124 ± 20	123 ± 26	121 ± 16	121 ± 12
	M	103 ± 7	158 ± 81	128 ± 27	138 ± 28	131 ± 26	127 ± 15	115 ± 8	138 ± 26	113 ± 23	116 ± 16	103 ± 29	110 ± 33	124 ± 45
	B	114 ± 10	154 ± 38	128 ± 10	128 ± 14	130 ± 16	141 ± 38	143 ± 8	158 ± 71	169 ± 75	154 ± 82	129 ± 26	142 ± 79	113 ± 26
f_R	C	34 ± 14	54 ± 23	55 ± 27	65 ± 22	61 ± 31	61 ± 29	59 ± 22	55 ± 24	51 ± 23	42 ± 23	36 ± 18	44 ± 18	48 ± 24
	M	33 ± 17	49 ± 27	51 ± 28	50 ± 28	52 ± 22	51 ± 18	54 ± 24	51 ± 24	38 ± 16	33 ± 14	31 ± 9	36 ± 13	35 ± 18
	B	39 ± 7	54 ± 31	61 ± 37	61 ± 36	67 ± 42	65 ± 46	53 ± 37	59 ± 37	62 ± 31	53 ± 28	43 ± 22	51 ± 16	65 ± 20
Intestinal	C	15 ± 2	13 ± 2	14 ± 2	15 ± 1	12 ± 2	13 ± 2	15 ± 1	16 ± 2	16 ± 1	16 ± 1	16 ± 2	15 ± 1	16 ± 1
motility	M	15 ± 1	13 ± 2	11 ± 4	8 ± 4*†	14 ± 3	14 ± 3	14 ± 1	14 ± 1	16 ± 2	14 ± 2	13 ± 2	14 ± 2	14 ± 1
	B	15 ± 2	13 ± 4	9 ± 2*†	9 ± 3*†	10 ± 3	11 ± 4	15 ± 2	14 ± 3	14 ± 3	16 ± 2	15 ± 3	15 ± 2	15 ± 1
T	C	37.8 ± 0.4	38.2 ± 0.9	38.4 ± 0.9	38.5 ± 0.8	38.6 ± 1.0	38.6 ± 0.8	38.4 ± 0.5	38.3 ± 0.3	38.2 ± 0.2	37.7 ± 0.4	37.6 ± 0.4	37.4 ± 0.2	37.4 ± 0.5
	M	36.9 ± 0.9	37.9 ± 0.7	38.3 ± 0.5*	38.2 ± 0.5*	38.7 ± 0.5*	38.7 ± 0.5*	38.6 ± 0.4*	38.4 ± 0.6*	38.1 ± 0.5*	37.8 ± 0.5	37.6 ± 0.8	37.3 ± 0.8	37.5 ± 0.4
	B	37.5 ± 0.6	38.3 ± 0.5	38.3 ± 0.6	38.5 ± 0.5*	38.5 ± 0.6*	38.5 ± 0.5*	38.6 ± 0.5*	38.4 ± 0.4*	38.4 ± 0.5*	38.3 ± 0.5	37.9 ± 0.5	37.7 ± 0.4	37.6 ± 0.7

HR — Heart rate; SAP — Systolic arterial pressure; f_R — Respiratory rate; T — Temperature.

† — Different from C at the same time.

* — Different from baseline.

Analysis of lameness in group M showed that the analgesic effect of epidural morphine started at 30 min. This latency period was similar to that obtained by other authors (17). In the present study, the analgesic effect of the morphine lasted for 12 h, although other studies (21,22) demonstrated that the use of epidural morphine did not promote analgesia in the thoracic limb region, suggesting that the cranial migration of the drug was insufficient to activate the opioid receptors in the cervical and thoracic region of the spinal cord. We believe that both the high volumes administered and the positioning of the catheter at the thoracolumbar region contributed to the efficacy of morphine in this study. In previous studies, the catheter was placed in the intervertebral sacrococcygeal space and only 10 cm of it was advanced through the epidural space (21) or at the first intercoccygeal intervertebral space and a volume of only 5 mL was administered (22). Although no radiographic examination was performed to identify the position of the catheter, the technique used to place the epidural catheter was judged to be successful using the criteria established by others (14,19,20,22).

As morphine does not act on the mediators involved in the inflammatory process induced by LPS, it is possible that the painful stimulus may have persisted at a lower intensity considering the improvement in the joint flexion angle. Thus, we hypothesize that an association of morphine and a non-steroidal anti-inflammatory drug would provide better analgesia. The aim of the study, however, was to evaluate the central analgesic effect of 2 opioids with different characteristics and find new alternatives for treating pain in equine thoracic limbs. The association with other analgesic drugs could interfere with the pain model used, thus impairing the observation of the analgesic effects attributed to the opioids.

The lameness observed in the animals from group B after treatment with buprenorphine improved significantly after 6 h and its effect remained for at least another 6 h. In humans, buprenorphine given epidurally had a latency period of 2 to 6 h due to its slow absorption and its distribution through fat tissues and consequent slow redistribution (16). However, buprenorphine did not show an initial improvement in the clinical signs. Moreover, the gradual decline in the lameness score in group C after 8 h suggests that buprenorphine did not provide satisfactory analgesia.

The cardiorespiratory parameters were not affected by the joint pain model, which corroborates with other studies (28,30,32,35). Although the intravenous administration of morphine (36) or buprenorphine (12,37) results in excitement and an increase in heart rate, blood arterial pressure, and cardiac index, the epidural use of these drugs did not cause any of those changes (13,14,17,18), which is probably indicated by the absence of behavioral changes.

The decreased intestinal motility observed in groups M and B may be attributed to the opioids as the same effect was not observed in group C. Although the animals had short periods of hypomotility, there was no occurrence of fecal retention or any sign of abdominal discomfort.

In spite of the higher temperature observed in opioid-treated animals, it was not different when compared with group C. However, the temperature values were significantly increased in the opioid groups when values were compared with the basal levels. This increase in temperature was expected in all the groups, including group C. Probably, this increase in temperature did not occur in group C because of its basal value. The dose of LPS was also lower, which minimized the inflammatory effect. Only higher doses of LPS than those used in this study may cause hyperthermia due to the direct action of LPS on the thermoregulatory center and the synthesis and release of endogenous pyrogens from neutrophils and mononuclear phagocytes that are activated by joint inflammation (32).

It was concluded that the behavioral and physiological changes observed in the pony that received rescue analgesia were due to individual variation. Other studies that used the same dose of LPS indicate that it does not induce systemic effects and the animals maintain their normal behavior and appetite and put weight on the affected limb (28,30,31).

This carpal synovitis model produced a painful stimulus for 12 h after the establishment of clinical signs characteristic of this pathology in ponies. The administration of epidural morphine provided better quality analgesia than buprenorphine, with a latency period of 30 min and adequate action for at least 12 h without the occurrence of side effects. It was concluded that morphine is a valuable analgesic option for alleviating joint pain in the thoracic limbs in ponies.

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