

EVALUATION OF AN INTRARTICULAR POLYACRYLAMIDE GEL FOR THE TREATMENT OF OSTEOARTHRITIS OF THE DISTAL JOINTS OF THE TARSUS IN HORSES.

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Summary: Osteoarthritis (OA) of the distal joints of the tarsus, is a degenerative joint disease that causes 60% of pelvic limb lameness in horses. However, the therapeutic approach to OA is palliative and the medical results are highly variable. A prospective, double-blind, controlled, intervention clinical trial was conducted to evaluate the clinical response of an intra-articular injection of a high-viscosity hydrogenated biopolymer (Noltrex[®]), in the short (1 month) and medium term (3 months) compared to the traditional treatment of sodium hyaluronate and triamcinolone acetate. When evaluating the clinical efficacy of the two treatments, the therapeutic response of Noltrex[®] in time was positive in relation to the resolution of lameness, being statistically significant ($p=0.015$), and the response to sodium hyaluronate and triamcinolone acetate, although it was also positive, it was better ($p<0.01$). It can be concluded that Noltrex[®] is a therapeutic alternative with a similar response to traditional pharmacological treatments, with the advantage of limiting the collateral and unwanted effects on cartilage that intra-articular drugs have.

Keywords: biopolymer, horses, intra-articular, Noltrex[®], osteoarthritis.

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Abstract: Osteoarthritis (OA) of the distal tarsal joints is a degenerative joint disease that causes 60% of the lameness of the pelvic limbs in horses. However, the therapeutic approach to OA is palliative and the medical results are highly variable. A prospective, double-blind, controlled clinical intervention trial was conducted to evaluate the clinical response of an intra-articular injection of a high-viscosity hydrogenated biopolymer (Noltrex®), short (1 month) and medium term (3 months) compared to the traditional treatment of sodium hyaluronate and triamcinolone acetate. In evaluating the clinical efficacy of the two treatments, the therapeutic response of Noltrex® over time was positive in relation to the resolution of lameness, being statistically significant ($p = 0.015$), and the response to sodium hyaluronate and triamcinolone acetate although it was positive, it was better ($p < 0.01$). It can be concluded that Noltrex® is a therapeutic alternative with a similar response to traditional pharmacological treatments, with the advantage of limiting the side effects and unwanted effects on the cartilage of intra-articular drugs.

Key words: biopolymer, horses, intra-articular, Noltrex®, osteoarthritis.

Introduction: Osteoarthritis (OA) is a very common clinical problem in horses (1), the literature estimates that up to 60% of lameness problems in horses are related to OA, which may occur early or later in the equine athlete's sporting life (2). The most important structure from a clinical point of view is hyaline cartilage, which is responsible for distributing the load functions within the joint and allowing the joint surfaces to slide virtually without friction during exercise (1). For this reason, in athlete horses, the distal joints of the tarsus have a higher incidence of OA (3). In horses, the management of OA is a multifaceted challenge that is usually addressed with intra-articular medication that allows a targeted, but palliative, therapy to the site of the pathology; a wide range of products are available for this use, which include the use of intra-articular corticosteroids (1,4,5). However, therapeutic tools to solve the degenerative problem that begins in articular cartilage are not yet available, nor are they possible to extrapolate *in vitro data* to clinical situations *in vivo* (3). Thus, this study seeks to evaluate the performance of a new therapeutic alternative, a

hydrogenated polyacrylamide gel called Noltrex[®], which acts as a biocompatible endoprosthesis without pharmacological effect and that would stabilize the intra-articular environment and with this recovery of cartilage; and compare it with the traditional treatment of sodium hyaluronate and corticosteroid in relation to the improvement of the main clinical sign caused by OA in Colombian criollo horses, different degrees of lameness.

Methodology: A prospective, double-blind, intervention controlled clinical trial was conducted. Population sampling was done for convenience between June 2016 and July 2017. Twelve horses were randomly divided into two groups of 6 horses each. In one group, intra-articular infiltration was performed with Noltrex[®] and in the other sodium hyaluronate with corticosteroids.

The animals included in the study were Colombian criollo horses with unilateral OA of tarsus grade 1, 2 and 3 proposed for this work, as follows: grade 1: positive for the joint stress test and intra-articular block, peri-articular osteophytes, no evident alteration in the subcondral bone and presence of joint space, grade 2: positive for joint stress test and intra-articular block, peri-articular osteophytes, moderate peri-articular bone proliferation, moderate decrease in joint space and, grade 3: positive for joint stress test and intra-articular block, defined peri-articular osteophytes, moderate peri-articular bone proliferation, sclerosis of the subcondral bone and moderate decrease in joint space.

Horses with more than one affected joint with OA, with OA secondary to a joint infection, with some joint undergoing arthroscopy up to 3 months before the start of the study, or under any other "anti-arthritis" treatment were excluded which was carried out two months before the start of the study. Horses that were receiving any additional treatment or had undergone surgery during the study period were also excluded; or

those classified as grade 4 proposed for this work, defined as: positive to joint stress test, positive to intra-articular block, defined peri-articular osteophytes, severe peri-articular bone proliferation, lysis of the subcondral bone and severe loss of joint space or fusion of joint space.

To determine whether each horse was included or excluded from the study, X-rays and clinical exams were performed. The imaging parameters were obtained by means of dorso-plantar, latero-medial, dorso-lateral plantar-medial oblique and dorso-medial oblique radiographic projections. The clinical parameters were obtained by means of an orthopedic examination, which made it possible to determine the initial degree of lameness and to record it in a standardized video where posterior and lateral views were obtained for subsequent evaluation.

In order to identify the area of joint pain, diagnostic approaches were carried out, such as joint stress tests, evaluation of walking, jogging and on different surfaces (1), with which the exacerbation of lameness was observed. Subsequently, an intra-articular anaesthetic block was diagnosed with a sterile anaesthetic salt (2% lidocaine) in the tarsus; for the tibio-tarsal joint a 1-inch 20G needle and 10-20 ml of 2% Lidocaine were used, for the distal inter-tarsal a 5/8-inch 20G needle and 3-5 ml of 2% Lidocaine were used, and for the tarso-metatarsal a 1.5-inch 20G needle was used and 3 to 5 ml of Lidocaine 2%, after 5 minutes the gait evaluation was performed to determine the degree of clinical improvement of lameness.

After diagnosis, the therapeutic intra-articular infiltration was performed, after surgical disinfection of the affected joint area, with an 18G needle for the experimental group treated with Noltrex[®] and for the control group treated with sodium hyaluronate and corticosteroids. A self-adhesive bandage was then applied to cover the tarsus for 36 to 48 hours and it was recommended that each horse remain in the stall for 8 days after intra-articular therapeutic infiltration.

Finally, the randomized and blind evaluation of the resolution of the clinical signs of OA, i.e., the degree of improvement or worsening of the lameness presented by each horse according to the AAEP scale, was performed by the designated veterinarians(1) and which was classified with the video recording described above; This evaluation was carried out in the same way the month and three months after the therapeutic infiltration.

Statistical analysis: A nonparametric statistical analysis was performed using a Friedman *test* to corroborate each treatment and its response over time. Additionally, a nonparametric Mann-Whitney U *test* was performed to compare treatments. The level of significance used was 0.05.

Results: A total of 12 horses were evaluated in this study. Initially all horses were included under the radiographic and clinical criteria that classify the degree of OA of each horse (1, 2, 3, 4, 5 according to degrees of AAEP) and the positive response to intra-block. They were subsequently evaluated in the medium and short term (Figure 1).

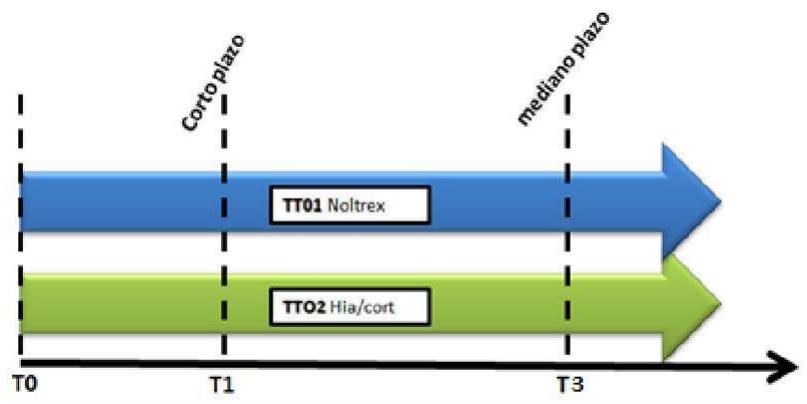


Figure 1. Evaluation of all horses in the short and medium term after intra-articular therapeutic infiltration. Clinical examination, radiographic examination and intra-articular infiltration were performed at time 0.

The therapeutic response to Noltrex® at time 1 and 2 was positive in relation to the resolution or improvement of lameness, being statistically significant ($p=0.015$) (Figure 2).

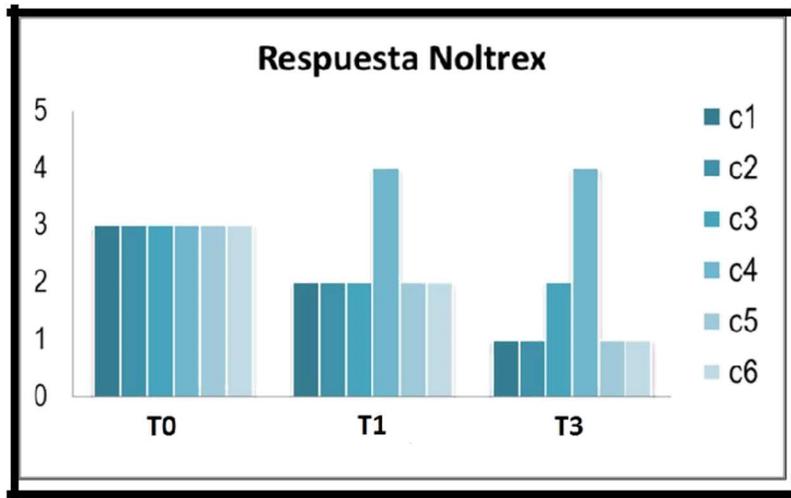


Figure 2. Evolution of horses treated with Noltrex® in the short (T1) and medium term (T3). The scale from 0 to 5 refers to the lameness degrees of AAEP. c1 to c6 correspond to each horse in this group.

The response of sodium hyaluronate plus Triamcinolone acetate was very positive in relation to the resolution of lameness, being highly significant ($p < 0.01$). (Figure 3). There was no statistically significant difference between sex ($p < 0.5$) the statistical analysis was done using *R-Project*)

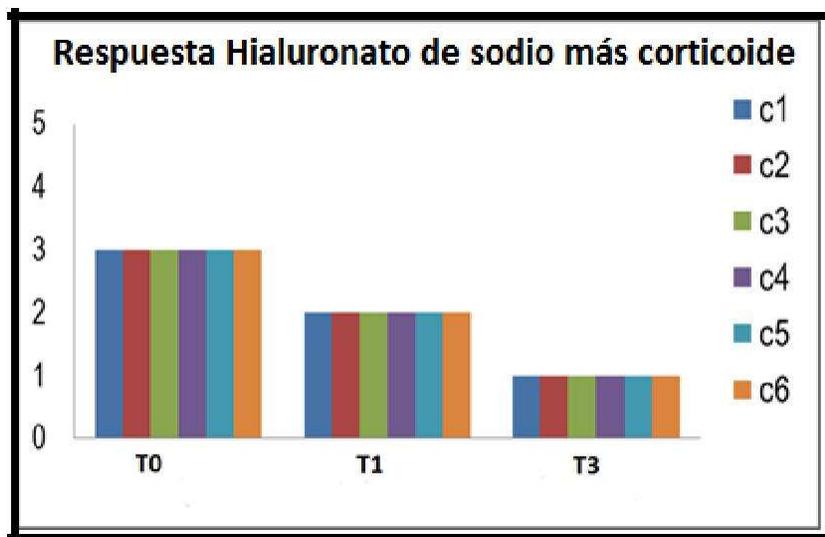


Figure 3. Evolution of hyaluronate-treated horses + short-term (T1) and medium-term (T3) corticosteroid. The scale from 0 to 5 refers to the degree of lameness of the AAEP.

The scale (c1, c2, c3, c4, c5, c6) refers to each horse in this group.

Discussion: The use of therapeutic alternatives with novel approaches represents a need in the daily work of veterinary doctors of horses and sports medicine. The use of a hydrogenated polyacrylamide gel, which plays the role of an endoprosthesis without pharmacological effects, represents a new alternative for the treatment of tarsal OA, since the traditional treatment of OA involves the use of intra-articular corticosteroids, which in the medium and long term generate deleterious effects on the articular cartilage (6-11).

Treatment with Noltrex[®], and sodium hyaluronate plus corticosteroids results in decreased clinical signs of OA, i.e., degree of lameness (2,8). However, in the group of horses treated with sodium hyaluronate plus corticosteroids, all the horses had a statistically significant improvement. The present study found that there was no significant difference between the two groups in the short and medium term, these results can be explained according to the comparative evaluation of the degree of initial lameness that each horse had and the degree that it presented in the short and medium term, showing a significant improvement as time passed, either by the homeostasis that Noltrex[®] generated in the joint or by the powerful anti-inflammatory effect of corticosteroid associated with sodium hyaluronate.

The degree of improvement that was evident after the use of the two visco supplementation products behaved similarly, going from an initial grade 3 (AAEP) to grade 2 or grade 1, being more representative in the medium term than in the short term.

Regardless of sex, both in the short and medium term, this study found that horses treated with Noltrex[®] and those treated with sodium hyaluronate and corticosteroid showed a similar behavior in the clinical response to treatment, showing a significant improvement in the degree of lameness initially evaluated.

Taking into account the reported deleterious effects of intra-articular corticosteroids such as necrosis and/or little chondrocyte differentiation, proteoglycan reduction and/or joint cartilage fibrillation (8,9), and decrease in matrix protein markers (10); and although in this research it was used in combination with sodium hyaluronate, it is important to emphasize that in this study no significant differences were observed in the recovery of the degree of lameness between both groups. Therefore, the therapeutic alternative of Noltrex[®] that fulfils a protective function in the form of an endoprosthesis (12) could be directed to the promising treatment of foals and young animals whose owners are willing to provide the recovery time without the independent competitive pressure of equestrian sport.

In the present study it can be inferred according to the clinical response of patients that Noltrex[®] creates an optimal environment in the joint space for a physiological stabilization and recovery of cartilage in the medium term, similar to what is reported in other long-term studies (2), since joint pain, and hence lameness as a clinical sign, is directly related to the structural and homeostatic involvement of cartilage (13,14). However, additional studies are required to evaluate the physiological morpho-recovery that may occur in cartilage. The use of Noltrex[®] as a non-pharmacological therapeutic alternative is appropriate and indicated when the clinical objective is determined from the preventive perspective, the prolongation of the athletic and competitive life of young horses with some degree of joint commitment; this in accordance with what is described in the literature, where in pharmacological therapy with corticosteroids in the medium and long term, the beneficial anti-inflammatory effects are overcome by the deleterious effects that these have, thus promoting the deterioration of the articular cartilage (6,9-11,15-19). From the same preventive perspective, the economic expenses incurred to treat OA and/or related orthopedic problems, can be reduced and attenuated, since the costs in veterinary doctors, drugs and rehabilitation related to this disease around the world are significantly high (20-23).

Conclusions: The use of hydrogenated polyacrylamide gel Noltrex[®] represents an effective alternative in the treatment of the clinical signs of OA of the tarsus in Colombian criollo horses, that is the improvement in the degree of lameness, evidence clinically similar behaviour to traditional treatment with sodium hyaluronate and corticosteroid.

Noltrex[®] is a therapeutic alternative with a clinical response similar to traditional pharmacological treatment, with the apparent advantage of limiting the undesired side effects on articular cartilage of intra-articular drugs in the medium and long term. However, more studies are required in equine models that evaluate the behavior of the cartilage structure versus the Noltrex[®] as have been done in other experimental models (24).

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