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Efficacy of intramuscular polysulfated glycosaminoglycan in a controlled study of equine carpitis

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Twelve healthy horses were subject to the monoioidoacetate (MIA) carpitis model, which was allowed to develop for 7 days. The horses were then randomly divided into two groups. Group A (control) received an intramuscular injection of normal saline every 4 days for a total of seven injections while group B received 500 mg of a PSGAG (SYNTEX CSY36) intramuscularly every 4 days for seven treatments. Efficacy of the PSGAG was evaluated by three clinical outcomes: lameness score, carpal circumference and maximum carpal flexion. Clinical outcomes were measured on days -8 (previous to carpitis induction), 0 (previous to drug treatment), 7, 14, 21, 28 and 35. Areas under the curve clinical outcome as function of time were built and used as variables for the statistical analysis. There was less joint circumference enlargement and lameness and greater carpal flexion in PSGAG-treated horses compared with that in controls. The studied compound has demonstrated to be efficacious on the treatment of a chemically induced carpitis in horses.

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INTRODUCTION

Osteoarthritis (OA) is the commonest type of arthritis in humans and animals and the most common cause of lameness in horses.

The management of osteoarthritis in animals involves both therapeutic and non-therapeutic measures. The latter includes, control of body weight and exercise level. However, therapeutic intervention is commonly necessary. For horses, the drug classes used most frequently to relieve pain and/or suppress inflammation are corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and agents described as disease modifying/chondroprotective.

Polysulfated glycosaminoglycans (PSGAGs) have been categorized by the International League against rheumatism (ILAR) as disease modifying osteoarthritis drugs (DMOADs). Therapy with this class of compounds can prevent, retard or reverse morphologic cartilaginous lesion of OA (Trotter, 1996). The exact mechanism of action of PSGAG has not yet been properly described. However, it has been reported that PSGAGs alter osteoarthritis progression by sustaining or promoting chondrocyte metabolic activity and inhibiting effects of cytokines or prostaglandins on cartilage (Carol, 2005). In recent years a number of effects for chondroitin sulfate on articular tissues have been reported. These effects, that could be extrapolated to PSGAGs, includes: (i) antiapoptotic effect by diminishing the activation of p38 mitogen-activated protein kinase (Verges *et al.*, 2004); (ii) increase of proteoglycan synthesis by providing building blocks for the synthesis and increasing sulfate incorporation in OA proteoglycans (Wang *et al.*, 2002); (iii) reduction of protease activation, specially MMP-3 (Verde *et al.*, 2006) and MMP-13 (Holzmann *et al.*, 2006) and (iv) reduction of PGE2 and NO synthesis and gene expression (Verde *et al.*, 2006; Chan *et al.*, 2005).

The objective of the present study was to evaluate the efficacy of a PSGAG molecule administered intramuscularly in a control randomized design applying an established model of equine carpal inflammation.

MATERIALS AND METHODS

Experimental design

A parallel randomized, blinded, controlled design was applied. Group A (control) received an intramuscular injection of normal saline every 4 days for a total of seven injections; while, Group B received 500 mg of PSGAG (SYNTEX CSY36) intramuscularly every 4 days for seven treatments.

Description of the PSGAG

The molecule tested in the present study (SYNTEX CSY36, Syntex Argentina S.A., Buenos Aires, Argentina) was a semisynthetic hypersulfated (3–4 sulfate groups per disaccharide unit) polysaccharide with a molecular weight of 5000–7000 Da. This is an experimental compound not commercially available.

Experimental animals

Twelve horses, weighing 425 ± 32 kg, were obtained through local suppliers. The horses met the following inclusion criteria: Over 2 years of age; Good nutritional status; No pregnant mares; Not have suffered any surgical procedure in the joint; Not suffer or being suffering any immunological disease; Not being receiving any chronic medication; Free of clinical signs of lameness (based on lameness examination); Normal radiographs for the right carpus.

All animal procedures were approved by the Institutional Animal Care and Use Committee, School of Veterinary, University of La Plata, Argentina.

Experimental model of arthritis

A previously described chemical carpitis model (Trotter *et al.*, 1989; Gustafson *et al.*, 1992) was induced in all horses on study day −7. After shaving and disinfection of the skin of the right carpus, 0.16 mg/kg of sodium monoiodoacetate (3% sterile solution) was injected into the right middle radial carpal joint using a 23- gauge 1 in. needle.

Treatments administration

After 7 days from arthritis induction, experimental horses were randomly assigned to two treatment groups by simple randomization:

Group A (control; $n = 6$) received an intramuscular injection of sterile normal saline every 4 days for a total of seven injections.

Group B ($n = 6$) received 500 mg of sterile PSGAG intramuscularly every 4 days for seven treatments.

Prior to injection, the site (the semimembranosus/semitendinosus muscle) was wiped with an alcohol-soaked gauze sponge

Evaluation of efficacy

Previously to the induction of the carpitis, as well as of the treatment administration, clinical measurements were done for building baselines for the different signs and/or clinical maneuvers applied. The first baseline (previous to the induction of carpitis) was used to evaluate the experimental model of inflammation, while the second baseline (after carpitis and before beginning of the treatments) was used to evaluate the efficacy of the polysulfated glycosaminoglycan.

After beginning of treatments, measurements were done weekly until day 35 posttreatment by a clinician (C. Verde) with no access to the treatment assignments.

The primary outcome measures were:

(i) Lameness score (0–3) [0 =normal no detectable lameness;1 = slight subtle lameness without overt head movement; 2 = moderate easily recognizable, head-bobbing lameness; 3 = severe definite lameness observed at a walk and at a trot].

The horses were observed at a walk and trot and while turning in both directions. The same attendant handled the horses all times for consistency.

(ii) Maximum carpal flexion was measured by slow flexing the carpus until the horse resisted. The angle was then measured in degrees using a home-made goniometer (Toutain *et al.*, 1994; Toutain & Cester, 2004).

(iii) Carpal circumference was measured at the level of the middle of the accessory carpal bone (in cm) using a flexible tape, with the limb extended (normal upright position) (Toutain *et al.*, 1994; Toutain & Cester, 2004).

The primary outcome measures were evaluated at study day −8, 1 day before model induction (normal premodel), at day 0, before the first treatment (diseased pretreatment) and weekly thereafter for 5 weeks (days 7, 14, 21, 28 and 35) . Blood samples were collected, and divided into two aliquots: the first was collected in a test tube containing EDTA (4 mL) for a complete haematology screen. The second 4 mL sample was collected in tubes with no anticoagulant, to evaluate clotting; the prothrombin time (PT) and partial prothrombin time (PTT) were determined using a fibrometer and standard laboratory techniques. Bleeding time measurement was performed as described by Jergens *et al.* (1987).

Blood fractions were kept on ice for subsequent centrifugation at 2200 ***g*** for 10 min at 4 °C. Synovial fluid was collected by aseptic arthrocentesis and stored frozen at −20 °C for future study of synovial fluid markers.

Performed activities can be summarized as follows:

DAY -8 →	1st Evaluation = NORMAL PRECARPITIS
DAY -7 →	INDUCTION OF CARPITIS
DAY 0 →	2nd Evaluation = DISEASED PRETREATMENT Beginning of Treatments
DAY 7 →	1st Evaluation = DISEASED POSTTREATMENT
DAY 14 →	2nd Evaluation = DISEASED POSTTREATMENT
DAY 21 →	3rd Evaluation = DISEASED POSTTREATMENT
DAY 28 →	4th Evaluation = DISEASED POSTTREATMENT
DAY 35 →	5th Evaluation = DISEASED POSTTREATMENT

Statistical analysis

Differences between outcome measures at day −8 and 0 (for evaluating the baseline model-induced deficit) were analyzed applying Wilcoxon-signed rank test using GraphPad Prism Ver.4 software (GraphPad Software Inc., San Diego, CA, USA). The level of significance was set at $P < 0.05$.

For the comparison between treatments, since the objective was to analyze modifications induced by treatments over a relatively long period of time, a scheme for repeated samples (Matthews *et al.*, 1990; Pham *et al.*, 1999; Schiff, 2003) was

applied, based on comparison of the areas under the curve clinical outcome vs. time. The area under the curve was calculated with the following equation:

$$AUC = 0.5 \sum_{1=0}^{n-1} (t_{i+1} - t_i)(y_i + y_{i+1})$$

where t is sampling time and y is the observed measurement.

Comparison of areas under the curve outcome measures as a function of time from time 0 to day 35 between control and PSGAG treated groups was performed by applying Wilcoxon-signed rank test using GraphPad Prism Ver.4 software. The level of significance was set at $P < 0.05$.

RESULTS

The model induction showed no complications with uniform responses in all experimental horses. Table 1 shows data treatment group mean for the three outcome measurements in all horses at days −8 (before arthritis induction) and day 0 (7 days after arthritis induction). These results reflect the uniformity of both treatment groups as well as the magnitude of the induced model. Mean lameness score increased from grade 0 to grade 3 in all experimental animals. Changes for carpal circumference and flexion were 12% and 30%, respectively. Horses during the study were eating and gaining weight and no use of analgesic was required.

Lameness score in both experimental groups was around 2 at day 7 posttreatment (see Fig. 1). Afterward, differences between groups were evident. Control group horses remained throughout the study with a similar score while, PSGAG treated group showed a decreased in lameness score, returning to baseline values at day 28 posttreatment. The *AUC* lameness score as a function of time (see Fig. 1, inner box and Table 2) was statistically greater ($P > 0.05$) in the control (73.5 ± 5.73 lameness score/day) than the PSGAG treated group (50.4 ± 23.3 lameness score/day).

The increase on carpal circumference in the control group was greater, in the range of 8–13%, than in the PSGAG treated group. The increase in the control group persisted up to the last sampling time (35 days posttreatment) (Fig. 2). PSGAG treated group had circumference values similar to baseline from the first sampling time after treatment (day 7).

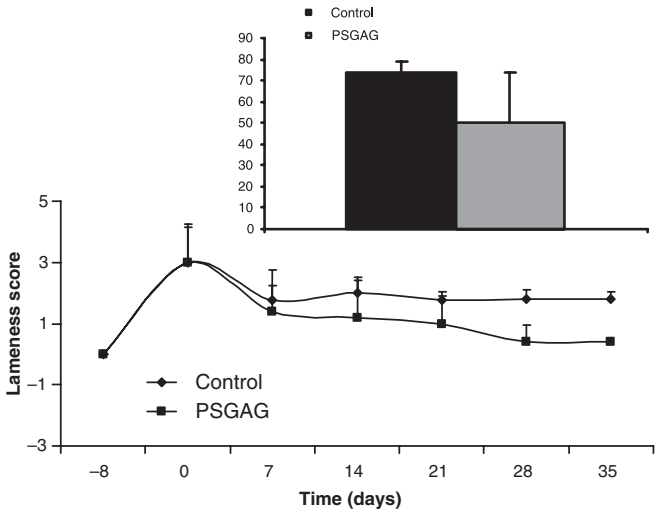

Fig. 1. Lameness score (mean ± SD) vs. time in arthritic horses after intramuscular administration of PSGAG, at a dose rate of 500 mg, and placebo every 4 days for seven treatments. *Inner Box*: Mean ± sd of the area under the curve (*AUC*) lameness score as a function of time in the experimental groups.

Table 2. Areas under the curve for lameness, flexion and carpal circumference as a function of time

	Lameness (score/day)	Maximum flexion (°/day)	Carpal circumference (cm/day)
PSGAG	50.4 ± 23.30*	1026.7 ± 192.41**	1156.6 ± 46.28**
Control	73.5 ± 5.72	1463.8 ± 178.89	1238.5 ± 23.75

Values are mean ± sd ($n = 6$). *$P < 0.05$; ** $P < 0.01$.

The *AUC* carpal diameter as a function of time (Fig. 2, inner box and Table 2) was 1238.56 ± 46.28 cm/day for the control group, while lower values were observed in the group treated with PSGAG (1156.61 ± 46.28 cm/day). Statistical analysis of the *AUC*s showed significant differences ($P > 0.01$) between treated groups.

Maximum flexion angle has been reported as an indicator of the possible analgesic potency of NSAIDs (Toutain & Cester, 2004). In the present study, the control group showed a greater and more sustained increase on carpal flexion angle than the

Table 1. Outcome measures at day −8 (previous to arthritis induction) and day 0 (before beginning of treatments) for evaluation of the experimental model of arthritis

	Day −8	Day 0	Change	% Change
Lameness				
PSGAG	0	3*	+3*	100
Control	0	3*	+3*	100
Maximum flexion (°)				
PSGAG	30.83 ± 1.47	44.00 ± 0.89*	+13.16 ± 0.58*	29.9
Control	31.00 ± 1.41	44.33 ± 1.03*	+13.33 ± 0.38*	30.07
Carpal circumference (cm)				
PSGAG	29.17 ± 1.03	32.58 ± 0.74*	+3.41 ±(–0.19)*	11
Control	28.75 ± 0.82	32.67 ± 0.41*	+3.91 ±(–0.40)*	13

Values are mean ± SD, except for % of change (only mean) ($n = 6$). *$P < 0.01$.

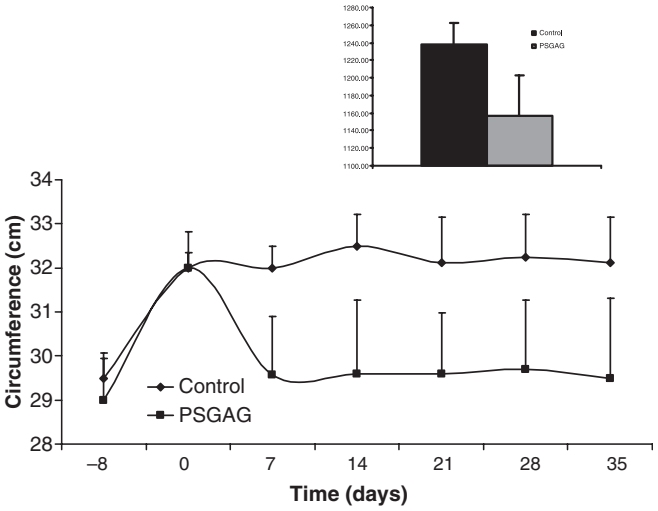

Fig. 2. Circumference of the inflamed join (mean ± SD) vs. time in arthritic horses after intramuscular administration of PSGAG at a dose rate of 500 mg and placebo every 4 days for seven treatments. *Inner Box*: Mean ± sd of the area under the curve (*AUC*) circumference of the inflamed join as a function of time in the experimental groups.

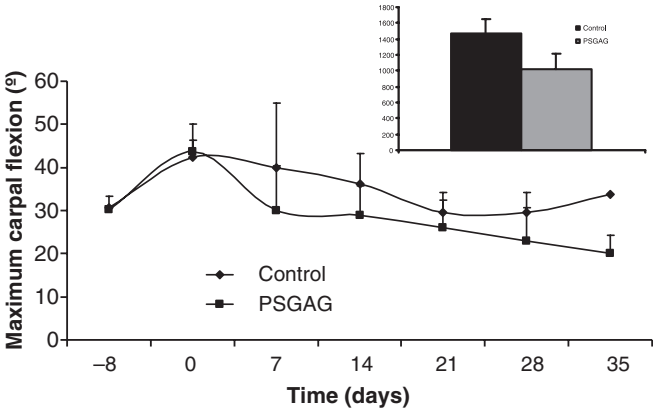

Fig. 3. Maximum flexion of the inflamed join (mean ± SD) vs. time in arthritic horses after intramuscular administration of PSGAG at a dose rate of 500 mg and placebo every 4 days for seven treatments. *Inner Box*: Mean ± sd of the area under the curve (*AUC*) maximum flexion of the inflamed join as a function of time in the experimental groups.

PSGAG treated group (see Fig. 3) This is clearly seen when comparing the values of *AUC* flexion angle as a function of time (Fig. 3, inner box and Table 2). The control group mean was 1463.87 ± 178.89°/day, while for the group treated with PSGAG this value was 1026.76 ± 192.41°/day. Statistical analyses of the *AUC*s indicated significant differences ($P < 0.01$) between PSGAG and control group.

In the PSGAG treated group all the measured clinical parameters had returned to basal values at day 35. Calculated recovery for the individual horses was between 90% and 100%.

None of the blood parameters evaluated showed values outside the normal range for horses. Due to the heparinoid character of PSGAGs, particular attention was paid to evaluation of parameters that reflect functioning of blood coagulation. Coagulation time, prothrombin time, partial prothrombin time and thrombin activity remained relatively content and within the normal range for the species, and no differences were observed between groups.

DISCUSSION

The MIA model of chemical carpitis (Trotter *et al.*, 1989; Gustafson *et al.*, 1992) induced a uniform and consistent carpitis with easily measured clinical deficits in lameness parameters. All experimental animals continue to eat and gain weight during the study. None of the horses required analgesia or withdrawal from the study. Regarding possible secondary effects of long-term administration of PSGAGs, none of the analyzed hematological variables was significantly modified.

The results observed in the PSGAG-treated group in the present study are consistent with results reported by other authors after intra-articular (IA) administration in naturally or chemically induced arthritis (Hamm *et al.*, 1984; Yovich *et al.*, 1987). Also, IA PSGAGs attenuated signs of OA in a study using a osteochondral defect model with subsequent exercise on a treadmill (Todhunter *et al.*, 1993). However, the number of clinical studies of PSGAGs after intramuscular administration is small. This is odd, since this is a very safe route of administration and anecdotal reports on efficacy are numerous (Kollias-Baker, 1999). Intra-articular injection of PSGAGs has been related to severe joint infections (Gustafson *et al.*, 1989a,b; Rashmir-Raven *et al.*, 1992). Other studies revealed that PSGAG potentiates intra-articular infection with *Staphylococcus aureus* through inhibition of both the classic and alternative pathways of complement activity (Gustafson *et al.*, 1989a). Further studies revealed that filtering the PSGAG prior to IA injection had no effect on the increase in infectivity, but intra-articular injection of 125 mg amikacin significantly decreased potentiation of infection by the PSGAG (Gustafson *et al.*, 1989b).

The results obtained in the present paper do not coincide with those reported by Trotter *et al.* (1989). These researchers, using the same chemical model of arthritis, reported no effect at all, after intramuscular administration of PSGAG (Adequan, Luitpold Pharmaceuticals, Shirley, NY, USA) at the same dose and administration design used here. However, it must be stated that in Trotter *et al.* study, two experimental models of arthritis were used simultaneously in the same experimental horses; in one carpal joint one full thickness articular cartilage defect was made on the central aspect of the distal articular surface of the radial carpal bone in one middle carpal joint and a partial-thickness articular cartilage defect was made on the axial aspect of the same bone, while in the contralateral carpal joint, articular cartilage degeneration was induced by intraarticular injection of sodium monoiodoacetate at the same dose used in the present study (50 mg). It is difficult to discuss the results reported by Trotter et al.; the use of two experimental models of arthritis simultaneously in the same animal for evaluating the efficacy of any drug is not advisable. It is expected that an animal with inflammation and pain in one carpal joint, shifts the body

weight to the contralateral limb, therefore, since both carpal joints are inflamed (with an unknown severity) is not possible to properly evaluate the effect of the treatments. On the other hand, the experimental animals were maintained in box stall during the study, while in the present study, the animals were maintained in a field allowing self-regulated exercise. It is important to highlight that in arthritic animals mild exercise is advisable to maintain joint mobility (Lees, 2003).

White et al. (2003) have reported the efficacy of a PSGAG (Adequan, Luitpold Pharmaceuticals) after intramuscular administration of 500 mg twice weekly for a total of seven injections, in a model of carpitis induced by complete Freund's adjuvant (CFA). In that study recovery of the model-induced deficit in carpal flexion (81% at day 33) and lameness (almost complete at day 33) was similar to that reported here. However, a lower recovery is informed for carpal circumference (33%). This difference could be consequence of the different experimental models. The complete Freund's adjuvant model of arthritis develops in two phases: an acute periarticular inflammation followed by a phase of bone involvement (Philippe *et al*., 1997). The acute phase is long lasting (around 1 month) and characterized by an oedematous acute synovitis with considerable diapedesis of the neutrophilic granulocytes (Haak *et al*., 1996). Contrarily, intraarticular injection of sodium monoiodoacetate induces a less acute local reaction with mild joint swelling (May, 1996).

Based on the findings reported, it can be concluded that the compound SYNTEX CSY36 is highly efficacious on the treatment of a chemically induced carpitis in horses. More studies on this PSGAG administered intramuscularly using different experimental models of arthritis as well as horses with naturally arthritis are needed.

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