Effect of Prophylactic Intramuscular Administration of Polysulfated Glycosaminoglycan on Developmental and Traumatic Joint Injuries in Thoroughbred Foals

Gary W. White, DVM, a G. Fredrick Fregin, VMD, b and Jules R. Selden, VMD, PhD c

ABSTRACT

The objective of this study was to determine whether a prophylactic regimen of intramuscular polysulfated glycosaminoglycans (PSGAG), administered to growing Thoroughbred foals, would significantly reduce the incidence or severity of osteochondritis dissecans (OCD) or traumatic joint lesions that had been found in untreated foals (historical controls) from the same farm during the preceding 3 years. The number of PSGAG-treated foals with clinically significant joint lesions was 44.1% lower than the number of foals with OCD/joint injuries that had been found in the untreated historical controls. Surgical intervention of the treated foals declined 87.7% from the incidence on the farm during the preceding 3 years. Although the incidence of OCD lesions of the hock, stifle, and fetlocks in treated foals was not significantly different from that found in the matched controls, the lesions in the PSGAG-treated foals resolved without surgery. These results suggest that PSGAG has the potential to improve the clinical course of osteochondrosis (OC) and OCD. Additional studies are underway to determine whether a shorter or more targeted prophylactic regimen will provide a similar benefit.

Keywords: Osteochondrosis; Osteochondritis dissecans; Articular cartilage; Osteoarthritis; Polysulfated glycosaminoglycan

INTRODUCTION

Osteochondrotic lesions of the stifle, hock, fetlock, or shoulder of growing foals caused by developmental orthopedic disease or trauma are common problems that may require medical or surgical intervention. 1 Osteochondrosis (OC) and osteochondritis dissecans (OCD), along with other diseases of the musculoskeletal system, contribute three times more to economic loss in the equine industry than do diseases of any other organ system. 2

Synovial joint disease in particular contributes prominently to wastage in racehorses as well as other equine athletes. The weight-bearing surfaces of synovial joints are composed of articular cartilage, subchondral bone, and trabecular bone, with each component’s biomechanical properties being dependent on the biochemical composition of their extracellular matrices (ECM). 2 The articular cartilage matrix is a unique combination of proteoglycans, collagen, and water arranged so that the joint surface may resist shearing forces and distribute loads evenly into the underlying bone. The extracellular matrix of bone is composed of 65% mineralized (hydroxyapatite) and 35% non-mineralized matrix, including collagens, proteoglycans, and water. Changes in the biochemical properties of cartilage and bone ECM and subsequent deterioration of the biomechanical properties of the cartilage or bone are thought to be important in the etiology of osteochondral diseases. 3

Early descriptions characterized OC as a focal failure or delay in endochondral ossification at predilection sites in the articular–epiphyseal cartilage complex or the metaphyseal growth plate. 4 Osteochondral abnormalities develop early in life and have been observed in the neonate and in radiographs of Standardbred and Dutch Warmblood foals between 1 and 3 months of age. 1 Osteochondrosis is a dynamic process in which lesions may become visible during the first few months of life and then partially or completely regress or progress into clinical OC. 1,5 When the delay in endochondral ossification leads to fissures or defects in the articular surface of the joint with the ensuing clinical signs of inflammation, joint swelling, and lameness, the syndrome is referred to as OCD. 6

Dorsal proximal injuries to the first phalanx (P1) of the fetlock, thought by some investigators to be developmental in origin and by others to be caused by trauma to the immature bone at the articular margin, can produce osteoarthritis or osteochondral fragmentation. 1,6 As with OCD, these P1 injuries can be costly to treat and may impact the potential value of the affected foals as future equine athletes.

Disturbances in the process of endochondral ossification occur in many equine breeds and may have different clinical
manifestations, depending on the predilection site and age of onset when the problems arise. OCD is common in Thoroughbreds and usually manifests clinically as lameness and joint distension by 1 year of age, whereas in Warmbloods, clinical signs are less frequently seen in horses younger than 2 years of age. Hock OCD is diagnosed in most equine breeds and appears to be particularly common in Standardbreds, in which joint swelling is a more common early finding than is lameness. Clinical signs of hock OCD are usually first noted as race training begins between 1 and 2 years of age. The most common site in Thoroughbreds for fetlock OCD is the sagittal ridge of the third metacarpal or metatarsal, with clinical signs characterized by joint swelling and variable lameness. Femoral OC is reported to be less common in Standardbreds than in other breeds, and tibial OC is reported less frequently in Quarter Horses. These findings support the contention that some of the clinical manifestations and predilection sites may have a breed predisposition.

Although the cause of OC and OCD may be multifactorial and putative factors in the growing foal include rapid growth, hereditary predisposition, nutritional imbalance, endocrine dysfunction, local ischemia, and trauma, the pathogenesis has yet to be clearly elucidated. Increasing knowledge of articular cartilage development in young animals points to the role of collagen metabolism, which is prominent in the process of endochondral ossification and in the remodeling of the cartilage extracellular matrix into a matrix that is typical for bone as a key factor. However, currently no proof exists that changes in collagen metabolism are the primary cause of OC.

Comparison of OC cartilage from the distal intermediate ridge of the tibia and articular cartilage from the same anatomical site in normal horses showed distinct biochemical, histochemical, and immunohistochemical differences that may reflect the inability of the chondrocyte of the developing OC-affected joint to alter the ECM to allow proper growth, mineralization, and putative factors in the growing foal include rapid growth, hereditary predisposition, nutritional imbalance, endocrine dysfunction, local ischemia, and trauma, the pathogenesis has yet to be clearly elucidated. Increasing knowledge of articular cartilage development in young animals points to the role of collagen metabolism, which is prominent in the process of endochondral ossification and in the remodeling of the cartilage extracellular matrix into a matrix that is typical for bone as a key factor. However, currently no proof exists that changes in collagen metabolism are the primary cause of OC.

The objective of this pilot study was to evaluate the effect of a prophylactic regimen of PSGAG in growing Thoroughbred foals. Our hypothesis was that there would be a reduction in the incidence or severity of OCD/traumatic joint lesions when compared with untreated historical and matched controls (based on breeding, date of birth, and sex) from the same Thoroughbred farm. The primary study endpoints were:

- Number/incidence and location of clinically significant developmental joint lesions diagnosed, including age of onset
- Estimated duration and progression of the clinical course for each affected foal
- Number/incidence of foals requiring surgery for OCD/traumatic joint lesions
- Number/incidence of adverse reactions/side effects to PSGAG

**MATERIALS AND METHODS**

Seventy-five foals born in 2003 on a Thoroughbred farm in central Kentucky were eligible for participation in the study. Each foal was enrolled at approximately 8 weeks of age after a screening physical examination. One foal with concurrent health problems was excluded from the trial. The initial signalment recorded for each foal included: date of birth, sex, sire/dam, body weight, vaccination and deworming status, and a summary of any pertinent health issues before enrollment. All foals were subjected to weekly physical
examinations, and body weight was recorded at monthly intervals. Additional physical examinations were performed on any foal that became ill or that was lame or had joint distension. Diagnostic procedures such as ultrasound or digital radiography and medical treatments initiated by the attending veterinarian were recorded in the foal’s medical record. Management practices, including infectious disease prevention, nutrition, parasite control, weaning schedules, and turn-out (exercise) were significantly unchanged during the study period from 2000 to 2004.

Polysulfated glycosaminoglycan (Adequan® IM, Luitpold Pharmaceuticals, Inc., Shirley, NY) was given by intramuscular injection at a dose of 1.1 mg/kg of body weight, beginning at 8 weeks of age and continued twice weekly for 4 weeks alternating with a 4-week period without treatment, until the foal was 1 year of age. This initial dose and treatment regimen is based on the approved dose regimen for PSGAG in adult horses (500 mg twice weekly for 4 weeks). A total of five 4-week treatment regimens were administered to each foal. On completion of the initial prophylactic regimen, weekly intramuscular injections of PSGAG were continued at the same dose rate (maximum dose of 500 mg) until November of the foal’s yearling year.

At the end of the treatment period, clinical data including the primary study endpoints as previously listed were tabulated from each foal’s medical record. Osteochondral abnormalities and dorsal proximal injuries to the first phalanx (P1) of the fetlock were judged by the attending veterinarian and farm management to be clinically significant, based on clinical signs (lameness and joint distension), radiographic appearance (size, number, location, and quality of the lesions), and on their experience with similar abnormalities in the untreated historical control population. Clinically significant joint lesions were expected to progress into chronic joint disease, resulting in lameness, poor performance, or requiring surgical intervention. The decision as to which foals required surgery was made subjectively, and surgery was limited to those lesions that might be expected to lead to permanent joint pathology that might preclude or significantly shorten a racing career. Examples include joints with osteochondral fragments and lesions with extensive disruption of the articular surface.

The historical control group included all foals (n = 233) born on the farm from 2000 to 2002. Medical records on these foals contained information similar to that of the test population (2003). Each foal in the 2003 crop was also matched to a foal from the 2002 crop, using in the order of significance dam, sire, date of birth, and sex. This was a non-blinded study with no positive or negative control group.

The historical control data were analyzed using a two-proportion z test. The following hypothesis was tested:

\[ \text{Ho: } p_1 = p_2 \text{ versus Ha: } p_1 \neq p_2 \]

where \( p_1 \) represents the control population proportion and \( p_2 \) represents the treated-group population proportion. The matched control data were analyzed using McNemar’s test. A P-value of .05 indicated statistical significance.

**RESULTS**

The overall incidence of clinically significant joint lesions in the historical control group of 29% (68/233) declined significantly in PSGAG-treated foals to 14.9% or 11 of 74 foals (\( P = .014 \)). Historically, the most frequently diagnosed joint abnormalities in foals at this farm were OCD of the hock, stifle, and fetlock (55.9%) and fragmentation of the dorsal proximal aspect of the first phalanx (44.1%). Thirty-eight of 233 (16.3%) historical control horses had OCD of the hock, stifle, or fetlock, whereas the incidence of OCD in the PSGAG-treated foals was 9 of 74 or 12.2% (\( P = .39 \)). The incidence of clinically significant proximal dorsal P1 chip fractures in the historical control group was 12.9% (30/233), with a significant decline in the PSGAG-treated foals to 2.7% or 2 of 74 foals (\( P = .013 \)) (Table 1).

Surgical intervention was required in 21.9% or 51 of 233 foals in the historical control group, but decreased significantly to 2.7% or 2 of 74 (\( P = .0001 \)) of the PSGAG-treated foals. None of the foals from the 2003 crop required surgery for OCD lesions of the hock, stifle, or fetlock (Table 2).

The foals in the 2003 (treated) crop showed a reduction in clinically significant joint lesions (\( P = .012 \)) and surgery

---

**Table 1.** Incidence of clinically significant joint lesions

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>Number of Lesions</th>
<th>% Affected Foals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Historical control (233)</td>
<td>68</td>
<td>29%*</td>
</tr>
<tr>
<td>Treated (74)</td>
<td>11</td>
<td>14.9%*</td>
</tr>
<tr>
<td>OCD of Hock, Stifle, and Fetlock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Historical control (233)</td>
<td>38</td>
<td>16.3%</td>
</tr>
<tr>
<td>Treated (74)</td>
<td>9</td>
<td>12.2%</td>
</tr>
<tr>
<td>Proximal Dorsal P1 Lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Historical control (233)</td>
<td>30</td>
<td>12.9%†</td>
</tr>
<tr>
<td>Treated (74)</td>
<td>2</td>
<td>2.7%†</td>
</tr>
</tbody>
</table>

*\( P = 0.014. \)
†\( P = .013. \)

---

**Table 2.** Incidence of surgery for clinically significant joint lesions

<table>
<thead>
<tr>
<th>Overall</th>
<th>Number of Lesions</th>
<th>% Affected Foals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical control (233)</td>
<td>51</td>
<td>21.9%*</td>
</tr>
<tr>
<td>Treated (74)</td>
<td>2</td>
<td>2.7%*</td>
</tr>
</tbody>
</table>

*\( P = .0001. \)
†Proximal dorsal P1 fragments; no hock or stifle OCD lesions required surgery.
for joint lesions \((P = .0005)\) compared with matched controls in the untreated 2002 crop. The PSGAG-treated foals also showed a reduction in clinically significant P1 lesions \((P = .007)\) and surgery for P1 lesions \((P = .005)\), compared with untreated matched controls. No significant difference was seen between the treated and matched controls for the incidence of OCD lesions of the hock, stifle, or fetlock.

Table 3 provides a summary of location, age of onset, and progression of OCD and P1 lesions for the treated and historical control groups.

**DISCUSSION**

Osteochondral injury and joint disease secondary to OC and OCD are an important cause of economic loss to horse breeders and owners. Osteochondrosis is a dynamic process in which radiographic abnormalities may become visible during the first few months of the foal’s life and then resolve uneventfully without any discernible clinical signs.\(^5\) In other foals, the lesions may persist, resulting in joint inflammation, swelling, lameness, and subsequent osteoarthritis. Recognizing that there is not always a good correlation between radiographic appearance and severity of the disease, the criteria for clinical significance were based on clinical signs (lameness and joint distension), radiographic appearance (size, number, location, and quality of the lesion), potential effect on racing career, and on the experience of the attending veterinarian with the historical control population of horses on the farm.\(^{25,26}\)

The use of historical control has limitations compared with other controlled study designs. The incidence of OC may be affected by many factors that induce stress (for example, drought and other weather extremes or systemic disease outbreaks) in a population of foals, and these factors may be impossible to control. Year-to-year variability in OCD incidence for unknown reasons is commonly observed and also cannot be controlled. Also, the subjective nature of the decision to go to surgery in this non-blinded study has the potential to introduce bias into the results. As far as possible, all management practices at this farm, including the selection of foals for surgery, remained the same for the 4-year period of the study.

The results from this study show that an extended prophylactic regimen of intramuscular PSGAG reduced the number of clinically significant joint lesions by almost 45\% in PSGAG-treated Thoroughbred foals compared with untreated historical controls. The need for surgical intervention in the treated foals declined 87.7\% from the incidence on the farm during the preceding 3 years. Two foals from the PSGAG-treated group required surgery for proximal dorsal P1 fragments. Whereas the incidence of OCD lesions of the hocks and stifles was not significantly reduced in the treated group, the lesions in the nine affected foals resolved without surgery; this finding is of clinical interest. The reason for the discrepancy in the efficacy of treatment in reducing the incidence of P1 fragments versus the incidence of hock and stifle OCD lesions is unclear. If the P1 fragment does indeed have a large traumatic component, this could explain why PSGAG had a more pronounced effect, because the drug is known for its efficacy in traumatic joint diseases.

The proposed pathogenesis of OC includes ischemia and trauma, as well as biochemical and molecular signaling derangements that affect cartilage differentiation and ossification.\(^9\) Because dysfunction of the articular ECM of OC cartilage has an apparent role in the failure of ossification, therapies aimed at promoting the health of articular cartilage matrix might be expected to improve the clinical course of OC and OCD. The mechanism for this effect may be related to the disease-modifying characteristics ascribed to PSGAG on injured or inflamed cartilage tissue. These effects have been previously summarized and include a decrease in enzymatic degradation of proteoglycan and collagen and an increase in endogenous synthesis of these matrix components.\(^{21}\) PSGAG also has been shown to have anti-inflammatory effects. These effects documented in articular cartilage also might be expected to occur in growth plate cartilage.

Despite the length of time the drug was given and the number of injections administered, no side effects or adverse reactions were observed.

<table>
<thead>
<tr>
<th>Table 3. Summary of OCD lesions by location, age of onset, time from onset to surgery, or time from onset to clinical resolution in non-surgical cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Historical Control Group</td>
</tr>
<tr>
<td>Hocks</td>
</tr>
<tr>
<td>Stifles</td>
</tr>
<tr>
<td>Fetlock (P1)</td>
</tr>
<tr>
<td>Treated Group</td>
</tr>
<tr>
<td>Hocks</td>
</tr>
<tr>
<td>Stifles</td>
</tr>
<tr>
<td>Fetlock (P1)</td>
</tr>
</tbody>
</table>

**NOTE.** All ages are expressed as months.

* Non-surgical.
This preliminary study examined a very long and expensive regimen of treatment, which is probably not economically feasible for most equine breeders. Further studies are underway to determine whether a shorter targeted prophylactic regimen will provide a similar benefit. The proposed studies will include bimonthly radiographic screening to document appearance and progression of the joint lesions. The timing and duration of the treatment for the current studies are based on the data on location, age of onset, and progression of past OCD lesions as summarized in Table 3.

REFERENCES


