Oral hyaluronan gel reduces post operative tarsocrural effusion in the yearling Thoroughbred

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Summary

Reasons for performing study: **Hyaluronan (HA) has been used to treat joint disease via intra-articular, i.v. and oral administration. The efficacy of intra-articular and i.v. use has been evaluated but the oral route has yet to be examined.**

Objectives: **To determine the effect of oral hyaluronan gel on joint effusion following arthroscopic surgery for osteochondritis dissecans (OCD) of the tarsocrural joint of yearling Thoroughbreds.**

Methods: **Forty-eight yearlings diagnosed with unilateral or bilateral osteochondritis dessicans (OCD) of the tarsus were arbitrarily chosen prior to arthroscopic surgery. The yearlings were included only if they had mild or no synovial effusion pre-surgery. Twenty-four of the yearlings (27 joints) were treated with 100 mg of HA orally for 30 days post operatively and 24 (30 joints) with a placebo orally for 30 days. At 30 days post operation, a blinded examiner scored the effusion of the dorsomedial tarsocrural joint individually using a scale of 0 to 5 (0 = no effusion, 1 = barely palpable effusion, 2 = palpable effusion [without plantar effusion], 3 = golf ball sized effusion with plantar effusion, 4 = tennis ball sized effusion with plantar effusion, 5 = > tennis ball sized effusion with plantar effusion). Half grades were allowed and OCD lesion sizes and locations were compared.**

Results: **A total of 57 joints were examined, of which 33 had OCD of the distal intermediate ridge of the tibia, 19 OCD of the distal lateral trochlear ridge of the talus and 5 OCD of the medial malleolus. The mean 30 day effusion score of the HA treated group (27 joints) was 0.67 while the mean of the 30 day placebo group (30 joints) was 2.05 (P≤0.0001). Similar results were noted when comparing treated vs. placebo for each lesion location as well as for lesion sizes.**

Conclusions and potential relevance: **Oral preparations of hyaluronan are being used to treat joint disease in horse. Anecdotal reports supporting the efficacy of these preparations already exist. This study provides objective evidence that oral HA reduces joint effusion post operatively following the arthroscopic removal of an OCD lesion in the tarsocrural joint.**

Introduction

Many Thoroughbred yearlings routinely undergo survey radiographs at age 10–12 months to detect the presence of bone abnormalities that may affect athletic performance. Many surgically correctable lesions are found during these surveys. Most lesions are found prior to the development of synovial effusion, however a few present clinically with lameness and/or joint effusion. A common surgical lesion is osteochondritis dissecans (OCD), which is most frequently located in the stifle (femoropatellar), hock (tarsocrural), fetlock, (metacarpophalangeal and metatarsophalangeal) and shoulder (scapulohumeral) joints. Osteochondritis dissecans is classified as a growth disorder within the developmental orthopedic disease complex and is considered a manifestation of osteochondrosis (Beeman and McIlwraith 1986; MacIlwraith 1993). Osteochondritis dissecans of the tarsocrural joint is found most frequently in Standardbreds, but has been documented in many other breeds including the Thoroughbred (McIlwraith *et al*. 1991). The most common sites involved, in order of decreasing frequency are the distal intermediate ridge of the tibia, distal lateral trochlear ridge of the talus and medial malleolus of the distal tibia.

Intra-articular hyaluronan (HA) has been used in the horse for the past thirty years (Rydell *et al*. 1970). More recently, i.v. administration has been shown to be effective in reducing the degree of lameness associated with joint disease (Kawcak *et al*. 1997). Oral HA formulated for the horse has been available for the past 4 years and anecdotal reports have suggested that its use has been effective in treating synovial effusion and lameness.

Hyaluronan is a glycosaminoglycan ubiquitous in all vertebrates and is an integral component of both synovial fluid and articular cartilage in normal synovial joints. Hyaluronan provides the viscoelasticity property to the synovial fluid and is responsible for the boundary lubrication of the synovial membrane and articular cartilage (Howard and McIlwraith 1996). Recent studies on HA have examined normal turnover and metabolism (Fraser and Laurent 1989), changes in lymphatic flow (Reed 1992), absorption through skin (Brown *et al*. 1999), changes in blood levels in various diseased states (Engstrom-Laurent 1989) and immunomodulary effects (Pirnazar *et al*.

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TABLE 1: Definitions of effusion scores used in study

Effusion score	Definition
0	No effusion palpable (normal)
1	Effusion barely palpable
2	Effusion palpable (no plantar effusion)
3	Golf ball size effusion (with plantar effusion)
4	Tennis ball size effusion (with plantar effusion)
5	>Tennis ball size effusion (with plantar effusion)

Half grades were also allowed.

1999). Hyaluronan has been shown to be absorbed by rats and beagles when administered *per os* (Schauss *et al*. 2004). Other glycosaminoglycans with physiological significance, such as chondroitin, dermatan and heparain sulphates have also been shown to be absorbed orally in rats and man (Silvestro *et al*. 1994; Dawes *et al*. 1989, 1991; Salartash *et al*. 1999). HA enters the bloodstream in significant amounts through the lymphatic system and is absorbed rapidly via a receptor into liver endothelial cells where degradation occurs (Laurent and Fraser 1986). The purpose of this blinded study was to evaluate objectively the effect of orally administered HA gel on post operative effusion of the tarsocrural joint.

Materials and methods

Cases

Forty-eight yearling Thoroughbreds admitted to Rood and Riddle Equine Hospital for arthroscopic OCD debridement of the tarsocrural joint between February and June 2004 were used for this study. Criteria for selection were: Pre-operative radiographic evidence of OCD in one or both tarsocrural joints, without or with mild pre-operative synovial effusion of the joint(s) and lesion size or anatomical location within the tarsocrural joint was not a limiting factor. Prior to the onset of the study, clients who owned the cases were sent a letter explaining the study. During the 5 month duration of the study, daily surgery schedule was checked arbitrarily for horses that fitted the criteria. Once selected and prior to surgery, owners were contacted for verbal consent. Their understanding of the study was confirmed at that time, although the type of treatment (HA vs. placebo) was not revealed. Less than 10% of all clients asked did not agree to participate.

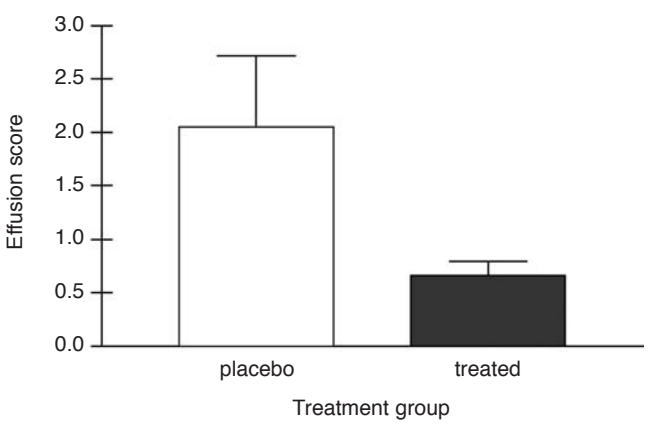

Fig 1: Overall mean joint effusion scores of oral HA Group 1 *(treated) group and* Group 2 *(placebo) group.*

Upon being included into the study each horse was assigned a number from 1 to 48 based on the order of presentation. Each joint was evaluated independently. Nine of the 48 had a lesion in each tarsus for a total of 57 joints. Anatomical locations included the distal intermediate ridge of the tibia (DIRT: n = 33), distal lateral trochlear ridge of the talus (DLTR: n = 19) and medial malleolus of the distal tibia (MM: n = 5).

In each case, size of lesion was graded as either ≤1 cm or >1 cm at its widest radiographic dimension. Forty-five of the lesions were ≤1 cm while 12 were >1 cm.

Selection criteria

All cases were assigned a number from 1–48 based on the order of presentation for surgery and grouped as follows. *Group 1* even numbers (n = 24) were administered a gel containing 100 mg of hyaluronan (Conquer)[1] orally once daily for 30 days post operatively, *Group 2* odd numbers (n = 24) were administered the same gel formulation without HA once daily for 30 days post operatively. Due to the arbitrary assignment, *Group 2* had 3 more cases of bilateral lesions (lesion in both left and right tarsus) than to *Group 1*. Therefore 30 joints were evaluated in *Group 2* vs. 27 joints in *Group 1*. After surgery, all yearlings were stall rested routinely for 2 weeks and subsequently stall rested and hand-walked for an additional 2 weeks.

At the 30 day examination, the blinded examiner (BJB) gave the post operative tarsus an effusion score. The scale used to grade synovial effusion is shown in Table 1.

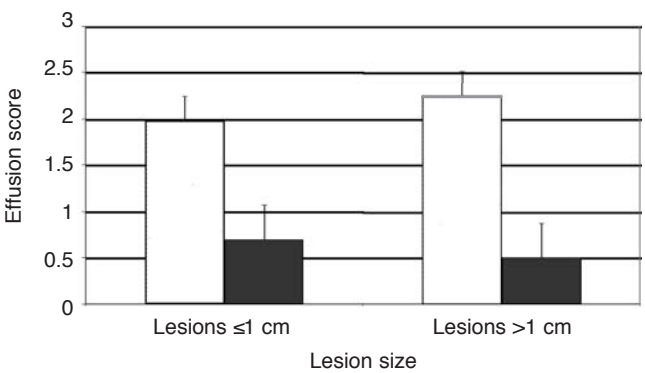

Fig 2: Mean joint effusion scores of oral HA Group 1 (*treated) and* Group 2 *(placebo) group by size of OCD lesion.*

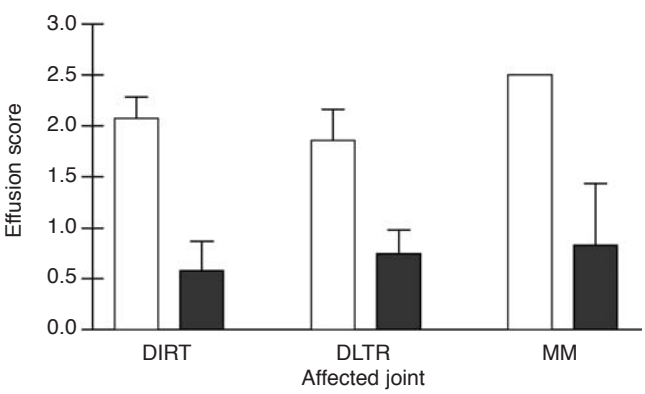

Fig 3: Mean joint effusion scores of oral HA Group 1 *(treated) and* Group 2 *(placebo) group by OCD lesion location.* □ *= placebo* ■ *= treated.*

Statistics

All score comparisons were done using 2 sided, 2 sample *t* tests assuming equal variances. The proportion of 0 scores were compared using Fisher's Exact Test. All P values were computed using JMP 4.0[2]. P<0.05 was considered significant. Means ± s.e. are reported.

Results

Mean 30 day effusion score of *Group 1* treated subjects was 0.67 while that of *Group 2* was 2.05 (P<0.0001: Fig 1). Retrospectively, note that this study was over-powered. A sample size of 8 in each group would have achieved 80% power, and a sample size of 10 in each group would have achieved 90% power. There were 11 scores of 0 (normal) in *Group 1* while only 2 scores of 0 in *Group 2* (P = 0.0035).

Of the 57 OCD lesions in the study, 45 were ≤1 cm and 12 >1 cm. When comparing treatment vs. placebo for ≤1 cm lesions (22–23 respectively), the 30 day mean effusion score of *Group 1* was 0.70 to that of *Group 2* 1.98 (P<0.0001) and vs. for >1 cm lesions, *Group 1* was 0.50 compared to *Group 2* of 2.25 (P = 0.0032: Fig 2).

A significant distinction was also shown when comparing groups with DIRT and DLRT lesions. In the DIRT operated group, there were 21 joints in *Group 1* and 12 in *Group 2*. Mean effusion score in *Group 2* was 2.07 while in *Group 1* it was significantly lower 0.58 (P = 0.0002). With DLTR lesions group, there were 7 joints in *Group 2*, mean score 1.86, compared to 12 in *Group 1* with significantly lower 0.75 mean (P = 0.0104: Fig 3). With MM lesions mean effusion score for *Group 1* was lower (0.67) than *Group 2* (2.5) but the difference was not considered statistically significant due to low sample size. All placebo treated horses, with an effusion score of ≥2 were given a free 30 day supply of the gel containing 100 mg of hyaluronan (Conquer)[1].

Discussion

Debridement of osteochondritis dissecans (OCD) lesions is a common surgical procedure in the horse that is normally performed arthroscopically. The purpose of surgery is to prevent degenerative joint disease and improve potential performance capacity (McIlwraith *et al*. 1991). Post operatively, rapid resolution of the inflammation within the joint and elimination of synovial effusion is one of the objectives of preventing initiation of, or interruption in the cycle of, joint degeneration. The effusion can be induced by either primary disease or by surgical manipulation, which can often result in inflammation and haemorrhage at the site of the OCD fragment removal. The post operative synovial effusion within the joint persists until haemorrhage ceases and fibrosis covers the site of the lesion removal. Once the raw bone is covered, the source of the inflammation within the joint is removed, allowing for the decrease in the inflammatory response created by surgical debridement. As a result, synovial fluid begins to improve in its concentration of HA and reduce in volume. If the cycle is not interrupted, the production of synovial effusion results in the initiation of inflammation and the release of destructive mediators leading to further articular degradation (McIlwraith 1996). This cycle can be considered self-replicating as it allows a renewal of effusion that promotes additional intra-articular irritation and results in the gradual production of more effusion.

Medical support of the surgical treatment is aimed at reducing effusion, resolving the inflammation and breaking the cycle of joint inflammation. This support is desirable both for the health of the joint and for the cosmetic aspects of resolving the effusion. Synovial fluid HA, synthesised by the synviocyte of the synovial membrane has been shown to have decreased concentrations in pathological human (Balazs *et al*. 1967; Howard and McIlwraith 1996) and equine (Hilbert *et al*. 1984, Howard and McIlwraith 1996) joints with traumatic arthritis. Numerous clinical and experimental studies have documented the beneficial effects of exogenous HA despite the remaining uncertainty of the exact mechanism through which this occurs. It has been suggested and demonstrated that there is a potential anti-inflammatory effect of exogenous HA on synovial fluid based on its ability to reduce the migration and interaction of articular degrading enzymes and other cells (Howard and McIlwraith 1996; Kawcak *et al*. 1997). Intra-articular and i.v. HA have been shown to be effective in improving the intra-articular condition of the joint, but the recent availability of oral HA provides an even more convenient method of delivery to the patient.

Based upon the blind comparison of this group of horses, oral treatment with hyaluronic acid was effective in reducing the synovial effusion significantly below that of the placebo controls. The examination was blinded as the material and packaging was identical and only the numerical sequential labeling of the tubes was different between horses in the study. The farm managers, attendants, attending veterinarians and independent grading veterinarian were all blinded as to the treatment being given. Their observations were made with no knowledge of what the horse was receiving. Only after the study was completed was the code broken.

The oral hyaluronic acid showed benefit over the orally administered placebo for all lesions at all locations and of all sizes. This study could not address how the orally administered HA would compare with parental administration, but the oral form is convenient and, therefore, may be preferable for routine use. This study establishes that oral administration of HA gel is effective in reducing synovial effusion following arthroscopic surgery for osteochondritis dissecans in the tarsocrural joint.

Manufacturers' addresses

[1]Kinetic Technologies, Lexington, Kentucky, USA.
[2]SAS Inc., Cary, North Carolina, USA.

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