



# HEALTH ZONE

## Joint Health

### Common Cause

BY AMANDA DUCKWORTH

**SOME ISSUES HORSES** struggle with, such as laminitis, can be difficult for people to comprehend fully because they are not afflictions humans face. When it comes to joint health, however, there is plenty of room for empathy.

Joint supplements are a standard part of the diet for many athletically inclined horses, but veterinarians also remain dedicated to researching and developing treatment for significant joint-related problems. As the science evolves, so do the options when it comes to healing and repairing damage along with managing the issues.

“Although joint therapy has been primarily targeted at Thoroughbred and Quarter horses, even miniature horses deal with the same sorts of problems,” explained Drs. Benjamin Espy and Justin Harper in “Lameness & Joint Medications” for the American Association of Equine Practitioners. “Breeding stallions and driving horses are especially prone to joint soreness.

“Traumatic joint disease in horses includes synovitis (inflammation of the flu-

id-producing membrane), capsulitis (inflammation of the fibrous joint capsule), articular cartilage and bone fragmentation, ligamentous tearing, and eventually osteoarthritis. In many cases the disease process primarily involves soft tissue

**Approximately 60% of lameness issues are related to osteoarthritis**

overuse and microtrauma to the bone surfaces and therefore can be challenging to diagnose without diagnostic anesthesia.”

Osteoarthritis is the most common cause of lameness in horses, leading to poor performance, and it is estimated that approximately 60% of lameness issues with horses are related to osteoarthritis.

In August 2019, PLOS One (a peer-reviewed open access journal published by the Public Library of Science) released “Comparison of Efficacy and Safety of Single Versus Repeated Intra-Articular Injection of Allogeneic Neonatal Mesenchymal Stem Cells for Treatment of Osteoarthritis of the metacarpophalangeal/metatar-

sophalangeal Joint in Horses: A Clinical Pilot Study.”

“Osteoarthritis (OA) of the metacarpophalangeal/metatarsophalangeal joints (MPJs) is one of the most common causes of lameness in sports horses,” explained the researchers. “Several local and systemic treatments have been described, including intra-articular viscosupplementation (hyaluronic acid, polyacrylamide gel), anti-inflammatory biological therapeutics (platelet-rich plasma), autologous conditioned serum (ACS or IRAP), polysulphated glycosaminoglycans (PSGAGS), and steroidal drugs (corticosteroids, stanozolol). Such intra-articular treatments have been shown to have predominantly symptom-modifying effects.

“Mesenchymal stem cell (MSC) therapy has been developed as a means of promoting scar-free tissue regeneration in a variety of musculoskeletal injuries in horses and has been characterized predominantly for the treatment of overstrain injuries of the superficial digital flexor tendon.”

The study was conducted to evaluate the effects of both single and repeated intra-articular administration of allogeneic, umbilical cord-derived, neonatal mesenchymal stem cells in horses with lameness due to osteoarthritis of a metacarpophalangeal joint.

For the study, 28 horses were divided into two groups, although six were eventually excluded for various reasons. All horses received an MSC injection at the beginning of the study. One group received a placebo one month later while the other received an MSC injection again.

Clinical assessments were done after one, two, and six months, including lameness evaluation, palpation, and flexion of the joint. Radiographs were conducted at the beginning and at the six-month mark. Additionally, a two-month rehabilitation program was recommended, which con-

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COADY PHOTOGRAPHY

Joint health is a key element in keeping Thoroughbreds racing at a high level



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MESSAGE FROM THE GRAYSON-JOCKEY CLUB RESEARCH FOUNDATION

## RESOLVING JOINT INFLAMMATION FROM INSIDE

BY DRS. BRUNO C. MENARIM AND LINDA DAHLGREN



Grayson-Jockey Club  
Research Foundation

**OSTEOARTHRITIS** is a major cause of joint disease, leading to poor performance and early retirement of horses; a heavy economic and emotional burden to the equine industry. Current treatments provide limited recovery of joint function, creating an urgent need for more efficient therapies. Development of new treatments requires a more comprehensive understanding of the mechanisms causing OA.

One fundamental characteristic of joint disease is sustained, low-grade inflammation. Cells called macrophages are the main drivers of joint inflammation; however, these complex cells can both incite and resolve inflammation, depending on the circumstances. Macrophages in the synovial (joint) membrane and fluid are essential in promoting joint health by clearing aggressors, by secreting key molecules required for optimal joint function, and by forming a shield that protects tissues undergoing repair, similar to a wound scab.

However, when the amount of tissue damage overwhelms these housekeeping functions, macrophages stimulate inflammation as a means of recruiting more cells to cope with increased demands for repair. If this response is efficiently accomplished, macrophages then resolve the inflammatory process, returning the joint to a healthy state.

The sequence of studies described herein focuses on understanding the dual function of macrophages in driving and resolving joint inflam-

mation, and ultimately in harnessing their therapeutic potential to treat joint disease.

The first study, funded by the American College of Veterinary Surgeons Research Foundation, compared the response of macrophages in normal and OA-affected joints. We observed that macrophages had a similar response in both healthy and OA-affected joints but were markedly activated in arthritic joints showing obvious, severe inflammation. Synovial fluid from OA joints had lower levels of a protein that recruits macrophages from the bone marrow following injury (SDF-1), and of a macrophage-derived anti-inflammatory protein called interleukin (IL)-10.

Our results suggest macrophage recruitment and associated anti-inflammatory mechanisms are impaired in OA-affected joints, preventing joint inflammation from being resolved, and that re-establishment of these functions could greatly aid in the treatment of OA.

Macrophages in the bone marrow (BMNC or bone marrow mononuclear cells) are used in people to treat inflammation in several chronically inflamed tissues and produce molecules essential for joint health, such as IL-10. Our second study, funded by the Grayson-Jockey Club Research Foundation, investigated the effects of injecting each horse's own (autologous) BMNC into normal and inflamed joints using an experimental model of joint inflammation in six Thoroughbred horses.

Inflamed joints treated with BMNC showed dramatic visual and measurable markers of improvement, with increasing macrophages and IL-10 in the joint fluid, which remained low in joints treated with placebo.

The results of this study confirmed that increasing macrophages in inflamed joints by BMNC injection recovered the macrophage- and IL-10-associated mechanisms required to resolve joint inflammation that are impaired during OA.

We conducted a third study, also funded by the GJCRF, that further investigated how BMNC (same group of horses as above) responded to laboratory culture in fluid from their normal and inflamed joints. Normal and inflamed joint fluid induced macrophages from BMNC to develop similar responses that precisely combined pro- and anti-inflammatory mechanisms, both essentially required for tissue repair and recovery of joint health. Such a balanced response was proportional to the inflammatory challenge. Macrophage proliferation and secretion of IL-10 and IGF-1 (both essential for cartilage metabolism) were highest for cultures in fluid from inflamed joints. BMNC cultured in normal or inflamed synovial fluid were ultimately comparable to cells native to normal joints, suggesting that the healthy state was recovered in inflamed joint fluid.

These observations suggest robust proliferation of BMNC in inflamed joint fluid provides a "bigger army"



to cope with the intensity of inflammation, allowing inflammation to be resolved and homeostasis (health) to be recovered.

Finally, a pre-clinical pilot study supported by the Virginia Horse Industry Board and the Veterinary Memorial Fund followed 18 Thoroughbred horses with naturally occurring OA treated with either BMNC, triamcinolone (commonly used corticosteroid), or placebo. Horses were evaluated for lameness (subjectively and

using Lameness Locator®) and synovial fluid analysis at 0, 7, and 21 days post-injection. BMNC injection was performed without adverse effects, with BMNC-treated horses being the only ones to show improved lameness during the study period.

In summary, BMNC injection is a safe, natural, point-of-care therapy that provides a promising means to recover and sustain macrophage-associated effects required for joint integrity while preserving mediators

of joint health often impaired by conventional therapies.

Currently, we are delving deeper, using cutting-edge “omics” techniques to define the molecular products of macrophages that drive resolution of inflammation and recovery of joint health.

Our long-term goal is to harness these natural processes to develop new treatments that stand to benefit thousands of OA patients of all species. **BH**

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sisted of stall rest with short, progressively increasing periods of controlled hand-walking daily. Following this program, horses were allowed to return to their normal routine.

The horses included in the study participated in a wide variety of disciplines, including jumping, dressage, pleasure riding, western riding, endurance, and Standardbred racing.

“There was a significant improvement

of the total clinical score for horses in both groups,” the study found. “There was no significant difference in the total clinical score between groups MSC1 and MSC2 at any point in the study. There was no significant difference in the total radiographic

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OA score, osteophyte score, joint space width score, and subchondral bone score between inclusion and M6.

“The eight-week period of rest and rehabilitation may also have helped the horse’s lameness grade improve through the study.

“It has been shown that it may be difficult to differentiate the beneficial effects of a rest and rehab program from those caused by a therapeutic agent administered concurrently in the treatment of equine osteoarthritis. However, the authors feel this is unlikely, as at least seven horses had already been rested for periods exceeding eight weeks without improvement before recruitment in the study, other horses had failed to respond to other treatments combined with rest, and the median time between OA diagnosis and MSC treatment was one year with a minimum of three months for horses in this study.”

Based on the results, researchers concluded MPJ OA improved significantly after treatment, but that there is no apparent clinical benefit of repeated intra-articular administration of MSCs at a one-month interval in horses with MPJ OA when compared to the effect of a single injection.

The November 2019 issue of *Equine Veterinary Journal* published a related study titled “The Use of Equine Chondrogenic-Induced Mesenchymal Stem Cells as a Treatment for Osteoarthritis: A Randomised, Double-Blinded, Placebo-Controlled Proof-Of-Concept Study.”

“Currently, treatment of OA is mainly focused on addressing the clinical signs,” explained the researchers. “The most commonly used treatments are corticosteroids, nonsteroidal anti-inflammatory drugs, hyaluronan, and polysulfated glycosaminoglycan. However, to date, none of these treatments halt the disease, let alone reverse it, so none of the current treatment modalities present a durable solution for OA.

“Regenerative medicine represents an interesting alternative for treating OA, since it has the potential to prevent further cartilage damage and even reverse the



COURTESY OF HEATHER SMITH THOMAS

### Regenerative medicine represents an interesting alternative for treating OA

sustained damage.”

In this study, osteoarthritis was induced in the metacarpophalangeal joint using an osteochondral fragment-groove model in 12 healthy horses. Five weeks after surgery, horses were randomly given either an intra-articular injection with chondrogenic-induced mesenchymal stem cells and equine allogeneic plasma or they were given a 0.9% saline solution to serve as a control group.

Horses underwent a weekly joint and lameness assessment from the time of surgery until the study concluded. At Week 11 the horses were subjected to euthanasia, and the metacarpophalangeal joints were evaluated macroscopically and histologically.

“No serious adverse events or suspected adverse drug reactions occurred during the study,” researchers found. “A signifi-



ANNE M. EBERHARDT

### In adult horses, fatalities are usually caused by joint contamination via wounds

cant improvement in visual and objective lameness was seen with the intervention compared with the control. Synovial fluid displayed a significantly higher viscosity and a significantly lower glycosaminoglycan concentration in the intervention group.

“Other biomarkers or cytology parameters were not significantly different be-

tween the treatment groups. Significantly less wear lines and synovial hyperaemia were present in the intervention group. The amount of cartilage oligomeric matrix protein, collagen type II, and glycosaminoglycans were significantly higher in the articular cartilage of the intervention group.”

Researchers found the results to be positive in the quest to treat osteoarthritis.

“Equine allogeneic chondrogenic-induced mesenchymal stem cells combined with equine allogeneic plasma may be a promising treatment for osteoarthritis in horses,” the study concluded.

Because soundness can be a struggle with performance horses, it is not unusual for veterinarians to recommend various types of joint injections. However, there has been some concern that in trying to treat joint issues via injection, joint infection can be an accidental result.

In good news for horse owners, a recent study concluded that the risk of joint infections after a horse receives a joint injection is low. “Synovial Sepsis Is Rare Following Intrasynovial Medication in Equine Ambulatory Practice” appeared in the September 2019 edition of *Equine Veterinary Journal*. “There are few observational studies regarding the potentially serious complication of synovial sepsis following intrasynovial medication in general equine practice,” the study explained. “Quantification of risk is fundamental to fully inform decision-making and owner consent prior to undertaking procedures.”

In the retrospective cohort study, in a large ambulatory equine practice between 2006-11 the occurrence of synovial sepsis following intrasynovial injections was examined. To conduct the study, medication records were cross-referenced against synovial cytology submissions and hospital admissions for synovial sepsis.

In all, 9,456 intrasynovial medications were performed in 4,331 sessions, and only four horses, or 0.04%, developed post medication synovial sepsis. The most frequently used medications were corticoste-



roids, hyaluronate, and amikacin sulphate. Two of the horses to develop synovial sepsis were given polysulphated glycosaminoglycans and hyaluronate while the other two had been given triamcinolone acetone and hyaluronate. All four were able to return to racing following joint lavage.

“The frequency of synovial sepsis in this population of horses was 0.04%,” the study concluded. “These data may be helpful in informing clients regarding the potential risks of adverse complications resulting from intrasynovial medication.

“Although the study was conducted in an ambulatory setting, the population included a high number of racehorses, limiting application to the general horse population.”

When it comes to joints, septic arthritis (joint infection) is a genuine concern because it creates soundness issues and impacts athletic ability. Additionally, joint infections can end up being fatal if left untreated. In adult horses, fatalities are usually caused by joint contamination via wounds. With foals, bacteria can enter the bloodstream resulting in the infection.

Earlier this year the *Journal of Orthopaedic Research* came out with an article on a new therapy that could be capable of combating persistent joint infections in horses. “Platelet-rich plasma lysate displays antibiofilm properties and restores antimicrobial activity against synovial fluid biofilms in vitro” was published in its June 2020 issue.

Researchers at North Carolina State University were funded by the Morris Animal Foundation to develop a platelet-rich plasma lysate that, when teamed with antibiotics, can eradicate bacterial biofilms common in joint infections.

“Infectious arthritis is difficult to treat in both human and veterinary clinical practice,” the study explained. “Recent literature reports *Staphylococcus aureus* as well as other gram-positive and gram-negative isolates forming free-floating biofilms in both human and equine synovial fluid that are tolerant to traditional antimicrobial therapy. Using an in vitro equine model, we investigated the ability of platelet-rich plasma (PRP) formulations to combat synovial fluid biofilm aggregates.”

Blood was taken from the research equine herd, and from there platelets were isolated. Researchers then created a super-concentrated product containing 50 times the number of platelets that would be found in an equal amount of blood. They lysed the platelets to release antimicrobial peptides, which are proteins that attack bacteria.

For the study researchers tested three methods to attack biofilms: antibiotics alone, lysate alone, and a combination of antibiotics and lysate. Results showed that antibiotics alone were ineffective; the lysate alone significantly decreased the bacterial load; and the antibiotic and lysate combination completely eradicated

KEN SULLINS PHOTOGRAPHY



**This radiograph of the hock reveals the horse has bone spavin, also called distal tarsitis osteoarthritis**

the biofilms and bacteria.

“Overall, PRP-L exhibited synergism with amikacin against aminoglycoside tolerant biofilm aggregates with greater activity against gram-positive bacteria,” the study found. “In conclusion, the use of PRP-L has the potential to augment current antimicrobial treatment regimens that could lead to a decrease in morbidity and mortality associated with infectious arthritis.”

Researchers did note, however, that the process to create the lysate was complicated and expensive, so they are now working toward finding a more efficient

way to produce it.

Joint health will always be a major concern for horse owners, and treatment options are routinely being researched by the scientific community. As with all other equine health worries, working with a veterinarian remains the best course of action when presented with a horse facing joint issues. **BH**

*Amanda Duckworth is a freelance writer based in Lexington.*

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