NEW DEVELOPMENTS IN TREATMENT of LAMENESS

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There have been many advances in the treatment of equine lameness during the last five years. This is a review of intra-articular medications, biologic/regenerative products, parenteral joint support medications and new oral supplements.

In my view, the hierarchy of effective treatment for lameness from most effective to least effective is:

- Intra-articular medication administered to the specific joint causing lameness
- Parenteral medication to manage musculoskeletal soreness
- Oral supplements

Parenteral, non-steroidal anti-inflammatory drugs (NSAIDs) also are part of basic treatment of joint inflammation and osteoarthritis. At times, NSAIDs are used concurrently with many of the treatment methods described.

INTRA-ARTICULAR MEDICATIONS

Traditionally, synovitis and osteoarthritis (OA) have been treated with administration of medications within the joint by injection, such as hyaluronan, steroids or a combination of the two. This approach is very effective for most common causes of joint soreness. The advantages of these medications are good results, quick onset of action and minimal adverse effects. The disadvantage of this method is that the medication is only effective within the treated joint(s). Also, with progression of OA, this traditional approach may require more frequent administration and may eventually become ineffective. Because of these limitations advanced approaches to intra-articular treatment have been developed. The new products include polyacrylamide hydrogel (PAHG), IRAP, intra-articular platelet-rich plasma, and intra-articular stem cells.

Polyacrylamide hydrogel

An early form of PAHG consisting of 2.5% crosslinked polyacrylamide is reported to become incorporated within the synovium following injection. This product was originally developed as a tissue filler for use in plastic surgery. It provides relief of OA pain by enhancing shock absorption within the joint. The gel becomes integrated with the synovium and a subsynovial layer of gel was found to remain at least 2 years after injection in horses with OA. (Arthramid Vet; Contura International, Soeborg, Denmark, 2010 package insert).[1] In a study of 43 horses with OA injected with 2.5% PAHG, 59% were sound at one month and 83% were sound and in full work at 24 months after injection.[2] This product was evaluated for treatment of middle carpal joint arthritis in racehorses. Treatment efficacy was compared for 2.5% hydrogel, triamcinolone and hyaluronan at 2, 4, and 6 weeks after injection. At 6 weeks, the percentage of sound horses for each group was: 83% hydrogel, 27% triamcinolone and 30% HA. The hydrogel treated horses were evaluated again at 12 weeks and all that were sound at 6 weeks remained sound at 12 weeks (Clifford, et al. AAEP Proceedings 2019).

A preliminary study of treatment of osteoarthritis in horses using 4% PAHG (NoltrexVet; BIOFORM, Moscow, Russia) in horses reported a significant improvement in lameness score,

with most of the horses maintaining the improvement in lameness to the end of the study at 90 days. Twenty-eight horses that met the study criteria (lameness evaluation, localization of the lameness using intra-articular anesthesia and radiography of the affected site) were included. Lameness grade, range of motion and joint swelling were outcome measures. Success was defined as improvement of at least one lameness grade or a reduction at least 3 grades of the combined scores for all outcome measures. Eight-two percent of the treated horses improved at least one lameness grade. Seventy-five percent of horses were considered successfully treated at 90 days, which was the end of the study period. No adverse responses to the injections were reported in this group.[3]

4% PAHG was injected into normal fetlock joints of 6 horses and compared to controls with synovial fluid analysis, histopathology of synovium and determination of cartilage metabolism. At 7 days following injection mild synovial fluid inflammation, synoviocyte hypertrophy, mononuclear infiltrate and increased cartilage metabolism were identified. The PAHG was found on the synovial surface at 7 days after injection, then integrated within the synovium on days 28 and 56 after injection. All horses remained sound and negative to joint flexion. Some treated joints had mild enlargement noted. Integration of PAHG appeared to be due to phagocytosis of the gel by synoviocytes. The synovial cell response to PAHG was theorized to have potential OA disease modifying effects such as improved synovial tissue function and by stimulating the release of anti-inflammatory cytokines.[3] 4% PAHG does not remain indefinitely within the synovium. It is gradually phagocytized with no significant inflammatory response Also, 4% PAHG does not induce or bind to inflammatory mediators or activate monocytes (White Paper: NoltrexVet, Nucleus Regenerative Technologies, Kennesaw, GA USA).

PAHG products have most commonly been used in horses that have not responded to other traditional joint therapies. Indications for use of PAHG are: 1) primary lameness is localized to a joint, 2) lameness has not responded to treatment with traditional intra-articular medications or 3) response to traditional therapy has been short lived. Further research may elucidate the disease modifying effects of PAHG.

Administration of PAHG is via routine aseptic joint injection. The gel is very viscous and requires a large gauge needle for administration, at least 19g and preferably 18g. Injection is also facilitated by warming the gel to body temperature. Amikacin injection (usually 1ml, 250mg/ml) is made with a separate syringe immediately after the needle is placed in the joint to verify correct needle placement and again following gel injection to 'clear' the needle of gel. Horses should be walked for about 3 minutes after injection to spread the gel throughout the joint. Horses are rested from full exercise for 7 days, then returned to light work.

BIOLOGICAL TREATMENTS

IRAP, ACS, APS

Advanced methodologies for attenuation of joint inflammation have become part of the equine practitioner's armamentarium. These products are referred to as IRAP (interleukin receptor antagonist protein), ACS (autologous conditioned serum), ACP (autologous conditioned plasma) or APS (autologous protein solution). ACS-type biological products require processing to concentrate the beneficial anti-inflammatory cytokines. The primary mechanism of action of these products is attenuating the inflammatory effect of IL-1. Processing requires contact of whole blood with glass beads and incubation. The ACS-type products are usually injected in the target joint three to four times. One proprietary processing system (Pro-Stride; Owl Manor Veterinary, Warsaw, IN USA) allows for stall-side processing with same-day administration.

Another proprietary product (MediVet ACS; Medivet Equine, Nicholasville, KY USA)) may be administered intra-articularly, but is primarily recommended for intravenous administration three times per week.

ACS contains multiple cytokines that reduce joint inflammation. These products primarily reduce the activity of IL-1, the primary inflammatory cytokine in joints. This allows for an alternate means to reduce joint inflammation compared to steroids and hyaluronan. Specifically, it has been reported that incubation of human whole blood with medical-grade glass beads exposed to chromium sulfate stimulates the production of IL-4, IL- 10, and interleukin receptor antagonist protein (IL-1ra) as well as fibroblastic growth factor-1, hepatocyte growth factor, and transforming growth factor-β1, resulting in higher concentrations of those cytokines and factors in human ACS. The increase in these anti-inflammatory mediators does not appear to be accompanied by an increase in the pro-inflammatory cytokines IL-1β or tumor necrosis factor-α. Because IL-1ra expression is as much as 140-fold greater than other anti-inflammatory proteins in ACS after such stimulation of whole blood, it has been assumed that IL-1Ra is one of the major mediators responsible for clinical improvement in patients with osteoarthritis.[4] Other studies have identified the following anti-inflammatory cytokines in IRAP processed from equine blood: IL-1ra and TNF-a.[5]

The first significant study of ACS in horses was published in 2007.[4] Using the Colorado State carpal chip model of OA, horses were injected with ACS four times at weekly intervals. Horses with experimental OA treated with ACS had significant improvement in lameness and significantly decreased synovial membrane hyperplasia, compared with placebo-treated joints. ACS-treated joints also appeared to have less gross cartilage fibrillation and synovial membrane hemorrhage. Synovial fluid concentration of IL-1ra was increased following treatment with ACS.

ACS is commonly produced by incubation for approximately 24 hours (for example: Orthokine, IRAP, IRAP II). Most processing systems result in 3 to 6 doses of ACS which are frozen until use. The ACS is injected in the affected joint 3 to 4 times at 7 to 10-day intervals.

A similar product, Autologous Protein Serum (APS), allows for stall-side processing of autologous blood and is administered with a single intra-articular injection (Pro-Stride). APS contains IL-1ra, white blood cells, and platelets. A group of 40 horses with naturally occurring osteoarthritis were randomly selected for treatment or control groups. Twenty horses received a single 5ml injection of APS and 20 horses were injected with 5ml of sterile saline. All horses were exercised on a treadmill and were evaluated for lameness grade, joint circumference, kinetic gait analysis, and range-of-motion for 14 days. Clients assessed and reported lameness before treatment and at 12 and 52 weeks following. The APS group had significant improvements in lameness, range-of-motion and gait symmetry by day 14. Clients reported improved lameness at 12 and 52 weeks over controls. Concentration of IL-1ra in APS was 5.8 times the level found in whole blood.[6]

The advantages of this product include stall-side convenience, no incubation period, single intra-articular injection and prolonged effect. In the last year I have used APS in joints where other IA treatment modalities have failed. Results have been very favorable and consistent with the paper described above.[6]

Platelet-rich plasma (PRP) and stem cells

Use of these biological products within the joint has been quite popular in human and animal medicine. In recent years there has been considerable research activity regarding PRP and

stem cells, yet there are many unknowns. The hard evidence for a positive effect with these treatments remains inconclusive for OA in horses.

In a meta-analysis of the use of PRP in human and equine OA, PRP's beneficial effects were observed in 47% of clinical studies, while the absence of positive effects was found in 43%. Seventy-three percent of experimental studies had positive results, and 8% yielded adverse effects. The methods employed for PRP preparation, administration and the selected outcome measures varied greatly between studies. Poor study design was a common feature of equine clinical trials. In studies that had positive effects, a majority had significant bias.[7]

In humans, a clinical study of PRP use for knee OA was conducted. Superior outcomes for up to 18 months were identified for the group that received two treatments spaced 14 days apart of intra-osseous and intra-articular (IA) PRP, compared to PRP IA and HA IA treatments.[8]

In a comparison of a single injection of PRP or HA in the human knee, patients were followed for 6 months. Both treatments led to improved function and pain. A non-statistically significant higher percentage of responders was observed in the PRP group (72.7%) than in the HA group (45.8%). The researchers determined that a single injection of PRP that contained low levels of inflammatory cytokines offered a significant improvement of knee OA.[9]

A counterpoint to the above study involved a comparison of PRP and HA for treatment of early hip OA in humans. Patients had their hips injected three times. PRP did not offer significantly better results compared with HA. The authors concluded that PRP should not be a primary treatment for early hip OA.[10]

A study in normal equine joints was used to determine the effect of PRP versus saline on cytokine concentrations and inflammatory indicators. In joints injected with PRP compared to saline controls, higher white blood cell counts, prostaglandin E2 and total protein levels were observed in the synovial fluid. There were no differences between the IL-1β, IL-1ra, TNF-α, chondroitin sulfate, or hyaluronic acid concentrations between PRP and control injected joints. PRP injection elicited a mild and self-limiting inflammatory response shortly after administration, without long-term deleterious effects on the joints.[11]

In a study of healthy equine joints, comparisons were made between plain PRP, $CaCl_2$-activated PRP and thrombin-activated PRP. It was determined that activation of PRP was not necessary for release of anti-inflammatory cytokines and growth factors. Thrombin-activated PRP resulted in more inflammation than plain PRP or $CaCl_2$-activated PRP.[12] In a similar study, plain PRP, $CaCl_2$-activated PRP and thrombin-activated PRP all caused inflammation in normal equine joints. Again, thrombin-activated PRP resulted in more inflammation than the other preparations.[13]

A group of 12 horses with moderate-to-severe OA in one joint were treated with autologous PRP obtained using a gravity filtration method and the responses were compiled. Outcome measures were force plate measurements and radiography. Significant differences in force plate response or radiographic findings were not identified over the 16-week study period.[14]

A combination of chondrogenic-induced mesenchymal stem cells (MSCs) and PRP has been found to effectively treat equine fetlock OA. The study was conducted in two phases: *Phase 1:* Twenty horses with mild-to-moderate fetlock OA of at least three months duration were studied. PRP and MSCs were obtained from the whole blood of a single donor, processed and frozen. The study population was divided into four treatment groups: 1) PRP only, 2) MSCs only, 3) MSCs and PRP, and 4) chondrogenic-induced MSCs and PRP. Horses were clinically evaluated before treatment and at 6 weeks, 12 weeks, 6 months and 12 months. Lameness grade, joint effusion and response to joint flexion were recorded. *Phase 2:* Thirty horses with

the same inclusion criteria as Phase 1 with the horses treated with either MSCs and PRP or chondrogenic-induced MSCs and PRP. In both study phases, the combination of MSCs and PRP improved the clinical scores of OA joints from 6 weeks until 12 months after treatment, compared to PRP alone. The Phase 2 study identified a statistically significant improvement in both MSC plus PRP groups.[15] This combination therapy may hold promise for treatment of OA in horses.

Another study in a large group of horses evaluated similar treatment approaches. The clinical outcome of allogenic, plain MSCs or chondrogenic-induced MSCs in combination with PRP for the treatment of OA was assessed in 165 horses. Joints treated included: stifle (n=30), fetlock (n=58), pastern (n=34) and coffin (n=43). After 6 weeks, 45% (plain MSCs) and 60% (chondrogenic-induced MSCs) of the treated patients returned to work and the beneficial effects of the treatment further increased after 18 weeks (78% for plain MSCs and 86% for chondrogenic-induced MSCs). Lower limb joints had better responses to therapy than did stifle joints.[16]

There is not enough scientific evidence that PRP use in equine joints is effective. MSCs with PRP may be an effective treatment for OA, but this still requires further confirmation. In April 2019 Boehringer-Ingelheim initiated marketing of chondrogenic-induced MSCs for use in equine joints (Arti-Cell Forte). It is a frozen, allogeneic stem cell product that was approved by the European Medicines Agency for use in EU countries.

Allogeneic dental pulp particles (Pulpcyte)

This is a recently available biologic product derived from the dental pulp of healthy equine fetuses that have died during birth. The pulp particles are minimally manipulated and processed on tight quality control. The product includes many anti-inflammatory proteins and mesenchymal progenitor cells that may have regenerative effects. In a placebo-controlled clinical study of osteoarthritis and soft tissue injuries in 40 horses, injection of allogeneic dental pulp particles resulted in improved lameness and less inflammation when compared to saline solution alone.[17]

Intraarticular osteoarthritis treatment with microparticles (Kush)

This intraarticular product consists of small ~100 micron particles that act to dampen mechanical joint forces and reduce friction. The web site describes the particles as 'small sponges' that absorb and release synovial fluid which results in the cushioning effects. The product is classified by the FDA as a medical device for horses and dogs. Treatment consists of 1-2ml of product to each affected joint. Duration of activity is claimed to be as long as one year. Safety and efficacy studies

INTRA-ARTICULAR STEROID

A recently developed intra-articular steroid has been reported to have chondroprotective and anabolic effects in joints. The product is a 1ml solution that contains 5mg stanozolol. Research studies on this type of product have been published since 2013[18-20]. The product (Sungate) is manufactured and approved for use in horses in Italy. Recommended intraarticular treatment is 1ml (5mg stanozolol) per medium-sized joint once per week for 2-6 treatments depending on the severity/chronicity of osteoarthritis.[19] The product has been reported to be undetectable in blood by 36 hours after administration.[20]

PARENTERAL MEDICATIONS

Medications in this classification include hyaluronan labelled for intravenous administration (Legend), polysulfated glycosaminoglycans labeled for the intramuscular route (Adequan), pentosan polysulfate administered in the muscle, and a variety of other medications. Legend and Adequan have been approved for use in horses in the United States by the Food and Drug Administration (FDA) and have passed safety and efficacy trials prior to approval. An FDA-approved version of pentosan plus glucosamine (PentAussie) was available in the USA at one time.

Pentosan

Pentosan polysulfate has been used to treat osteoarthritis in humans, dogs and horses since the 1990s. Pentosan is a semi-synthetic polysulfated xylan which was initially obtained as an extract of beechwood hemicellulose. It was initially used as an anti-thrombotic, antilipidemic agent. In multiple animal studies pentosan has been found to reduce cartilage deterioration by inhibiting inflammatory cytokine MMP-3[21], stimulating the production of hyaluronan by synoviocytes[22], and stimulating proteoglycan synthesis by chondrocytes.[23] In sheep with experimentally induced OA, pentosan resulted in improved radiographic and Mankin scores.[23]

A review of parenteral joint medication use by Australian equine practitioners reported that pentosan was the most common drug used for preventive/maintenance therapy prior to competition. Forty-eight percent of practitioners responded that pentosan was highly efficacious. Pentosan was reported to be used with other therapies such as hyaluronan and glucosamine. The most commonly reported dose regime was 3 mg/kg IM once per week for 4 weeks with maintenance at once per month.[24]

Horses with a carpal-chip model of OA were evaluated, with 8 horses treated with a combination of pentosan, glucosamine and hyaluronan and compared to 8 horses administered saline. Horses had treadmill exercise following surgery. Treated horses were medicated intravenously with this combination for 10 weeks. Radiographic scores and gross pathology of synovium and cartilage were significantly reduced in treated horses. Treated horses had increased synovial fluid protein and white blood cell counts compared to controls. However, microscopic pathology, histochemical and biochemical findings did not statistically differ between treated and control groups.[25]

A study using the same carpal chip model with treadmill exercise where pentosan was administered intramuscularly 4 times at 1-week intervals also found a subtle beneficial effect.[23] Treated horses had significantly reduced cartilage fibrillation and a trend to lower cartilage histologic scores over controls. Pentosan treated horses had increased chondroitin 846 epitope in both chip-fracture and control joints. This biomarker is consistent with cartilage repair. The disease modifying effects of pentosan may be beneficial in reducing the progression of mild OA.

There is often concern regarding the efficacy of medications administered in the muscle for treatment of joint inflammation. Calcium pentosan polysulphate at 2 mg/kg IM was found in joint fluid at therapeutic levels 4 hours after injection.[26] Plasma levels of pentosan were insignificantly low at 8 hours following injection.[27] It is theorized that pentosan accumulates in connective tissues, which act as a reservoir for the medication.[27] Formulations of pentosan may also be administered intravenously. One source formulates pentosan 250mg/ml with glucosamine 150mg/ml and hyaluronic acid 2.5mg/ml (Pentosan Platinum, Racehorse Meds, Richmond,

British Columbia, Canada) and pentosan 250mg/ml. Both preparations are formulated for intravenous or intraarticular administration.

Indications for administration of pentosan include: horses with mild to moderate OA, mild to moderate positive joint flexion results with minimal degenerative changes on radiographic evaluation, and long-term support of horses that are being treated primarily with intra-articular injections. For joint maintenance pentosan is administered at 3 mg/kg IM every two weeks.

ORAL SUPPLEMENTS

Oral joint supplements have been available as adjunct treatment and for maintenance of horses with OA for a considerable period of time. Oral supplements for treatment of joint disorders most commonly include glucosamine and chondroitin as the basic components. Other additives such as hyaluronan, MSM, avocado/soybean unsaponifiables (ASU), among others, are often included.

In vitro studies of equine cartilage indicate that inflammatory mediators are attenuated with clinically relevant levels of glucosamine present.[29] When used at the appropriate dosage, glucosamine/chondroitin supplements have been reported to prolong the interval for joint treatments to alleviate pain.[30]

Resveratrol supplements

Resveratrol has become available as a primary supplement and as an additional component in many oral joint products.

Resveratrol is a natural compound found in plants such as grape skin. In animals, the compound has been found to act as an anti-oxidant and anti-inflammatory. Resveratrol has been identified as the compound in red wine that may be partially responsible for reduced heart disease in humans. Anti-inflammatory effects of resveratrol have been reported such as: down regulation of cyclooxygenase, inhibition of IL-1β and scavenging of free radicals.[31]

One resveratrol supplement has undergone clinical research in horses.[32] Forty-five horses with lameness localized to the lower hock joints were included. All horses had triamcinolone injected in the lower hock joints. Horses were fed either 1000 mg resveratrol (Equithrive, Lexington, KY USA) or placebo twice daily for four months. Riders reported reduced lameness and better performance in the resveratrol group compared to placebo group. Objective measurement of lameness improved from pre-treatment to 4 months in the resveratrol group compared to placebo.

Resveratrol for horses in ‘pure form’ is available in two preparations: a standard powdered product (Equithrive) and a capsule form (Resvantage Equine; Advantage Partners, Newport Beach, CA USA).

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