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Advances in diagnosis and clinical management of equine arthritis: A review

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Abstract

Arthritis is one of the most frequently reported causes of lameness, poor performance, decreased competitive lifespan and premature retirement of horses. It affects the major joints of the body whose correct functioning is critical for the athletic performance of horses. The present review aims at focusing the current trends in diagnosis and clinical management of equine arthritis that can help in normalizing the inflamed joint as quickly as possible before permanent damage occurs.

Keywords: Equine, arthritis, diagnosis, clinical management

Introduction

The horse has always taken a special position among the species that have been domesticated by human kind. The main purpose of the horse's domestication was for physical power and athletic capacity. The cardio-respiratory and musculo-skeletal systems are the most critical body systems for athletic performance. It may not be surprising that orthopedic malfunction or other musculoskeletal disorders account for the vast majority of reasons to consult an equine practitioner. Joints are complex structures of the musculoskeletal system, whose correct functioning is critical for the athletic performance of horses (McIlwraith *et al.*, 2016) [8].

Arthritis is a non-specific term denoting inflammation of joints. All joint diseases of animals have an inflammatory component to varying degrees. Arthritic entities of importance include septic or infective arthritis, traumatic arthritis, osteoarthritis, osteochondritis dissecans and subchondral cystic lesions. Arthritis is one of the most frequently reported causes of lameness, poor performance, decreased competitive lifespan and premature retirement of horses. In a survey of U.S. horse owners in 1998 it was estimated that 60% of all lameness was related to osteoarthritis (McIlwraith *et al.*, 2016) [8]. Osteoarthritis (OA) compromises the equine industry, not only due to the costs of treatment, but also as a consequence of delayed return to athletic performance. It is impossible to prevent joint stress; however the aim remains at normalizing the inflamed joint as quickly as possible before permanent damage occurs (Souza, 2016) [10]. The objective of this topic is to review the information related to advances in diagnosis and treatment of arthritis, which helps in early detection and prompt treatment, for the management and prevention of joint damage.

Morpho-physiology of joints

The best way to prevent arthritis is to arm ourselves with a clear understanding of the normal structure of joints and factors contributing to joint disease. Three different types of joints exist: synarthroses (immovable), amphiarthroses (slightly movable) and diarthroses (movable). Diarthrodial or synovial joints account for the greatest number in the body. A synovial joint is more than a collection of tissues with separate characteristics and functions and is seen as a complex multi-composite structure.

Bone, articular cartilage, synovial fluid, joint capsule and ligamentous structures make up the components of a synovial joint. The function of synovial joints depends on the integrity of normal anatomy and proper cellular function of each of its components. A healthy joint provides a smooth and frictionless system with superior efficiency. The constituting elements act together to ensure proper joint function. Pathologic states arise, usually because of dysfunction of one or more components (Auer and Stick, 2012).

Classification of Arthritis

Any type of joint disease can create inflammation and cause swelling, heat and redness of the affected area. Arthritis generally results in pain and altered function of the joint. Horses that are used for jumping, dressage, racing, reining and other high-impact sports are more susceptible to arthritis. Equine arthritis can affect any joint in the body but the weight-bearing joints of limbs, especially fetlocks, knees and hocks are more susceptible. Extra stress, trauma and infection to any joint can lead to arthritis. There are several arthritis conditions, but the most common are Septic/Infectious arthritis, Traumatic arthritis and Osteoarthritis.

Septic/Infectious arthritis-

Septic or infective arthritis results from bacterial infection in a joint. It is usually characterized by severe lameness and distention of the joint with cloudy, turbid synovial fluid. The primary cause may be either an abnormal exposure to pathogens or an abnormal weakness of the host defense. Infection of a joint develops in three main ways: hematogenous infection (common in foals), traumatic injury with local introduction of infection and iatrogenic infection associated with joint injection or surgery.

In adult horses, penetrating injuries and injections are the most common cause of septic arthritis and is typically caused by *Staphylococcus aureus*, which is one of the most common and most resistant joint infections to manage. Synovial sepsis in horses is life threatening but accurate diagnosis and prompt treatment can improve the survival. The typical clinical signs of septic arthritis are heat, swelling, pain, severe lameness, variable pyrexia, variable depression and variable peripheral white cell changes (Higgins and Snyder, 2006) ^[6].

Traumatic arthritis

Traumatic arthritis includes traumatic synovitis and capsulitis, intra-articular chip fractures, ligamentous tears (sprains) and meniscal tears. Lameness varies from a mild gait change to severe lameness. Traumatic arthritis and degenerative arthritis are usually closely linked. More commonly, low-grade repetitive trauma initiates a destructive cycle that results in osteoarthritis (Higgins and Snyder, 2006) ^[6].

Osteoarthritis

Osteoarthritis is a progressive degradation of articular cartilage. Osteoarthritis is characterized by inflammation within a joint that sparks an inflammatory cascade resulting in the production of a large amount of inflammatory enzymes, which causes the progressive destruction of articular cartilage. Osteoarthritis manifests as thinning and erosion of the articular cartilage and progresses to osteophyte formation and periarticular soft tissue changes such as formation of new bone at the joint capsule attachments. The development of osteoarthritis can often progress un-noticed because the onset of lameness can be insidious. Eventually, as the cartilage becomes more damaged, the bone beneath the pad of cartilage becomes damaged as well. The horse will then experience more discomfort. In more advanced cases, small bony growth called osteophytes may be seen on X-ray and may be felt around the affected joint (Baxter, 2011) ^[2].

The most common signs of osteoarthritis are stiffness, pain, warmth and swelling of joints, tenderness of affected limb, lameness, and reluctance to exercise, slight swelling or puffiness of lower leg, appetite loss and trouble walking.

Diagnosis of Arthritis

Arthritis can occur well before what we think. An accurate diagnosis of the cause of joint pain, stiffness and lameness in horses is critical to select the most appropriate treatment plan and rehabilitation regimen. Prompt attention to minor lameness or injury helps to minimize unsoundness.

Diagnosis of joint disease involves a variety of diagnostic tools including clinical examination, diagnostic imaging techniques and synovial fluid analysis. Nuclear scintigraphy and other computer-assisted imaging techniques are becoming more widespread in availability, but are still primarily confined to referral centers (Higgins and Snyder, 2006) ^[6]. After taking a history of the problem, various diagnostic techniques are used to gain information about the condition of the bones, cartilage and fluid of a particular joint.

Clinical examination

The first step toward a definitive diagnosis of arthritis is clinical examination. It is a routinely used method to locate the joint responsible for the manifestation of lameness, but severity or duration of the joint disease often cannot be determined. It includes visual inspection, palpation of the affected joint, flexion test, diagnostic nerve blocks and motion analysis (Auer and Stick, 2012) ^[1].

Diagnostic imaging techniques

We move to diagnostic imaging for accurate diagnosis, treatment plan and prognosis. Commonly used imaging techniques are radiographs (X-rays), ultrasound and arthroscopy. Nowadays some latest tools like, computed tomography (CT), magnetic resonance imaging (MRI), nuclear scintigraphy, thermography and optical coherence tomography (OCT) are also used for better imaging of joints. (McIlwraith, 2010) ^[7].

Synovial fluid Analysis

Examination of the synovial fluid should be a routine procedure in the evaluation of arthritic conditions. The conventional analysis will not provide a specific diagnosis; however, it does give an indication of the degree of synovitis and metabolic derangement within the joint. The most common and important application for synovial fluid analysis in equine patients is to distinguish between septic and non-septic arthritis.

Total nucleated cell count, percentage of neutrophil and total protein in synovial fluid are used to diagnose and monitor synovial sepsis; however, their concentrations can be equivocal and are affected by common treatments such as synovial lavage and intra-synovial amikacin. The most specific diagnostic test for septic arthritis is microbiological culture from synovial fluid or visualization of bacteria on synovial fluid smear, but their sensitivity is low. Therefore, early diagnosis can be difficult and investigation into other indicators of synovial sepsis is warranted (Robinson *et al.*, 2017) ^[9].

Biomarkers detection in synovial fluid and serum are very useful for specific and early diagnosis of different types of arthritic conditions. In joint disease, these molecules may

appear in the synovial fluid. Investigation of synovial fluid markers more accurately identifies articular cartilage damage and advanced stages of joint disease. (Bertone *et al.*, 2001) [3]. Certain biomarkers under study are Cytokines, eicosanoids, Epitope CS846, Epitope CPII, Glycosaminoglycan (GAG), Epitope Col CEQ, Osteocalcin, C-terminal of type I collagen (CTX1), etc. The eicosanoids, prostaglandin E₂ (PGE₂), prostaglandin F_{1-α} (PGF_{1-α}), thromboxane B₂ (TBX₂) and leukotriene B₄ (LTB₄) are also inflammatory mediator found in synovial fluid.

Treatment of Arthritis

The principal aim of the treatment of joint problems in the horse focuses on pain relief and minimization of progression of joint deterioration. There is no cure for osteoarthritis at this time. Once the cartilage in a joint is gone, it is very difficult to repair it. Arthritis is almost unavoidable as a horse ages but can be managed with conscientious care. The treatment of arthritis is divided into two parts: therapeutic and surgical treatment.

Therapeutic treatment

Arthritis requires prompt treatment to avoid irreparable damage to the joint. Medical treatment regimens used for treatment includes antimicrobial therapy, use of corticosteroids, NSAIDs and other biologically active ingredients like Hyaluronan, Polysulfated Glycosaminoglycan, Pentosan polysulfate, Polyacrylamide hydrogel (PAAG) and Stanazolol.

Systemic antibiotics like Penicillin, Gentamicin, Trimethoprim-sulfonamide, Ceftiofur, Enrofloxacin, Flucloxacillin, etc. Systemic antibiotic treatment is often combined with intra-articular antibiotics to achieve more effective sterilization of the joint. The most frequently used IA drugs are amikacin (250 mg-1 g IA) and gentamicin (300-500 mg IA) (Higgins and Snyder, 2006) [6].

Corticosteroids are the most potent anti-inflammatory medications used to treat osteoarthritis are corticosteroids. Their actions are complex and include stabilization of lysosomal membranes, inhibiting prostaglandin, free radical, interleukin-1 and collagenase release, and decreasing vasodilation, edema formation and fibrin deposition. They also suppress leukocyte function, as well as inhibiting other inflammatory pathways. Commonly used corticosteroids are Betamethasone acetate, Triamcinolone acetonide, Methylprednisolone acetate, Dexamethasone sodium phosphate and Isoflupredone acetate. The deleterious effects of corticosteroids are considered to be a result of decrease in proteoglycan content and cartilage elasticity which can result in cartilage degeneration. However, recent studies have shown that triamcinolone has very few adverse effects when administered IA and the potent anti-inflammatory effects of this medication are well documented (Higgins and Snyder, 2006) [6].

NSAIDs may have a role in mediating joint pain at the level of the spinal cord as well as locally. The medication blocking cyclooxygenase (COX) affects prostaglandins alone and this could therefore be considered focused anti-inflammatory therapy. Commonly used NSAIDs are Phenylbutazone, Carprofen, Flunixin meglumine, Ketoprofen, Firocoxib and Meloxicam. Phenylbutazone is the most commonly used NSAID in the horse and is considered one of the more potent NSAIDs for symptom-modifying effects in equine musculoskeletal disease

(McIlwraith *et al.*, 2016) [8].

Hyaluronan acts as lubricant. The other major function attributed to it is a barrier that regulates fluid exchange at the level of the synovial membrane, thus controlling the intraarticular synovial environment. Its role in diseased joints is to both maintain a lubricating environment and to help minimize the mediators of joint disease such as white blood cells (WBCs), free radicals, and pro-inflammatory cytokines. Intra-articular injections of high molecular-weight sodium hyaluronan (SH), have been implemented as part of the treatment for OA in horses (McIlwraith *et al.*, 2016) [8].

Polysulfated glycosaminoglycan (PSGAG) belongs to a group of polysulfated polysaccharides. These drugs are disease-modifying osteoarthritic drugs (DMOADs). The principal GAG in PSGAG is CS, and the product is made from an extract of bovine lung and trachea modified by sulfate esterification. Adequan is marketed for both intra-articular (IA) and intramuscular (IM) use (Higgins and Snyder, 2006) [6].

Pentosan polysulfate (PPS) was used initially in humans as an anticoagulant, then as an anti-inflammatory and most recently as the major treatment for interstitial cystitis. PPS is made from beech wood (plant) shaving and is inexpensive. PPS stimulates chondrocytes to synthesize new cartilage matrix and inhibits multiple degradative enzymes and inflammatory mediators, thereby attenuating catabolic events responsible for the loss of cartilage matrix in OA joints. Substantial evidence demonstrates that PPS can stimulate the synthesis of HA by synoviocytes and that PPS stimulates the release of tissue plasminogen activator, consequently increasing fibrinolysis with resulting improvement in synovial membrane and subchondral blood flow. In horses, CaPPS was found to reduce lameness post-racing when administered at a dose of 2 mg/kg intramuscularly once weekly for 4 weeks (Higgins and Snyder, 2006) [6].

A new treatment for osteoarthritis in horses has better clinical efficacy and longer duration. The treatment consists of an injection into the affected joint of a polyacrylamide hydrogel (PAAG). It is a breakthrough therapy, which is highly promising with respect to the products that are otherwise available for the treatment of osteoarthritis. PAAG is a non-particulate homogenous gel similar to sodium hyaluronan (SH) gel in overall structure and tissue compatibility, but with a longer-lasting viscous effect, as it is non-degradable.

Biological therapy

Joint cartilage destruction is caused by several substances that increase when inflammation occurs in the joint. One of the main substances responsible for cartilage destruction is interleukin-1 (IL-1). Antibodies produced against IL-1, have a beneficial effect in arresting cartilage damage. Interleukin-1 Receptor Antagonist Protein (IRAP) therapy is a novel approach in treating osteoarthritis (OA) in horses. It is especially helpful in reducing joint inflammation and preventing continued degeneration and progression of osteoarthritis. IRAP is a natural anti-inflammatory protein released by leukocytes (McIlwraith *et al.*, 2016) [8].

Stem cell therapy is designed to regenerate injured or damaged tissues through the use of stem cells derived from the horse's own body. The stem cells can be collected from the horse's bone marrow. Stem cells are injected directly

into the site that requires treatment. They develop into new cells of the desired tissue type to help in repair of damaged tissue.

Stem cells have already been deployed therapeutically in a number of clinical settings, in particular the use of mesenchymal stem cells (MSCs) to treat osteoarthritis in horses and dogs. Current commercial MSC-based therapies for the treatment of osteoarthritis involve injecting a suspension of MSCs into the joint space. MSCs introduced in this fashion do not engraft into the endogenous cartilage and directly affect repair. The combination of cells and biomaterials with a supporting matrix or scaffold is used, in an attempt to regenerate damaged or diseased tissues. Scaffolds, hydrogels and other matrices aim to organize the cells into a three-dimensional pattern that closely replicates that found in the endogenous tissue (Whitworth and Banks, 2014) ^[11].

Surgical treatment

Surgical approaches to treat joint disorders have been grouped into four categories: palliative (arthroscopic debridement and lavage, osteophyte removal, articular cartilage curettage), reparative (marrow stimulation techniques), restorative (osteochondral grafting, autologous chondrocyte implantation or ACI) and salvage (arthrodesis).

Palliative treatments/Arthroscopic surgery

Arthroscopy has many advantages over traditional joint surgery (arthrotomy), primarily in that the joint does not have to be opened completely, which usually significantly reduces the recovery time. The success rate may be greater due to a decrease in trauma to the connective tissues around the joint. Arthroscopic surgery generally involves two very small (8mm) keyhole incisions. The first incision is to insert the arthroscope, and the second small incision to insert the surgical instrument to perform the procedure (Carmelt and Wilson, 2005) ^[4].

Surgical debridement is the first-line palliative treatment. Removal of free bodies and excision of osteophytes have been shown to decrease pain and improve joint function. The goal of debridement of full-thickness cartilage defects is to create a contained lesion to stimulate spontaneous repair. The depth of the debridement and the angles of the lesion affect the formation of repair tissue in the defect. Debridement should be thorough, but not overly aggressive (Cokelaere *et al.*, 2016) ^[5].

Reparative techniques: Bone marrow stimulation techniques (BSTs)

Bone marrow stimulation techniques are among the first-line surgical treatment options for symptomatic articular cartilage defects. BSTs are based on the penetration of the subchondral bone plate at the base of the cartilage defect, evoking an endogenous repair response. Bleeding from the bone marrow under the subchondral plate will bring a low number of pluripotent stem cells and growth factors to the defect that are embedded in the blood-clot that forms at the base of the defect and are crucial for the early stages of repair. Surgically, penetration of the subchondral bone spaces can be accomplished with small drill bits (subchondral drilling), microfracture or abrasion arthroplasty (Cokelaere *et al.*, 2016) ^[5].

Restorative techniques: Transplantation procedures (grafting)

Tissue-engineering approaches are potentially promising. Cells, 3D-scaffolds and growth factors are the three main components in tissue-engineering. Scaffolds, in different physical forms like fibres, meshes and gels, can be derived from biological or synthetic materials or combinations and can be functionalized with growth factors (such as BMP-2, TGF- β 1, PRP) and mimicking peptides. Scaffolds can be used seeded with chondrocytes or stem/progenitor cells as scaffolds are not only a carrier system, but may also have an intrinsic regenerative ability. They temporarily fill the defect and are ideally degraded and replaced simultaneously in a synchronized process by neo-tissue. Scaffolds may be based on the natural extracellular matrix (ECM) of a variety of tissues, which are decellularised and otherwise processed before being implanted (Cokelaere *et al.*, 2016) ^[5].

Arthrodesis

Arthrodesis refers to the surgical fusion of a joint, resulting in bony ankylosis. The procedure is solely for salvage for pasture activity for a broodmare, stallion or valued retiree. It is used for relief of pain associated with severe degenerative joint disease that is no longer responsive to anti-inflammatory medications, loss of supporting soft tissue structures and treatment of complicated articular fractures. This procedure expects to alleviate the pain associated with movement of the joint and to salvage the animal for nonathletic function. Conversely, arthrodesis of low-motion joints often carries a reasonable prognosis for athletic soundness and can be accomplished using surgical, chemical, or laser-based techniques. This is especially true for the proximal interphalangeal, tarsometatarsal, carpometacarpal, and distal intertarsal joints. Some risks have been identified with chemical fusion of joints because unexpected anatomic communications with other synovial and nonsynovial structures can be encountered (Auer and Stick, 2012) ^[1].

Joint Replacement

When reparative surgical procedures have failed, and the patient is unresponsive to medical management, many end-stage cases of osteoarthritis in people are treated using joint replacements. Relatively high morbidity is associated with such procedures, especially related to implant loosening. The cost of implant design and manufacturing difficulties with prolonged non weight bearing and surgical morbidity continue to keep equine joint replacement out of mainstream clinical practice (Auer and Stick, 2012) ^[1].

Conclusion

Arthritis is one of the most frequently reported cause of lameness, compromises the equine industry, not only due to the cost of treatment but also as a consequence of delayed return to athletic performance. It is impossible to prevent joint stress; however the aim remains at normalizing the inflamed joint as quickly as possible before permanent damage occurs by using various treatment and surgical regimens that depends upon a quick and correct diagnosis of the underlying cause. Use of various conventional and advanced diagnostic and treatment techniques can alleviate the condition and prevent the loss.

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