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Equine osteoarthritis: An overview of different treatment strategies.

Elhussein E. Mahmoud[1*#], Ahmed S. A. Hassaneen[2#], Mohammed A. Noby[1], Amany S. Mawas[3], Abdel-Nasser A. Abdel-Hady[1]

[1]Department of Surgery, Anaesthesiology, and Radiology, College of Veterinary Medicine, South Valley University, Qena 83523, Egypt, [2]Department of Theriogenology, Obstetrics, and Artificial Insemination, College of Veterinary Medicine, South Valley University, Qena 83523, Egypt, [3]Department of Pathology & Clinical Pathology, College of Veterinary Medicine, South Valley University, Qena 83523, Egypt.

Abstract

Osteoarthritis (OA) has been considered the most common cause of lameness in equine, especially athletic horses. Different therapies are used for the treating of OA; hyaluronic acid (HA), a component of the articular cartilage matrix, has been shown to reduce OA-related lameness in horses. Recently, another biological therapy named platelet-rich plasma (PRP) is used for the treatment of OA. PRP consists of several growth factors which would be useful to inhibit the OA progression, till now, the obtained results of using either HA or PRP are still of contradictory effects on OA. Subsequently, one other novel alternative treatment option has been recently emerged in the veterinary field for treating musculoskeletal disorders. This novel treatment is known as stem cell therapy. In the present review, we explain different treatments of the OA such as HA, PRP, and stem cells therapy that would be effective to control lameness and locomotor disorders in equine.

Keywords:

Athletic horses, Lameness, Mesenchymal stem cells, Platelet-rich plasma, Regenerative medicine.

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1. Introduction

Articular cartilage repair remains a great challenge for veterinarians and researchers due to its avascular nature. If not treated, the articular cartilage lesions lead to osteoarthritis (OA) which is characterized by degradation of the articular cartilage and exposure of the subchondral bone. Osteoarthritic lesions not only involved the articular cartilage but also the whole structures of the joint including the subchondral bone, ligaments, synovial membrane (Synovitis), and meniscus (meniscal tears) (Mahmoud et al., 2019).

Till now, the real cause of the OA is still unclear; it is likely of traumatic origin, as reported by many research groups. However, many predisposing factors such as age, sex, and malconfirmation would be involved. It was reported that the metacarpophalangeal, and then the carpal joints are the most common affected joints with spontaneous OA in racehorses (Neundorf et al., 2010).

The OA affection is considered as the common problem of lameness in athletic horses, and it causes large economic losses due to medical cost, bad performance, and further culling. Joint injury represents about 60% of equine lameness, and the OA affects over 80% of horses >15 years of age and up to 2/3 of thoroughbred race horses, making it one of the highest causes of wastage and loss of use in this particular population (Ireland et al., 2012). Moreover, it was found that the OA can be developed in young horses and foals (Di Filippo et al., 2019). The diagnosis of the OA can be performed by radiographically where there are three main radiographic findings including osteophytes, increased subchondral density, and narrowing the joint space at its late stage. In the next section, we discuss the recent studies on different treatment options (Fig. 1) that have been developed to improve joint lesions especially the OA in equine.

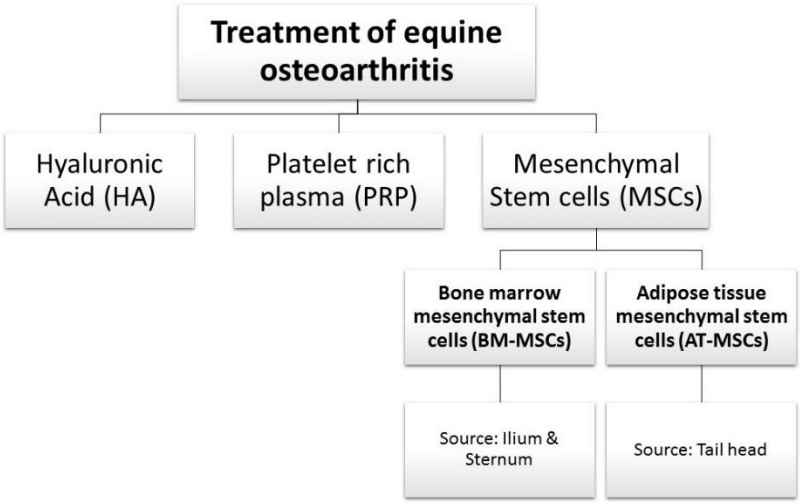

Fig.1. Schematic diagram showing different treatment options of osteoarthritis in equines.

2. Different treatment options for OA:

2.1. Hyaluronic acid (HA):

Hyaluronic acid is an essential component of the articular cartilage matrix, it is naturally synthesized by chondrocytes. HA acts as the substantial part of the proteoglycans aggregate in the extracellular matrix, and the compressive stiffness in articular cartilage depends on the integrity

of the extracellular matrix proteoglycans (Howard and McIlwraith, 1993). It has been previously shown that HA was experimentally and clinically effective to reduce OA-related lameness in horses. Although the exact mechanism by which the HA reduces lameness is still not fully understood (Kawcak et al., 1997), the HA treatment is likely beneficial in OA-related equine lameness by reducing synovial membrane inflammation and cartilage fibrillation (Goodrich and Nixon, 2006), either in mild or moderate synovitis (Goldberg and Buckwalter, 2005). Another study using experimentally-induced OA showed that the HA treated group had less articular cartilage fibrillation when compared with the control group, but no significant reduction was reported in synovial membrane vascularity and subintimal fibrosis (Frisbie et al., 2009a). Neuenschwander et al. (2019) has been recently reported that HA has chondroprotective and joint-preserving effects on lipopolysaccharide-induced synovitis and OA, possibly, through inhibition the digestion of cartilage proteoglycans efficiently and synovial fluid HA breakdown.

On the other hand, a controlled study using orally-administered HA products could not find significant effectiveness in joint lesions of equines (Carmona et al., 2009). However, another clinical study evaluating the effect of HA oral treatment revealed a significant reduction in postoperative synovial fluid effusion, after arthroscopic surgery, in the HA-orally treated horses (Bergin et al., 2005). The limitation of intravenous administration of HA was clinically demonstrated by Frisbie et al., (2016) who reported the harmful effect of prophylactic HA on articular cartilage in equine, and this harmful effect had been confirmed by both clinical and radiological outcomes. Prophylactic horses with HA were significantly worse in carpal flexion tests than prophylactic horses treated with saline. Additionally, HA-treated OA affected horses had bone proliferation at the joint capsule, osteophyte formation, and subchondral sclerosis, which were greater than those of placebo-treated OA affected horses. Also, clinical outcome of HA on OA is limited due to possible toxicity and biodegradation by-products with their adversely effects on chondrocytes (Knudson et al., 2000; Getgood et al., 2009).

2.2. Platelet-rich plasma (PRP):

Platelet-rich plasma, an autologous biological product from the whole blood, contains several growth factors such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), which induce cell proliferation and matrix production (Schmidt et al., 2008; Semple et al., 2011). Also, fibroblast growth factor-2 (FGF-2) stimulates MSC and chondrocyte proliferation (Solchaga et al., 2005). In addition, Insulin-like growth factor-1 (IFG-1) promotes MSC proliferation with modulation of chondrogenesis (Longobardi et al., 2006). These growth factors are involved in tissue healing, as previously reported (Barrientos et al., 2008). Although TGF plays important role in chondrogenesis through increase in collagen type II and aggrecan without upregulation of hypertrophic chondrocyte marker such as collagen type 10 and matrix metalloprotease 13 (MMP13) (Desancé et al., 2018), increased TGF stimulates synovial fibrosis (Bakker et al., 2001) and osteophytes formation with OA (van der

Kraan et al., 2012). Moreover, PRP is rich in cytokines including interleukin 1-beta, and tumor necrosis factor alpha (Kamm et al., 2010), these cytokines induce cartilage degeneration as catabolic cytokines. A placebo-controlled experimental study found that PRP treatment enhanced tissue healing in musculoskeletal injuries of horses (Bosch et al., 2010). The effectiveness of PRP treatment is a possible result of its anti-inflammatory and anabolic effects that promote chondrogenesis (Wu et al., 2011). Interestingly, PRP decreases apoptosis in osteoarthritic chondrocytes (Moussa et al., 2017). Therefore, the effectiveness of using PRP in the treatment of OA opened the door to the use of PRP in other species such as rabbits (Saito et al., 2009). In addition, there are no standard procedures for PRP preparation (Kisiday et al., 2012). Several methods are used such as one step centrifugation method for 15 minutes at 3200rpm (Hede et al., 2019), two step centrifugations (Kisiday et al., 2012), and filtration system using kits (Hessel et al., 2015). The results of experimental and clinical use of PRP in the treatment of OA-related lameness were controversial because it had either favourable (Carmona et al., 2007) or unfavourable outcomes (Smit et al., 2019). Clinical use of PRP in equine practice is limited due to the variability of cellular content of PRP products depending upon breed, age, sex, and processing technique (Garbin and Oliver, 2020).

2.3. Stem cells therapy:

The use of mesenchymal stem cells (MSCs) started to increase in the veterinary field especially for the treatment of musculoskeletal disorders in equine (Yingling and Nobert, 2008), based on the unique characteristics of MSCs.

Mesenchymal stem cells have the ability for high proliferative rates, wide differentiation ability into different mesenchymal lineages such as chondrocytes, osteoblasts, and adipocytes, ease accessibility from different sources in a safe manner (Pittenger et al., 1999). Therefore, the use of MSCs has been emerged as a unique promising strategy for cell-based musculoskeletal regeneration especially in equines. In addition, MSCs can be easily isolated due to their strong adherence to cell culture plastic. MSCs cultures generally represent a heterogeneous population of cells. It is clear that, MSCs themselves secrete several bioactive molecules that have immunoregulatory functions (Chen et al., 2006; Uccelli et al., 2007) and/or regenerative activities (Kan et al., 2007). The bioactive factors have been reported to inhibit tissue scarring, suppress apoptosis, enhance angiogenesis, and stimulate mitosis of tissue-intrinsic stem or progenitor cells (Caplan and Dennis, 2006). As long as.one of the MSCs properties is the immunomodulatory effect, it is more possible that, MSCs regulate inflammation rather than replace damaged tissue (Wyles et al., 2015). In spite that, the exact mechanisms that direct homing of delivered MSCs are not fully known, especially in systemic homing of MSCs which are administered into the bloodstream, and then entrapped into lung tissue, this may be due to low expression of CXCR4 on MSCs (Ullah et al., 2019). Therefore, we suggest that intra-articular use of MSCs would be a superior novel choice for treatment of OA and other musculoskeletal disorders in equines.

Many different sources for MSCs have been previously reported. Bone marrow-MSCs (BM-MSCs) and adipose tissue-MSCs (AT-MSCs) are the most common culture-expanded MSCs used, with dominating of BM-MSCs than Ad-MSCs in the veterinary field for both clinical and research purposes (Fortier and Travis, 2011). In horses, BM-MSCs are aseptically obtained from the sternum or ilium with Jamshidi needle (Kasashima et al., 2011; Arnhold et al., 2007); however, in middle-aged horses, it was found that, samples harvested from the sternum have a greater MSCs density than those harvested from the ilium (Delling et al., 2012). Therefore, the sternum is commonly used as the recommended harvest site in middle-aged to older horses. The bone marrow aspirate can be either cultured for about 2–3 weeks in order to obtain BM-MSCs or immediately centrifuged to produce what is known as bone marrow concentrate (BMC). Bone marrow concentrate concentrates both stem cells and platelets compared to raw bone marrow aspirate; however, it yields a much lower number of stem cells compared to BM-MSCs (Fortier et al., 2010). Adipose tissue-mesenchymal stem cells are generally collected from the tail head and then subjected to collagenase digestion and subsequent culturing for several weeks to harvest AT-MSCs (Gutierrez-Nibeyro, 2011).

Other different sources of equine stem cells have been reported including fetal fibroblasts (Watts et al., 2011), umbilical cord blood, umbilical cord tissue/matrix (Wharton's Jelly) (Koch et al., 2009), placental tissue (Violini et al., 2012), amniotic fluid (Iacono et al., 2012), peripheral blood (Dhar et al., 2012), and synovial fluid (Zayed et al., 2018). It was reported that, the efficacy of using stem cells therapy for equine OA and cartilage injuries has been evaluated in the form of both research and clinical studies with more promising results for BM-MSCs than AT-MSCs (Ferris et al., 2014; Frisbie et al., 2009b).

Intra-articular injection is the most convenient method for delivery of MSCs into the osteoarthritic joint. Single intra-articular injections of adipose-derived stromal vascular fraction (SVF) or BM-MSCs had been previously tested in the equine OA model. The only significant change was a greater improvement in synovial fluid prostaglandin E2 (PGE2) levels with BM-MSCs intra-articular injection compared with placebo and SVF intra-articular injections. The overall findings of this trial were not promising enough to recommend the use of stem cells for the treatment of equine OA model (Frisbie et al., 2009b). Although, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) are the most predominant pro-inflammatory cytokines in osteoarthritic joints, a recent study reported that TNFα increased the in vivo MSCs benefit in Achilles tendon injury rat model (Aktas et al., 2017). Moreover, another research group recently found that interferon (IFN)γ-stimulated equine MSCs showed enhanced effects in a murine OA model, supporting the potential of this strategy (Maumus et al., 2016). These factors were used to induce the immunomodulatory effect of equine BM-MSCs to improve the safety and therapeutic efficacy of the allogeneic MSCs transplantation into equine OA model. It was proved that repeated intra-articular administration of stimulated and naïve allogeneic MSCs has beneficial effects on

equine model chemically induced-OA in early stage. These beneficial effects are likely due to both the limitation of the induced-inflammation and subsequent cartilage degradation (Barrachina et al., 2018). These findings were in consistent with a new study using surgically induced OA in a rabbit model through cutting of the anterior cruciate ligament; three consecutive injections of allogeneic BM-MSCs promoted the conditions of all joint structured lesions when compared with single injection of MSCs (Mahmoud et al., 2019), one possible reason is to reduce pain but not overcome the degenerative changes of OA (van Buul et al., 2014). Alternatively, surgically induced OA in equines was recently performed using osteochondral fragments in 12 healthy horses. In this equine surgically induced OA model, using allogeneic chondrogenic MSCs with plasma as a novel therapy for OA revealed high amounts of collagen II and GAG (Broeckx et al., 2019).

Recently, clinical trials for treatment of OA were published. In this an in-vivo study a repeated intra-articular injection of allogeneic adipose stem cells has been used for treatment of OA in eight horses ranged from 2-20 years old, with reduction of lameness (Marinas-Pardo et al., 2018). One more recent study revealed safety and efficacy of single versus multiple allogeneic umbilical cord-derived, neonatal mesenchymal stem cells in horses with lameness due to OA of metacarpophalangeal joint in 28 horses, where lameness produced by OA, was declined in both groups, but there was no clinical apparent difference between both groups (Magri et al., 2019). This is likely due to the adverse immunological reaction against allogeneic MSCs compared with autologous MSCs (Joswig et al., 2017).

Conclusion:

Different therapies are used for treating of OA which is of great clinical importance as the most common cause of lameness in equine. These treatments include HA, PRP, and MSCs therapy. HA has been shown to reduce OA-related lameness in horses, and PRP is recently used for treatment of the OA. However, till now, the results of using either HA or PRP were of contradictory effects. On the other hand, the MSCs therapy would be a novel good option for treatment of equine OA either by single injection to reduce pain and lameness or by multiple injections to improve different lesions resulting from OA.

Conflict of interest:

The authors declare that there is no any conflict of interest.

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