Domaniža M, et al., J Stem Cell Res Dev Ther 2021, 7: 083
DOI: 10.24966/SRDT-2060/100083

HSOA Journal of
Stem Cells Research, Development & Therapy

Review Article

Mesenchymal Stem Cell-Based Treatment of Osteoarthritis in Dogs - A Review

Domaniža M*, Trbolová A, Hluchý M and Čížková D

Small Animal Clinic, Centre for Experimental and Clinical Regenerative Medicine, University of Veterinary Medicine and Pharmacy, Komenského 73, 041 81 Košice, Slovakia

Abstract

Osteoarthritis (OA) is Degenerative Joint Disease (DJD) associated with pain, inflammation and cartilage degradation resulting in lameness. This state is irreversible and actual conventional therapies are not able to provide regeneration of damaged tissue. Current therapies, mainly NSAIDs, have many adverse effects and are not able to stop degenerative process. Joint supplements, weight management, and rehabilitation therapy often fail to provide a long-term response in inflamed joint. Adult Mesenchymal Stem Cells (MSCs) might serve as an alternative therapy for OA, because they can differentiate into osteo-chondral lineages. In addition, they have shown ability to decrease pain and inflammation as well as promote cartilage function and healing in patients with OA. Thus, the aim of present review is to clarify the findings associated with MSCs application in the treatment of OA by means of synovial fluid analysis, gait analysis, clinical and x-ray examination often used in veterinary practice

Keywords: Cartilage; Inflammation; Mesenchymal Stem Cells; Osteoarthritis

Introduction

Articular cartilage is hyaline cartilage and is principally composed of water (65-85 %), collagen (10-20 %, collagen type II is 90-95%), proteoglycans (10-20 %) and chondrocytes (1-5 %). Cartilage consists of four layers - superficial layer, transitional layer, deep layer and layer of calcified cartilage. Hyaline cartilage is a free of vascular, lymphatic and neural structures. Nourishment is accomplished through diffusion from synovial fluid and vessels in synovial membrane [1-4].

***Corresponding author:** Domaniža M, Small Animal Clinic, Centre for Experimental and Clinical Regenerative Medicine, University of Veterinary Medicine and Pharmacy, Komenského 73, 041 81 Košice, Slovakia, E-mail: domaniza.michal@gmail.com

Citation: Domaniža M, Trbolová A, Hluchý M, Čížková D (2021) Mesenchymal Stem Cell-Based Treatment of Osteoarthritis in Dogs - A Review. J Stem Cell Res Dev Ther 7: 083.

Received: September 27, 2021; **Accepted:** October 05, 2021; **Published:** October 12, 2021

OA is described as a main reason of dog lameness which is also first clinical sign observed by owners [5]. Most important clinical signs are joints pain and decreased range of motion. Prescription of Non-Steroidal Anti-Inflammatory Drugs (NSAID) by veterinarian is still the number one choice in OA treatment. NSAIDs application is associated with some adverse effects, which is not required for long-term use [6,7]. There have been used alternatives of NSAIDs such as hyaluronic acid [8]. Mesenchymal Stem Cell (MSC) therapy is a new and safe therapeutic method in OA treatment in veterinary medicine [9-11]. For MSC treatment is typical high therapeutic index and long-term influence on joint microenvironment, despite the MSCs will not last long *in vivo* [12]. MSCs interact with the microenvironment of inflamed joint, through large cytokines variety, micro-vesicles (exosomes), growth factors which results in immunomodulatory, trophic, anti-fibrotic, and anti-apoptotic effects [13,14]. Stromal vascular fraction from visceral fat is comparable with MSCs from joint tissues. MSCs from bone marrow have high tendency for chondrocytes hypertrophy and bone tissue proliferation [15,16], which is not required. MSCs from synovial membrane are ideal for cartilage regeneration [17].

Pathophysiology of Osteoarthritis

OA is characterized by cartilage destruction, loss of cartilage matrix, bone remodeling and intermittent inflammation. The degradation of cartilage is not the only pathological process in the joint. OA involves complex changes that affect the subchondral bone and the surrounding soft tissues (synovium, joint capsule, ligaments, and muscle) [18].

Osteoarthritis development can be connected with aging changes in body constitution, such as loss of muscle mass or atrophy, increased fat tissue, a low-grade inflammatory state, less growth-promoting hormones, decreased bone mass structure, and increased microtrauma resulting from decreased proprioception and balance [19,20].

There are detectable changes at early stage of OA in subchondral bone or synovium. Increase in cartilage matrix synthesis occurs in parallel with increased degradation. Synovial and cartilage-derived proteases are key factors in cartilage matrix degradation. Matrix metalloproteinases – calcium depended and zinc containing peptidases (MMPs) and aggrecanases - proteolytic enzymes are responsible for catabolic processes in cartilage [18].

Osteoarthritis includes following changes in articular and periarticular tissue

Degeneration of the articular cartilage

Synthesis and degradation of collagen and proteoglycans is caused by release of wide spectrum of cytokines, mainly the matrix metalloproteinases and collagenases, along with growth factors [18].

Changes in bone

Marginal osteophytes and subchondral sclerosis are two visible signs of OA by X-ray, CT or arthroscopy examination [18].

Changes in synovial membrane

Inflammatory mediators are responsible for an increase in cells in the synovial lining layer and subsynovial layer. Permeability in capillaries increase fluid in the subsynovial layer, leads to thickening of the synovium and increase fluid in the joint (joint effusion). Flexibility in the thickened synovium is decreased in comparison with normal synovium, resulting in decreased range of motion [18].

Changes in articular cartilage

Early changes in articular cartilage are characterized by changes in colour and structure. Cartilage is not more white and smooth, but became yellow with soft or velvety areas [18].

Clinical signs

Most common clinical sign of OA is pain. Joint pain occurs after the hard joint loading, or during palpation and manipulation with the OA joints. Stiffness is another clinical sign, is associated with inflammation, and can be result of oedema of periarticular tissues or joint effusion. Joint crepitus is defined as sound or vibration detected with movement of the joint. It is most commonly associated with irregular joint surfaces that result from the loss of cartilage and osteophytes formation [9,18,21].

Regenerative Medicine for OA Treatment

In areas where tissue is not responding by healing in traditional circumstances, innovated strategies of regenerative medicine are suggested. Every tissue is able to heal or perform scarring after traumatic damage. Some tissues are able to heal to their previous structure and resilience. Cartilage does not heal itself as well as most other tissues because chondrocytes rarely replicate or repair, thus their self-repair capacity is very limited. The objective of regenerative medicine is to promote cartilage healing, decrease inflammation and pain and secure return the functionality of the damaged cartilage.

Autologous/Allogeneic Conditioned Serum (ACS) and Platelet Rich Plasma (PRP) are most often used in regenerative cell based therapies. However, Interleukin-1 Receptor Antagonist Protein (IRAP) enjoys great popularity in last years, especially in horse medicine. Other products such as bone marrow aspirate concentrate, adipose derived MSCs, cultured bone marrow derived stem cells, synovium derived mesenchymal stem cells, allantois and placenta can be also a source of stem cells for various cell-based therapies. These products contain growth factors, chemokines, cytokines and cells, which can secure anti-inflammatory or immune-mediated response Furthermore they can heal and regenerate damaged tissue, stimulate neovascularization, activate adult stem (resident) cells, produce a scaffold for new tissue and its protection against scar formation [22-24].

Isolation and Cultivation of Bone Marrow from Dogs - Derived MSC *In Vitro*

The bone marrow can be easily obtained from epiphysis of the proximal *humerus,* proximal *femur* (great trochanter, trochanteric fossa), pelvis (iliac crest), *sternum*, rib under general anaesthesia. For bone marrow, sample collection is suitable Jamshidi™ Bone Marrow Biopsy Needles. The surgical site is aseptically prepared and surgical site is draped. Incision of the skin and subcutis can be made with scalpel blade. Needle for bone marrow biopsy is applied to bone with firm pressure and slightly twisting motion [25]. Post procedural analgesia is maintained with NSAIDs or opioids. Donors must be healthy, young dogs without any neoplastic process or hemopoetic problems (Figure 1).

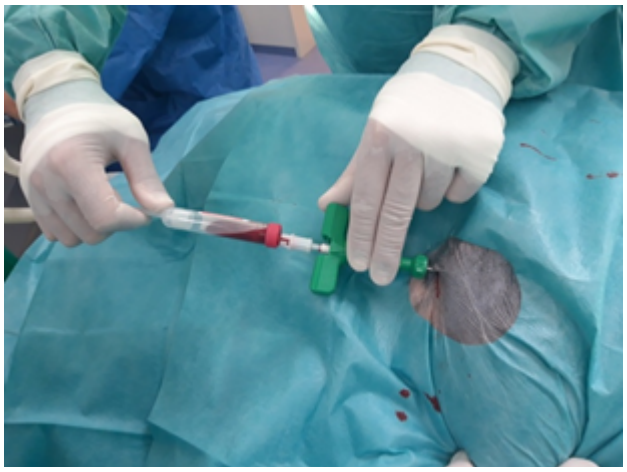

Figure 1: Bone marrow biopsy with Jamshidi needle.

Because of high risk of contamination stem cells must be handled carefully. The samples are collected and send to the laboratory, centrifugation of samples is at 500 x g for 10 minutes. The mononuclear fraction can be applied directly to the patient or used for cultivation of MSCs. Isolated bone marrow is diluted in phosphate buffered saline, which contains antibiotics. Cells are counted using trypan-blue method and then laid on T75 cell culture flask in 5 x 10^7 cells/cm^2 density in commercial culture medium Dulbecco's Modified Eagle Medium (DMEM) or in Minimum Essential Medium Eagle - alpha modification (alpha MEM) containing 100 units/ ml of penicilin, 100mg/ml of streptomycin and 2.7 µg/ml of amphothericin B. Temperature and humidity (usually at 37°C and 5% CO_2) are strictly controlled. The cells remain under these conditions in special tissue culture flasks until they will reach 80% confluence. Thus, the MSCs are characterized by forming cellular monolayer and displaying fibroblast-like morphology in phase-contrast microscope [26].

During the stem cell cultivation is crucial to remove other cell types from culture, this process is called *cell passage*. After repeated cell passage, reaching required confluence are MSCs characterized. Cultivated MSCs must meet criteria for MSCs according to The International Society for Cellular Therapy.

MSCs Secretome in OA Joints

MSCs are able to secrete wide range of cytokines and chemokines after exposure to the inflammatory environment [27].

MSC stem cells injected to the synovial joints migrate to synovial membrane and to articular cartilage. After migration to the synovial membrane, MSCs produce trophic factors such as PRG-4, BMP-6 a TSG-6 for chondroprotection and immunosuppression [28]. In early state of cartilage damage intraarticulary injected MSCs migrate to cartilage defect, while residual MSCs migrate to synovial membrane to produce trophic factors. Good results have been obtained with MSCs and hyaluronic acid combination [29] or combination with platelet rich plasma [30].

Apoptosis

Apoptosis of chondrocytes is associated with degenerative OA [31,32]. There is no evidence of direct MSC- cell based antiapoptotic effect in OA joints, but exosomes released from human MSCs inhibit IL-1 induced apoptosis in *ex-vivo* cultivated OA- chondrocytes [33].

Anti-inflammatory effect

IFNγ, TNFα, IL-1β, and IL-17 are responsible for induction of MSCs into anti-inflammatory state. High level of inflammation in environment will cause higher production of anti-inflammatary and immunomodulatory factors by MSCs. These factors are mainly TSG-6, IL-6, PGE2. This means that the immunomodulatory effect of MSCs depends on the severity of joint inflammation [11,12,14,34-37].

Tissue metabolism

MMPs reduce extracellular matrix and are regulated by TIMPs (tissue inhibitors of metalloproteinases). In OA joint is unbalance between catabolic and anabolic factors. In OA cartilage are MMP-2,-9 and -13 detectable in higher concentrations [23]. MMP-2 and MMP-9 are inhibited by TIMP-2 and TIMP-1, which are secreted from MSCs. Secretion is increased in environment with higher concentrations of IL-1β, TNF-α and hypoxia, to counterattack catabolic activity. TIMP-1 can inhibit most MMPs [38], this means MSCs are capable to keep metabolic balance in OA cartilage. In pathologic circumstances are concentrations of TIMP-1 increased.

Antifibrotic effect

Antifibrotic effect is based on decreasing decreasing fibrotic markers such as MMP-13, alkaline phosphatise, collagens type I,III,IV and vimentin. Some studies discovered that antifibrotic effect is maintained through secretion of bFGF and adrenomedullin [10,24].

Chondrogenesis

Chondrogenesis and bone proliferation in damaged cartilage is provided by thrombospondin (TSP-2), which is secreted by MSCs via autocrine mechanism ([39,40]. TSP-2 is responsible for cartilage tissue differentiation and to avoid cartilage hypertrophy [40].

Immunosuppression

Immunosuppression can be described as a potential of allogeneic MSC to suppress T-cells in recipient organism. [41,42]. PGE2 is one of the most important effectors of MSC mediated immunosupresion and is produced by MSCs. (IFN)-γ, TNF-α [43], or IL-1β [44] stimulate production of PGE2. Indoleamine 2,3-dioxygenase (IDO) is responsible for breakdown of tryptophan, causing suppression of T-cells [45]. MSCs secrete IDO after IFN-γ stimulation [42].

MSCs Application

General health condition of the recipient must be evaluated, which include blood examination (PCV, TP, CREA, BUN), capillary refill time, heart and lungs auscultation, measurement of body temperature. To diagnose the stage of osteoarthritis is necessary X-ray or CT examination. MSCs are administered intraarticulary in volume of 0.5 ml. Patient is sedated or conscious during application. After MSCs administrations is important to keep dog in restricted motion for 1–2 days. Every complications including redness, swelling of the joint or inability to use limb must be recorded. Four applications every 8–10 days are usually required to reach therapeutic effects [28,29,46].

Cartilage Regeneration after MSC Therapy

MSC stem cells injected to the synovial joints migrate to synovial membrane and to articular cartilage. After migration to the synovial membrane, MSCs produce trophic factors such as PRG-4, BMP-6 a TSG-6 for chondroprotection and immunosuppression [28]. In early state of cartilage damage intraarticularly injected MSCs migrates to cartilage defect, while residual MSCs migrate to synovial membrane to produce trophic factors. Good results have been obtained with MSCs and hyaluronic acid combination [46,47] or combination with platelet rich plasma [30].

Recommendations associated with MSC Therapy

Since MSCs have anti-inflammatory effect it is not recommended to use them with NSAIDs because of false results or conclusions [8,48]. NSAIDs and corticosteroids can inhibit differentiation, proliferation and migration of stem cells, so during MSC treatment it is proposed to avoid their use [49-51]. Cooling joints after application is not recommended, because cold can slow the differentiation of stem cells *in vitro* [52,53]. Low-level laser therapy (LLLT) IIIb class and rehabilitation exercises are recommended every week in first 12 weeks after stem cells therapy, because it stimulates stem cells proliferation and viability [54-56]. Other methods of rehabilitation are not recommended in first 8 weeks after therapy because their effect on stem cells is still not well discovered.

Methods for Measuring Efficacy of MSCs Treatment

OA can be diagnosed with clinical and radiographic examination. For describing grades of OA is recommended to use OA clinical scoring systems [57,58]. Subjective methods for treatment efficacy include owner questionnaire (Liverpool Osteoarthritis in Dogs – LOAD, Helsinki chronic pain index) about pain and lameness. Gait analysis using a force platform is objective method to evaluate the efficacy of MSCs treatment [59,60]. Force platform is modern equipment for measuring ground reaction forces from feet of the dog during the motion [61]. Joints range of motion can be detected by goniometry.

Kinetic and kinematic gait analysis in dogs

Gait analysis can be performed with special devices, which are able to record numeric comparisons between normal and abnormal gait [62,63].

Science of animal motion is kinesiology. Kinetics (the forces that affect motion) and kinematics (the temporal and geometric characteristics of motion) [63].

Kinetic gait analysis can be performed using a force plate to obtain objective notice of the forces occurring between the foot and the surface of the plate during the stance phase of the walk (ground reaction forces) [63]. Data relative to the swing phase of the walk are not measured. A single force plate cannot measure successive strides during locomotion; however, a series of plates or a force plate built into a treadmill can be used to evaluate consecutive strides [47,64].

Kinematic gait analysis performed using several cameras situated in measuring path, so they are able capturing reflection of the light from reflective targets placed on the dog's skin over required anatomic points [65,66].

Computer systems are able to measure the flexion, extension, angles, velocity during movements of joints in two or three dimension. In ideal scenario, camera analysis is combined with force plate

measuring ground forces so that dynamic 3-D characteristics of limb motion are evaluated with ground-reaction force measurements [66].

Synovial fluid analysis

Biomarkers of the synovial fluid are objective indicators for the efficacy of MSCs therapy. Synovial fluid from the OA joints should be examined before and after the MSCs treatment in order to have comparable results. Proteins or enzymes that are directly or indirectly responsible for joint inflammation and pain are present in synovial fluid and may act as biomarkers for OA and provide information about treatment efficacy [67].

There is wide spectrum of markers associated with OA inflammation in joints such as interleukin-1 (IL-1), tumour necrosis factor (TNF), IL-6, MMPs, GM-CSF, PGE2. Synovial fluid from osteoarthritic joints reveal increased content of cytokines (IL-1, IL-6, and TNF), MMPs and other inflammatory mediators [68].

Synovial fluid is usually collected via arthrocentesis procedure, performed to aspirate fluid from a joint. Synovial fluid after collection is examined for cell types and numbers, protein, viscosity, and glucose content. Before synovial fluid collection, there must be hair clipping and surgical scrubbing to reduce possibility of joint infection. Surgeon must perform arthrocentesis carefully to avoid damage of cartilage. Visible synovial fluid in the needle confirms proper needle placement. Joint disease is presenting with synovial fluid effusion, what makes synovial fluid sampling easier [18]. Synovial fluid is aspirated using a 3 ml syringe [69]. The sample of synovial fluid must be stored at -80 °C until assayed. Several diagnostic methods are able to provide synovial fluid markers detection, such as ELISA, flow cytometry or Luminex Assays system.

Conclusion

Many studies described positive therapeutic effect after *in vivo* MSCs application in dogs. Study of MSC in dogs is perspective and needs to be further explored much more. Despite difficulties associated with cell processing and unknown mechanisms underlying MSC-mediated cartilage repair, it can be considered as an alternative treatment for OA and cartilage repair in veterinary orthopedics.

Acknowledgment

Study was supported by: APVV 19-0193, VEGA 1/0376/20

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