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STEM CELL THERAPY FOR KNEE OSTEOARTHRITIS- A COMPREHENSIVE REVIEW

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Abstract:

Background: *Knee osteoarthritis is a condition which cannot be treated easily even surgery isn't a good option due to obesity and other comorbidities. Regenerative medicine utilizing stem cells, platelet rich plasma (PRP), amniotic fluid, and cytokine modulation is very promising in the treatment of KOA.*

Objective: *Review of articles to calculate the current evidence about regenerative medicine therapies in the treatment of KOA.*

Methods: *An online search of PubMed and Cochrane library database was performed to find out related literature using the keywords of "treatment, stem cell, knee osteoarthritis," limited to the English language. Only those articles were recruited which met the inclusion criteria rest were filtered out.*

Results: *Out of 268 articles, only 18 articles met the inclusion criteria and were included in this study.*

Limitation: *There is still less literature about the efficacy of regenerative medicine in the treatment of KOA. Large clinical trials are required to make sure about the evidence.*

Conclusion:

Current investigations conclude that regenerative medicine procedures have good evidence in the treatment of knee osteoarthritis. But still in greater depth study to explore more ideal way to overcome present difficulties is required.

Key words: *Knee osteoarthritis, platelet rich plasma, stem cell, cartilage degeneration.*

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INTRODUCTION:

Osteoarthritis is a chronic joint disease characterized by pain and articular degeneration. The earliest pathology which occurs in osteoarthritis is articular cartilage degeneration [1]. It usually affects larger weight bearing joints such as hip, knee, and spine and later followed by distal interphalangeal joints. Knee osteoarthritis is the most common among all of them, causing pain, stiffness, inflammation that leads to decreased mobility and negative impact on quality of life [2][3]. Clear etiology of knee OA is still unknown. It has multifactorial pathology which is still unclear. It may be related to age, gender, obesity, mechanical damage, or joint trauma and some other factors. Symptoms are knee pain, joint stiffness, and pain and muscle weakness [4].

Some literature concluded that inflammation which has caused by hyperplasia and chondrocyte apoptosis are directly linked with cartilage degenerative lesion [5] [6]. The prevalence is remarkably high in women than men. Decrease in the sub-chondrol blood vessels lead to the cartilage related physiological and biomechanical abnormalities. With the increase in age, chondrocytes are no longer produced with long chain of hyaluronic acid and poyglucose, the results in cartilage softening, loss of elasticity, wear and tear, and structural damage. This pathological process leads to joint fibrosis which is the main cause of joint stiffness [7] [8].

The aim of knee OA treatment is to decrease joint pain, correct deformity, restore joint function, and improve quality of life. There are so many treatments used in clinical practice for the treatment of knee OA. But these methods are only used to minimize the pain, improve the functional ability, and to minimize the disability. These treatments are not helping in cartilage regeneration. OA is characterized by degeneration of extracellular matrix that causes articular cartilage damage [9] [10] [11]. According to the expertise, there are some regenerative medicines for the treatment of KOA which can potentially result in repair, replacement, restoration, and regeneration of injured tissues. Some mechanisms of regenerative therapy include stem cells, platelet rich plasma and amniotic fluid. In this new technology era, researchers are working on the technical methods of regeneration targeting discs, ligaments, joints, and cosmetic applications. These therapies reach up to the field of OA treatment. Many of researchers have tried to repair the damaged articular cartilage through regenerative therapies and providing a new way towards restoring the joint structure and function [12]

METHODS:

A computer based online search of PubMeD and Cochrane library databases to search related articles using the keywords of stem cell, treatment, knee osteoarthritis limited to English language. Articles were critically reviewed and analyzed.

RESULTS:

Total 268 articles were in the favor of stem cells in treating KOA. Case studies, reviews, or mechanistic studies were excluded because the only aim of the current study was to include clinical trials and 18 controlled studies were identified.

Articular cartilage injury mechanism

According to the biological progression of disease, OA can be divided into forms; primary OA and secondary OA. Primary OA is voluntary mechanism of erosive inflammation of specific joint. This pathology might be due to abnormal biomechanical abnormalities or some genetic changes. This mechanical pressure reduces the maintaining capacity of a joint tissue structure and increase the range of damage [13] whereas secondary OA is multifactorial that affects the joint distribution and loading. The end result of both primary and secondary OA is articular cartilage damage. However normal articular cartilage is white, translucent, soft and shiny. Cartilage matrix and chondrocytes are main component of a joint. Its cartilage matrix made up of proteoglycans and collagen. 50% collagen mostly type II collagen fibers which are extending form sub chondral plate to cartilage surface in upward and oblique manner [14] [15]. The defined composition of fiber in different direction lead to a mesh arch structure. Chondrocyte are arranged in parallel direction to collagen fibers. Chondrocytes are supposed for the production and decomposition if the matrix, which is the main ingredient in cartilage composition. This composition and arrangement have the ability to adapt stress. When the articular cartilage load increases, it increase the intra-articular pressure, which in turn affects the secretion of synovial fluid and decreases nutrition to chondrocytes, leading to dehydration, condensation, fragmentation, and necrosis. Focal injuries of articular cartilage penetrate and reach up to sub-chondral bone. [16] [17]

Status of stem cell therapy

Articular cartilage tissue itself have the capability to regenerate up to some extent, including chondrocytes,

cartilage matrix, and elastic fibers. Even though the regeneration process is slow and unable to bear the heavy pressure placed on the joint. Mesenchymal stem cells which are present in the synovial fluid have cartilage regenerating potential but there differentiating capacity is weak even if the joint is under minimal pressure. Moreover the number of MSCs in articular cartilage is less and the process of differentiation into cartilage is slow [18] [19]. MSCs are comprehensively distributed all over the body such as bone marrow, periosteum, trabecular bone, fat pad tissue, synovial membrane and teeth. Nevertheless of the tissue origin, they have the ability to differentiate. Therefore scientists have derived number of cellular therapies for the treatment of KOA. [20] [21]

Autologous chondrocyte Implant

The implementation of autologous chondrocyte implantation (ACI) requires assets of cartilage tissue from healthy joints, separation of chondrocytes from them and the expansion of culture, and then injection into the defect of the cartilage tissue. In 1997 food and drug administration approved this technology. Cells are introduced into the joint with the help of arthroscopy or open surgery [22]. Literature reports that autologous chondrocyte implantation is better than autologous osteochondral graft mosaic angioplasty [23]. There is no remarkable difference in the effects of these techniques whereas effects of ACI in long term appear to better [24]. A study who had long term follow up over 10 years has confirmed that in ACI there has less chances of failure and better recovery of joint function as compared to autologous osteochondral mosaic [25]. Another study of 20 years has reported that ACO has more positive outcome than autologous bone cartilage transplantation, mosaic angioplasty, and microfracture technology [26]
Implantation of stem cell

To achieve the maximum therapeutic effect of stem cell there must be appropriate selection of implantation method [27]. There are some following implantation methods

MSC stent implantation

A stent is implanted into the micro environment as a carrier for nutrients. They can be divided as per requirement into collagen, fiber, hyaluronic acid and other. Researchers conducted an experiment on rabbit by injecting MSCs into their bone marrow with hyaluronic acid gel sponge as a carrier which can effectively repair damaged articular cartilage. After 12 week of the transplantation they observed healthy articular cartilage synthesis around the injured articular cartilage [28]. Another study by walitani et al supported this technique [29]

Local injections of MSCs

Local application of MSCs has many advantages that not only strengthens the joint but also repair and reduce the induced degeneration. It is the simple and easiest method for treating KOA [30]. A study conducted my Murphy et all has found that transplantation of bone marrow MSCs in goats can stimulate meniscus regeneration and decrease the damage to the injured part [31]. Another study stated that they kept observing 24 weeks by MRI tracking and found that transplanting of MSCs can stimulate cartilage growth and decrease the pain in degenerating joints [32]

Mixed injections

To boost up the effectiveness cytokines or growth factors have been mixed with a scaffold. Mixed injection enhances efficacy by implanting a scaffold mixed with cytokines or growth factors. Mrugala et al used fibrin gel containing sheep MSCs with or without the addition of chitosan and TGF-β3 to treat OA in joints. The authors reported that the addition of chitosan and TGF-β3 sheep MSCs can produce therapeutic effects [33]. PRP is an autologous tissue of cartilage growth factor rich in TGF-β and platelet-derived growth factor, which can be used as a source of tissue for the treatment of cartilage injury [34]. Koh et al have demonstrated that combining MSCs and PRP when injecting into the joint cavity in the treatment of OA achieves significant improvement [35]. Haleem et al have suggested that implantation of a platelet-rich fibrous gel cell scaffold containing autologous bone marrow MSCs in the joint may be a more effective treatment for repairing articular cartilage injury [36]. Seo et al have found that the combined use of double gel/beta-tricalcium phosphate with stem cells, chondrocytes, BMP-2, and PRP in the treatment of malocclavian cartilage injury can stimulate cartilage regeneration [37]. Koh et al conducted another study which administered injections of patients' stem cells prepared with PRP as a novel biological scaffold. These studies have demonstrated safety, efficacy in reducing pain, and improvement in function in patients with KOA [38].

DISCUSSION:

Stem cell therapy has been most successful in recent years by experiencing on animals and in vitro experiments. Tissue engineering technology which is based on cartilage cells and MSCs to repair the cartilage and to restore the cartilage regeneration has

given very positive outcome. Cartilage tissue containing only chondrocyte cell is ideal for tissue engineering and repairing. Clinical feedback of ACI application is very appreciating from the last 20 years or more in the treatment of kOA. A randomized controlled single blinded study report that MSC treatment can effectively enhance repair of articular cartilage [39]

Aghdami et all investigated the effects of intra articular injections in the patient having moderate to severe symptoms with a 9 month follow up. They compared the intervention group with placebo group. The outcomes of intervention group were very positive. Initially patients have decreased subchondral edema and the thickness of cartilage was increased [40].

Another study conducted by Lamo-espinosa et all, they used patients autologous bone marrow after culture, then randomly assigned them to either intra-articularly administered hyaluronic acid alone or together. The follow up was of 12 months. Intervention group had more good results especially in patients who were given high dose. They had improved both VAS and WOMAC scale, used to measure pain. Whereas in control group there was reduction in knee joint space in control group, which was not seen in treatment group. In high dose treatment group there was decreased joint damage [41] Gupta et al also conducted a similar study. They tried different doses of cells (25, 50, 75, or 150 million cells) to be injected into the knee joint, followed by 2 mL hyaluronic acid (20 mg). The 25-million-cell dose demonstrated the most effective pain reduction. However, there was no significant change in MRI findings compared with the placebo group [42]. In addition, Vangsness et al found that allogeneic human MSCs can induce meniscus regeneration and relieve pain caused by KOA [43]. Sekiya et al used patient's synovium-derived stem cells to treat OA and achieved significant therapeutic effects [44]. Saw et al demonstrated after arthroscopic subchondral drilling into grade 3 and 4 chondral lesions, postoperative intraarticular injections of autologous peripheral blood stem cells in combination with hyaluronic acid resulted in an improvement of the quality of articular cartilage repair [45].

CONCLUSION:

Stem cell therapies have good outcome in the field of regenerative medicine. A well designed randomized controlled trail specifically for KOA repair is still needed for the most effective approach.

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