REVIEW

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The use of mesenchymal stem cells in the treatment of vertebral diarthroses degeneration (Facet Syndrome)

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ABSTRACT

The standard therapy of Facet Syndrome includes physical therapy, steroid injection or even surgical treatment. Tissue engineering offers us the choice of using Mesenchymal Blast Cells that act over the vertebral diarthroses by regenerating the joint cartilage. It is widely accepted that using blast cells helps many patients suffering from pain due to spinal trauma. When the weight bearing surfaces of the spine change, e.g. due to exaggerated lordosis, Facets get injured and pain emerges. While we can use steroid injection in treating these patients, its painkilling capacity wears off over a period of 6 months approximately, then the pain reemerges more strongly. Using mesenchymal stem cells to treat Facet Syndrome is helpful only in the case that the balance axis of the body and spine remains intact in coronal and sagittal level.

Moving towards this need, mesenchymal stem cells injection has been used in patients resulting in Facet cartilage regeneration. The ability of mesenchymal stem cells to reduce the body's inflammatory response mainly by inhibiting the action of macrophages is well known. They can also stimulate anabolic pathways by secreting certain substances. After being injected intra-articularly and with the help of synovial fluid, they act directly over cartilage defects, thus restoring them.

There is the question of which is the best site for harvesting mesenchymal stem cells. The first tissue to be examined was bone marrow, which easily differentiates into cartilage. On the other hand, mesenchymal stem cells taken from the fat require an easier procedure like aspiration or small incision, and suffice for the needs of several Facets. In any case, whether taken from the fat or the bone marrow, mesenchymal stem cells have justified their place in the treatment of Facet Syndrome. Further experimental and clinical trials are required in order to shed light on every possible aspect of this novel and pioneering therapy.

KEY WORDS: mesenchymal stem cells, facets joints, vertebrae diarthroses, Facet cartilage regeneration.

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VOLUME 70 | ISSUE 4 | OCTOBER - DECEMBER 2019

Introduction

Osteoarthritis of vertebral diarthrosis (Facet Syndrome) is considered to be one of the most frequent and serious reasons for causing degeneration-related lower back pain. Treatment includes physiotherapy, intra-articular drug injection, cautery-thermoregulation of spinal nerves through radio frequencies, as well as surgical operation. Tissue engineering is quite promising in treating a variety of musculoskeletal diseases and anomalies. Mesenchymal Stem Cells (MSCs) have their own multi-potent characteristics and are able to differentiate between various tissues, including joint cartilage.

Vertebral diarthroses (Facet joints) are laminar joint junctions between two neighboring vertebrae spanning from the neck to the lumbar spine. Two vertebral diarthroses exist in the posterolateral area of every kinetic level. Vertebral diarthrosis is shaped between two articular apophyses – the apophysis of proximal vertebra and the superior apophysis of distal vertebra. Articular apophyses are covered by hyaline cartilage and are surrounded by joint capsule and bursa that allows movement with little friction, just as in all capsular joints (knees, hips, shoulders etc.).

Facets and stem cells

Is there a possibility that the stem cells may interfere with the pain resulting from Facets? That depends on whether the joint has been injured due to trauma, which is a case occurring frequently in cervical vertebrae. In this case we expect a good outcome. However, Facet-related lower back pain is mostly due to joint degeneration and long- lasting rub. Individuals with a normal lumbar lordosis have their torso and upper spine's loads shared between vertebral body and the intervertebral disc. Facets are located in the posterior surface of the vertebrae and help with the junction, stability and natural movement in a normal lumbar spine. When lumbar lordosis is exaggerated due to various reasons, Facets' loads are increased and that leads to greater degeneration of articular surfaces and neighboring soft tissue (bursa and ligaments).

In this case, injection of local anesthetics and steroids (cortisol) inside the Facets is very common. The satisfactory clinical outcome of this procedure lasts usually for six months before the pain reappears. The first reason for pain relapse is simple. Steroids, although they present a good anti-inflammatory action, tend to destroy Facet cartilage at the same time. That is why when their action has stopped, the pain gets worse than before. The second reason for relapse is indirect and has to do with a general imbalance of the body and the spine in coronal and sagittal level. When the axis of balance of both lumbar and cervical spine has changed, there is no use in injecting stem cells locally into the Facets. There will be no significant pain reduction unless the factors contributing in coronal and sagittal balance, as well as pelvis inclination and spine curvature, will be corrected.

From all the above, we can conclude that the intra-dermal use of Mesenchymal Blast Cells - especially the ones coming from bone marrow - that are multipotent and have anti-inflammatory and growth action due to their own anti-inflammatory and growth factors, may benefit affected Facets in patients with embio-mechanically normal pelvis and spine.

Mesenchymal stem cells and the regeneration of Facet joint cartilage

As in all capsular joints, Facets are prone to degeneration and joint cartilage tear. Facet osteoarthritis has been described as a main contributing factor for pain in a degenerated spine and the term Facet Syndrome has been added to the literature. Based on various diagnostic criteria, Facet Syndrome's incidence ranges between 5% and 90% in patients with low back pain. There is a higher incidence in the elderly, and tends to become a serious clinical issue. Self-renewable cells that can differentiate between bone, cartilage, fat, tendon, muscle or fibrous tissue in vitro, were first described in 1968 [1]. In 1991, the term Mesenchymal Stem Cells was described and it is still used [2].

Mesenchymal stem cells have been used with success in the treatment of joint cartilage defects (e.g. on knees) and in regenerating inter-vertebral disc. They have also been used in repairing various bone

VOLUME 70 | ISSUE 4 | OCTOBER - DECEMBER 2019

Figure 1. *Intraoperative fluoroscopy showing the exact placement of the needles into the facet joints of L4–L5 and L5–S1.*

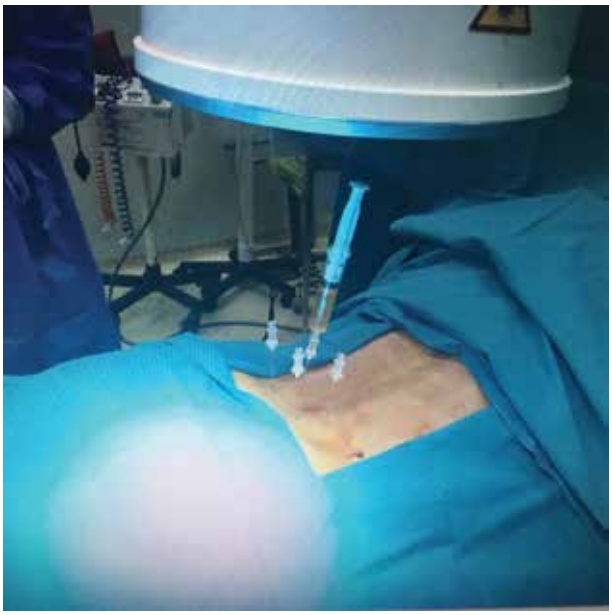

Figure 2. *Intraoperative picture showing the way of injecting MSC's into to the facet joints of the lumbar spine.*

defects, either in long bones or in the head (mandible, zygomatics).

It is a fact that none of the methods used today for the treatment of Facet Syndrome can succeed in regenerating the Facet joint. Thus, there is a dire need to find a novel technique for that purpose. Intra-articular injections of rh-BMP seem to be capable of boosting joint cartilage regeneration, as was observed in lab animals suffering from Facet arthritis [3]. In recent years, mesenchymal stem cells injections (**fig. 1**) are used with the purpose of regenerating Facet joint cartilage [4].

Mechanism of tissue regeneration

Mesenchymal stem cells are heterogeneous body cells that can be found in bone marrow, fat, skeletal muscle, capsules and other connective tissue. Animal experiments uncovered a possible mechanism by which mesenchymal stem cells can trigger joint cartilage regeneration. In an animal model for osteoarthritis, Van Ley et al [5] have shown that mesenchymal stem cells can deactivate macrophage cells, which are triggered by the joint cartilage decay byproducts, thus inhibiting joint cartilage catabolism. This study has shown that mesenchymal stem cells are capable of deactivating macrophage cells and also boosting their ability to secrete anabolic cytokines. That third mechanism of cartilage regeneration seems to be of great importance, as far as using mesenchymal stem cells in the treatment of degenerated Facets is concerned.

Mesenchymal stem cells can easily proliferate in cultures, maintaining their multi-potent character. That makes them a very promising choice in tissue regeneration [6]. These cells can differentiate into cells of the mesodermal line, resulting in the creation of tissues and organs such as cartilage, bone, fat, inter-vertebral disc, ligament or muscle [7]. Using specific growth factors while culturing mesenchymal stem cells, we have the capacity to differentiate them into chondrocytes, myocytes, adipocytes, osteoblasts or tendon cells [8]. Paracrine mechanisms may play a crucial role in tissue regeneration with mesenchymal stem cells. Mesenchymal stem cells are capable of producing several cytokines including Transforming Growth Factor–b (TGF-b), Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF) and other paracrine factors [9]. As a result, mesenchymal stem cells can augment and indirectly adjust tissue regeneration.

After injecting mesenchymal stem cells intra-articularly, various cytokines are released by them and, with the help of synovial fluid, they reach the cartilage defects (**fig. 2**).

Sources of mesenchymal stem cells

There are questions as to which is the ideal source of mesenchymal stem cells that can be used for repairing the Facet joint. Mesenchymal stem cells in adults can be taken from various anatomical sites like bone marrow, subcutaneous adipose tissue, skeletal muscle and via simple procedures like fat or bone aspiration and muscle biopsy [10]. It has been proven that a smaller difference between the tissue of origin and the tissue of mesenchymal stem cells injection leads to a better outcome as far as differentiation is concerned [11, 12].

Mesenchymal stem cells from bone marrow are the first to be studied, as they were also the first to be discovered. However, mesenchymal stem cells are being harvested from other sites as well, just like subcutaneous adipose tissue (A-MSCs) and this seem to have many advantages [13]. Harvesting mesenchymal stem cells from fat is easier and is associated with less morbidity. Great quantities of mesenchymal stem cells can easily be harvested from subcutaneous adipose tissue either by making a small incision and fat aspiration, or by excision of a small part of adipose tissue [14]. Mesenchymal stem cells concentration in adipose tissue is said to be up to 500 times bigger than that in bone marrow, especially in the elderly [15]. Bearing in mind the relatively small size of the Facet, we conclude that the quantity of mesenchymal stem cells taken from adipose tissue (A-MSCs) is enough to meet the needs of few Facets, without having to undertake local culture of MSCs.

Several in vitro studies have shown that the mesenchymal stem cells taken from adipose tissue present low capacity to differentiate into cartilage, as compared to the ones coming from bone marrow [16]. Other researchers believe that there is no difference in chondrogenic ability between mesenchymal stem cells from bone marrow and the ones from adipose tissue. Furthermore, the same researchers believe that the initial low chondrogenic capacity of A-MSCs can reach that of bone marrow mesenchymal stem cells, if they are combined with growth factors. In any case, studies have shown that MSCs both from the bone marrow and the fat are useful in restoring Facets [17].

Post injection treatment

Apart from the types of cells, the sources, the technique of harvesting and injecting of MSCs in Facet cartilage defects, another crucial factor for the clinical outcome is the post-operational treatment. The development and maintenance of joint cartilage is considered to be related with mechanical stimulation on it [18]. Early mobilization has been proven to be critical in regenerating joint cartilage [19]. Many mobilization protocols suggest constant passive movement or active exercises starting from the day of procedure [20].

Experimental studies on animals with inter-vertebral disc regeneration have not shown any need for post operational immobilization. It is generally accepted that post- operational mobilization programs need to be personalized according to the type of injury, patient's personality and surgical procedure [20]. A specific programme of mobilization needs to be scheduled when a Facet MSCs injection is planned.

Conclusion

There is the choice of using mesenchymal stem cells in treating joint cartilage defects, as well as strong indications that they play an important role in Facet Syndrome's treatment. Further experimental and clinical studies are required in order to investigate every aspect of this promising topic.

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Not applicable.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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