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# Stem Cell Therapy in Osteonecrosis of the Femoral Head

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## CURRENT STATUS OF STEM CELL THERAPY IN OSTEONECROSIS OF THE FEMORAL HEAD

Stem cell research began as a potential means of identifying new treatment options for intractable and lethal diseases. In the orthopaedic field, diseases in which current treatment methods are unsatisfactory, inefficient, or incapable of providing durable results are targets for stem cell therapy[1,2]. Osteonecrosis of the femoral head (ONFH) is a cause of premature total hip arthroplasty in young patients. In ONFH, osteocytes die from an obstruction to the blood supply, thus preventing dead tissue from repairing microcracks and leading to a gross collapse of femoral head structural integrity[3]. Stem cell therapy for ONFH–first suggested by Hernigou et al.[4]–started with the premise that no existing treatments could regenerate dead bone. They added bone marrow aspirate concentrate (BMAC) after core decompression, and in a sense, BMAC injection represents a primitive form of stem cell therapy. However, bone marrow aspirate contains various cell types, of which a low proportion is stem cells, and thus is not considered a genuine stem cell therapy[1].

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Several studies from other groups followed on the application of BMACs or culture-expanded mesenchymal stem cells (MSCs) to treat ONFH, and most reported a beneficial effect of the implantation of BMACs or culture-expanded MSCs[5,6]. Except for a few controlled studies, the majority of reported studies are, unfortunately, uncontrolled case series. Local implantation of BMAC to the core decompression tract was most commonly used, however, some recent studies used culture-expanded BMSCs. Scaffolding materials include fibrin glue, platelet rich plasma, $\beta$-tricalcium phosphate, autologous bone, and tantalum rod. While it is difficult to compare individual studies because of heterogeneous methods of application, BMAC or bone marrow MSC (BMSC) treatment seems to have reasonable, if not remarkable, effects in early stage (Ficat I or II) ONFH in terms of symptomatic relief and preventing progression of femoral head collapse[1].

A recent meta-analysis of stem cell therapy in ONFH revealed a very low complication rate (2.8%); these complications were all minor (hematoma, wound infection and pain at the site of bone marrow aspiration)[7]. Transformation of implanted cells is a potential serious complication in implantation of culture expanded MSC; however, to date no major cell-related complications were reported in stem cell implantation for ONFH.

## POINTS FOR CONSIDERATION AND POTENTIAL WAYS TO IMPROVE STEM CELL THERAPY IN ONFH

Like any treatment modality, stem cell therapy requires an understanding of the underlying pathophysiology of the disease. It is imperative that clinicians who adopt these new strategies into their practice possess a good understanding of the natural course of targeted disease[1].

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One surprising aspect of stem cell application in ONFH is that the fate of implanted cells was not characterized in any studies. While stem cells are applied with the expectation that these cells will: i) survive, ii) be taken up in the recipient area, and iii) differentiate into bone, it is not known whether these implanted cells will survive. Stem cell tracking studies in other organs reveal that injected or implanted stem cells usually exert paracrine effects, and then perish from the site. In the case of osteonecrosis, reduced vascularity of the implantation site would make the local environment even more hostile to the survival of stem cells. The less-than-satisfactory results of stem cell implantation in controlled studies may be explained by this understanding. It is expected that most implanted cells will undergo massive cell death in a short period, probably exerting some paracrine effect before they die. Therefore, if we wish to increase the survival capacity of implanted cells and ensure that they become osteoblasts within the implanted area, some measures to enhance the vascularity and osteogenic potential of the stem cells area are necessary.

While the most commonly used stem cell is BMSC, adipose stem cells (ASCs) have the advantage of promoting angiogenesis. Our group had previously demonstrated that co-culture of a BMSC and ASC had a synergistic effect on angiogenesis and osteogenesis *in vitro* compared with either one of the cells alone. When these cells were implanted into bone defects of rats, enhanced bone formation was also observed[8]. Our group had also implanted BMSC and ASC together in the ONFH model of minipig, and demonstrated significantly enhanced bone formation, compared with an unimplanted control[9].

Another potential mechanism of enhancing angiogenesis and prolonging implanted cell survival is to concomitantly introduce angiogenic factors with the stem cells. Vascular endothelial growth factor (VEGF) can be impregnated into various scaffolds, and released in a controlled way to enhance angiogenesis. VEGF can be also transfected to ASCs, and the transfected cells can release VEGF for a period of time, before blood supply is established, aiding implanted cell survival. Our group has transfected the VEFG gene to ASCs using electroporation. When co-cultured with BMSCs, as little as 5% of ASC to BMSCs were effective in enhancing angiogenesis and osteogenesis *in vivo* and *in vitro*[10].

## SUMMARY AND PERSPECTIVES

In summary, there are a handful of reports that investigated applying stem cells as a treatment for ONFH; however, more than half of these studies used BMAC, which are not true stem cells. Furthermore, there is a very limited number of well-controlled studies. Although many studies report positive results, it remains unclear whether stem cell implantation can genuinely alter the natural history of ONFH. In addition, the adequate dose of cells has yet to be determined. To understand the place of stem cell therapy and maximize its therapeutic effect, the mode of action should be determined. If the paracrine effect is not sufficient for bone regeneration in ONFH, methods to enhance the survival of implanted cells and support their differentiation into bony tissue should be employed. To prolong the survival of implanted cells, rapid vascularization of the implantation site is necessary. To prove the mode of action in stem cell implantation, robust animal models are necessary to track the implanted cells, and observe their therapeutic effects. The well-known difficulty in establishing an animal model in ONFH adds up to the obstacles to resolving the fate of implanted stem cells in ONFH. For bone regeneration, ONFH has been the greatest focus for cell therapy. More evidence will be required to confirm the effectiveness of stem cell treatment in arresting the progression of the disease. In addition to scientific matters, regulatory issues complicate cell therapies. The implantation of culture-expanded cells needs approval from regulation agencies in most developed countries. The process is even tougher for allogeneic or genetically modified cells, adding up the cost of cell therapy.

For treating physicians, it is also important to have an enhanced understanding of different cell sources, with analysis of the reported population of native stem and progenitor cells. Precise use of definitions and nomenclatures regarding cell sources and cell types is mandatory, as is distinguishing between culture-expanded cells and native cells and between autologous and allogeneic sources. It will also help to have a basic knowledge on the use and availability of methods for the quantification and characterization of the cells, and the efficiency of harvest, processing, and delivery procedures. It is also highly recommended that the concomitant use of established measures is not thrust aside until stem cell therapy is proven worthy in terms of safety, efficacy and cost[1].

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## CONFLICT OF INTEREST

The author declares that there is no potential conflict of interest relevant to this article.

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