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Original Research Article

The comparison of knee osteoarthritis treatment with single-dose bone marrow-derived mononuclear cells vs. hyaluronic acid injections

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ABSTRACT

Objective: The aim of this study was to compare treatment methods of the knee joint degenerative osteoarthritis, using autologous bone marrow-derived mononuclear cells and hyaluronic acid injections and observe prevalence of adverse effects in both groups.
Materials and methods: A prospective randomized controlled clinical trial was carried out. The analysis of pain and changes in osteoarthritis symptoms after a single intra-articular bone marrow-derived mononuclear cell injection into the knee joint in the Kellgren–Lawrence stage II–III osteoarthritis during the 12-month period were performed. The results were compared with the control group treated routinely by hyaluronic acid injections therapy. A therapy group of patients ($n = 28$) received single bone marrow-derived mononuclear cell intra-articular injections. A control group of patients ($n = 28$) was treated with a total of three sodium hyaluronate intra-articular injections each one performed a week apart. The clinical results were obtained using the knee osteoarthritis outcome score (KOOS) and the knee society score (KSS) before and 3, 6, and 12 months after injection.
Results: A statistically significant improvement was observed in the mononuclear cell group over the starting point in all scores. At the endpoint at month 12, the KOOS score improved significantly ($P < 0.05$) on the pain subscale (+25.44), activity and daily living subscale (+21.36), quality of life subscale (+28.83), and total KOOS (+18.25). The KSS score also demonstrated a significant improvement on the symptoms subscale (+25.42) and the function subscale (+38.32) ($P < 0.001$). The KOOS symptoms and sports subscales improved without statistical significance. The difference between the control group treated with

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hyaluronic acid versus the bone marrow-derived mononuclear cells group at time points 6 and 12 months demonstrated a statistically significant ($P < 0.05$) superiority in the KOOS pain subscale over the hyaluronic acid group. In both groups serious adverse effects were not observed.

Conclusions: The intra-articular injection of bone marrow-derived mononuclear cells is a safe manipulation with no side effects during the 12-month period. This treatment provides statistically significant clinical improvement between the starting point and 1, 3, 6, and 12 months after. When compared to hyaluronic acid treatment, better pain relief in the long-term period of mononuclear cell group was observed.

1. Introduction

Treatment options in the OA treatment have been expanded using the ability of tissue self-renewal properties. The results of platelet rich plasma, growth factors and autologous chondrocyte implantation have been well documented [1–3]. Despite of this, new strategies using mesenchymal stem cells (MSCs) have been actively explored in the last decade. The ability of the MSCs to differentiate into chondrocytes and synoviocytes could be utilized in the cartilage repair and the OA treatment [4,5]. This biological solution could offer a potential treatment option for the younger patient group and all other patients affected by the OA, where joint replacement would not be considered as the best treatment option. For cartilage repair, the MSCs are mainly acquired from the bone marrow (BM). However, other sources such as the adipose tissue (ASC), the synovial membrane and the umbilical cord have been described. All of these MSCs are expressing the same markers as embryonic stem cells and show also similar pluripotent properties [6,7].

In clinical practice both the ASC and the BMSCs have been used for cell based cartilage restoration. However, both of them have their own advantages. Certain studies show the advantage of the BMSC is in ability to produce the collagen type II and sulphated glycosaminoglycans [8,9].

In regenerative medicine, the BMSCs used can be divided into the following subgroups: the bone marrow aspirate concentrate, mononuclear cells, the isolated MSCs without in vitro expansion and the cultured MSCs. The bone marrow sample can be separated into plasma, red blood cells, platelets, and mononuclear cells by applying density gradient centrifugation. A mononuclear cell fraction contains a variety of progenitors including the MSCs population. Most of these mononuclear cells are CD34+ hematopoietic lineage progenitors, while very few are actually the MSCs capable to differentiate into bone, cartilage and synovial tissue [10]. Estimated frequency of the MSC in the BM nucleated cell population differs in range from 0.0017 to 0.034% [11]. Easy access to the mononuclear cells makes them advantageous in orthopedic practice. In literature we found a variety of clinical studies and case reports about the use of the BMSC in the treatment of isolated cartilage lesions and the OA patients [12,13]. These clinical studies describe the use of the MSC from both autologous and allogenic cell sources such as the bone marrow, the adipose tissue and the peripheral blood. Different MSC concentration methods and cell expansion ex vivo, additional augmentation with growth factors, hyaluronic acid and cell introducing methods have been used. A uniform BMSC based therapy analysis of clinical benefits on larger patient groups in orthopedic practice is still missing.

The primary aim of this study was to find out clinical effectiveness, analyze pain and changes in the OA symptoms, after a single intra-articular injection of the BM-MNC on KL stage II–III affected joints over a period of 12 months and to compare it to the clinical effectiveness of the patient group treated with sodium hyaluronate injections. The secondary aim was to observe any presence of adverse events associated with applied therapy.

2. Materials and methods

2.1. The patient randomization and the study design

The level of evidence: level II, randomized controlled trail (RCT). Between 2012 and 2015, 72 patients with the KL stage II–III OA in knee were screened, 56 were included in the study according inclusion exclusion criteria outlined in Table 1.

The patients were randomly divided into two groups: the bone marrow-derived mononuclear cells (BM-MNC) group and the sodium hyaluronate (HA) as a control group. The patient randomization process is represented in Fig. 1.

The State Central Medical Ethics Committee approved this clinical study. All patients provided an informed consent for the study according to the Helsinki Declaration and all patients voluntarily agreed to participate and signed the informed consent forms. The enrolled patients were randomized into study and control groups 1:1. The mean age in the study group was 53.44 ± 15 years, and there were 15 males (53%) and 13 females (47%). The control group included 10 males (34%) and 21 females (66%) with mean age 58.55 ± 13 years. The OA progression stage according Kellgren–Lawrence classification was 7 (25%) OA stage II and 21 (75%) OA stage III in the control group. The study group contained 9 (32%) OA stage II and 19 (68%) OA stage III patients. Patients in the therapy group underwent a single intra-articular injection of BM-MNC. Patients in the control group received total three Na hyaluronate (HA) intra-articular injections with an interval of one week, starting at the week 1 and finishing at the week 3.

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