IN STEP WITH CONTEMPORARY TRENDS-STEM-CELL THERAPY AS A KEY DRIVER OF REGENERATIVE ORTHOPEDICS AT THE CLINICAL CENTER OF VOJVODINA – PRELIMINARY DATA FOR THE TREATMENT OF KNEE OSTEOARTHRITIS AND OSTEochondRAL LESIONS

U KORAK SA SAVREMENIM TRENDOVIMA – TERAPIJA MATIČNIM ĆELIJAMA KAO KLJUČNI PO-KRETAČ REGENERATIVNE ORTOPEDIJE U KLINIČKOM CENTRU VOJVODINE – PRELIMINARNI REZULTATI LEČENJA OSTEOARTHRITISA I OSTEOHONDRLNIH LEZIJA

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Summary

Introduction. In the treatment of various orthopedic conditions, regenerative therapies, including platelet rich plasma and autologous stem-cell therapy, have recently been advancing. Knee cartilage lesions are a debilitating disease resulting in fibrillation and subsequent degradation which can also involve the subchondral bone and lead to the development of osteoarthritis. Bone marrow mesenchymal stem cells are a heterogeneous mixture of cells involved in cartilage formation and regenerative repair, whereas other mesenchymal stem cells have the capacity to play a role as immunomodulatory and trophic factors. Nowadays, stem-cell therapy is widely used for the treatment of knee osteoarthritis and cartilage lesions. The purpose of this study was to evaluate preliminary clinical data of treatment of knee osteoarthritis with stem cell injection and treatment of osteochondral lesions with stem-cell scaffold. Material and Methods. Stem cells were obtained by concentrating the content taken with aspiration needles from the bone marrow my means of Arthrex Angel Bone Marrow Aspirate Concentrate centrifuge. Results. The study sample consisted of 39 patients who were included in knee osteoarthritis treatment. Surgical implantation was performed in 7 patients from the osteochondral group. In the first group, an average Visual Analogue Scale pain felt before intervention decreased statistically significantly three days after the intervention (from 7.27 to 2.12, p≤0.05) and remained 1.2 until the check-up after 3 months. The same results were achieved in the average Western Ontario and McMaster Universities Arthritis Index score (prior to intervention=51.5; after 1 month=72 and after 3 months= 76). For the second group, an average pre-intervention Visual Analogue Scale pain decreased statistically significantly three days after intervention (from 8.1 to 2.7) and remained 1.2 until the check-up after months. The same results were achieved on the Knee injury and Osteoarthritis Outcome Score pain (p<0.05). Both procedures were proved as safe providing pain relief and function improvement of treated knee joints.

Key words: Stem Cell Transplantation; Bone Marrow Cells; Regenerative Medicine; Osteoarthritis, Knee; Osteochondritis; Cartilage, Articular; Orthopedic Procedures; Pain Measurement

Sažetak

Uvod. Regenerativna medicina danas je klinička realnost u tretmanu mnogih ortopedskih stanja unazad nekoliko godina. Pored terapije platelet rich plasma, terapija matičnim čelijama postaje sve popularnija. Lezije hrgavice predstavljaju onesposobljavajuću bolest koja vremenom progredira ka zdravoj hrgavici i suphondralnoj kosti; dovodeći do razvoja osteoartritisa. Ma-tične čelije porekom iz koštane srži su heterogena mešavina čelija koje učestvuju u formiranju i regeneraciji hrgavice, ali imaju i imunomodulatorna i trofička svojstva. Danas je korišćenje terapije matičnim čelijama široko rasprostranjeno za lečenje kako osteoartritisa tako i za lečenje lezije hrgavice velikih zglobova. Cilj ovog rada bio je da se predstave preliminarni klinički rezultati lečenja osteoartritisa injekcijama matičnih čelija kao i lečenja osteohondralnih lezija skafoldima od matičnih čelija. Materia l i metode. Matica čelije su dobijene koncentravljašanjem sadržaja uzetog punkcijom iz koštane srži uz pomoć Arthrex Angel centrifuge. Rezultati. U našoj ustanovi, 39 pacijenata lečeno je injekcijama matičnih čelija, dok je sedam pacijenata lečeno implantacijom matičnih čelija u autologi biojksi skafold. Kod prve grupe, skala bola Visual Analogue Scale značajno je pala tri dana nakon intervencije (od prosечно 7,27 na 2,12, p≤0.05) i održavala se niskom do trećeg meseca sa rezultatom 1,2. Slični rezultati su postignuti i na skali Western Ontario and McMaster Universities Arthritis Index (pre-interventno = 51,5; prvi mesec = 72 i treći mesec = 76). U drugoj grupi, skala bola Visual Analogue Scale značajno je pala tri dana nakon intervencije (od prosечно 8,1 na 2,7, p≤0.05) i održavala se niskom do trećeg meseca sa rezultatom 1,2. Slični rezultati postignuti su i na skali bola Knee injury and Osteoarthritis Outcome Score. Zaključak. Obe procedure su dokazane kao bezbedne po pacijentima sa dramatičnim poboljšanjem funkcije tretiranog kolena i smanjenjem bola. Ključne reči: transplantacija stem čelija; čelije koštan srži; regenerativna medicina; osteoartritis kolen; osteochondritis; zglobna hrgavica; ortopedski procedure; merenje bola
Abbreviations

- BMAC – Bone Marrow Aspirate Concentrate
- FASSG – autologous scaffold covered by bio-regenerative glue augmented with growth factors
- IL – Interleucin
- KCV – Clinical Center of Vojvodina
- MSc – mesenchymal stem cells
- OA – osteoarthritis
- OH – osteochondral
- PRP – platelet rich plasma
- PRF – platelet rich fibrin
- TNF – tumor necrosis factor
- VEGF – vascular endothelial growth factor

Introduction

At the very beginning, we would like to present a short historical overview of regenerative orthopedics at the Department of Orthopedic Surgery and Traumatology, Clinical Center of Vojvodina (CCV) which is at the disposal of our patients. Our Center is the only state-owned hospital having modern equipment and well educated teams capable of offering adequate, contemporary and state-of-the-art regenerative orthopedic procedures. The first regenerative procedures were established 3 years ago when our Center was equipped with the VivoStat® System and a sufficient number of Platelet Rich Fibrin sets (PRF). Early pioneers of these procedures were focused on intra-articular injections of PRF for treatment of osteoarthritis (OA) and soft tissue infiltrations for treatment of painful syndromes such as tennis and golf elbow, rotator cuff tear, subacromial bursitis, muscle and ligament injuries, etc. Unfortunately, there were no methodological records of follow-up results. Encouraged by great results and high levels of patient’s satisfaction following the functional improvement our surgeons continued to widen the spectrum of potential regenerative options and to extend their knowledge base. Surgical implantation of bioregenerative scaffold with stem cells from bone marrow aspirate concentrate (BMAC) for treatment of osteochondral (OH) lesion was performed for the first time in our country in November 2015, at the Clinical Center of Vojvodina. It was conducted by Prof. Dusan Maric, Prof. Dragan Savic and Dr. Vaso Kecojevic and supervised by Prof. Stefano Zanasi from the Rizzoli Institute, Bologna, Italy. At the end of 2015, the Clinical Center of Vojvodina applied for the Provincial state funding with a Project for Treatment of OA and osteochondral lesions with BMAC. Upon the approval of budget, the Department was equipped with an Arthrex®Angel centrifuge as well as a number of sets for BMAC and PRP production with the aim of offering the most modern therapy options for our clients but also to extend the base for scientific research. Nowadays, BMAC and PRP therapy is widely used for treatment of OA in knee and hip, OH lesions, avascular necrosis of femoral head and condyles, non-union fractures and a wide range of soft-tissue pathologies. This project has consequently opened the door for a number of clinical studies approved by ethical and state authorities for research of clinical application of stem cells in different orthopedic conditions.

Regenerative adjunctive treatment is the next logical step in the progression of surgical intervention. Biologically augmented or regenerative techniques are at the very forefront of modern treatment and have the potential to transform the practice of medicine and surgery significantly in a very short period. Although the basic science remains in its infancy, especially in the areas of signaling, regulation, and mechanism, regenerative knowledge has expanded significantly in volume and across disciplines [1]. In the treatment of various orthopedic conditions, regenerative treatments have recently been advanced, including platelet-rich plasma and autologous stem-cell therapy. The term orthobiologics has been used to describe these various bio-logic agents that are obtained directly from our bodies tapping into our own intrinsic capabilities to heal [2]. Multiple studies on platelet-rich plasma have been published that demonstrate the modulation of pain and inflammation in degenerative arthritis of the knee [3–7] and the healing capabilities of this treatment for chronic refractory tendinopathies [8, 9]. On the other hand, studies are emerging that support the benefit of mesenchymal stem cells (MSC) for cartilage pathology including osteoarthritis and osteochondral lesions. Positive functional outcomes have been reported 12 (for OA) to even 60 months after implantation of stem cells in different types of treatment options for OH lesions, but future work is required to assess long-term outcomes with respect to other treatment modalities [10–14]. Besides varying degrees of beneficial clinical outcomes, most currently published articles have reported that the application of BMAC is a safe procedure without any complications which occur in general population according to the statistics [15].

Articular cartilage lesions are a debilitating disease resulting in fibrillation and subsequent degradation which can also involve the subchondral bone and lead to the development of OA [16, 17]. One limiting factor in the repair of these defects is the well-known low intrinsic regeneration potential of cartilage, which might be due to the difficulty encountered by progenitor cells from the blood, bone marrow, or even other compartments in entering the defect and the inability of resident articular chondrocytes that are entrapped within the surrounding matrix to migrate into the lesion to secrete a reparative matrix [18]. The avascular, aneural, and lymphatic nature of articular cartilage hinders repair and regeneration potential once injured. Articular cartilage lesions may be focal defects resulting from direct trauma, avascular necrosis (AVN), or osteochondritis dissecans. These lesions are described as chondral (limited to the cartilage surface) or osteo- chondral (extending beyond the calcified
cartilage layer into the subchondral bone). Chondral lesions have a poor intrinsic ability to repair themselves because they lack blood vessels that are critical for circulation and delivery of progenitor cells as a part of the normal healing processes. Instead of progenitor cells filling chondral defects, cells from the synovial membrane migrate to the articular cartilage defect and fail to integrate completely, leading to continued degeneration. In contrast, osteochondral lesions have access to the bone marrow, which provides a supply of mesenchymal stem cells that can create the repair tissue [18]. This tissue, however, resembles fibrocartilage, which does not integrate well with the adjacent matrix and does not withstand mechanical stress, resulting in eventual degeneration over time. Articular cartilage lesions may also be more generalized, or diffuse and lacking lesion margins as in degenerative joint disease or OA. Once early OA begins, the repair capacity of articular cartilage is further compromised by a cascade of catabolic events including inflammation, recruitment of cells that release pro-inflammatory factors, and proteinase activation that leads to degeneration and cell senescence with apoptosis. Disease progression is believed to result from an imbalance between pro-inflammatory cytokines (including interleukin 1α (IL-1α), IL-1, and tumor necrosis factors (TNF) and anti-inflammatory cytokines (including IL-4, IL-10, and IL-1ra) [18]. This cytokine imbalance is thought to promote proteolytic enzymes, which lead to cartilage deterioration [19–22]. In addition, the subchondral trabecular bone is thought to play an important role in OA because subchondral bone changes are potentially both a result and a cause of cartilage loss [23].

Bone marrow MSCs are a heterogeneous mixture of cells with at least two different functions. Some of these cells are already involved in the osteogenic pathway and accelerate bone formation and regenerative repair [24–27], whereas other MSCs have the capacity to play a role as immunomodulatory and trophic factor [28]. These MSCs are formed at broken and inflamed blood vessels where the local pericyte detaches from the vessel and becomes an activated MSC. This in situ MSC secretes a curtail of bioactive agents that locally inhibit the over-aggressive immune system from sending in integrating cells. This is the body’s first line of control and defense against establishing an autoimmune reaction against the antigens exposed by the injured tissue [1].

The “trophic” effects of MSCs establish a regenerative microenvironment at the site of injury by (a) inhibiting ischemia-related apoptosis, (b) by inhibiting scar formation, (c) by stimulating angiogenesis by secreting large amounts of vascular endothelial growth factor (VEGF) and by transforming some of the MSCs back into pericytes that function to stabilize the fragile, newly forming capillaries, and (d) by secreting tissue progenitor-specific mitogens so that the slow process of tissue regeneration is enhanced [29]. In conclusion, MSCs serve as “drug stores” [28, 29] for sites of injury and/or inflammation by providing an array of bioactive molecules tailored for that site and the injury [1]. MSCs are characterized on the basis of surface expression markers as CD73, CD90, and CD105 positive, and CD34 and CD45 negative [30].

Adult stem cells consist of 2 general classifications: hematopoietic stem cells, which are responsible for the formation of blood products, and mesenchymal stem cells (MSCs) [8]. In the early 1990s, adult MSCs were discovered to have an active role in connective tissue repair [31]. Since that time, impressive progress toward the development of safe clinical applications for MSC-mediated therapy has been achieved. It is now technically feasible to harvest tissue cells, culture them (if needed) to expand the cell population, and then inject these cells directly into areas of injury. Several injectable stem-cell therapies with differing cell origins now abound, including MSCs, tenocyte-derived stem cells, adipose-derived stem cells, amniotic-derived cells, and dermal fibroblasts. The most well-studied sources of MSCs include bone marrow derived MSCs and adipose-derived stem cells [8].

Bone marrow concentrate contains bone marrow derived mesenchymal stem cells, hematopoietic stem cells, platelets (containing growth factors), and cytokines. Bone marrow cells consist of erythroblasts, neutrophils, eosinophils, basophils, mononuclear cells (monocytes containing mesenchymal stem cells and macrophages), lymphocytes, and plasma cells [18]. These cells are present in various stages of differentiation [32]. The hematopoietic progenitor cells can morph into mesenchymal stem cells, differentiate into chondrocytes, and are more osteoinductive than adipose-derived cells [33]. Following the knowledge base derived from pre-clinical, basic studies about the role of MsC in an inflammatory environment in the knee, a ratio for the treatment of OA and OH with stem cells from different sources is justified.

The purpose of this study is to evaluate preliminary clinical data of treatment of knee OA with BMAC injection and treatment of osteochondral lesions with BMAC and Fully Autologous Scaffold covered by bioregenerative glue augmented with growth factors (FASGG).

**Material and Methods**

The group included into osteoarthritis treatment (OA group) consisted of 39 outpatients complaining of knee pain who underwent physical examination, laboratory test and X-ray from April 2016 to a thorough clinical history. The study was performed only if the patients understood and agreed to the treatment method and procedure. After careful review of all the test results, the following exclusion criteria for this study were set: knee instability, severe
misalignment, flexion contracture of more than 10, inflammatory arthritis such as rheumatoid arthritis and ankylosing spondylitis, presenting muscle pain, and underlying diseases such as hematologic disorders, septicemia, coagulopathy, neoplasm, active infection, and immune deficiency. According to these criteria, 39 patients who were diagnosed with degenerative arthritis (Kellgren-Lawrence grade from 2 to 4) of the knee were included in this study.

For the procedure, the patient was placed in supine position, following preparation and draping of tuberosity, then local anesthesia (Marcaine, 10 ml) was infiltrated from skin to periosteum. Autologous bone marrow of 100 cc was aspirated using Arthrex Angel BMAC set with aspiration needles. The punctured bone marrow was injected into the plastic bag including the anti-coagulant inside the kit and then mixed. The Arthrex Angel centrifuge was used to separate 6 ml cc of BMAC and an injection of BMAC was injected into the treated knee. After the intervention, the patients were allowed to go back home to return to their daily lives with a recommendation to decrease activities in next 5 to 7 days and not to take any NSAID therapy for 2 weeks. After 7 days, there was no limitation on daily routines other than the instruction to refrain from extreme exercise for 3 weeks following the intervention. The patients were followed up for VAS pain and swelling 3 and 7 days after intervention and invited for the check-up after 1 and 3 months. The clinical results were also analyzed using the WOMAC score.

For the osteochondral lesion treatment (OH group), the procedure and surgical method of implantation were performed on 7 patients. Previously, they were recruited for the study after physical examination and magnetic resonance imaging (MRI) confirmation of cartilage lesion presence. Having given their signed consent, they were operated on under general anesthesia. For the procedure, the patient was placed in supine position, with the knee prepared for arthroscopic surgery. An amount of 100 ml cc blood was taken for PRP and platelet poor plasma (PPP) preparation and sent to a separate centrifuge for production of FASSG. Autologous bone marrow of 100 cc was aspirated by means of Arthrex Angel BMAC set. The punctured bone marrow was injected into the plastic bag including the anti-coagulant inside the kit and then was mixed. The Arthrex Angel centrifuge was used to separate 6 ml cc of BMAC. Then, the presence of lesions was confirmed by means of knee arthroscopy. The lesion was approached through the mini arthrotomy. Debridement of lesion was conducted on the borders of the damaged cartilage including the healthy cartilage tissues, and the subchondral bone of the lesion which was exposed. After the microfracture had been performed, BMAC was placed, then FASSG was placed and at the end after FASSG changed consistency and became solid, bioregenerative fibrin (BFR) was sprayed to cover the scaffold. The remaining BMAC and PRP were injected into the knee, and the wound was closed. When it was necessary to control the pain, the use of oral non-steroidal anti-inflammatory drugs was not allowed, and Acetaminophen pain relievers or opioids were prescribed. When the stitches were removed, the patients were sent to rehabilitation. The patients were banned from weight bearing in the next 4 to 6 weeks during which the patients themselves conducted the joint angle exercise until the full range of motion (ROM) was reached with an increase after 6 weeks. After that, the patients were allowed to return to their daily routines with the progression to full sports activities about 3 months after the operation. The clinical evaluation was based on the survey completed at outpatient visits before the operation and 1 and 3 months after the operation, the physical examination, and the direct follow-up. This study evaluated the degree of pain of patients through the visual analogue scale (VAS) scores, and the clinical results were analyzed by means of the International Knee Documentation Committee (IKDC). Both procedures were approved by the Ethics committee. Statistical analyses were performed with ANOVA model analyzing the differences among group means. IBM SPSS 20.0 was used for statistical calculations.

Results

No serious adverse events were reported either in the OA or in the OH group. The OA group consisted of 25 male (64%) and 14 female (36%) patients, whose mean age was 56 years, ranging from 38 to 75 years. The average body mass index BMI was 28.19. The average number of total nucleated cells per 1 ml was 17.2 million. The viability of cells was 98.6%. The degree of degenerative arthritis was evaluated by K–L grade (Kellgren–Lawrence grading scale) on standing anteroposterior (AP) view: there were 15 (38%) cases of grade II, 21 (53%) cases of grade III, 8 (9%) cases of grade IV. The average VAS pain was 7.27 before intervention; 2.12 after 3 days; 1.5 after 7 days; 1.3 after 1 month and 1.2 after 3 months. There was a statistically significant difference between the pre-intervention values and other values on follow-up starting from 3 days to 3 months. (p ≤ 0.05). The average VAS swelling was 1.7 before intervention; 1.1 after 3 days, 0.91 after 5 days; 0.6 after 1 month and 0.5 after 3 months (Graph. 1). There was a statistically significant difference between the pre-intervention values and other values on follow-up starting from 3 days to 3 months. (p ≤ 0.05). The average WOMAC score was 51.5 before intervention; 72 after 1 month and 76 after 3 months (Graph. 2).

There were 6 (86%) male and 1 (14%) female patients in the OH group, whose mean age was 43 years, ranging from 30 to 59 years. The average BMI core was 28.92. The average number of total
nucleated cells per 1 ml was 19.4 million. The viability of cells was 99.1%. There were 1 medial condyle lesion, 1 lateral condyle lesion, 3 cases with both medial and lateral condyle, 1 trochlear lesion and 1 patient with lateral condyle and patella lesion. The average VAS pain was 8.1 before intervention; 2.7 after 3 days; 2.1 after 7 days; 1.5 after 1 month and 1.2 after 3 months. There were statistically significant differences between the values prior to intervention and other results starting from 3 days follow up ($p<0.05$). The average VAS swelling was 5.6 before intervention, 4.3 after 3 days, 1.8 after 7 days; 1 after 1 month and 0.5 after 3 months (Graph. 3). There were also statistically significant differences between the values before intervention and other results starting from 3 days follow up ($p<0.05$). The average KOOS pain score was 37.7 prior to intervention, 59.5 after 1 month and 69.4 after 3 months (Graph. 4). There were statistically significant differences between the values before intervention and other results starting from 1 month follow-up ($p<0.05$).

Discussion

Osteoarthritis of the knee is a highly prevalent joint disease with prominent symptoms affecting the daily lives of millions of people. The most current evidence-based therapies focus on the symptom improvement or total joint replacement versus prevention or improvement in the progressive destruction of OA joints. The concept of intra-articular delivery of MSCs opens up novel treatment options for this disease process [34]. Consistent with previously published results from other publications, these preliminary results have shown that BMAC injection in the knee is a safe procedure, without any serious adverse effects. Significant improvement of knee function and pain relief, with immense analgesic effect in a previously painful knee (measured by a significant decrease in VAS pain score after 3 days and continuation of good results measured by a decrease of pain and an increase of joint function as far as 3 months after one injection), were confirmed. Besides, preliminary results among the patients treated with a FASSG have shown very encouraging results with a dramatic increase of KOOS and a decrease in VAS pain score starting from one month after surgical intervention followed by further improvement after 3 months.

Not much is known about this topic which is confirmed by numerous pre-clinical studies; whereas studies done at the clinical level are characterized by methodological shortcomings, small study samples and short follow-up period. Nonetheless, the available studies suggest a potential for these cell-based treatments to be developed in many directions, with different available cell sources, the possibility to use them concentrated or expand them in vitro, to apply them as a simple minimally invasive injective approach, or to be delivered surgically, alone or augmented with growth factors or scaffolds, and many other improvements are being developed. Mesenchymal stem cells in cartilage regeneration represent a promising new approach with preliminary interesting findings ranging from focal chondral defects to articular OA degeneration. How-
ever, many aspects are still controversial, and they have to be clarified [35].

Safety of the BMAC therapy was investigated in many trials, both for scientific, clinical or regulatory purposes [10, 15, 35, 36]. Our safety results are similar to previously published reports of BMAC use in osteoarthritic knees as they were without pain. There was no clinical evidence to suggest that treatment with MSCs (alone or in mixture with other stem cells or PRP) increase a risk of neoplasm, immunological or other related diseases. Having performed an investigation in multi-center analysis among 2,372 adults undergoing autologous stem-cell therapy Centeno C. et al. concluded that the rate of reported neoplasms is even lower in treatment group in comparison with the general population [15]. Lack of any adverse events is logical; BMAC, with its ingredients is fully autologous so there is no single substance which could elicit to any foreign body reactions which could induce reactions to foreign body, immunological attacks or toxic spreads. With these interventions, we simply transplant specific body cells from one body part to the other because there is no way to be transported through circulation.

There is a general agreement among researchers about pain relief reaction after BMAC injection in the knee [18, 37–39]. Therefore, theories of MSC paracrine signaling mechanisms to modulate joint homeostasis have further been corroborated by many BMAC studies demonstrating symptomatic pain relief, despite low cell numbers compared with culture-expanded techniques [29, 40, 41].

Having analyzed our preliminary results after surgical transplantation of BMAC in FASSG, we are encouraged with almost full absence of knee pain, which was a dominant sign before the surgery. In addition, a dramatic increase of joint function additionally supports our belief in this method. Although it is very early for arthroscopic or MRI diagnostic of cartilage defect consistency, we believe that after these clinical signs, a regenerative biological process is ongoing inside the knee at the site of implantation which is expected to result in the full creation of cartilage-like tissue. Wakitani et al. [42] injected autologous BM-MSCs embedded in the collagen gel directly into the articular cartilage defect of osteoarthritic knee joints. Twelve patients received autologous bone marrow cell transplants, and twelve were cell-free controls. A better arthroscopic and histological score was observed in the cell-transplanted group even though no clinical improvement was demonstrated after 6 months. Another non-randomized study, performed by Nejadnik H. et al. [43], compared 36 patients with autologous chondrocyte implantation (ACI) and 36 patients with autologous BM-MSCs. After 2 years, similar outcomes were obtained for the two procedures but the autologous BM-MSC-based approach was safer and less expensive. This year, Gobbi et al. [14] published a paper with clinical outcome data on the five-year follow up after the same concept of cartilage surgery as we did in this study with a conclusion that cartilage repair using HA-BMAC leads to successful medium-term outcomes independent of age or lesion size. All these studies generally reported the presence of a hyaline-like cartilage repair tissue within the primitive cartilage defects. Weaknesses in this study are clear—very short follow-up period and a small size of study sample to yield systematic clinical conclusions. Despite these shortcomings, the consistency, strength, and rapidity of improvement suggest that more extensive and more strongly designed prospective observational studies are warranted and we will continue to perform these procedures at our Department.

Conclusion

Cellular-based therapies for osteoarthritis are rapidly evolving; however, much remains to be understood regarding their efficacy and mechanism of action. Mesenchymal stem cells therapy may be a valid alternative treatment for chronic knee osteoarthritis. The intervention is simple, it does not require hospitalization or surgery, it provides pain relief, and significantly improves cartilage quality.
References


