ELMER PRESS

Short Communication

J Clin Med Res. 2020;12(11):747-751

A Retrospective Study of Stromal Vascular Fraction Cell Therapy for Osteoarthritis

Brian Mehling[a], Milan Hric[b], Adriana Salatkova[b], Robert Vetrak[b], Doreen Santora[a], Miriama Ovariova[c], Renata Mihalyova[c], Marine Manvelyan[a, d]

Abstract

Background: Osteoarthritis (OA) is progressive degenerative damage to articular cartilage. Current therapeutic options are reduced to control the OA-associated symptoms, leaving the degenerative changes to progress until a joint replacement becomes mandatory. Therefore, therapeutic alternatives are warranted to improve the patient's quality of life. Cell-based therapy is a developing therapeutic modality, showing promising results in the regeneration of injured cartilage and reduction of on-going inflammation within the affected joint. The current retrospective chart review study was aimed to analyze changes in pain and mobility of subjects with OA after stromal vascular fraction (SVF) cell therapy.

Methods: Three hundred fifty subjects with hip and knee OA, treated with autologous SVF cells at the Malacky Hospital (Bratislava, Slovakia) in the period from 2015 to 2018, were included in the retrospective chart review study.

Results: Seven days after SVF cell therapy, 45.2% of subjects experienced improved pain levels and mobility. Three, 6, and 12 months after therapy, improvement in pain levels reached 75.3%, 84.4%, and 84.9%, and improvement in mobility reached 75.2%, 84.4%, and 84.9%.

Conclusions: Our study of 350 subjects with hip and knee OA showed a significant improvement in pain levels and mobility 3, 6, and 12 months compared to 7 days after autologous SVF cell administration. The treatment demonstrated a strong safety profile with no severe adverse events or complications reported. The results of the study are showing that SVF cell therapy was more effective in subjects with arthritis stage III compared to arthritis stages I, II, and IV.

Keywords: Stromal vascular fraction; Osteoarthritis; Autologous; Mesenchymal stem cells; Platelet-rich plasma; Cell therapy

Manuscript submitted September 17, 2020, accepted October 8, 2020
Published online November 3, 2020

[a]BHI Therapeutic Sciences, 214 State Street, Hackensack, NJ 07601, USA
[b]Malacky Hospital, Nemocnicna, Duklianskych hrdinov 34, 901 22 Malacky, Slovakia
[c]Blue Horizon International, Grosslingova 17, 801 29 Bratislava, Slovakia
[d]Corresponding Author: Marine Manvelyan, BHI Therapeutic Sciences, 214 State Street, Hackensack, NJ 07601, USA.
Email: mmanvelyan@bluehorizoninternational.com

doi: https://doi.org/10.14740/jocmr4354

Introduction

Osteoarthritis (OA) is the common cause of pain and disability in adult individuals. It is characterized by degeneration of articular cartilage, inflammation of the synovium tissue, and tendon [1, 2]. Pathogenesis of OA involves multiple factors, including age, joint trauma, genetic factors, altered biomechanics, and obesity [3]. Knee OA-associated pain is well-recognized as typically transitioning from intermittent weight-bearing pain to a more persistent, chronic pain [4]. Fatigue, sleep trouble, psychological stress, poorer perceived health, reduced activity, function decline, disability, and reduced independence are consequences of knee OA-associated pain [5]. An increase in C-reactive protein (CRP) level was associated with the presence and progression of knee OA, particularly with synovial fluid interleukin 6 (IL-6) and degree of synovial fluid infiltration, symptoms of pain, and stiffness [6]. Cartilage destruction is the result of molecular damage and inability to effectively manage mechanical forces, leading to the production of a host of inflammatory mediators, which include cytokines and chemokines [7]. Early OA is characterized by increased mononuclear cell infiltration and overexpression of inflammatory mediators compared with a late disease [8]. Treatment options targeting inflammatory processes in this stage might be most productive for the prevention and therapy of OA [3]. Current therapeutic strategies for OA include drugs for control of pain and inflammation, such as nonsteroidal anti-inflammatory drugs, analgesics, locally administered corticosteroids, and viscosupplementation [9]. Tectorigenin has a positive role in OA restriction because of its anti-inflammatory and antioxidant activities. Wang et al demonstrated the chondroprotective potential of tectorigenin in the OA process and prevention of articular cartilage degeneration and chondrocyte apoptosis via the NF-κB P65 pathway [9]. Stem cell therapy is a developing therapeutic modality in the treatment of OA. Adipose tissue-derived stromal vascular fraction (SVF) contains a variety of cells, including mesenchymal stem cells (MSCs), which is a promising therapeutic option for OA. With the application of conventional liposuction and isolation methods, SVF in adipose and connective tissues can be easily obtained from patients [10]. Michalek et al showed significant improvement

in OA symptoms, particularly pain reduction and decrease in nonsteroidal anti-inflammatory drug usage in a large group of 1,128 patients with OA [11]. Numerous clinical studies have been published about OA treatment with autologous adipose SVF. However, a limited number of clinical studies include a large group of subjects. Efficacy assessments mostly include evaluation of pain, joint movement, joint stiffness, and non-steroidal anti-inflammatory drug usage in the general group of OA patients. In the present retrospective chart review study, we analyzed not only changes in pain and mobility parameters but also the correlation of improved parameters with the arthritis stage in a group of 350 subjects with OA.

Materials and Methods

Study subjects and methods

Three hundred fifty subjects with hip and knee OA, treated with autologous SVF cells at the Malacky Hospital (Bratislava, Slovakia) in the period from 2015 to 2018, were included in the retrospective chart review study. There were 202 male subjects (58%) and 148 female subjects (42%), aged 27 - 79 in the male group, 54.5 ± 0.7 (mean ± the standard error of the mean (SEM)) and 20 - 79 in the female group (56.3 ± 0.9). Affected areas included knee (63%), hip (31%), knee with the hip (6%). Based on clinical and X-ray or magnetic resonance imaging (MRI) examination, 64 (18.3%) subjects were diagnosed with stage II, 63 (18%) with stage III, 57 (16.4%) with stage II - III, 50 (14.3%) with stage III - IV, 27 (8%) with stage IV of OA. The reaming 89 subjects (25%) had different combinations of stages I - IV of the knee and hip OA. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Evaluation of BMI showed the following distribution: one subject was underweight (0.3%) (BMI is below 18.5), 55 subjects (15.7%) had normal BMI (BMI is 18.5 - 24.9), 132 subjects were overweight (37.7%) (BMI is 25.0 - 29.9), and 162 subjects (46.3%) were obese (BMI is 30.0 and above). The mean BMI was 30.1 ± 0.3. Habits evaluation showed the following: the smoking group included 84 subjects (24.9%), and the alcohol-consuming group included 97 subjects (28.8%). The group with pre-existing conditions included 90 subjects (25.7%). All subjects provided informed consent. All subjects underwent standard tumescent liposuction under the local anesthesia to obtain 50 - 150 mL of lipoaspirate. The adipose tissue was processed using the centrifugation techniques in the cell processing room of the hospital following the standard operating procedures. In this procedure, autologous SVF cells were produced without culture. SVF cells were resuspended in the patient's platelet-rich plasma and saline solution and administered into hip and knee joints via intra-articular injection. The study was approved by the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (IRCM-2017-137) and by the Ministry of Health of the Slovak Republic. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Data collection, outcomes assessed, and scales

Patients charts were reviewed, and the following data were collected: age, gender, BMI, pre-existing conditions (stroke, high blood pressure, diabetes, respiratory illness, chronic kidney disease, cardiovascular disease), habits (smoking and alcohol consumption), pain and mobility scales data, arthritis stage. Pain and mobility assessment scales indicated current changes in pain intensity and mobility compared to that before treatment. The assessment scales were administered 7 days, 3, 6, and 12 months after therapy. Pain intensity and mobility changes were graded using the following scale: (-1) worse; (0) no change; (1) improved; (2) much improved.

Statistical analysis

Quantitative data are given as mean ± SEM. Differences between the two groups were quantified using the Mann-Whitney Rank Sum Test. When comparing the differences between several groups, the one-way analysis of variance was used. A significant level of 0.05 was used for all statistical tests. Statistical analysis was performed with the application of SigmaStat 3.5 software.

Results

No complications associated with the processing of adipose tissue or preparation of SVF cells were noticed. Follow-up examination of subjects 7 days, 3, 6, and 12 months after SVF therapy showed that subjects did not experience adverse reactions connected to treatment, further demonstrating the safety of SVF therapy.

Pain and mobility assessments were conducted 7 days, 3, 6, and 12 months after SVF cell therapy. Seven days after treatment, 45.2% of subjects experienced improved pain levels. Three, 6, and 12 months after treatment, the number of subjects with improvement in pain levels reached 75.3%, 84.4%, and 84.9% correspondingly (Table 1). A statistically significant improvement in subjects' pain levels was observed 3, 6, and 12 months compared to 7 days after treatment ($P < 0.05$). No statistically significant difference was observed in the subjects' pain levels between 3-, 6- and 12-month post-therapy time.

Improvement in mobility was in 45.2% of subjects 7 days after therapy. The subjects' number with improvement in mobility reached 75.2% 3 months, 84.4% 6 months, and 84.9% 12 months after treatment (Table 2). Improvement in subjects' mobility was statistically significant 3, 6, and 12 months compared to 7 days after treatment ($P < 0.05$). The difference in subjects' mobility between 3-, 6- and 12-month post-therapy period was not significant.

After adipose tissue-derived SVF cell therapy, the better outcome was observed in subjects with arthritis stage III compared to arthritis stages I, II, and IV. Improvement in pain levels and mobility was observed in 52.6% of subjects with arthritis stage III (Table 3).

Table 1. Changes in Pain Levels After SVF Cell Therapy

Follow-up interval (n of evaluated subjects)	Improvement, n (%)	No change, n (%)	Deterioration, n (%)
7 days (345 subjects)	156 (45.2%)	180 (52.2%)	9 (2.6%)
3 months (339 subjects)	255 (75.3%)	76 (22.4%)	8 (2.3%)
6 months (346 subjects)	292 (84.4%)	46 (13.3%)	8 (2.3%)
12 months (344 subjects)	292 (84.9%)	44 (12.8%)	8 (2.3%)

SVF: stromal vascular fraction.

The number of overweight and obese patients with arthritis stages III - IV and IV were statistically different from the underweight and normal weight having patients ($P < 0.001$). The small number of patients in the smoking and alcohol-consuming groups did not allow to do a statistical correlation of these factors with arthritis stages III - IV and IV. One hundred ninety-five subjects did not experience improvement in pain levels after SVF therapy. Among them, 43 subjects (47.8% from the general number of 90 subjects with pre-existing conditions) had pre-existing conditions. Statistical analysis showed that a high percentage of patients with pre-existing conditions in the group of patients who did not experience improvement in pain levels are not random ($P < 0.001$). Statistical analysis did not reveal the impact of pre-existing conditions on the improvement of mobility after SVF therapy. Because most subjects were overweight (294 subjects, 84.0%), the statistical correlation of SVF treatment efficacy to the BMI was not revealed. There was no statistically significant impact of smoking and alcohol consumption on the efficacy of SVF treatment.

Discussion

In the present study, we reported the safety and efficacy of adipose tissue-derived SVF cell therapy in 350 subjects with hip and knee OA.

OA is a multifactorial disease characterized by changes in the structure and function of the whole joint. Mechanical factors have a central role in this multifactorial process [12-14]. The most commonly used existing treatments for OA (such as nonsteroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, and total joint replacement) are causing adverse events compared with conservative interventions such as exercise, weight loss, braces, and orthotics [15]. To date, there is no cure from OA, and current therapeutic strategies are primarily aimed at reducing pain and improving joint function. Cell-based therapy is a new investigational approach that holds promise to enhance recovery from OA [16]. SVF cell therapy for OA is a rapid, effective, and safe method that significantly improves the quality of life in patients with OA [17]. The cell types found in the SVF include preadipocytes, fibroblasts, adult mesenchymal stem cells, monocytes, macrophages, lymphocytes, as well as pericytes related to angiogenesis [18]. Mesenchymal stem cells can migrate to sites of injury, inhibit pro-inflammatory pathways, and promote tissue repair through the release of anabolic cytokines and direct differentiation into an array of specialized connective tissue cells [19]. Autologous blood products such as platelet-rich plasma act as an adjuvant of surgical treatment and its intra-articular delivery showed beneficial effects for OA treatment [20]. In our study, to maximize the therapeutic effect, SVF cells were combined with platelet-rich plasma and administered via intraarticular injection.

Published clinical studies have mostly analyzed the efficacy of SVF cell therapy on a small number of patients. Also, these studies do not describe the correlation of improved symptoms with the arthritis stage. In the current retrospective chart review study, we analyzed the effect of SVF cell therapy on the improvement of pain levels and mobility in 350 subjects with OA. The results of the study are concordant with several previ-

Table 2. Changes in Mobility After SVF Cell Therapy

Follow-up interval (n of evaluated subjects)	Improvement, n (%)	No change, n (%)	Deterioration, n (%)
7 days (341 subjects)	154 (45.2%)	178 (52.2%)	9 (2.6%)
3 months (342 subjects)	257 (75.2%)	77 (22.6%)	7 (2.2%)
6 months (346 subjects)	292 (84.4%)	26 (13.3%)	8 (2.3%)
12 months (344 subjects)	292 (84.9%)	44 (12.8%)	8 (2.3%)

SVF: stromal vascular fraction.

Table 3. Correlation of Measures of Treatment Efficacy With the Arthritis Stage

Measures of treatment efficacy	Arthritis classification (n of evaluated subjects)		
	I, I - II, II, II - III (216)	III (57)	III - IV, IV (77)
Improvement in pain, n (%)	86 (39.8%)	30 (52.6%)	19 (24.7%)
Improvement in mobility, n (%)	81 (37.5%)	30 (52.6%)	16 (20.7%)

ous clinical studies [20-22]. Furthermore, for the first time, the results of the current study indicate that autologous SVF cell therapy is more effective in subjects with arthritis stage III. The limitations of this study are retrospective nature and the lack of a placebo group. The efficacy of SVF cell therapy for OA needs to be confirmed by further controlled long-termed studies.

In conclusion, our study of 350 subjects with hip and knee OA demonstrated a significant improvement in pain levels and mobility 3, 6, and 12 months compared to 7 days after autologous SVF cell therapy. Cell therapy demonstrated a strong safety profile with no severe adverse events or complications reported. Subjects with arthritis stage III showed better outcomes after SVF cell therapy, compared to arthritis stages I, II, and IV. Autologous SVF therapy is a rapid, effective, and safe method that significantly improves the quality of life in patients with OA.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Informed Consent

Written informed consents were obtained from all participants.

Author Contributions

BM and MH contributed to the conception, design of the study and the acquisition of data. AS and RV provided critical revision of the manuscript. DS, MO, RM, and MM analyzed and interpreted the data, obtained the ethical approval, and drafted the manuscript. All authors read and approved the final version of the manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

References

1. Chen D, Shen J, Zhao W, Wang T, Han L, Hamilton JL, Im HJ. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Res. 2017;5:16044.
2. Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, Zheng MH. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. Arthritis Res Ther. 2013;15(6):223.
3. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis. 2013;5(2):77-94.
4. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1145-1153.
5. Rayahin JE, Chmiel JS, Hayes KW, Almagor O, Belisle L, Chang AH, Moisio K, et al. Factors associated with pain experience outcome in knee osteoarthritis. Arthritis Care Res (Hoboken). 2014;66(12):1828-1835.
6. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, Pepys MB. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum. 1997;40(4):723-727.
7. Anandacoomarasamy A, March L. Current evidence for osteoarthritis treatments. Ther Adv Musculoskelet Dis. 2010;2(1):17-28.
8. Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis. 2005;64(9):1263-1267.
9. Wang CL, Li, Wang CD, Xiao F, Zhu JF, Shen C, Zuo B, et al. Anti-inflammatory and anti-osteoarthritis effects of tectorigenin. Biol Open. 2017;6(8):1130-1136.
10. Darinskas A, Paskevicius M, Apanavicius G, Vilkevicius G, Labanauskas L, Ichim TE, Rimdeika R. Stromal vascular fraction cells for the treatment of critical limb ischemia: a pilot study. J Transl Med. 2017;15(1):143.
11. Michalek J, Moster R, Lukac L, Proefrock K, Petrasovic M, Rybar J, Chaloupka A, et al. Stromal vascular fraction cells of adipose and connective tissue in patients with osteoarthritis: a case control prospective multi-centric non-randomized study. Global Surg. 2017;3(3):1-9.
12. de Rezende MU, de Campos GC, Pailo AF. Current concepts in osteoarthritis. Acta Ortop Bras. 2013;21(2):120-122.
13. Hunter DJ, Felson DT. Osteoarthritis. BMJ. 2006;332(7542):639-642.
14. Man GS, Mologhianu G. Osteoarthritis pathogenesis - a complex process that involves the entire joint. J Med Life. 2014;7(1):37-41.
15. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145-1155.
16. Diekman BO, Wu CL, Louer CR, Furman BD, Huebner JL, Kraus VB, Olson SA, et al. Intra-articular delivery of purified mesenchymal stem cells from C57BL/6 or MRL/MpJ superhealer mice prevents posttraumatic arthritis.

Cell Transplant. 2013;22(8):1395-1408.
17. Michalek J, Vrablikova A, Darinskas A, Lukac L, Prucha J, Skopalik J, Travnik J, et al. Stromal vascular fraction cell therapy for osteoarthritis in elderly: Multicenter case-control study. J Clin Orthop Trauma. 2019;10(1):76-80.
18. Miana VV, Gonzalez EAP. Adipose tissue stem cells in regenerative medicine. Ecancermedicalscience. 2018;12:822.
19. Freitag J, Bates D, Boyd R, Shah K, Barnard A, Huguenin L, Tenen A. Mesenchymal stem cell therapy in the treatment of osteoarthritis: reparative pathways, safety and efficacy - a review. BMC Musculoskelet Disord. 2016;17:230.
20. Mehranfar S, Abdi Rad I, Mostafav E, Akbarzadeh A. The use of stromal vascular fraction (SVF), platelet-rich plasma (PRP) and stem cells in the treatment of osteoarthritis: an overview of clinical trials. Artif Cells Nanomed Biotechnol. 2019;47(1):882-890.
21. Hurley ET, Yasui Y, Gianakos AL, Seow D, Shimozono Y, Kerkhoffs G, Kennedy JG. Limited evidence for adipose-derived stem cell therapy on the treatment of osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2018;26(11):3499-3507.
22. Bansal H, Comella K, Leon J, Verma P, Agrawal D, Koka P, Ichim T. Intra-articular injection in the knee of adipose derived stromal cells (stromal vascular fraction) and platelet rich plasma for osteoarthritis. J Transl Med. 2017;15(1):141.