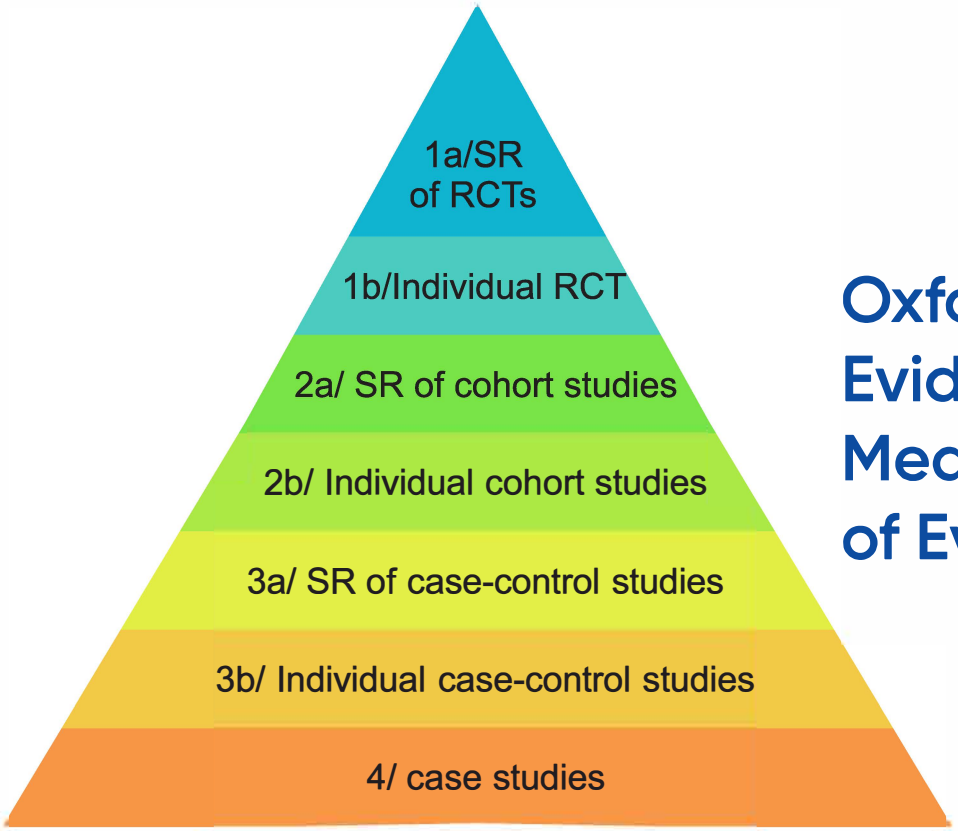
#Evidence based
SAHAJ THERAPY
Innovative Surgical Procedures

Global Level I and II Evidence of Stromal Vascular Fraction in treatment of Osteoarthritis

SUMMARY OF LEVEL OF EVIDENCE ADIPOSE DERIVED CELLULAR FRACTION (SVF) IN OSTEOARTHRITIS



SR: Systematic reviews | RCT: Randomized controlled trial

Oxford Centre for Evidence-Based Medicine: Levels of Evidence

Autologous Adipose-Derived Cellular fraction(SVF) has the level I & II Evidence to use in the treatment of Osteoarthritis & has Recommendation A

CONTENT

Sr.No.	Level of Evidence	Title
1.	1a	Yang Y et al., Effect of intra-knee injection of autologous adipose stem cells or mesenchymal vascular components on short-term outcomes in patients with knee osteoarthritis: an updated meta-analysis of randomized controlled trials PMID: 37563715 Link: https://pubmed.ncbi.nlm.nih.gov/37563715/#:~:text=Conclusions%3A%20In%20conclusion%2C%20in%20osteoarthritis,cartilage%20status%20were%20also%20shown.
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3.	1a	Graza JR et al., Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis: A Double-Blinded Prospective Randomized Controlled Clinical Trial. Am J Sports Med. 2020 Mar;48(3):588–98., PMID: 32109160 Link: https://pubmed.ncbi.nlm.nih.gov/32109160
4.	1a	Yubo M et al., Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: A meta-analysis, PLoS One. 2017 Apr 27;12(4):e0175449. doi: 10.1371/ journal.pone.0175449, PMID: 28448518; Link: https://www.ncbi.nlm.nih.gov/pubmed/28448518
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8.	2a	Bolia et al., Clinical Efficacy of Bone Marrow Aspirate Concentrate Versus Stromal Vascular Fraction Injection in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. , Am J Sports Med. 2022 Apr;50(5):1451-1461. doi: 10.1177/03635465211014500. Epub 2021 Jun 8. PMID: 34102078 Link: https://pubmed.ncbi.nlm.nih.gov/34102078/

CONTENT

Sr.No.	Level of Evidence	Title
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10.	2b	Anil U et al., The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials, Knee . 2021 Oct;32:173-182. doi: 10.1016/j.knee.2021.08.008. Epub 2021 Sep 6. PMID: 34500430 Link: https://pubmed.ncbi.nlm.nih.gov/34500430/
11.	2b	Muthu S et al., Is Culture Expansion Necessary in Autologous Mesenchymal Stromal Cell Therapy to Obtain Superior Results in the Management of Knee Osteoarthritis?—Meta-Analysis of Randomized Controlled Trials. doi: 10.3390/bioengineering8120220 PMID: 34940373 Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8698637/pdf/bioengineering-08-00220.pdf
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Arthritis Research & Therapy

REVIEW

Open Access

Effect of intra-knee injection of autologous adipose stem cells or mesenchymal vascular components on short-term outcomes in patients with knee osteoarthritis: an updated meta-analysis of randomized controlled trials

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Abstract

Objective Assess the efficacy of single and multiple intra-articular injections of autologous adipose-derived stem cells (ASCs) and adipose-derived stromal vascular fraction (ADSVF) for the treatment of knee osteoarthritis (OA).

Methods We conducted a thorough and systematic search of several databases, including PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov, to identify relevant studies. The included studies were randomized controlled trials (RCTs) that involved single or multiple intra-articular injections of autologous ASCs or ADSVF for the treatment of patients with knee osteoarthritis, without any additional treatment, and compared to either placebo or hyaluronic acid.

Results A total of seven RCTs were analyzed in this study. The results of the meta-analysis show that compared to the control group, both single and multiple intra-articular injections of ASCs or ADSVF demonstrated superior pain relief in the short term ($Z=3.10$; $P<0.0001$ and $Z=4.66$; $P<0.00001$) and significantly improved function ($Z=2.61$; $P<0.009$ and $Z=2.80$; $P=0.005$). Furthermore, MRI assessment showed a significant improvement in cartilage condition compared to the control group. ($Z=8.14$; $P<0.000001$ and $Z=5.58$; $P<0.00001$).

Conclusions In conclusion, in osteoarthritis of the knee, single or multiple intra-articular injections of autologous ASCs or ADSVF have shown significant pain improvement and safety in the short term in the absence of adjuvant therapy. Significant improvements in cartilage status were also shown. A larger sample size of randomized controlled trials is needed for direct comparison of the difference in effect between single and multiple injections.

Keywords Adipose-derived stem cells, Knee osteoarthritis, Stromal vascular fraction

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META-ANALYSIS

Comparative effectiveness of adipose-derived mesenchymal stromal cells in the management of knee osteoarthritis: A meta-analysis

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Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis

A Double-Blinded Prospective Randomized Controlled Clinical Trial

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Investigation performed at the Rothman Orthopaedic Institute, Philadelphia, Pennsylvania, USA; Cooper University Health Care, Camden, New Jersey, USA; and Texas Plastic Surgery, San Antonio, Texas, USA

Background: Currently, there are limited nonoperative treatment options available for knee osteoarthritis (OA). Cell-based therapies have emerged as promising treatments for knee OA. Autologous stromal vascular fraction (SVF) has been identified as an efficient medium for intra-articular administration of progenitor cells and mesenchymal stem cells derived from adipose tissue.

Hypothesis: Patients receiving intra-articular SVF would show significantly greater improvement than patients receiving placebo injections, and this improvement would be dose dependent.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: This was a multisite prospective double-blinded randomized placebo-controlled clinical trial. Adult patients with symptomatic knee OA were eligible. Thirty-nine patients were randomized to high-dose SVF, low-dose SVF, or placebo (1:1:1). SVF was obtained via liposuction, processed to create the cellular implant, and injected during the same clinical visit. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and magnetic resonance images were obtained preoperatively and at 6 and 12 months after injection. The Wilcoxon rank sum nonparametric test was utilized to assess statistical significance, and the Hodges-Lehmann location shift was used to assess superiority.

Results: The median percentage change in WOMAC score at 6 months after injection for the high-dose, low-dose, and placebo groups was 83.9%, 51.5%, and 25.0%, respectively. The high- and low-dose groups had statistically significant changes in WOMAC scores when compared with the placebo group (high dose, $P = .04$; low dose, $P = .02$). The improvements were dose dependent. The median percentage change in WOMAC score from baseline to 1 year after injection for the high-dose, low-dose, and placebo groups was 89.5%, 68.2%, and 0%, respectively. The high- and low-dose groups displayed a greater percentage change at 12 months when compared with the placebo group (high dose, $P = .006$; low dose, $P = .009$). Magnetic resonance image review revealed no changes in cartilage thickness after treatment. No serious adverse events were reported.

Conclusion: Intra-articular SVF injections can significantly decrease knee OA symptoms and pain for at least 12 months. The efficacy and safety demonstrated in this placebo-controlled trial support its implementation as a treatment option for symptomatic knee OA.

Registration: NCT02726945 (ClinicalTrials.gov identifier)

Keywords: progenitor cells; stem cells; osteoarthritis; cartilage; knee; stromal vascular fraction; adipose

Knee osteoarthritis (OA) is highly prevalent among older adults in developed countries and is a significant cause of chronic pain and disability.[24] The definitive surgical treatment for knee OA is total knee arthroplasty, a major surgical procedure. Given the complications and intense rehabilitation process associated with total knee arthroplasty, physicians

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PLOS ONE

RESEARCH ARTICLE

Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: A meta-analysis

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Purpose

The aim of this study was to evaluate the therapeutic efficacy and safety of mesenchymal stem cells (MSCs) for the treatment of patients with knee osteoarthritis (OA).

Materials

We performed a meta-analysis of relevant published clinical studies. An electronic search was conducted for randomized controlled trials (RCTs) of MSC-based therapy in knee OA. The visual analogue scale (VAS), International Knee Documentation Committee (IKDC) form, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne algofunctional indices (Lequesne), Lysholm knee scale (Lysholm), Tegner activity scale (Tegner) and adverse events (AEs) were evaluated.

Results

Eleven eligible trials with 582 knee OA patients were included in the present meta-analysis. We demonstrated that MSC treatment could significantly decrease VAS and increase IKDC scoresafter a 24-month follow-up compared with controls ($P<0.05$). MSC therapy also showed significant decreases in WOMAC and Lequesne scores after the 12-month follow-up ($P<0.01$). Analysis of Lysholm (24-month) and Tegner (12- and 24-month) scores also demonstrated favorable results for MSC treatment ($P<0.05$).

Conclusion

Overall, MSC transplantation treatment was shown to be safe and has great potential as an efficacious clinical therapy for patients with knee OA.

Intra-articular Injection of Autologous Adipose-Derived Stem Cells or Stromal Vascular Fractions: Are They Effective for Patients With Knee Osteoarthritis? A Systematic Review With Meta-analysis of Randomized Controlled Trials

Abstract

Background: Intra-articular injection of adipose-derived stem cells, which are divided into adipose-derived mesenchymal stem cells (ASCs) and adipose-derived stromal vascular fractions (ADSVFs), has been reported to be a viable treatment modality for knee osteoarthritis (OA); however, its efficacy remains limited.

Purpose: This study aimed to provide comprehensive information about the efficacy and safety of intra-articular injections of autologous ASCs and ADSVFs without adjuvant treatment in patients with knee OA.

Study design: Meta-analysis; Level of evidence, 1.

Methods: A systematic search of the MEDLINE, Embase, Web of Science, and Cochrane Library databases was performed to identify randomized controlled trials (RCTs) that evaluated the efficacy and safety of intra-articular injections of autologous ASCs or ADSVFs without adjuvant treatments compared with placebo or hyaluronic acid in patients with knee OA. Clinically, the 100-mm visual analog scale for pain relief and the Western Ontario and McMaster Universities Osteoarthritis Index for functional improvement were implemented. Radiologically, cartilage status was assessed using magnetic resonance imaging (MRI). Procedure-related knee pain, swelling, and adverse events (AEs) were evaluated for safety. Additionally, we performed subgroup analyses comparing ASCs versus ADSVFs. Methodological quality was assessed using the modified Coleman Methodology Score (mCMS).

Results: A total of 5 RCTs were included in this study. Based on the meta-analysis, ASCs or ADSVFs showed significantly better pain relief at 6 months ($Z = 7.62$; $P < .0001$) and 12 months ($Z = 7.21$; $P < .0001$) and functional improvement at 6 months ($Z = 4.13$; $P < .0001$) and 12 months ($Z = 3.79$; $P = .0002$), without a difference in procedure-related knee pain or swelling compared with controls. Although a meta-analysis with regard to cartilage improvements was not performed owing to heterogeneous MRI assessment, 3 studies

cells

MDPI

Systematic Review

Meta-Analysis of Adipose Tissue Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis

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Abstract: Osteoarthritis (OA) is a degenerative disorder associated with cartilage loss and is a leading cause of disability around the world. In old age, the capacity of cartilage to regenerate is diminished. With an aging population, the burden of OA is set to rise. Currently, there is no definitive treatment for OA. However, cell-based therapies derived from adipose tissue are promising. A PRISMA systematic review was conducted employing four databases (MEDLINE, EMBASE, Cochrane, Web of Science) to identify all clinical studies that utilized adipose tissue derived mesenchymal stem cells (AMSCs) or stromal vascular fraction (SVF) for the treatment of knee OA. Eighteen studies were included, which met the inclusion criteria. Meta-analyses were conducted on fourteen of these studies, which all documented WOMAC scores after the administration of AMSCs. Pooled analysis revealed that cell-based treatments definitively improve WOMAC scores, post treatment. These improvements increased with time. The studies in this meta-analysis have established the safety and efficacy of both AMSC therapy and SVF therapy for knee OA in old adults and show that they reduce pain and improve knee function in symptomatic knee OA suggesting that they may be effective therapies to improve mobility in an aging population.

Keywords: osteoarthritis; degenerative changes; knee; adipose tissue; mesenchymal stem cells; stromal vascular factor

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1. Introduction

1.1. The Burden of Osteoarthritis

Osteoarthritis (OA) is a progressive degenerative joint disorder associated with aging. It is a leading cause of disability around the world. In 2019, the Global Burden of Disease Study reported that musculoskeletal disorders account for over 5% of worldwide disability adjusted life years (DALY) [1]. The World Health Organization (WHO) estimate that approximately 10% of all men and 18% of all women aged over 60 have OA [2]. Out of these individuals, they estimate that 80% have limitations in movement and 25% cannot perform major daily activities of life [2].

In addition to physical symptoms, there is evidence to suggest that OA is associated with mental health problems as well. A longitudinal cohort study, conducted by the Osteoarthritis Initiative, found that there was a greater risk of developing depressive symptoms in patients with hip or knee OA than those without [3]. Another observational study found that OA was associated with 1.27 times increase odds of suicidal ideation [4]. There is also evidence that OA increases the risk for myocardial infarction, with one meta-analysis reporting a 1.31 times increased risk for myocardial infarction [5].

These, among many other studies have highlighted the burden OA has on the individual. In addition to this, OA carries significant economic burden on societies across the world. When adjusted for age, sufferers are shown to be at high risk of sick leave and

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ORIGINAL PAPER

Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial

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Abstract

Objective The purpose of this study was to compare the clinical and radiological efficacy of autologous adipose-derived stromal vascular fraction (SVF) versus hyaluronic acid in patients with bilateral knee osteoarthritis.

Methods Sixteen patients with bilateral symptomatic knee osteoarthritis (K-L grade II to III; initial pain evaluated at four or greater on a ten-point VAS score) were enrolled in this study, which were randomized into two groups. Each patient received 4-ml autologous adipose-derived SVF treatment (group test, $n=16$) in one side of knee joints and a single dose of 4-ml hyaluronic acid treatment (group control, $n=16$) in the other side. The clinical evaluations were performed pre-operatively and post-operatively at one month, three months, six months, and 12-months follow-up visit, using the ten-point visual analog scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the knee range of motion (ROM). The whole-organ assessment of the knees was performed with whole-organ magnetic resonance imaging score (WORMS) based on MRI at baseline, six months and 12-months follow-up. The articular repair tissue was assessed quantitatively and qualitatively by magnetic resonance observation of cartilage repair tissue (MOCART) score based on follow-up MRI at six months and 12 months.

Results No significant baseline differences were found between two groups. Safety was confirmed with no severe adverse events observed during 12-months follow-up. The SVF-treated knees showed significantly improvement in the mean VAS, WOMAC scores, and ROM at 12-months follow-up visit compared with the baseline. In contrast, the mean VAS, WOMAC scores, and ROM of the control group became even worse but not significant from baseline to the last follow-up visit. WORMS and MOCART measurements revealed a significant improvement of articular cartilage repair in SVF-treated knees compared with hyaluronic acid-treated knees.

Conclusion The results of this study improve function, and repair cartilage defects in patients with knee osteoarthritis.

Keywords Osteoarthritis · Adipose-derived stromal vascular fractions · Intra-articular injection · Articular cartilage

Introduction

Osteoarthritis (OA) results from degeneration of joint cartilage and subchondral bone and is one of the leading causes of joint pain and disability [1, 2]. The knee is the most frequently involved weight-bearing joint [3]. As a Bwear to tear^ disease, OA is associated with significant morbidity and healthcare expenditure [4, 5]. Many treatment modalities for knee OA such as lifestyle modification, pharmaceutical, and surgery have been advocated [6]. Intra-articular injection of hyaluronic acid (HA) is effective in improving symptoms and slowing down the progression of OA [7, 8], but fail to reverse or repair the degenerative cartilage or bone [9].

Regenerative cell therapies for knee OA such as adipose-derived stromal vascular fraction (SVF) have been recently investigated [10–14]. Adipose-derived stromal cells (ADSC) included in SVF have the potential of differentiating into adipogenic, osteogenic, chondrogenic, and other mesenchymal lineages, and have been widely applied to knee OA

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Clinical Efficacy of Bone Marrow Aspirate Concentrate Versus Stromal Vascular Fraction Injection in Patients With Knee Osteoarthritis

A Systematic Review and Meta-analysis

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Background: Knee injection using either bone marrow aspirate concentrate (BMAC) or stromal vascular fraction (SVF) from adipose tissue has been shown to result in symptomatic improvement in patients with knee osteoarthritis (OA). It is still unclear whether one of these therapies is superior over the other.

Purpose: To systematically report the clinical studies evaluating BMAC and SVF in the treatment of knee OA and to compare the clinical efficacy of these 2 injection therapies.

Study Design: Meta-analysis; Level of evidence, 4.

Methods: This meta-analysis was performed per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Studies were included if they reported the clinical outcomes after a single BMAC or SVF injection in the knee joint of patients with OA. Studies evaluating preparations of culture-expanded stem cells were excluded. A random effects model was used; the clinical efficacy of BMAC or SVF injection was assessed using the standardized mean difference (SMD) and compared. Visual analog scale (VAS) scores for pain and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) knee index were the primary outcomes. The level of statistical significance was set at $P < .05$.

Results: Ten studies and 472 patients with knee OA who received either BMAC (233 patients) or SVF (239 patients) were included. Patients who received an injection had improved VAS outcomes (mean ± SD): from 5.8 ± 1.3 to 2.6 ± 17 for BMAC and from 6.4 ± 1.4 to 3.4 ± 0.5 for SVF. They also experienced significantly reduced pain (SMD [VAS], 2.6 for BMAC and 3.4 for SVF) and improved function (SMD [WOMAC], 1.4 for BMAC and 1.2 for SVF). However, the SVF injection had a significantly greater effect on pain reduction than did the BMAC injection ($P < .0001$). Based on WOMAC, the clinical effect of BMAC versus SVF knee injection in patients with knee OA was equivalent ($P = .626$). Results were limited by the presence of publication bias as well as variability in the preparation methods utilized in the BMAC and SVF injection protocols. Complications were reported in 50% of the BMAC studies (knee stiffness, persistent knee swelling) and 67% of the SVF studies (knee swelling, knee pain, positive SVF cultures without symptoms of infection, and bleeding at the abdominal harvest site).

Conclusion: A single BMAC or SVF injection into the knee joint of patients with OA resulted in symptomatic improvement at short-term follow-up. However, SVF seemed to be more effective than did BMAC in the reduction of knee pain. There was significant variation in the BMAC and SVF injection preparation techniques used across the studies and a lack of stratification of outcomes based on the radiologic classification of OA. Therefore, these results should be taken with caution.

Keywords: bone marrow aspirate concentrate; BMAC; stromal vascular function; SVF; outcomes; knee; osteoarthritis

Osteoarthritis (OA) is a leading cause of disability and health care costs worldwide, with an estimated 27 million individuals having clinical OA of some joint.[13,32] When direct and indirect expenditures are combined, the total annual average cost for OA and associated disorders is

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Does the Source of Mesenchymal Stem Cell Have an Effect in the Management of Osteoarthritis of the Knee? Meta-Analysis of Randomized Controlled Trials

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Abstract

Study Design. Meta-analysis. *Objectives*. To compare the efficacy and safety of bone marrow(BM)–derived mesenchymal stem cell(MSCs) and adipose-derived(AD) MSCs in the management of osteoarthritis of knee from randomized controlled trials(RCTs) available in the literature. *Materials and Methods*. We conducted electronic database search from PubMed, Embase, and Cochrane Library till May 2020 for RCTs analyzing the efficacy and safety of MSCs in management of osteoarthritis of knee. Visual Analog Score(VAS) for Pain, Western Ontario McMaster Universities Osteoarthritis Index(WOMAC), Lysholm Knee Scale(Lysholm), Whole-Organ Magnetic Resonance Imaging Score(WORMS), Knee Osteoarthritis Outcome Score(KOOS), and adverse events were the outcomes analyzed. Analysis was performed in R platform using OpenMeta[Analyst] software. *Results*. Nineteen studies involving 811 patients were included for analysis. None of the studies compared the source of MSCs for osteoarthritis of knee and results were obtained by pooled data analysis of both sources. At 6 months, AD-MSCs showed significantly better VAS($P<0.001$,$P=0.069$) and WOMAC($P=0.134$,$P=0.441$) improvement than BM-MSCs, respectively, compared to controls. At 1 year, AD-MSCs outperformed BM-MSCs compared to their control in measures like WOMAC($P=0.007$,$P=0.150$), KOOS($P<0.001$; $P=0.658$), and WORMS($P<0.001$,$P=0.041$), respectively. Similarly at 24 months, AD-MSCs showed significantly better Lysholm score($P=0.037$) than BM-MSCs($P=0.807$) although VAS improvement was better with BM-MSCs at 24 months ($P<0.001$). There were no significant adverse events with either of the MSCs compared to their controls. *Conclusion*. Our analysis establishes the efficacy, safety, and superiority of AD-MSC transplantation, compared to BM-MSC, in the management of osteoarthritis of knee from available literature. Further RCTs are needed to evaluate them together with standardized doses.

Keywords

mesenchymal stem cells, bone marrow–derived mesenchymal stem cells, adipose-derived mesenchymal stem cells, cartilage regeneration, knee osteoarthritis, meta-analysis

Introduction

Osteoarthritis (OA) of the knee is the most common degenerative joint disorder among adults that poses major morbidity affecting the functional quality of everyday life. OA knee results from an imbalance between the rate of degeneration and repair due to limited intrinsic potential for cartilage to heal.[1] It is characterized by the gradual wear of hyaline cartilage resulting in the formation of bony spurs at the margins of the joints and development of subchondral sclerosis and cysts.[2] Hence, cartilage has been targeted to regenerate and rejuvenate with the help of orthobiologics. These bioactive molecules bridge a gap between conservative and surgical management in the treatment of osteoarthritis knees.

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Review

The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: Osteoarthritis (OA) is a debilitating joint disease characterized by progressive loss of articular cartilage. Intra-articular injections are a mainstay of nonoperative treatment, however, there is controversy as to the optimal injectable for these patients. The purpose of the current study is to perform a network meta-analysis of the randomized control trials in the literature to ascertain whether there is a superior injectable nonoperative treatment for knee OA.

Methods: The literature search was conducted based on the PRISMA guidelines. Randomized control trials (RCTs) evaluating intra-articular injectables in osteoarthritic knees were included. Data was extracted and Visual Analogue Scale (VAS) scores and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, where available were analyzed at 1, 3, 6 and 12 months. Clinical outcomes were compared using a frequentist approach to network meta-analysis, with statistical analysis performed using R. The treatment options were ranked using the P-Score.

Results: Seventy-nine RCTs with 8761 patients were included in this review. Intra-articular injectables evaluated included autologous conditioned serum (ACS), bone marrow aspirate concentrate (BMAC), botulinum toxin, corticosteroids (CS), hyaluronic acid (HA), mesenchymal stem cells (MSC), ozone, saline placebo, platelet-rich plasma (PRP), plasma rich in growth factor (PRGF), and stromal vascular fraction (SVF). At 4–6 weeks and 3 months of follow-up, the treatment with the highest P-Score for WOMAC score was high molecular weight (HMW) HA + CS [P-Score = 0.9500 and 8503, respectively]. At 6-months follow-up, the treatment with the highest P-Score for WOMAC score was PRP [P-Score = 0.7676]. At all post-injection time points, the treatment with the highest P-Score for VAS score [P-Score Range = 0.8631–9927] and Womac score at 12 Months [P-Score = 0.9044] was SVF.

Conclusions: The current evidence shows that SVF injections result in the greatest improvement in pain and functional outcomes in patients with knee OA at up to 1 year of follow-up.

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Review

Is Culture Expansion Necessary in Autologous Mesenchymal Stromal Cell Therapy to Obtain Superior Results in the Management of Knee Osteoarthritis?—Meta-Analysis of Randomized Controlled Trials

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Abstract: Study Design: Meta-analysis. **Objectives:** We aimed to analyze the impact of cultured expansion of autologous mesenchymal stromal cells (MSCs) in the management of osteoarthritis of the knee from randomized controlled trials (RCTs) available in the literature. **Materials and Methods:** We conducted independent and duplicate electronic database searches including PubMed, Embase, Web of Science, and Cochrane Library until August 2021 for RCTs analyzing the efficacy and safety of culture-expanded compared to non-cultured autologous MSCs in the management of knee osteoarthritis. The Visual Analog Score (VAS) for pain, Western Ontario McMaster University's Osteoarthritis Index (WOMAC), Lysholm score, Knee Osteoarthritis Outcome Score (KOOS), and adverse events were the analyzed outcomes. Analysis was performed in R-platform using OpenMeta [Analyst] software. **Results:** Overall, 17 studies involving 767 patients were included for analysis. None of the studies made a direct comparison of the culture expanded and non-cultured MSCs, hence we pooled the results of all the included studies of non-cultured and cultured types of MSC sources and made a comparative analysis of the outcomes. At six months, culture expanded MSCs showed significantly better improvement ($p < 0.001$) in VAS outcome. Uncultured MSCs, on the other hand, demonstrated significant VAS improvement in the long term (12 months) in VAS ($p < 0.001$), WOMAC ($p = 0.025$), KOOS score ($p = 0.016$) where cultured-expanded MSCs failed to demonstrate a significant change. Culturing of MSCs did not significantly increase the complications noted ($p = 0.485$). On sub-group analysis, adipose-derived uncultured MSCs outperformed culture-expanded MSCs at both short term (six months) and long term (12 months) in functional outcome parameters such as WOMAC ($p < 0.001$, $p = 0.025$), Lysholm ($p < 0.006$), and KOOS ($p < 0.003$) scores, respectively, compared to their controls. **Conclusions:** We identified a void in literature evaluating the impact of

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What is the clinically significant ideal mesenchymal stromal cell count in the management of osteoarthritis of the knee? – Meta-analysis of randomized controlled trials

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ABSTRACT

Study design: Meta-analysis.
Objectives: We aim to identify the clinically significant ideal Mesenchymal Stem Cell (MSC) count in the management of osteoarthritis of knee from Randomized Controlled Trials (RCTs) available in the literature.
Materials and methods: We conducted independent and duplicate electronic database searches including PubMed, Embase, Web of Science, and Cochrane Library till August 2021 for RCTs conducted in the management of knee osteoarthritis using MSC therapy specifying the quantity of MSCs delivered. We categorized the studies based on the MSC count utilized in them into four groups namely $<1 \times 10^7$ MSCs (Group I), 1-5x10^7 MSCs (Group II), 5-10 $\times$ 10^7 MSCs (Group III), and $>10 \times 10^7$ MSCs (Group IV). Visual Analog Score (VAS) for Pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, Knee Osteoarthritis Outcome Score (KOOS), and adverse events were the outcomes analyzed. Analysis was performed in R-platform using OpenMeta [Analyst] software.
Results: 14 studies involving 564 patients were included for analysis. We noted incremental decrease in the VAS with increasing dosage of MSCs at 12 months [Group I,WMD = 2.641(p = 0.854); Group II, WMD = −4.853(p = 0.379); Group III, WMD = −12.154 (p = 0.316); Group IV, WMD = −15.935(p = 0.116)], and 24 months [Group I,WMD = −6(p = 0.001); Group II, WMD = −15(p = 0.001); Group IV, WMD = −20(p = 0.001)]. We also noted incremental improvement in the WOMAC, KOOS with increasing dosage of MSCs at 12 months [Group I, WMD = 7(p = 0.001); Group II, WMD = 28(p = 0.001); Group IV, WMD = 30(p = 0.001)] and [Group II, WMD = −2.562(p = 0.676); Group III, WMD = 7.670(p = 0.099); Group IV, WMD = 13.475(p = 0.261)] respectively. However, we noted significant reduction in the Lysholm score in Group IV, compared to the others at 12 months (WMD = −12.5, 95%CI[-25.883,0.883]) and 24 months (WMD = −6.6, 95%CI[-23.596,10.396]). We did not find any significant increase in the adverse events with incremental dosage of MSCs in any of the groups compared.
Conclusion: Compared to the four dosage groups of MSCs analyzed, Group III showed consistent significant improvement in pain and functional outcomes analyzed compared to the other groups. Hence, we recommend a cell volume of 5-10 $\times$ 10^7 cells to be delivered to the target site to obtain superior benefits out of the procedure. However, we urge future trials of sufficient quality to validate our findings to arrive at a consensus on the ideal count of MSCs to be delivered in the cellular therapy for knee osteoarthritis.

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Time- and Kellgren–Lawrence Grade-Dependent Changes in Intra-Articularly Transplanted Stromal Vascular Fraction in Osteoarthritic Patients

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Abstract: Knee osteoarthritis (OA) is one of the most prevalent disorders in elderly population. Among various therapeutic alternatives, we employed stromal vascular fraction (SVF), a heterogeneous cell population, to regenerate damaged knee cartilage. OA patients were classified on the basis of age, gender, body mass index (BMI), and x-ray-derived Kellgren–Lawrence (KL) grade. They were treated with SVF and followed-up for 24 months. Visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index were used to determine treatment efficacy. Cartilage healing was assessed using the MRI-based Outerbridge score (OS) and evaluation of bone marrow edema (BME) lesions, while a placebo group was used as a control. Time- and KL-dependent changes were also monitored. We observed a decreasing trend in VAS score and WOMAC index in the SVF-treated group up to 24 months, as compared with the placebo group. Besides, a significant increase and decrease in Lysholm and OS, respectively, were observed in the treatment group. Compared with the values before treatment, the greatly reduced WOMAC scores of KL3 than KL2 groups at 24 months, indicate more improvement in the KL3 group. Highly decreased BME in the treated group was also noted. In conclusion, the SVF therapy is effective in the recovery of OA patients of KL3 grade in 24 months.

Keywords: knee osteoarthritis (OA); KL grade; stromal vascular fraction (SVF); MRI; WOMAC; VAS; OS; BME

1. Introduction

Knee osteoarthritis (OA) is one of the most common progressive joint disorders, especially among elderly population in the United States and other developed countries [1–3]. Cartilage devolution, stiffness, loss of joint function, bone loss/rearrangement, and pain are primary

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Comparative Clinical Observation of Arthroscopic Microfracture in the Presence and Absence of a Stromal Vascular Fraction Injection for Osteoarthritis

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Key Words. Osteoarthritis • Stromal vascular fraction • Platelet-rich plasma • Arthroscopic microfracture

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ABSTRACT

Osteoarthritis (OA) is a degenerative cartilage disease that is characterized by a local inflammatory reaction. Consequently, many studies have been performed to identify suitable prevention and treatment interventions. In recent years, both arthroscopic microfracture (AM) and stem cell therapy have been used clinically to treat OA. This study aimed to evaluate the clinical effects of AM in the presence and absence of a stromal vascular fraction (SVF) injection in the management of patients with OA. Thirty patients with grade 2 or 3 (Lawrence scale) OA of the knee participated in this study. Placebo group patients (n = 15) received AM alone; treatment group patients (n = 15) received AM and an adipose tissue-derived SVF injection. The SVF was suspended in platelet-rich plasma (PRP) before injection into the joint. Patient groups were monitored and scored with the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Lysholm, Visual Analog Pain Scale (VAS), and modified Outerbridge classifications before treatment and at 6, 12, and 18 months post-treatment. Bone marrow edema was also assessed at these time points. Patients were evaluated for knee activity (joint motion amplitude) and adverse effects relating to surgery and stem cell injection. Treatment efficacy was significantly different between placebo and treatment groups. All treatment group patients had significantly reduced pain and WOMAC scores, and increased Lysholm and VAS scores compared with the placebo group. These findings suggest that the SVF/PRP injection efficiently improved OA for 18 months after treatment. This study will be continuously monitored for additional 24 months. STEM CELLS TRANSLATIONAL MEDICINE *2017;6:187–195*

SIGNIFICANCE STATEMENT

Arthroscopic microfracture (AM) and stem cell therapy have been used clinically to treat osteoarthritis (OA). This study evaluated the clinical effects of AM in the presence (treatment group) and absence (placebo group) of a stromal vascular fraction (SVF) injection in the knee for OA. The SVF was suspended in platelet-rich plasma (PRP) before injection. Treatment efficacy differed significantly between placebo and treatment groups. All treatment group patients had significantly improved pain and arthritis index scores compared with the placebo group. These findings suggest that the SVF/PRP injection efficiently improved OA after 18 months. This study will be continuously monitored for 24 months.

INTRODUCTION

Osteoarthritis (OA) is a chronic progressive disease characterized by cartilage degeneration, osteophyte formation, bone reorganization, and loss of joint function [1]. OA is the most frequent cause of disability among adults in the United States, and it occurred in >10% of the U.S. adult population in 2009. In 2009, 905,000 knee and hip replacements were carried out in OA patients, costing approximately $42.3 billion in total.

At present, OA is mainly treated with pharmaceuticals [2, 3], hyaluronic acid [4], and neridronate [5, 6]. However, these treatments only reduce symptoms and pain or control the inflammation process [7–9]; none of these drugs actually prevents the progression of OA [10, 11].

Arthroscopic microfracture (AM) has recently gained popularity as a therapy for OA [12–14], with some studies reporting significant symptom and functional improvement following the procedure [15]. Consequently, AM is indicated as a routine treatment for OA. However, meta- and systematic analyses indicate that although AM initially improves OA symptoms [16, 17], this effect is only short term [16]. In some cases, particularly among older people, AM can be harmful [16, 18, 19].

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Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis

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ABSTRACT

Purpose: The aim of the study was to determine if isolated mesenchymal stem cells (MSCs) derived from the infrapatellar fat pad could effectively improve clinical results when percutaneously injected into arthritic knees.

Level of evidence: Therapeutic case–control study; Level III.

Methods: Twenty five stem cell injections combined with arthroscopic debridement were administered to patients with knee OA. A mean of 1.89×10^6 stem cells were prepared with approximately 3.0 mL of platelet-rich plasma (PRP) and injected in the selected knees of patients in the study group.

Results: The mean Lysholm, Tegner activity scale, and VAS scores of patients in the study group improved significantly by the last follow-up visit. No major adverse events related to the injections were observed during the treatment and follow-up periods. The results were compared between the study and control groups, in which the patients had undergone arthroscopic debridement and PRP injection without stem cells. Although the preoperative mean Lysholm, Tegner activity scale, and VAS scores of the study group were significantly poorer than those of the control group, the clinical results at the last follow-up visit were similar and not significantly different between the two groups.

Conclusions: The short-term results of our study are encouraging and demonstrate that infrapatellar fat pad-derived MSC therapy with intraarticular injections is safe, and provides assistance in reducing pain and improving function in patients with knee OA.

1. Introduction

Osteoarthritis (OA) is a cartilage degenerative process involving the immune system, wherein local inflammatory reactions occur with the production of proinflammatory cytokines. Currently, no treatment is available to improve or reverse the process. OA of the knee joint has a particularly significant impact on the affected individual's ability to perform activities of daily living, and combined with the high cost of its management, it poses a major social issue, especially in populations with a long life expectancy [1]. Current treatment options for articular injury and OA itself aim to relieve inflammation and pain, but they do little to delay disease progression [2]. Various surgical methods have been proposed to regenerate articular cartilage, but they all are associated with complications, leaving many patients with inadequately treated cartilage lesions. When left untreated, cartilage lesions can progress to more extensive defects and, ultimately, they may require joint replacement surgery, subject to failure of conservative options. This consequence is the driving force behind numerous ongoing efforts to develop new tissue engineering-based strategies for the treatment of OA [3].

Because of their multilineage potential, immunosuppressive activities, limited immunogenicity, and relative ease of growth in culture, mesenchymal stem cells (MSCs) have attracted attention for clinical use. Although ethical and political issues surround the use of embryonic stem cells, the use of MSCs generally is well accepted by society. Furthermore, MSCs are an autologous source of cells, eliminating concerns regarding rejection and disease transmission, and they are less tumorigenic than their embryonic counterparts [4]. Therefore, MSCs have been suggested for use in the cell-based treatment of cartilage lesions.

In this study, we present the preliminary results (at a minimum of 12 months of follow up) of 25 cases of knee OA treated with intraarticular injections of autologous MSCs. Autologous MSCs were separated from the infrapatellar fat pad of OA patients, isolated in vitro, and then injected into the patients' knee joints. The aim of the study was to determine whether isolated MSCs derived from the infrapatellar fat pad are safe and can effectively improve clinical results when percutaneously injected into arthritic knees.

2. Patients and methods

2.1. Patients

Between January 2010 and September 2010, 25 stem cell injections combined with arthroscopic debridement were administered

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Review Article

Cartilage Regeneration in Human with Adipose Tissue-Derived Stem Cells: Current Status in Clinical Implications

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Osteoarthritis (OA) is one of the most common debilitating disorders among the elderly population. At present, there is no definite cure for the underlying causes of OA. However, adipose tissue-derived stem cells (ADSCs) in the form of stromal vascular fraction (SVF) may offer an alternative at this time. ADSCs are one type of mesenchymal stem cells that have been utilized and have demonstrated an ability to regenerate cartilage. ADSCs have been shown to regenerate cartilage in a variety of animal models also. Non-culture-expanded ADSCs, in the form of SVF along with platelet rich plasma (PRP), have recently been used in humans to treat OA and other cartilage abnormalities. These ADSCs have demonstrated effectiveness without any serious side effects. However, due to regulatory issues, only ADSCs in the form of SVF are currently allowed for clinical uses in humans. Culture-expanded ADSCs, although more convenient, require clinical trials for a regulatory approval prior to uses in clinical settings. Here we present a systematic review of currently available clinical studies involving ADSCs in the form of SVF and in the culture-expanded form, with or without PRP, highlighting the clinical effectiveness and safety in treating OA.

1. Introduction

Osteoarthritis (OA) is a common painful and debilitating disorder in the elderly [1, 2]. All current medical treatments for OA, such as nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and hyaluronic acids (HAs), physical therapy, aim to remedy the symptoms, as opposed to treating the underlying causes. When failed with symptomatic medical treatments, patients usually resort to receiving total knee replacement (TKR) or total hip replacement (THR) surgery. Both TKR and THR surgeries carry relatively high morbidity and mortality rates [1, 2]. Even with improved surgical technique, anesthesia, and rehabilitation, the thirty-day mortality rate after total knee arthroplasty is reported to be 0.18%, and 5.6% of the patients experienced complications [3]. Also, the overall 30- and 90-day mortality rates for total hip arthroplasty are reported to be 0.24% and 0.55%, respectively [4]. These approaches do not address the morbidity associated with early disease or the limitations of arthroplasty surgery, which include the possibility of adverse outcomes and the finite lifespan of prostheses [5].

Mesenchymal stem cells (MSCs) are found in numerous human tissues including bone marrow and adipose tissue [6, 7]. These MSCs have been shown to differentiate into bones, cartilage, muscle, and adipose tissue [6–8]. Because of their potential capabilities in regenerating cartilage, MSCs have been successfully used in animals [9, 10]. In 2008, Centeno et al. have showed successful cartilage regeneration in humans with MSCs [11]. Subsequently, in 2010, the same group also reported safety data of using MSCs in humans for cartilage regeneration [12].

Adipose tissue-derived stem cells (ADSCs) are one type of MSCs. In 2001 and 2002, Zuk et al. showed that adipose tissue in the form of stromal vascular fraction (SVF) contains stem cells that have the capacity to differentiate into cartilage, bone, muscle, and adipose tissue, similar to MSCs [13, 14]. Likewise,

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REVIEW Open Access

Current use of autologous adipose tissue-derived stromal vascular fraction cells for orthopedic applications

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Abstract

Autologous adipose stromal vascular fractions (SVFs) containing adipose tissue-derived stem cells (ASCs) are currently being used in clinical settings for various orthopedic applications for human patients. Due to its potential capability of regenerating cartilage, bone, and tendons, autologous adipose SVFs are being tried in treating patients with osteoarthritis (OA), chondromalacia, meniscus tear, osteonecrosis of the femoral head, and tendon injuries. Here, we have reviewed available human clinical studies with regard to patient applications of autologous adipose SVF containing ASCs, specifically assessing effectiveness and safety in the field of orthopedic disorders. All studies reviewed in this article presents potential benefits of autologous adipose SVF in various orthopedic applications without any serious side effects.

Keywords: Mesenchymal stem cell, Stromal vascular fraction, Autologous adipose tissue-derived stem cells, Effectiveness and safety, Orthopedic applications

Background

Musculoskeletal injuries and damage are common health problems in both young and old patients [1]. Various treatment modalities are available for such musculoskeletal injuries. However, most of these modalities provide only symptomatic relief [2]. The regenerative potential of injured and damaged tissue with stem cells is a promising new treatment strategy in the field of orthopedics. Stem cells can be categorized into two major forms: embryonic stem cells and adult stem cells [3]. Adult stem cells, which include mesenchymal stem cells (MSCs), can be further divided into non-culture expanded forms, also known as stromal vascular fractions (SVF), and culture expanded forms [3]. Often, the SVFs are autologous in nature and the process of obtaining SVFs may require a procedure with a physician. On the contrary, culture expanded stem cells involve cell growth and cell expansion using various nutrients in a laboratory setting. Thus, culture expanded stem cells are usually considered to be a pharmaceutical product requiring government regulatory clearance and approval in Korea [4]. Due to such government regulatory issues, adipose SVF has been more commonly used for various orthopedic applications in clinical settings. Currently two common forms of SVFs are readily available: bone marrow and adipose tissue [5].

Although MSCs can be found in numerous human tissues, a clinically applicable quantity of autologous non-culture expanded MSCs can be obtained only from bone marrow and adipose tissue [5, 6]. MSCs contained in adipose tissue are called adipose tissue- derived stem cells (ASCs) and are considered to be one specific type of MSCs, and they have been shown to differentiate into bones and cartilage [5–9]. In 2001 and 2002, Zuk et al. showed that adipose tissue contains MSCs in SVF and that these MSCs have the capacity to differentiate into cartilage and bone [8, 9]. The earliest clinical application of autologous adipose SVF with one surgical procedure to treat widespread traumatic calvarial defects was reported in 2004 by Lendeckel et al. [10].

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The use of stromal vascular fraction (SVF), platelet-rich plasma (PRP) and stem cells in the treatment of osteoarthritis: an overview of clinical trials

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ABSTRACT

Osteoarthritis (OA) is a major cause of disability across the world, which its prevalence is relatively high in elder population. Current accepted therapies such as exercise, anti-inflammatory drugs and intra-articular inoculation of corticosteroids are aimed at controlling symptoms in the affected patients. Surgical options including arthroplasty, osteotomy and joint replacement are other choices of treatment, which are invasive and can be applied in case of failure of conventional therapies. In the last few decades, efforts to treat musculoskeletal diseases are being increasingly focused on regenerative cellular therapies. Stromal vascular fraction (SVF), which obtained from adipose tissue, contains a variety of cells include mesenchymal stem cells (MSCs) and has shown to be effective in cartilage repair. Autologous blood products such as platelet-rich plasma (PRP) act as an adjuvant of surgical treatment and its intra-articular delivery has shown beneficial effects for OA treatment. Given the efficacy of such treatment approaches in OA, this paper discusses both preclinical and clinical evidence with major focus on clinical trials.

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KEYWORDS
Clinical trial; osteoarthritis; stem cell; platelet-rich plasma; stromal vascular fraction

Introduction

Osteoarthritis (OA) is the most prevalent degenerative joint disease, which mostly impairs mobility and subsequent quality of life in elder individuals. Patients experience signs of pain, morning stiffness and a grating sound during joint motion known as crepitus. Although the pathogenesis of OA has been poorly understood, it has often defined with changes in articular cartilage. Tissue fluid, proteoglycans and type 2 collagen form the main structure of cartilage. Furthermore, chondrocytes, as the main cell type found in this area, can generate and maintain the extracellular environment. It has been reported that chondrocytes have no mitotic and regenerating capacities under physiologic condition. These cells can maintain the minimal turnover of collagens to make permanent structures in front of mechanical forces exerted on the joints. However, any mechanical stress or injury can stimulate chondrocytes to proliferate and increase their ability to synthesize the extracellular matrix as part of the repair process. The subsequent changes in matrix composition can induce chondrocytes to release catabolic factors leading to cartilage degradation. This can cause friction between bones and make pain and immobility in the affected patients [1].

Several risk factors include genetic, ageing, obesity and low-grade systemic inflammation have been described and are being the subject of ongoing research in OA [2]. Data from twin and familial aggregation studies have estimated 40–65% genetic risk for OA. The strongest genetic association has been reported with growth differentiation factor 5 (*GDF5*) gene, which originally identified with candidate gene-based approach. Moreover, during the last 10 years, genome-wide association studies (GWAS) have established the remaining association with 21 genetic loci. These associated loci include genes that are involved in pathways related to cell signalling, apoptosis, mitochondrial damage and extracellular matrix remodelling. Although each individual allele exerts moderate to small risk in OA pathogenesis, their identification helps to discover the whole mechanism of the disease. In addition, it helps to find biomarkers to detect high-risk individuals or improve disease outcomes in the affected patients [3].

Among several aforementioned risk factors of OA, the most prevalent one is ageing. Evidence has shown that OA and ageing are two linked but independent processes. To date, several mechanisms have been proposed to declare how the ageing-associated changes promote OA development [4]. The low-grade systemic inflammation, as one of the OA risk factors, is created when the mass of muscle decreased and the fat mass increased in the body. This metabolic condition, as seen in obesity, can change mechanical loading, which further increases adipokines and cytokines in the joint space [5]. Other mechanisms include mitochondrial

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Systematic Review

Intra-articular Mesenchymal Stem Cells in Osteoarthritis of the Knee: A Systematic Review of Clinical Outcomes and Evidence of Cartilage Repair

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Purpose: To provide a systematic review of the clinical literature reporting the efficacy of mesenchymal stem cells (MSCs) in terms of clinical outcomes including pain and function and cartilage repair in patients with osteoarthritis. **Methods:** We systematically reviewed any studies investigating clinical outcomes and cartilage repair after the clinical application of cell populations containing MSCs in human subjects with knee osteoarthritis through MEDLINE, EMBASE, the Cochrane Library, CINAHL, Web of Science, and Scopus. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Studies with a level of evidence of IV or V were excluded. Methodological quality was assessed using the Modified Coleman Methodology Score. Clinical outcomes were assessed using clinical scores, and cartilage repair was assessed using magnetic resonance imaging and second-look arthroscopy findings. **Results:** A total of 17 studies that met the criteria of 50 full-text studies were included in this review, with 6 randomized controlled trials, 8 prospective observational studies, and 3 retrospective case-control studies. Among 17 studies, 8 studies used bone marrow–derived MSCs, 6 used adipose tissue–derived stromal vascular fraction, 2 used adipose tissue–derived MSCs, and 1 used umbilical cord blood–derived MSCs. All studies except 2 reported significantly better clinical outcomes in the MSC group or improved clinical outcomes at final follow-up. In terms of cartilage repair, 9 of 11 studies reported improvement of the cartilage state on magnetic resonance imaging, and 6 of 7 studies reported repaired tissue on second-look arthroscopy. The mean Modified Coleman Methodology Score was 55.5 ± 15.5 (range, 28-74). **Conclusions:** Intra-articular MSCs provide improvements in pain and function in knee osteoarthritis at short-term follow-up (<28 months) in many cases. Some efficacy has been shown of MSCs for cartilage repair in osteoarthritis; however, the evidence of efficacy of intra-articular MSCs on both clinical outcomes and cartilage repair remains limited. **Level of Evidence:** Level III; systematic review of level I, II, and III studies.

See commentary on page 289

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Articular cartilage has a limited capacity for spontaneous healing; therefore, any damage from trauma or degeneration ultimately progresses to osteoarthritis.[1] The current treatment approach to osteoarthritic cartilage defects is mainly palliative. A limited number of studies have reported that microfracture has led to improvements in pain and function in patients with osteoarthritis[2,3]; however, microfracture is understood to be most appropriate for small-sized lesions <2 to 4 cm and to deteriorate within a few years.[4,5] Although autologous chondrocyte implantation has been associated with improved structural and functional outcomes in young patients with focal chondral defects at long-term follow-up,[6-8] this technique is less optimal in elderly patients because of senescence or dedifferentiation of the proliferated chondrocytes.[9] Abrasion arthroplasty can be a valid treatment for cartilage lesions, but particularly for young patients

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REVIEW ARTICLE OPEN

Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation

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This systematic review with a meta-analysis aimed to summarize the current evidence of the effectiveness of mesenchymal stem cell (MSC) treatment for knee osteoarthritis (OA) and to examine whether rehabilitation is an effect modifier of the effect estimate of MSC treatment. A literature search yielded 659 studies, of which 35 studies met the inclusion criteria ($n = 2385$ patients; mean age: 36.0–74.5 years). The meta-analysis results suggested that MSC treatment through intra-articular injection or arthroscopic implantation significantly improved knee pain (standardized mean difference [SMD]: −1.45, 95% confidence interval [CI]: −1.94, −0.96), self-reported physical function (SMD: 1.50, 95% CI: 1.09, 1.92), and cartilage quality (SMD: −1.99; 95% CI: −3.51, −0.47). However, the MSC treatment efficacy on cartilage volume was limited (SMD: 0.49; 95% CI: −0.19, 1.16). Minor adverse events (knee pain or swelling) were reported with a wide-ranging prevalence of 2–60%; however, no severe adverse events occurred. The evidence for these outcomes was "very low" to "low" according to the Grades of Recommendation, Assessment, Development and Evaluation system because of the poor study design, high risk of bias, large heterogeneity, and wide 95% CI of the effects estimate. Performing rehabilitation was significantly associated with better SMD for self-reported physical function (regression coefficient: 0.881, 95% CI: 0.049, 1.712; $P = 0.039$). We suggest that more high quality randomized controlled trials with consideration of the potential rehabilitation-driven clinical benefit would be needed to facilitate the foundation of effective MSC treatment and regenerative rehabilitation for patients with knee OA.

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INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis.[1] OA ultimately results in cartilage degeneration, chronic knee pain, and disability. In 2010, knee OA was the 11th leading cause of disability worldwide, with increasing incidence over the last 2 decades.[2] Current treatments have little impact on the progressive degeneration of articular cartilage; therefore, developing effective and financially viable disease-modifying therapies is a critical medical priority.

Mesenchymal stem cells (MSCs) have emerged as a cell type with great potential for cell-based articular cartilage repair in patients with knee OA.[3] Clinical trials that investigate the effects of MSC treatments in patients with knee OA have recently begun emerging,[4] and results of clinical studies are continuously reported.[5,6] Several meta-analyses summarize the effects of MSC treatment in patients with knee OA;[7–10] these studies contribute to the establishment of effective cell-based therapies for degenerative cartilage disease. However, some of these systematic reviews included patients with focal cartilage lesions[8–10] or focused on pain and physical function as treatment outcomes,[7,9,10] with a large heterogeneity and lack of evaluation of bias risk.[7–9] As knee pain would be discordant with articular cartilage status, understanding the effects of MSC treatment against OA joint degeneration and exploring the mechanisms underlying symptom-modifying MSC treatment are important. In addition, confidence in the effects estimate from meta-analysis depends on the quality of the included studies and analytical process,[11] as the former can be evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[12] However, no meta-analysis has examined the effects of MSCs on knee OA considering the GRADE approach.

Physical factors such as rehabilitation programs are potential effect modifiers that were not well addressed in previous meta-analyses.[7–10] Physical factors regulate MSC differentiation and tissue development, pointing to a potential therapeutic strategy for enhancing the MSCs injected or implanted into the knee joint,[13,14] such as the recently proposed new field "regenerative rehabilitation".[15] Regenerative rehabilitation is defined as the integration of principles and approaches from the fields of rehabilitation science and regenerative medicine.[16] The efficacy of regenerative medicine may be enhanced when coupled with mechanical input. Weight-bearing might influence the structural outcome in the postoperative phase of autologous chondrocyte implantation in adults with cartilage defects.[17,18] Thus, further investigation of the effects of MSC treatment in patients with knee OA and the potential role of rehabilitation (i.e., regenerative rehabilitation) as an effect modifier would be of interest.

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Review

Cartilage Regeneration in Humans with Adipose Tissue-Derived Stem Cells and Adipose Stromal Vascular Fraction Cells: Updated Status

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Abstract: Adipose tissue-derived stem cells (ASCs) in the form of stromal vascular fraction (SVF) and cultured expansion have been applied in clinical settings in some countries to treat osteoarthritis (OA) of knees, one of the most common debilitating, incurable disorders. Since the first report of successful cartilage-like tissue regeneration with autologous adipose SVF containing ASCs, there has been a gradual increase in the number of publications confirming such results. Thus far, most of the reports have been limited to treatments of OA of knees. Recently, successful applications of adipose SVF in treating OA of ankles and hips have been reported. In addition, several groups have reported modified methods of applying adipose SVF, such as combining bone marrow stimulation with adipose SVF or adding additional extracellular matrix (ECM) in treating OA. Here, we present an updated, systematic review of clinical effectiveness and safety in treating OA of knees, ankles, and one hip since 2016 using ASCs in the form of adipose SVF or in cultured expansion, along with a description and suggestion of potential biological mechanisms of cartilage regeneration.

Keywords: adipose tissue-derived stem cells; stromal vascular fraction; human cartilage regeneration; osteoarthritis

1. Introduction

Current medical therapies for degenerative joint disease (DJD) are limited only to symptomatic treatments. Nonsteroidal anti-inflammatory drugs (NSAIDs), hyaluronic acid (HA) joint injections, physical therapy, steroid injections, and even arthroscopic lavage provide only symptomatic relief without addressing the underlying causes of osteoarthritis (OA). Although cartilage regeneration is not the "cure-all" remedy for OA, it can be considered to be a form of curative therapy. When these medical therapies fail, arthroplasty for knee (TKR) or arthroplasty for hip (THR) is the only alternative option of treatment available. However, these surgical measures carry relatively high risks of morbidity and mortality [1,2]. In total, 5.6% of the patients who have received these surgeries experience complications [3,4]. Furthermore, the possibility of adverse outcomes and the finite lifespan of the implanted prostheses necessitating repeated surgical procedures are additional potential limitations of the surgery [5].

RESEARCH ARTICLE

Use of Autologous Adipose-derived Stromal Vascular Fraction Grafting in Treatment of Knee Osteoarthritis: A Safety and Efficacy Study

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ABSTRACT

Autologous adipose-derived stromal vascular fraction (SVF) grafting done in a single surgical sitting was used to treat 201 osteoarthritic knees of grades II or III (as per Kellgren and Lawrence classification scale) under an IEC-approved protocol for its safety and efficacy study in Indians. The primary objective of this study was to determine if adipose-derived SVF can be safely used for intra-articular injection of the knee. The secondary objective of this study was to evaluate the efficacy of an intra-articular grafting of adipose-derived SVF for pain relief in osteoarthritic knees. SVF was obtained through lipoaspirated adipose tissue without using enzymes or chemicals or animal products which is grafted into the intra-articular space of effected joint. Patient pain data were obtained at per SVF grafting as well as post grafting at 3-, 6-, 9-,12- and 24-month follow up using Knee injury and Osteoarthritis Outcome Score (KOOS) to access statistical significance for the 5 subscales; pain, other symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QOL) to access improvisation.

Adipose-derived SVF of adipose tissue is a rich source of preadipocytes, Pericytes, endothelial progenitor cell, T cells, B cells, mast cells as well as adipose tissue macrophages obtained from loose connective tissue can significantly improve outcome of degenerative OA leading to a better QOL.

A total of 201 joints mainly knee OA were treated with autologous grafting of SVF done in a single surgical sitting. A total of 201 joints studied out of which 60 joints were followed up for 24 months, 107 joints followed for 12 months, 127 joints are followed for 9 months, 160 joints followed for 6 months and finally all 201 joints were followed for minimum 3 months for safety and efficacy. Modified KOOS Clinical Score was used to evaluate clinical effect and was based on pain, non-steroid analgesic usage, limping, extent of joint movement, and stiffness evaluation before and at pre-operative, 1, 6, 9, 12 and 24 months post-op after grafting. No side effects, systemic infection or cancer were associated with autologous grafting of SVF. There was a significant improvement from pre-op to post-op in all the followed patients. Average KOOS score improved from pre-operative 45.09 to post-operative 24 months average 80.27, which is a very significant improvement in all grades. All sub-scale parameters for pain, symptoms, activity of living and QOL showed significant improvement. Higher grade of OA was associated with comparatively slower healing. Autologous grafting of SVF in single surgical sitting is a novel and promising treatment approach for patients with degenerative OA. This treatment method was found to be minimal invasive, safe and cost-effective treatment modality for osteoarthritis.

KEYWORDS Autologous adipose derived stromal vascular fraction, SVF, Osteoarthritis, KOOS, Pericyte, Autologous grafting, Stromal vascular fraction

INTRODUCTION

Osteoarthritis (OA) or degenerative joint disease is a common chronic, progressive musculoskeletal disorder characterized by gradual loss of articular cartilage. The disease most commonly affects the middle-aged and elderly, although it may begin earlier as a result of injury or overuse. It is often more painful in weight-bearing joints such as the knee and hip.

It can be caused by aging, heredity and injury from trauma or disease. OA is the most prevalent form of arthritis in the world. The CDC combined data from the National Health Interview Survey (NHIS) years 2010-2012, sample adult core components to estimate average annual arthritis prevalence in the civilian, and non-institutionalized US adult population aged 18 years or older. Overall, 22.7% (52.5 million) of adults reported doctor-diagnosed arthritis, with significantly higher age-adjusted prevalence in women (23.9%) than in men (18.6%). Arthritis prevalence increased with age[1].

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ORIGINAL ARTICLE

Functional Outcome Analysis of Autologous Stromal Vascular Fraction (SVF) (Sahaj Therapy®) Using Direct Sonication in Osteonecrosis of the Femoral Head (ONFH): A 6-Year Follow-Up Study

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Abstract

Introduction We investigated the safety, efficacy, functional, and clinical outcomes of intra-osseous implantation of mechanically isolated, autologous stromal vascular fraction (SVF), an Australian patented direct ultrasonication technology (Sahaj Therapy®) in osteonecrosis of the femoral head (ONFH).

Materials and Methods A total of 32 cases of ONFH were enrolled in the study after confirming with an MRI of the affected hip. All cases were treated with an intra-osseous autologous SVF implantation [4–5 cc with the cellular dosage of 8.0×10^7 cells with a viability of > 85% SVF cells] on the same surgical sitting. All the cases were followed up clinically, functionally, and radiologically at regular intervals. A comparison of mean HOOS scores at different follow-ups was done using Paired '*t*'-test. A *P* value of < 0.05 was considered significant.

Results In our study, male preponderance was seen (53.1%). According to the modified Ficat and Arlet classification, the most common grade of ONFH was grade 2 [right: 25 hips and left: 25 hips]. There was a statistically significant improvement in the mean HOOS score of the right hip ($n = 10$) and left hip ($n = 9$) from preoperative time till 72 months ($P < 0.05$). The follow-up MRI of the affected hips shows improved osteogenesis without any further worsening of the contour of the femoral head. No adverse effects were seen in any of the study participants.

Conclusion For individuals with ONFH, treated with intra-osseous autologous SVF implantation in the same surgical procedure is an innovative and promising treatment modality. Even after 6 years of follow-up, the study participants with ONFH have shown good clinical and functional outcomes with autologous SVF.

Keywords Adipose tissue · Stromal vascular fraction · Osteonecrosis · Femoral head

Introduction

Osteonecrosis of the femoral head (ONFH) is an advancing disease that is delineated by the spontaneous demise of the cellular element of the subchondral part of the bone as a result of loss of blood supply that causes osteoarthritis [1], the deficiency of blood supply can be because of various factors like trauma, genetic predilection, systemic abnormalities, metabolic components, drugs, and other local causes [2, 3]. The mechanism of development is not

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clear but the endpoint is reinstating the bone that is dead with thin fragile trabeculae that is susceptible to fracture and collapse with stress [1].

The pathogenesis behind ONFH remains ambiguous [4, 5], it is commonly perceived that the various causes predetermine the perilous blood supply to the femoral head, which in turn results in ischemia of the bone that triggers the demise of the cells of the bone and ultimately causes the collapse of the necrotic section of bone [6–8]. The sequel of the above-mentioned leads to the collapse of the femoral head and secondary arthritic changes of the affected hip [9, 10]. In a high number of patients, without early diagnosis and appropriate treatment, osteonecrosis progresses to collapse of the femoral head with the destruction of the hip joint and necessitates total hip arthroplasty (THA) to bring back effective function of the hip joint [11]. In the recent past, many young individuals are affected and THA at a young age will not increase the lifetime of the patient and so hip-conserving treatment options are mainly in need for these young individuals in the early stages of ONFH disease [12, 13].

Among the various available stem cells, the mesenchymal stromal cells (MSCs) are one of the most common subsets used, which is distributed in a vast range of tissues viz, peripheral circulation, adipose tissue, bone marrow, Wharton's jelly, umbilical cord, amniotic fluid, dental pulp, hair follicle, dermal papillae, etc. [14–20]. MSCs can delineate into osteoblasts and endothelial cells to propagate the repair of bones and angiogenesis and also would crop growth factors to induce blood supply to the areas of necrosis by paracrine modes [21–24]. Stem cell therapy has been serving as one of the hip-conserving treatment choices for the past two decades since the first case report of stem cell treatment for ONFH [25]. In the past few years, there has been rapid progress in the field of tissue engineering and cell biotechnology, which has led to encouraging results in ONFH treatment.

Adipose tissue-derived mesenchymal stromal cells (AD-MSCs) are a good stem cell source for ONFH therapy and have many advantages such as easily attainable, greater productivity, and analogous potential for differentiation as bone marrow stem cells [26, 27]. The by-products of AD-MSCs are adipose tissue-derived stem cells (ADSC), microfat, nanofat, stromal vascular fraction, microvascular fragments, and exosomes [28]. The excessive expression of vascular endothelial growth factor (VEGF) could increase the osteogenesis capacity and neoangiogenesis by AD-MSCs [29]. In our study, we investigated the safety, efficacy, functional, and clinical outcomes of intra-osseous grafting of mechanically isolated, autologous stromal vascular fraction (SVF) Australian Patent technology (Sahaj Therapy®) in osteonecrosis of the femoral head (ONFH).

Materials and Methods

After obtaining the institutional ethical clearance [IMCHRC/IEC/2015/013 dated 02.05.2015], the present prospective observational study was conducted on 32 patients [from May 2015 to May 2021] suffering from osteonecrosis of the femoral head (ONFH) with modified Ficat and Arlet classification grades I to III. Voluntary written informed consent was obtained from the patient and/or his/her legally acceptable representative for participation in the study.

Inclusion Criteria

The patients with idiopathic ONFH of age between above 18 years, patients with modified Ficat and Arlet classification grades I to III ONFH, patients with self-reported difficulty in at least one of the following activities such as lifting and carrying groceries, walking 400 m, getting in and out of a chair, or going up or down the stairs, patients with an adequate renal (serum creatinine < 1.5 mg/dl), cardiovascular, and respiratory functions, patients with PT/INR < 1.5 and normal APTT value, and patients with an adequate immune system function and no known immunodeficiency were included in the study.

Exclusion Criteria

The patients with ages less than 18 years, patients with modified Ficat and Arlet classification grades IV ONFH and secondary ONFH, patients with an active neoplastic disease diagnosed in the last 3 years, patients with a BMI more than 35, patients with a history of any surgery including arthroscopy or major trauma to the affected hip joint in the last 12 months, patients with the signs of active infection or inflammation over the joint, patients with inflammatory joint diseases or laxity in joint, patients who are positive HIV, HbsAg, HCV or VDRL were excluded from the study.

Surgical Procedure

After obtaining consent for participation and other consents relevant to the treatment, the isolation and implantation of autologous SVF into hip joints were performed. The whole procedure from harvesting the autologous adipose tissue to the isolation and implantation of autologous SVF into the hip was done in the same surgical sitting which took around 90 min. The following steps were performed as depicted in Fig. 1.

Lipoaspiration

The patient was prepared for the procedure with all aseptic precautions. Pre-procedural antibiotics, anxiolytics, and/or opioid-based pain medications were administered

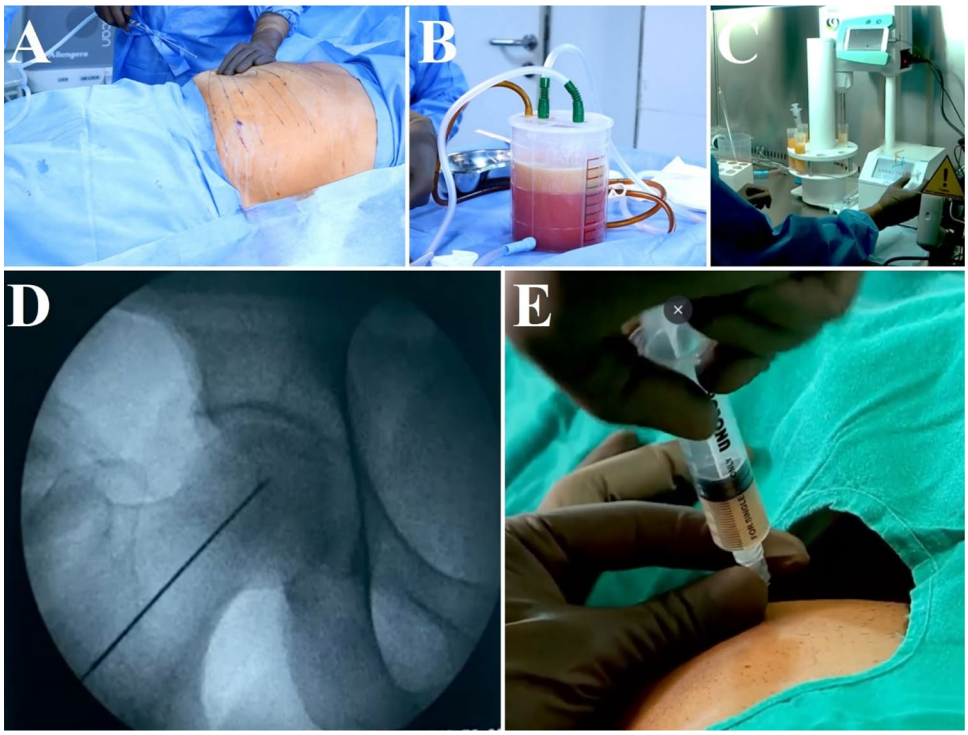

Fig. 1 Preparation of stromal vascular fraction (SVF). **A** Marking of the abdomen for lipoaspiration, **B** lipoaspiration in the canister, **C** adipose tissue disruption by direct ultrasonic cavitation process, and **D**, **E** intra-osseous SVF grafting in same surgical sitting in the right femoral head

if needed. Under sedation/short general anesthesia, a stab incision on the abdomen using a #11 blade was made for cannula entry after local infiltration with 1% lidocaine with epinephrine 1:100,000. 40 ml of 2% lidocaine plus 1 ml of 1% epinephrine was added to a 1000 ml bag of 0.9% normal saline and was infiltrated with the tumescent anesthesia on the infraumbilical area of the abdomen. Approximately, 200–250 cc of adipose tissue was aspirated into the patented sterile Lipoaspiration Jar (Design No. 316580–001) containing 0.9% sterile normal saline and sodium bicarbonate.

Recovery of the Autologous Adipose Tissue (ACRU Unit)

Approximately 300–450 cc of autologous adipose tissue was harvested. In Class II Bio-Hood, the sample was divided into 50 ml tubes and tissue fragmentation was done using direct ultrasonic cavitation (Australian Patented Technology) which was used to separate the SVF or cellular fraction from fat. These 50 ml tubes were centrifuged with a pellet being formed at the bottom of the tube. The tube was turned upside down after screwing a tube filter to the 50 ml tube. The pellet separated was the SVF or cellular fraction, which is the heterogeneous population of cells. The cell count and viability were checked using the Muse Cell Flow cytometer.

Intra-osseous Autologous SVF Grafting

Under local anesthesia and mild sedation, chlorhexidine was used for hip preparation. Under c-arm guidance, a 18-gauge bone marrow needle was inserted into the necrotic area of the femoral and the prepared autologous SVF of 4–5 cc with the cellular dosage of 8.0×10^7 cells with a viability of > 85% SVF cells were implanted intraosseously into the affected femoral head under C-arm guidance.

Follow-up

Patients with autologous SVF implantation into the affected hips were instructed to contact the surgeon in case of fever, pain, and any other adverse events. Patients were followed up regularly functionally by Hip Disability and Osteoarthritis Outcome Score (HOOS) at the end of 3, 6, 12, 24, 36, 48, 60, and 72 months after the procedure by telephone, email, or in person for radiological documentation as depicted in Figs. 2, 3, 4 and 5. The patients were allowed to walk with support for first 3 weeks immediately after the surgical procedure and complete weight bearing was allowed after 3rd week in the post-operative period.

Statistical Analysis

Statistical software, SPSS version 26.0, IBM Chicago, Illinois was used for statistical analysis. Descriptive statistics were presented as numbers and percentages. Paired '*t*'-test was applied to compare the preoperative HOOS score at various follow-ups. A P value of < 0.05 was taken as statistically significant.

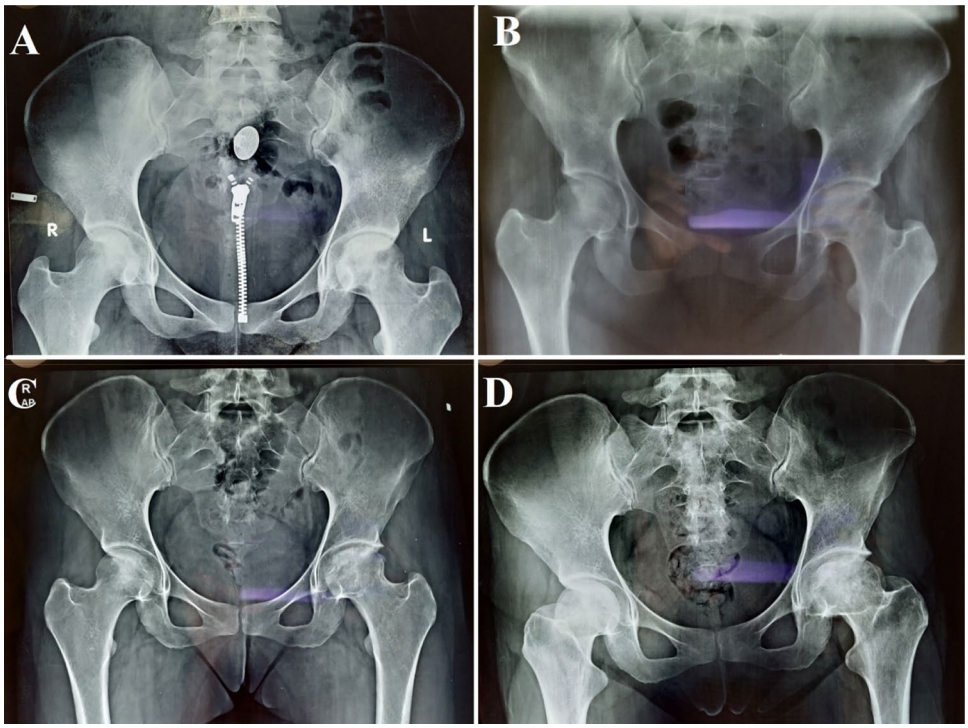

Fig. 2 Plain radiograph of pelvis with bilateral hips (AP) showing **A** stage 2b left ONFH, **B** immediate follow-up x-ray of SVF implantation over the left femoral head, **C** 1-year follow-up x-ray with osteogenic activity over left femoral head, and **D** 4-year follow-up x-ray with maintained femoral head contour

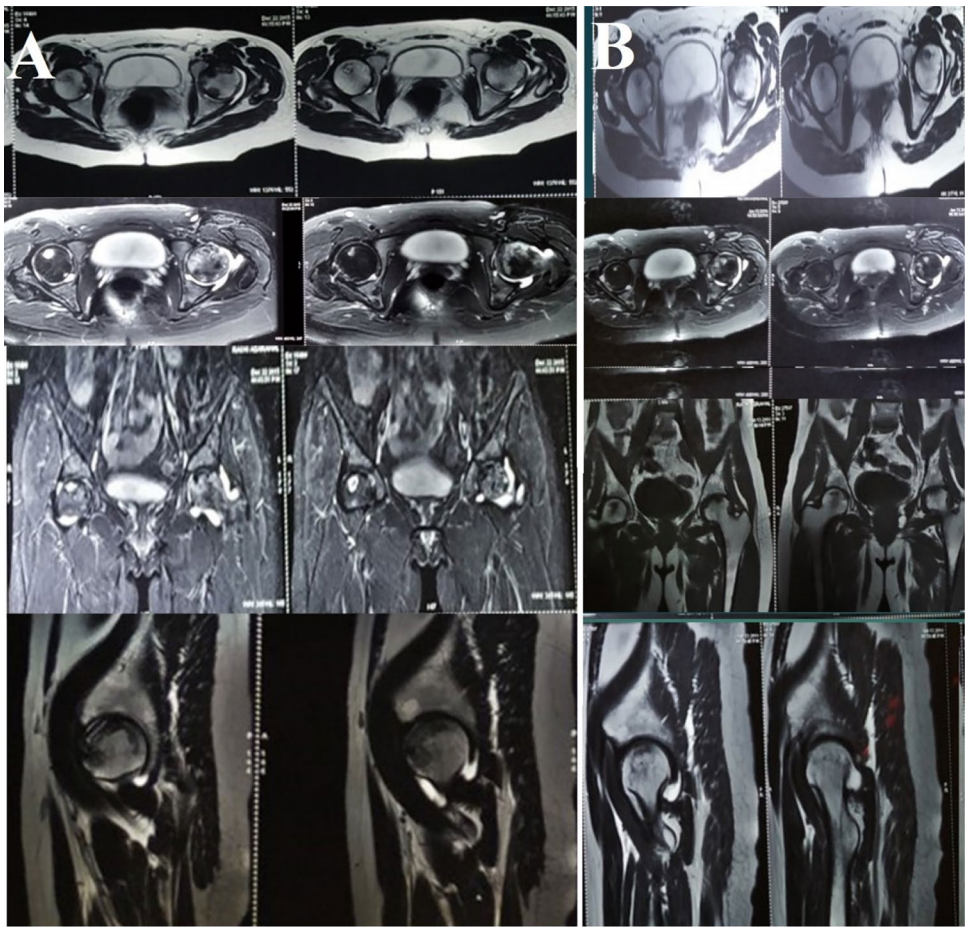

Fig. 3 **A** MRI of bilateral hips showing stage 2b left ONFH and **B** 4 years follow-up MRI of bilateral hips showing maintenance of left femoral head contour with improved osteogenesis

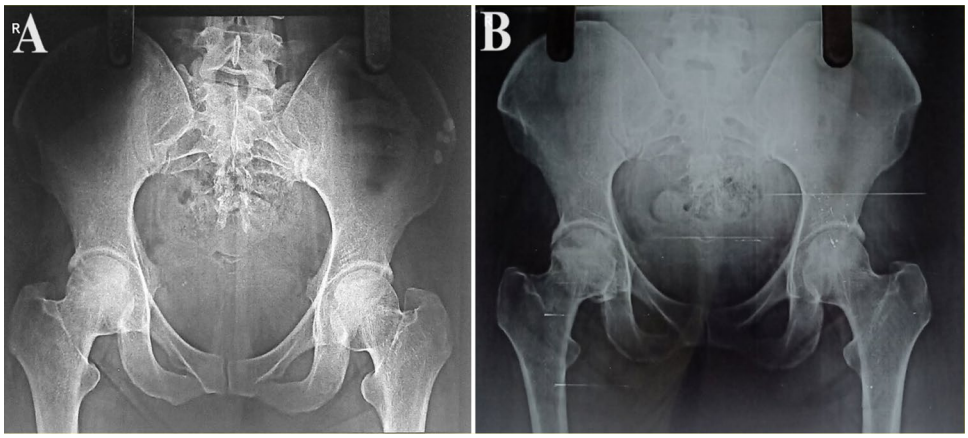

Fig. 4 Plain radiograph of pelvis with bilateral hips (AP) showing **A** stage 2a ONFH of right hip and **B** 5-year follow-up x-ray with osteogenic activity over right femoral head with maintained femoral head contour

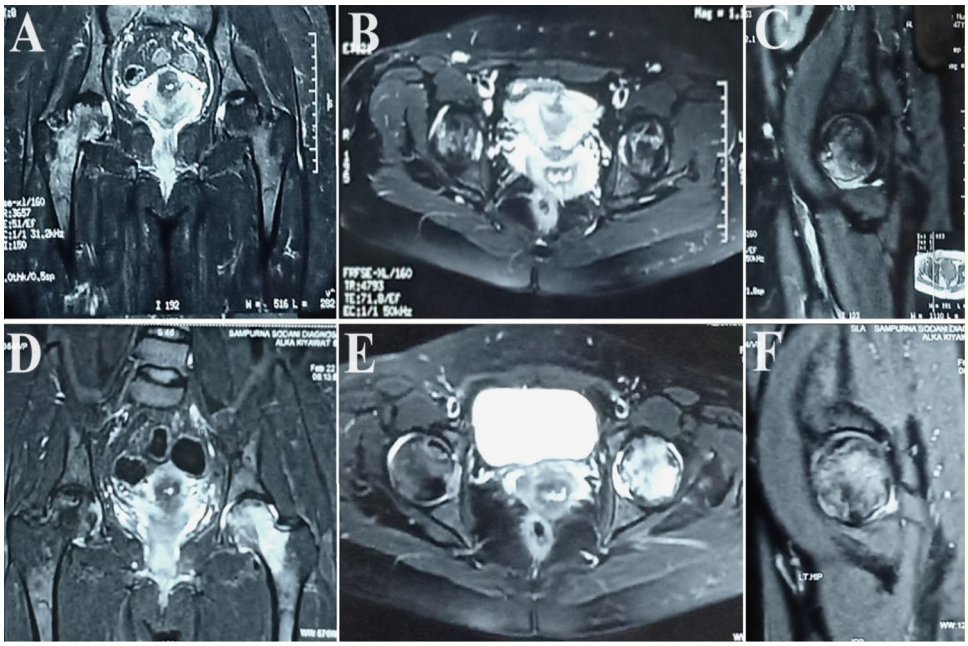

Fig. 5 **A**–**C** MRI of bilateral hips showing stage 2a right ONFH and **D**–**F** 5 years follow-up MRI of bilateral hips showing maintenance of right femoral head contour with improved osteogenesis

Results

A total of 32 patients with ONFH treated with intra-osseous SVF implantation were analyzed and followed up at regular intervals. The demographic characteristics were tabulated in Table 1. The majority of the patients were in the age group 21–40 years (53.1%) and the least was more than 60 years age group (9.4%). The mean age of the patients was 41.97 ± 12.53 years (range: 21 to 62 years). Males were slightly more than the females in our series (53.1% vs. 46.9%). 43.8% of patients were in the normal weight group, 40.6% of patients were overweight and 12.5% of patients were obese. Patients with ONFH of 31 right hips (modified Ficat and Arlet classification: grade 1—4 hips; grade 2a—12 hips; grade 2b—13 hips, and grade 3—4 hips) and 28 left hips (modified Ficat and Arlet

Table 1 Demographic characteristics of study participants ($N = 32$)

Demographic characteristics	Frequency	Percentage
Age		
21–40 years	17	53.1
41–60 years	12	37.5
> 60 years	3	9.4
Gender		
Female	15	46.9
Male	17	53.1
BMI category		
Underweight	1	3.1
Normal weight	14	43.8
Overweight	13	40.6
Obese	4	12.5
Total	32	100.0

classification: grade 1—2 hips; grade 2a—15 hips; grade 2b—10 hips, and grade 3—1 hip) underwent autologous SVF implantation. The distribution of patients available at each follow-up is depicted in Table 2.

Preoperatively, the mean HOOS score of the right hip was 44.07 ± 10.39, at 3 months it was 55.82 ± 10.61, at 6 months it was 59.26 ± 9.75, at 12 months it was 65.06 ± 9.09, at 24 months it was 70.09 ± 9.42, at 36 months it was 73.71 ± 9.73, at 48 months it was 75.64 ± 9.51, at 60 months it was 77.27 ± 9.47 and at 72 months it was 79.65 ± 10.16 as mentioned in Fig. 6. There was a statistically significant improvement in the mean HOOS score of the right hip from preoperative time till 72 months ($P < 0.05$) as shown in Table 3.

Preoperatively, the mean HOOS score of the left hip was 44.21 ± 9.55, at 3 months it was 56.14 ± 8.40, at 6 months it was 59.89 ± 9.52, at 12 months it was 65.88 ± 8.95, at 24 months it was 70.79 ± 9.24, at 36 months it was 74.28 ± 9.51, at 48 months it was 76.12 ± 9.98, at 60 months it was 78.20 ± 8.28 and at 72 months it was 79.60 ± 8.16 as mentioned in Fig. 7. There was a statistically significant improvement in the mean HOOS score of the left hip from preoperative time till 72 months ($P < 0.05$) as shown in Table 4. None of the patients were deteriorated which have not necessitated the need for total hip replacement.

Table 2 Number of patients available at each follow-up ($N = 32$)

Follow-up	Right hip	Left hip
3 months	31	28
6 months	31	28
12 months	27	24
24 months	22	20
36 months	20	18
48 months	18	16
60 months	15	14
72 months	10	9

Discussion

In the recent past, adult stem cell-based therapy has provided assuring results in increasing the formation of collateral vasculature in ischemic conditions [29, 30]. For a prolonged duration, the bone marrow-derived mesenchymal stromal cells (BM-MSCs) have been abundantly utilized for therapeutic purposes, which require neovascularization. They are progenitor cells with the property of multipotency, which is the ability to diversify into vascular cells and perpetuate neovascularization [30–32].

Other sources of easily accessible adult autologous stem cells include adipose tissue in adults that possess a high quantity of endothelial progenitor cells and MSCs with the property of multipotency [33]. Adipose tissue in the body has abundant vascularity and there is a major role in the remodeling process of the persistent vessels in the physiological behavior of the adipose tissue [34]. Zuk et al., for the first time in history, defined a group of look-alike cells that resembles the fibroblast cells in adipose tissue-derived SVF, which could disseminate in vitro into myogenic, osteogenic, chondrogenic, and adipogenic cells [35].

The contents of SVF include endothelial cells (ECs), smooth muscle cells, fibroblasts, mural cells, macrophages, smooth muscle cells, and MSCs/phenotypes of other progenitor cells [28, 36]. Of these, the focus has been kept on the characteristic features and functional capability of AD-MSCs in the mechanism of neovascularization. Though

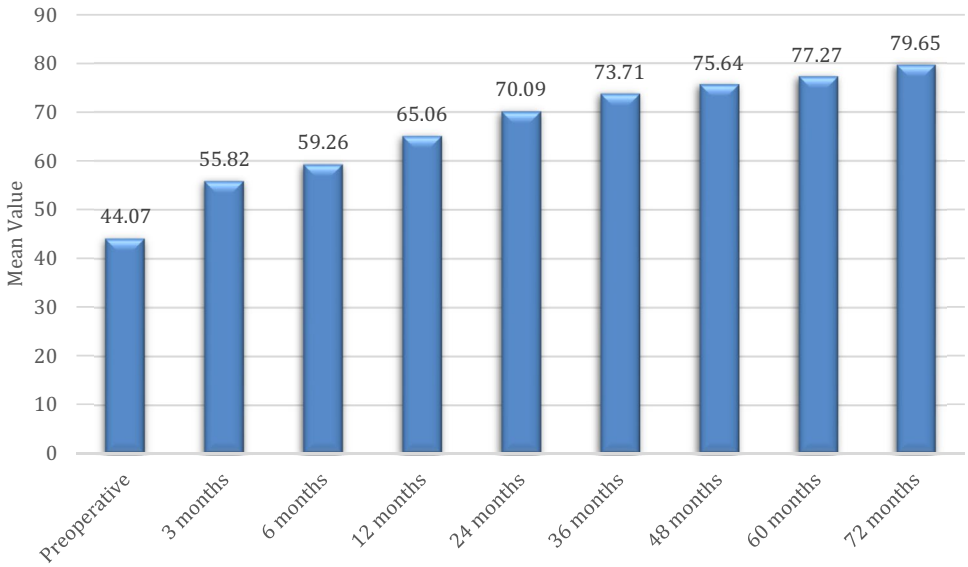

Fig. 6 Comparison of mean HOOS score of the right hip at different time intervals

Table 3 Comparison of mean HOOS score of the right hip at different time intervals ($N=31$)

Pair	Time interval	No	Mean ± SD	't' value, df	P value
Pair 1	Preoperative	31	44.07 ± 10.39	− 6.542, $df=30$	0.001*
	3 months	31	55.82 ± 10.61		
Pair 2	3 months	31	55.82 ± 10.61	− 2.656, $df=30$	0.013*
	6 months	31	59.26 ± 9.75		
Pair 3	6 months	27	60.68 ± 9.42	− 6.884, $df=26$	0.001*
	12 months	27	65.06 ± 9.09		
Pair 4	12 months	22	65.94 ± 9.51	− 6.375, $df=21$	0.001*
	24 months	22	70.09 ± 9.42		
Pair 5	24 months	20	70.29 ± 9.74	− 7.880, $df=21$	0.001*
	36 months	20	73.71 ± 9.73		
Pair 6	36 months	18	73.28 ± 10.16	− 5.690, $df=17$	0.001*
	48 months	18	75.64 ± 9.51		
Pair 7	48 months	15	75.67 ± 10.29	− 2.762, $df=14$	0.015*
	60 months	15	77.27 ± 9.47		
Pair 8	60 months	10	78.30 ± 10.82	− 2.680, $df=9$	0.025*
	72 months	10	79.65 ± 10.16		

Paired 't' test was applied. P value < 0.05 was taken as statistically significant

ADSCs have competency in the field of regenerative and reconstructive medicine, SVF has proven to have exceptional results in comparison to only AD-MSC therapy [37]. The unique feature of SVF cells is their capability to gather into a hierarchical, divided, infused vasculature in vivo [36].

The ECs and their precursors have CD31 as their prototype surface marker and CD34 is manifested by the duo-the ECs and hematopoietic stem/precursor cells [38]. Klar et al. [39] separated the SVF cellular components into CD34+/CD31+ cells and CD34+/CD31− cells by the technique of flow cytometry. Their observation lead to the findings viz CD31+ cells comprised of only 25% of the total cell content in SVF and they express a particular endothelial phenotype that could assert CD31 and vascular endothelial growth factor receptor 2 (VEGFR2) and can assimilate fluorescent labeled acetylated low-density lipoprotein. On the other hand, the CD31- cells separated from the human adipose tissue displayed properties of stromal stem cells, exhibited surface markers specific to MSCs, and showed positivity for CD90 and vimentin [39]. Morris et al. have found that myeloid cells of mice comprise 22% of SVF cells [40].

In the initiation of osteogenic differentiation, transplantation of autologous AD-MSCs can increase osteogenesis and elevate bone density and bone mass in ONFH [41]. The excessive expression of VEGF can propagate osteogenesis and angiogenesis by AD-MSCs [29]. Abudusaimi et al. stated that core decompression along with transplantation of AD-MSCs enhanced the osteogenic potential of the necrotic patches by enhancing the osteocalcin expression of ONFH [42]. Pak et al. injected autologous adipose SVF into the hip by percutaneous means and observed that there was an improvement in the symptoms & there was a promotion of bone regeneration in the osteonecrotic areas [43].

It is easy to obtain adipose tissue-derived MSCs and have some similar biological features and properties to BM-MSCs, also enormous amounts of MSCs can be obtained without any necessity for ex-vivo culture [44]. There are various comments that the ischemic surrounding reduces the osteoprogenitor cell count in the healthy part of the head of the femur which in turn provides the process of necrosis an upper hand and leads to the spread of the lesion because of the inability to repair the disease progress [43]. Lee et al. elaborated on the potentiality for the repair of the human AD-MSCs, which when implanted into mice by activating

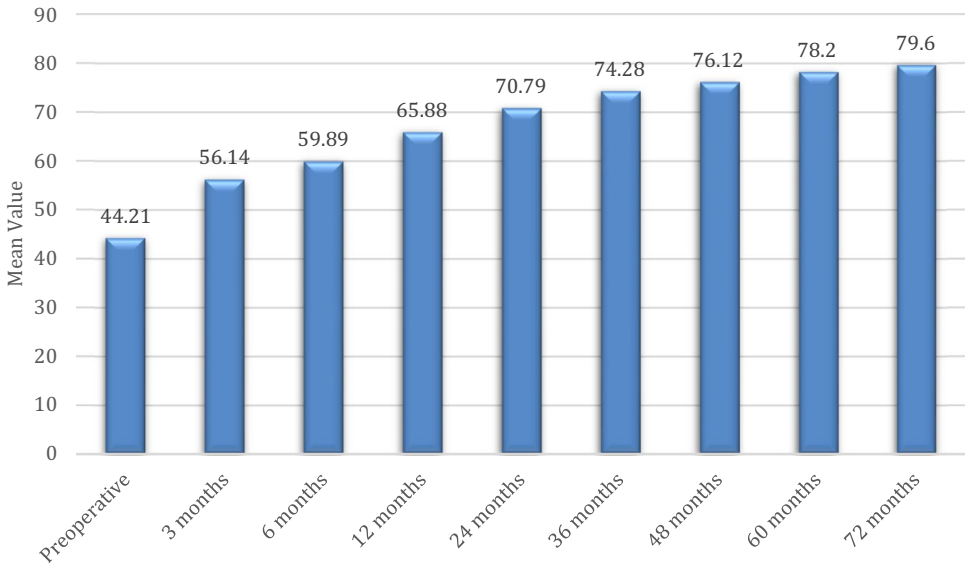

Fig. 7 Comparison of mean HOOS score of the left hip at different time intervals

Table 4 Comparison of mean HOOS score of the left hip at different time intervals ($N=28$)

Pair	Time interval	No	Mean ± SD	'*t*' value, *df*	*P* value
Pair 1	Preoperative	28	44.21 ± 9.55	− 10.353, *df* = 27	0.001*
	3 months	28	56.14 ± 8.40		
Pair 2	3 months	28	56.14 ± 8.40	− 4.383, *df* = 27	0.001*
	6 months	28	59.89 ± 9.52		
Pair 3	6 months	24	61.41 ± 8.99	− 7.527, *df* = 23	0.001*
	12 months	24	65.88 ± 8.95		
Pair 4	12 months	20	66.94 ± 9.16	− 6.217, *df* = 19	0.001*
	24 months	20	70.79 ± 9.24		
Pair 5	24 months	18	71.36 ± 8.95	− 6.296, *df* = 17	0.001*
	36 months	18	74.28 ± 9.51		
Pair 6	36 months	16	74.20 ± 9.77	− 4.157, *df* = 15	0.001*
	48 months	16	76.12 ± 9.98		
Pair 7	48 months	14	76.07 ± 10.62	− 2.305, *df* = 13	0.038*
	60 months	14	78.20 ± 8.28		
Pair 8	60 months	9	77.96 ± 9.49	− 2.582, *df* = 8	0.033*
	72 months	9	79.60 ± 8.16		

Paired '*t*' test was applied. *P* value < 0.05 was taken as statistically significant

an excessive amount of osteoblasts and osteoclasts activeness in the bone, and inferred that AD-MSCs would be a helpful tool in the treatment of osteoporosis and repair of bones [45]. Jeyaraman et al. concluded that a combination of core decompression with BM-MSCs implantation provides better osteogenesis at the necrosis of the femoral head than core decompression alone [21].

From recent studies, it has been proven that the potential of differentiation and repair of the AD-MSCs are equivalent to the mandible-derived MSCs (MD-MSCs) with actual dominance in regards to culture, harvest, and interventional safety [46]. Researchers are working on the details regarding the optimization of the treatment modalities in bone lesions and defects. Mihaila et al. conducted a study that demonstrates the fact that by acquiring the needful amount of subpopulation of adipose tissue of humans, we will be able to procure the relevant type of cells needed for the manufacturing of vascularized bone tissue-engineered scaffolds, whereas Behr et al. delineated the fact that invitro employment of particular growth factors may improve the osteogenic potential of AD-MSCs [47].

Core decompression, often with augmentation, stands as a widely accepted treatment for early-stage ONFH. The overall success rate is 65% and varies widely with the success rate showing significant difference on the outcomes of different stages [48]. Core decompression predominantly aims to relieve bone pressure. In contrast, our approach capitalizes on the regenerative potential harbored within adipose-derived stem cells from the stromal vascular fraction. These cells exhibit promising attributes in fostering tissue rejuvenation, dampening inflammation, and facilitating angiogenesis. Despite its relative minimally invasive nature, core decompression involves drilling and can entail a protracted recovery span (typically around 6 weeks before full weight-bearing is advised). Conversely, the SVF technique's less invasive procedure involves adipose tissue extraction, subsequent SVF processing, and targeted injection into the afflicted region, yielding briefer recuperation periods. Notably, our technique even permits immediate weight-bearing. This study underscores the distinct edge of the SVF approach. Choosing between the two methodologies pivots on factors like the patient's status, inclinations, and disease stage. Enhanced comprehension of the comparative efficacy in tackling ONFH necessitates additional research and comprehensive clinical trials.

In our study, there was a statistically significant improvement in the mean HOOS score of the right hip ($n=10$) and left hip ($n=9$) from preoperative time till 72 months ($P<0.05$). The follow-up MRI of the affected hips shows improved osteogenesis without any further worsening of the contour of the femoral head. No adverse effects were seen in any of the study participants. The limitations of the study are the small sample size of study participants with a shorter duration of follow-up, only 20% of the study participants were followed-up for 6 years, and no comparison group to compare the effectiveness of autologous SVF in ONFH. We recommend a large blinded controlled trial to validate the results of our study.

Further research is essential to comprehensively unravel the precise mechanisms of SVF's action, as these potential actions hold promise in contributing to the alleviation of ONFH. The potential mechanisms of action could include:

(a) The ability of MSCs to differentiate within SVF into various cell types, including bone-forming cells (osteoblasts), aiding in the formation of new bone tissue and repairing the damaged bone,
(b) Beyond their direct differentiation potential, the MSCs within SVF secrete various bioactive molecules through paracrine signaling. These molecules encompass growth factors, cytokines, and extracellular vesicles, which can significantly impact local cells, promoting their survival, proliferation, and regeneration, and
(c) Inflammation is often intertwined with ONFH, exacerbating tissue damage. SVF also contains anti-inflammatory cytokines that can modulate the immune response and mitigate inflammation in the affected region. This reduction in inflammation can foster an environment supportive of tissue recovery.

Conclusions

In our study, significant improvements in HOOS scores and enhanced osteogenesis, evident in postoperative MRI, underscore the positive impact of SVF treatment on ONFH over a 6-year follow-up period. The absence of adverse effects among participants is encouraging. Nevertheless, the study's limitations, such as a small sample size and short follow-up duration for some participants, call for a larger, controlled trial to validate our findings and better compare the effectiveness of autologous SVF therapy in ONFH. This research direction holds the potential for SVF to become one tool in orthopedics approach to treatment of OFNH.

Author Contributions Conceptualization—VT, RS; Data procurement—MBP, AKS; Data analysis—RS; Manuscript writing—MJ, AN; Manuscript revision—MJ, AN; and Project administration—VT, RS. All authors agreed to publish the manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study informed consent is not required.

IEC approval IMCHRC/IEC/2015/013 dated 02.05.2015.

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