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ORIGINAL ARTICLE

Prospective Study

Efficacy of stromal vascular fraction for knee osteoarthritis: A prospective, single-centre, non-randomized study with 2 years follow-up

Madhan Jeyaraman, Naveen Jeyaraman, Tarun Jayakumar, Swaminathan Ramasubramanian, Rajni Ranjan, Saurabh Kumar Jha, Ashim Gupta

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Madhan Jeyaraman, Naveen Jeyaraman, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai, Tamil Nadu 600077, India

Madhan Jeyaraman, Saurabh Kumar Jha, Department of Biotechnology, School of Engineering and Technology, Sharda University, Greater Noida, Uttar Pradesh 201310, India

Madhan Jeyaraman, Ashim Gupta, Department of Orthopaedics and Regenerative Medicine, South Texas Orthopaedic Research Institute, Laredo, TX 78045, United States

Tarun Jayakumar, Department of Orthopaedics, KIMS-Sunshine Hospital, Hyderabad, Telangana 500032, India

Swaminathan Ramasubramanian, Department of Orthopaedics, Government Medical College, Omandurar Government Estate, Chennai, Tamil Nadu 600002, India

Rajni Ranjan, Department of Orthopaedics, School of Medical Sciences and Research, Sharda University, Greater Noida, Uttar Pradesh 201306, India

Saurabh Kumar Jha, Department of Zoology, Kalindi College, University of Delhi, New Delhi 110008, India

Ashim Gupta, Department of Orthopaedics and Regenerative Medicine, Regenerative Orthopaedics, Noida 201301, Uttar Pradesh, India

Ashim Gupta, Department of Orthopaedics and Regenerative Medicine, Future Biologics, Lawrenceville, GA 30043, United States

Ashim Gupta, Department of Orthopaedics and Regenerative Medicine, BioIntegrate, Lawrenceville, GA 30043, United States

Co-corresponding authors: Madhan Jeyaram and Saurabh Kumar Jha.

Corresponding author: Madhan Jeyaraman, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai, Tamil Nadu 600077, India. madhanjeyaraman@gmail.com

Abstract

BACKGROUND

Current osteoarthritis (OA) treatments focus on symptom relief without addressing the underlying disease process. In regenerative medicine, current treatments have limitations. In regenerative medicine, more research is needed for intra-articular stromal vascular fraction (SVF) injections in OA, including dosage optimization, long-term efficacy, safety, comparisons with other treatments, and mechanism exploration.

AIM

To compare the efficacy of intra-articular SVF with corticosteroid (ICS) injections in patients with primary knee OA.

METHODS

The study included 50 patients with Kellgren-Lawrence grades II and III OA. Patients were randomly assigned (1:1) to receive either a single intra-articular SVF injection (group A) or a single intra-articular ICS (triamcinolone) (group B) injection. Patients were followed up at 1, 3, 6, 12, and 24 months. Visual analog score (VAS) and International Knee Documentation Committee (IKDC) scores were administered before the procedure and at all follow-ups. The safety of SVF in terms of adverse and severe adverse events was recorded. Statistical analysis was performed with SPSS Version 26.0, IBM Corp, Chicago, IL, United States.

RESULTS

Both groups had similar demographics and baseline clinical characteristics. Follow-up showed minor patient loss, resulting in 23 and 24 in groups A and B respectively. Group A experienced a notable reduction in pain, with VAS scores decreasing from 7.7 to 2.4 over 24 months, compared to a minor reduction from 7.8 to 6.2 in Group B. This difference in pain reduction in group A was statistically significant from the third month onwards. Additionally, Group A showed significant improvements in knee functionality, with IKDC scores rising from 33.4 to 83.10, whereas Group B saw a modest increase from 36.7 to 45.16. The improvement in Group A was statistically significant from 6 months and maintained through 24 months.

CONCLUSION

Our study demonstrated that intra-articular administration of SVF can lead to reduced pain and improved knee function in patients with primary knee OA. More adequately powered, multi-center, double-blinded, randomised clinical trials with longer follow-ups are needed to further establish safety and justify its clinical use.

Key Words: Knee osteoarthritis; Adipose tissue; Stromal vascular fraction; Regenerative medicine; Orthobiologics

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Core Tip: The clinical study presents a comprehensive analysis of the efficacy of stromal vascular fraction (SVF) in managing knee osteoarthritis, highlighting its superiority over corticosteroid injections in reducing pain and improving joint function. The research emphasizes the need for standardizing SVF therapy protocols to enhance its clinical application.

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INTRODUCTION

Osteoarthritis (OA) is a highly prevalent degenerative joint disease that affects approximately 43 million people, contributing to the 11th most debilitating disease worldwide[1]. Its incidence is most common in people aged 60 and over, with a higher prevalence in women than men[2,3]. Among the different types of OA, knee OA is the most frequently encountered, with a prevalence of 181.2 cases per 100000 people[4]. Knee OA significantly impairs quality of life and presents substantial clinical and financial challenges due to its associated symptoms of pain, stiffness, and restricted joint mobility/range of motion (ROM)[4,5]. The disease is characterized by the degradation of articular cartilage, the formation of peripheral osteophytes, subchondral cysts, and bone sclerosis[6,7]. While the current therapeutic approaches for OA mainly focus on symptomatic relief through lifestyle modifications, physical therapy, and pharmacological interventions such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, and viscosupplementation, these treatments often provide temporary relief without addressing the underlying root cause of disease progression[8-11].

Given the limited intrinsic capacity for cartilage repair in the knee, there has been growing interest in exploring regenerative medicine as a promising avenue for managing knee OA. In particular, cellular therapy utilizing mesenchymal stem/stromal cells (MSCs) has emerged as a potent option, especially when traditional therapies are ineffective[12,13]. Autologous MSCs can be derived from various sources, including bone marrow and adipose tissue[14].

Adipose-derived mesenchymal stem cells (AD-MSCs), or Adipose-derived stem cells (ASCs), are a subset of mesenchymal stem cells traditionally viewed as biologically inert but later recognized for their dynamic role in adipose tissue, especially after the discovery of adipokines[15-17]. These cells are conveniently harvested from abundant adipose tissue and share regenerative properties akin to other MSCs, making them promising for regenerative medicine and tissue engineering applications[15,18-20]. They can differentiate into various mesodermal tissues like bone, cartilage, muscle, and adipose tissue[14,21,22]. AD-MSCs are categorized based on size: (1) Macro fat, with particles larger than 1 mm; (2) minifat, with particles between 0.5 and 1 mm; (3) micro fat, with particles between 0.2 and 0.5 mm; and (4) nanofat, with particles smaller than 0.2 mm, primarily containing SVF cells and free lipids. The stromal vascular fraction (SVF) is a mixed cellular product from adipose tissue, containing ASCs, endothelial cells, pericytes, fibroblasts, and immune cells. SVF-gel, an extracellular matrix/SVF blend, retains viable SVF cells and adipose tissue structure[23,24]. SVF has demonstrated superior safety and consistent efficacy in improving pain and functional outcomes[13].

The SVF, a heterogeneous cell population derived from adipose tissue, has been identified as a promising candidate for regenerative medicine in OA[12]. Preclinical models have shown promising results regarding the therapeutic potential of SVF, which is rich in AD-MSCs, in terms of cartilage regeneration[25]. Clinical studies have also begun to explore the use of SVF, with some reporting significant improvements in pain, ROM, functional rating, and functional outcome scores in OA patients receiving intra-articular SVF injections[26-29]. These positive outcomes were often accompanied by low donor-site morbidity and minimal adverse events[26]. Comparative studies have further supported the therapeutic potential of SVF, highlighting its superiority over other treatments such as hyaluronic acid in terms of pain relief, functionality, and structural improvement[30,31]. The lack of standardized SVF products and variability in concomitant treatments present challenges in interpreting and comparing different clinical studies[29,32].

This study acknowledges the existing heterogeneity in the literature regarding the effectiveness of SVF in OA management, which can be attributed to variations in SVF formulation protocols employed across different studies[33,34]. To address this variability, our research presents a meticulously standardized SVF formulation protocol and conducts a comprehensive assessment of its therapeutic efficacy. This scholarly endeavor is positioned to lay a robust foundation for forthcoming studies in the field of OA management, with the overarching goal of promoting a uniform and effective application of SVF therapy in clinical practice.

MATERIALS AND METHODS

A prospective, longitudinal, comparative study was conducted at a single tertiary care institute between September 2021 to August 2023 after obtaining institutional ethical committee clearance [SU/SMS&R/76-A/2021/113]. A total of 50 adult patients with primary OA knee were eligible for recruitment in this study. Patients having grade 2 or grade 3 OA knee according to the Kellgren-Lawrence (K-L) scale who showed no symptomatic relief from the conservative line of management (NSAIDs, physiotherapy, weight loss) for 6 months and were fit for the procedure were included in the study. Exclusion criteria consisted of patients with grade 1 or grade 4 OA knee (K-L scale), severe deformity (> 10° in the coronal or sagittal plane), body mass index (BMI) > 35, concomitant meniscal/ligament involvement, inflammatory arthritis, rheumatological or other systemic diseases, malignancy, patients on immunosuppressive medication, previous history of knee surgeries or intra-articular injections of steroids or hyaluronic acid in the past 6 months, previous history of intra articular stem cell procedures post-traumatic arthritis and infections.

Group allocation

After obtaining informed consent, patients were divided into two groups in an alternating manner. Group A (n = 25) comprised patients who were allocated to receive a single injection of SVF intra-articularly, with a dosage of 10 cc containing 5.0 × 10^7 cells/10cc and 85% viability. On the other hand, Group B (n = 25) consisted of patients who received a single intra-articular corticosteroid injection (40 mg of triamcinolone (Tricort 40 mg, Cadila Pharmaceuticals Ltd., India).

SVF preparation

Under strict aseptic precautions, a stab incision on the lower part of the abdomen on both iliac fossa just above the ASIS using a No.11 blade was made for cannula entry after local infiltration with 1% lidocaine with epinephrine 1:100000. 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 anaesthesia on the infraumbilical area of the abdomen. Approximately 200 cc of adipose tissue was aspirated. Aspirated adipose tissue was washed with saline and subjected to centrifugation at 3000 rpm for 10 mins. The oil layer was discarded and adipose mass was subjected to fragmentation by intra-syringing (30 passages) and then subjected to centrifugation at 3000 rpm for 10 mins. The pellet separated was the SVF which contains the heterogeneous population of cells. The harvesting of adipose tissue to prepare SVF and intra-articular SVF implantation was performed with minimal manipulation of cells under the same surgical sitting.

Intra-articular SVF implantation (Group A)

Under strict aseptic precaution, the prepared autologous SVF (10 cc with a cellular dosage of 5.0 × 10^7 cells with a viability of > 85% (range: 82%–91% SVF cells) was implanted intra-articularly into each knee joint through the medial infrapatellar

fossa with the knee flexed to 90 degrees.

Intra-articular corticosteroid injection (Group B)

Under strict aseptic precaution, the corticosteroid (40 mg of triamcinolone) was injected intra-articularly into each knee joint through the medial infrapatellar fossa.

Post-operative protocol

Patients were started on full-weight-bearing mobilization immediately post-surgery. Physiotherapy included quadriceps and hamstring strengthening exercises and patients were permitted to do light activities as tolerated. All patients were made to avoid oral NSAIDs for at least 4 weeks following the procedure.

Outcome measures

All 50 patients were followed up regularly at 1, 3, 6, 12, and 24 months after the procedure. Patients were evaluated using a VAS pain score (0-10, with 10 being the most severe); and an International Knee Documentation Committee (IKDC) score (ranging from 0 to 100, with 100 representing the highest possible level of function and lowest degree of symptoms) both pre-operatively and at all follow-ups in-person *via* direct examination. Complications in both the groups and overall patient satisfaction at the final follow-up of 2 years were also documented along with magnetic resonance observation of cartilage repair tissue 2.0 knee score (MOCART 2.0) (0-100, with a higher score indicating better cartilage repair).

Statistical analysis

Statistical analysis was performed using a 2-tailed independent samples *t*-test for continuous data parameters such as VAS and IKDC scores. The Chi-square test or Fisher's Exact test was used for categorical data parameters. Statistical analysis was performed using SPSS Version 26 (International Business Machines- IBM, Armonk, NY, United States). Assuming a power of 80% and 95% confidence intervals, a *P* value less than 0.05 was considered significant.

RESULTS

A total of 50 patients were recruited during the study. Demographic and baseline clinical characteristics of the study population are summarized in Table 1. The mean age of the participants in the study was 48.23 12.07 years (Range: 31-70) with almost equal gender distribution. Both groups were comparable in terms of age, gender, BMI, and Kellgren-Lawrence grading with no statistical difference between the groups. Throughout the study, two patients from Group A (SVF) and one patient from Group B (Triamcinolone) were not contactable and lost to follow-up leaving a total of 47 patients (Group A, $n = 23$ and Group B, $n = 24$) eligible for final analysis.

Visual analog scale score

Group A exhibited a substantial reduction in visual analog scale (VAS) scores over 24 months, decreasing from 7.7 ± 1.1 pre-procedure to 2.4 ± 0.88 at 24 months ($P < 0.001$). Conversely, Group B also saw a decrease in VAS scores, but with a less pronounced change, going from 7.8 ± 0.8 pre-procedure to 6.2 ± 1.1 at 24 months. There were no significant differences in VAS scores between the two groups at baseline ($P = 0.71$). However, starting from the 3-month mark, significant differences emerged. Group A had a VAS score of 6.5 ± 1.8 compared to 7.6 ± 1.6 in Group B ($P = 0.03$). This difference became more pronounced at 6 months (4.3 ± 1.4 in Group A *vs* 6.8 ± 1.2 in Group B, $P < 0.001$) and remained highly significant at 12 and 24 months ($P < 0.001$) (Table 2 and Figure 1A).

IKDC score

Group A showed substantial improvement in their IKDC scores, increasing from an initial mean of 33.4 ± 10.20 to 83.10 ± 18.25 at the 24-month follow-up. In contrast, Group B had a less notable increase, starting at 36.7 ± 9.17 and reaching 45.16 ± 12.35 at 24 months. There was no significant difference in baseline IKDC scores ($P = 0.23$). However, starting at 6 months, Group A exhibited significantly higher IKDC scores compared to Group B (62.6 ± 13.27 *vs* 50.16 ± 12.35, $P = 0.001$) (Table 3 and Figure 1B). This difference continued to widen at 12 and 24 months ($P < 0.001$), emphasizing the sustained superiority of Group A's outcomes. The improvement in Group A was statistically significant from 6 months and maintained through 24 months.

Adverse effects

Throughout the study duration, no patients in either group reported complications related to the procedure, including donor site morbidity, local reactions around the knee, hematoma, or paraesthesia, underscoring the safety profile of both treatments.

Radiological analysis

At baseline, both groups demonstrated similar MOCART 2.0 scores with Group A showing a mean score of 52.7 ± 6.2 and Group B having a mean score of 53.3 ± 4.7. The difference between the groups was not statistically significant ($t = 0.37$, $P = 0.71$), indicating comparable conditions prior to the commencement of the respective treatments, as detailed in Table 4 and Figure 2. Remarkably, at the 24-month follow-up, the SVF group exhibited a significant improvement in MOCART 2.0 scores, averaging 91.8 ± 5.1. In contrast, the corticosteroid group presented a more modest improvement, with an

Table 1 Demographic characteristics of the study population, *n* (%)

Parameters	Group A (*n* = 25)	Group B (*n* = 25)	*P* value
Age (yr)			0.95
31–40	3 (12)	4 (16)	
41–50	6 (24)	5 (20)	
51–60	7 (28)	8 (32)	
61–70	9 (36)	8 (32)	
Sex			0.57
Male	12 (48)	14 (56)	
Female	13 (52)	11 (44)	
BMI			0.94
18.5-24.9	9 (36)	9 (36)	
25.0-29.9	8 (32)	9 (36)	
30.0-35.0	8 (32)	7 (28)	
K-L grading			0.58
II	11 (44)	13 (52)	
III	14 (56)	12 (48)	

Chi-square test. BMI: Body mass index.

Table 2 Visual analog score in various time-points

Time-point	Group A (*n* = 23)	Group B (*n* = 24)	Standard error	95%CI	*t*	*P* value
Pre-procedure	7.7 ± 1.1	7.8 ± 0.8	0.272	-0.44-0.64	0.37	0.71
1 month Follow-up	7.0 ± 1.8	7.2 ± 1.0	0.41	-0.62-1.02	0.48	0.561
3 months Follow-up	6.5 ± 1.8	7.6 ± 1.6	0.48	0.13-2.06	2.28	0.03
6 months Follow-up	4.3 ± 1.4	6.8 ± 1.2	0.36	1.75-3.24	6.78	< 0.001
12 months Follow-up	2.3 ± 0.20	6.1 ± 0.80	0.16	3.47-4.13	23.04	< 0.001
24 months Follow-up	2.4 ± 0.88	6.2 ± 1.1	0.27	3.25-4.34	13.97	< 0.001

Independent *t*-test.

Table 3 International Knee Documentation Committee score in various time-points

Time-point	Group A (*n* = 23)	Group B (*n* = 24)	Standard error	95%CI	*t*	*P* value
Pre-procedure	33.4 ± 10.20	36.7 ± 9.17	2.743	-2.22-8.82	1.20	0.23
1 month Follow-up	58.14 ± 17.23	56.6 ± 18.25	5.02	-11.63-8.55	-0.307	0.76
3 months Follow-up	60.3 ± 14.21	54.2 ± 13.25	3.88	-13.91-1.71	-1.57	0.12
6 months Follow-up	62.6 ± 13.27	50.16 ± 12.35	3.62	-19.72 to -5.15	-3.431	0.001
12 months Follow-up	78.3 ± 12.24	48.76 ± 12.17	3.45	-36.48 to -22.59	-8.56	< 0.001
24 months Follow-up	83.10 ± 18.25	45.16 ± 12.35	4.40	-46.80 to -29.07	-8.61	< 0.001

Independent *t*-test.

Table 4 Magnetic resonance observation of cartilage repair tissue 2.0 knee score at baseline and 24-month follow-up

Time-point	Group A (*n* = 23)	Group B (*n* = 24)	Standard error	95%CI	*t*	*P* value
Baseline	52.7 ± 6.2	53.3 ± 4.7	1.60	-2.62-3.82	0.37	0.71
24 months follow-up	91.8 ± 5.1	61.2 ± 8.4	2.03	-34.70 to -26.49	-15.01	< 0.001

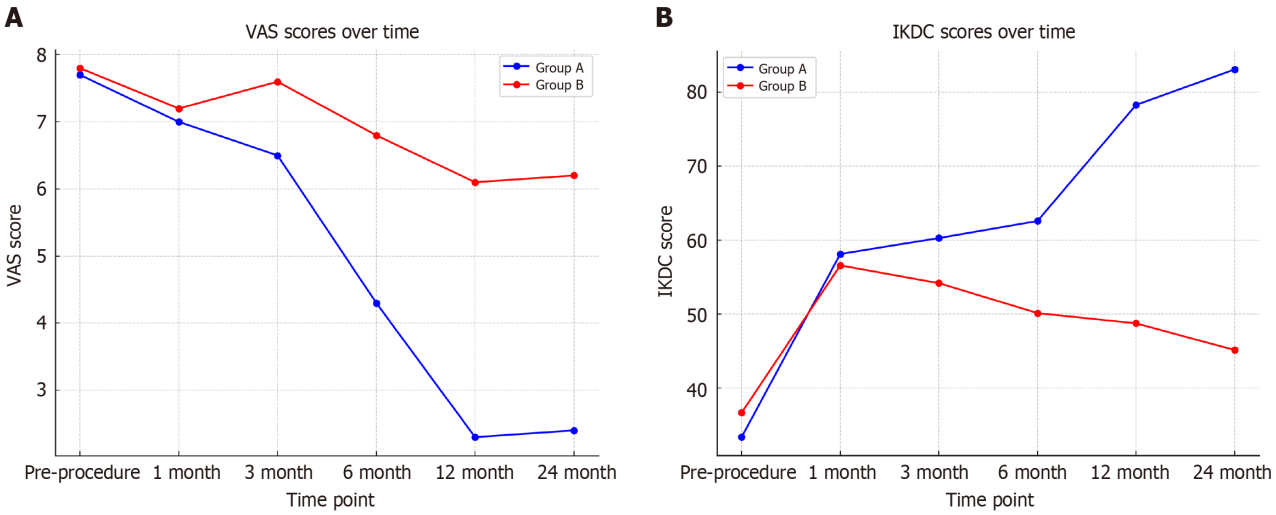


Figure 1 Graphical chart. A: Representation of Visual Analog Score over various time-points; B: Representation of International Knee Documentation Committee scores over various time-points. VAS: Visual Analog Score; IKDC: International Knee Documentation Committee.

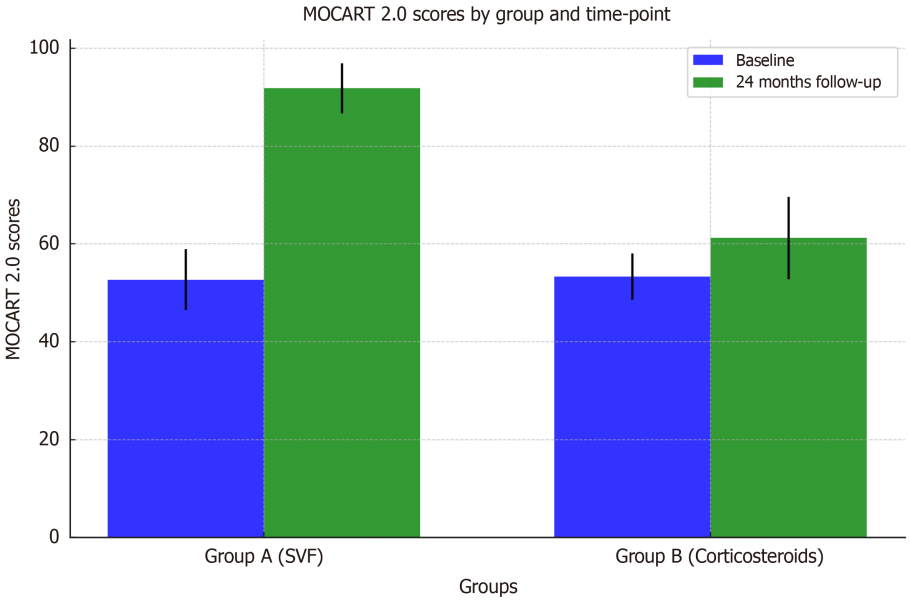


Figure 2 Magnetic resonance observation of cartilage repair tissue 2.0 knee score at baseline and 24-month follow-up.

average score of 61.2 ± 8.4. The difference between the groups at this time-point was statistically significant (t = -15.01, P < 0.001) with a 95% confidence interval ranging from -34.70 to -26.49, as reported in Table 4. This substantial difference indicates a markedly superior efficacy of SVF therapy over corticosteroids in improving KOA over a 24-month period. A representational case from group A and group B are depicted in Figures 3 and 4 respectively.

DISCUSSION

This research critically examines the utilization of SVF in the management of knee OA, a chronic and debilitating condition that affects millions worldwide. The evidence generated in this research is part of an expanding body of

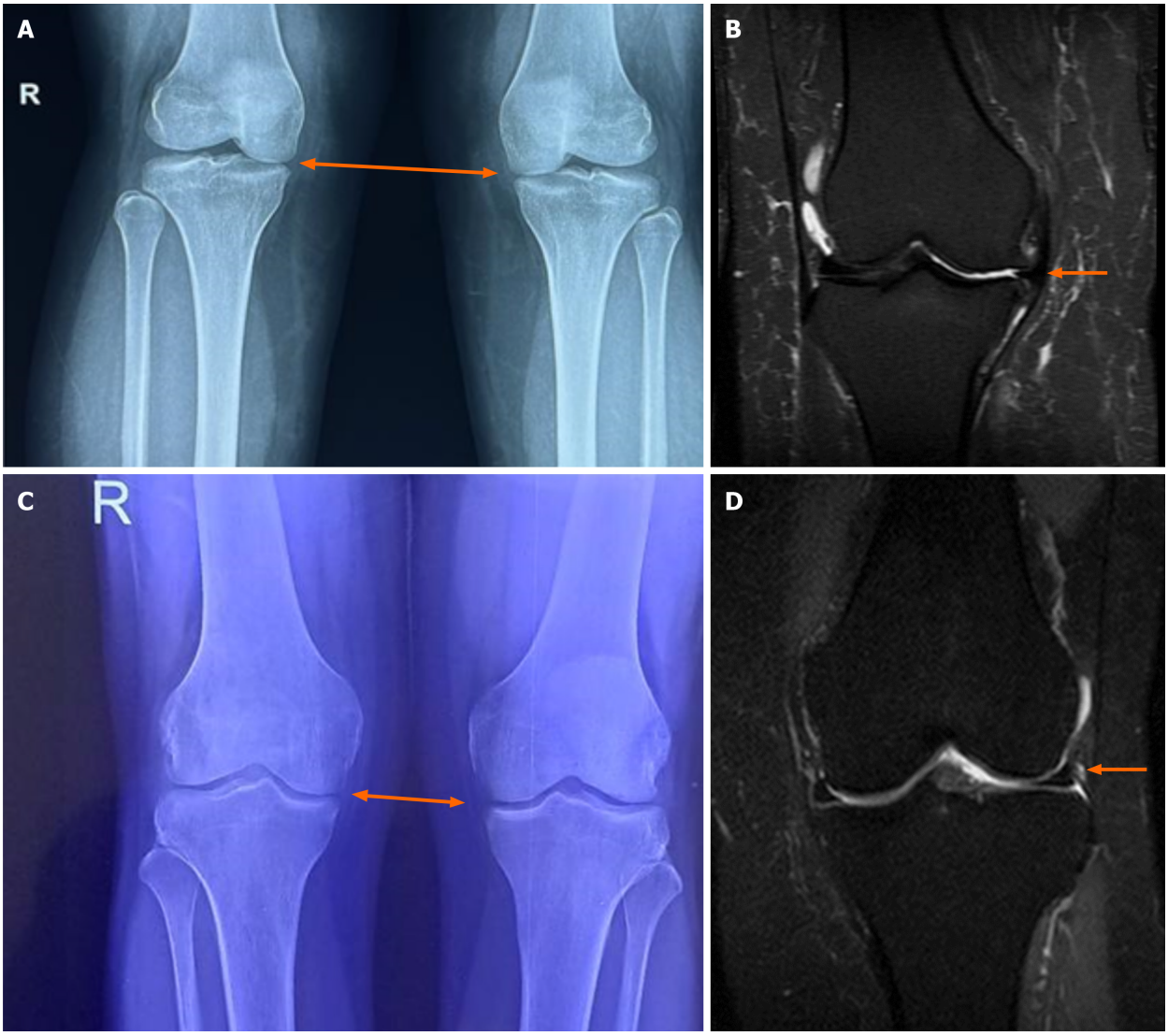


Figure 3 A representational case from group A. A: Pre-procedural radiograph of bilateral knees (anteroposterior (AP) view on standing position) showing decreased medial joint line in bilateral knees suggestive of Kellgren-Lawrence grade II knee osteoarthritis (OA); B: Pre-procedural T2W magnetic resonance imaging (MRI) (coronal section) showing hyperintensity with thinned out cartilage along the medial femoral condyle close to the medial meniscus suggestive of OA knee; C: 2-years follow-up radiograph of bilateral knees (AP view on standing position) showing subtle increase along with the maintenance of medial joint line in bilateral knees; D: 2-years follow-up T2W MRI (coronal image) showing increased cartilaginous thickness with relatively maintained cartilaginous signal indicating response to stromal vascular fraction therapy.

evidence that underscores both the safety and efficacy of SVF in the management of OA knee. Our study aligns with a growing consensus that AD-MSCs and SVF hold significant promise in the treatment of OA[13,22,35,36]. Previous studies report a range of positive outcomes from adipose-derived cell therapy, similar to our results[13,22,35,36]. These include reductions in pain, improvements in joint function, and enhanced quality of life. By adding our findings to this growing pool of research, we contribute further evidence to the potential of intra-articular administration of SVF in knee OA patients.

Our study utilized lipoaspirates as the source of AD-MSCs and SVF, similar to previous research[12,37,38]. However, the methodology employed for the extraction and application of these cells varied considerably across studies. Some studies used enzymatic digestion for the extraction of AD-MSCs, while others like ours relied on mechanical methods[12, 37,39]. The heterogeneity in cell preparation methodologies demonstrably impacted the purity, viability, and efficacy of the resultant cells, consequently influencing treatment outcomes. In response to this variability, initiatives were undertaken to achieve standardization of the cell formulation, thereby enhancing the repeatability and reproducibility of results. This standardization was underpinned by meticulous characterization of the cellular components. Our results demonstrate that adipose-derived therapies, especially the administration of SVF, can be a promising approach to managing knee OA, an outcome that corroborates the evidence from several previous investigations[37-39].

In light of the findings from our study, there is clear evidence pointing towards a substantial improvement in MOCART 2.0 Scores among participants in Group A, who were treated with SVF, when compared to Group B, who received corticosteroid treatment. This observed improvement from baseline to the 24-month follow-up underscores the potential efficacy of SVF as a therapeutic intervention for knee osteoarthritis (Figure 5). Our results resonate with the

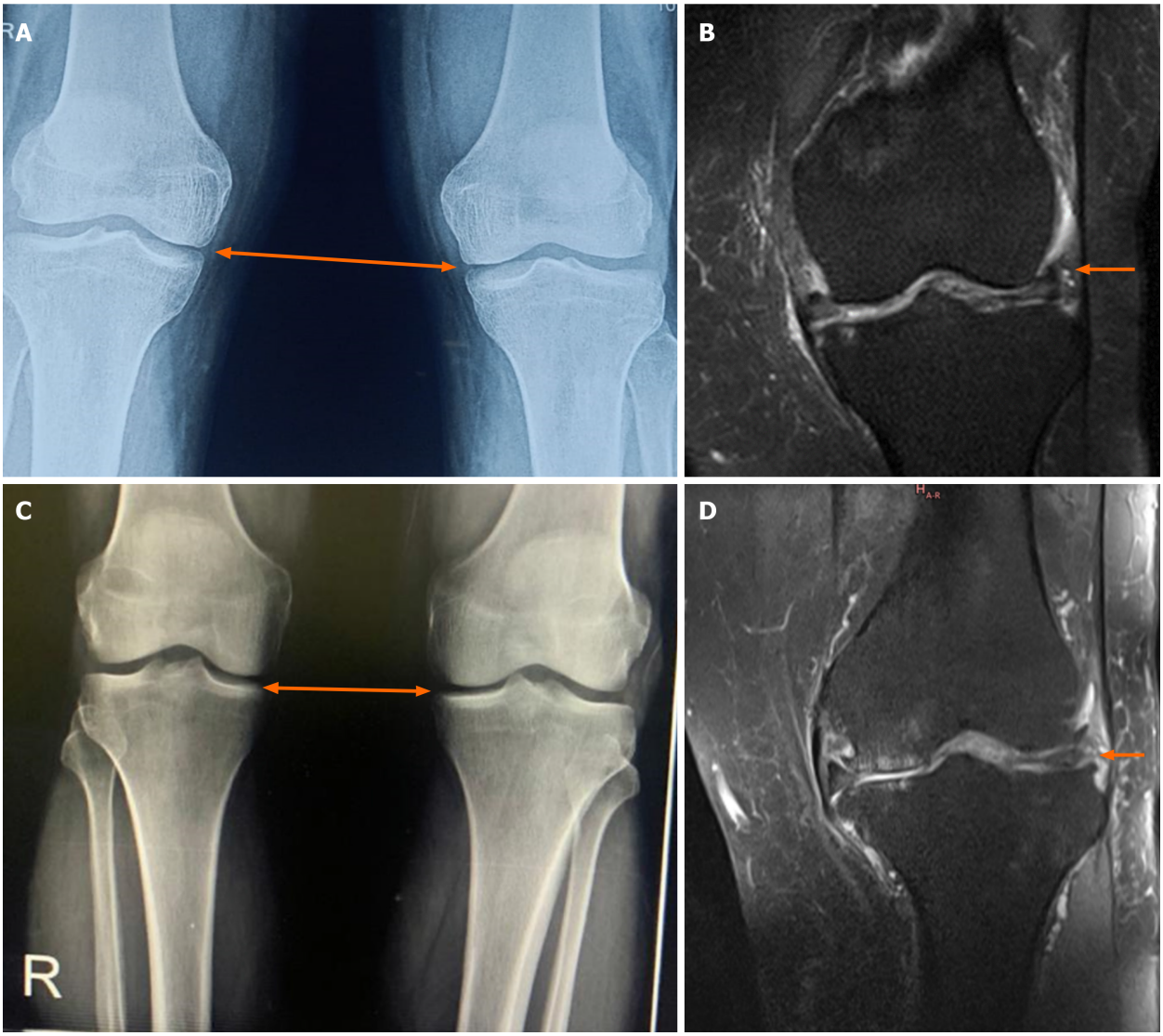


Figure 4 A representational case from group B. A: Pre-procedural radiograph of bilateral knees (anteroposterior (AP) view on standing position) showing decreased medial joint line in bilateral knees suggestive of Kellgren Lawrence grade II knee osteoarthritis (OA); B: Pre-procedural T2W magnetic resonance imaging (MRI) (coronal section) showing hyperintensity with thinned out cartilage along the medial femoral condyle suggestive of OA knee; C: 2-years follow-up radiograph of bilateral knees (AP view on standing position) showing no improvement in the thickness of medial joint line in bilateral knees; D: 2-years follow-up T2W MRI (coronal image) showing no cartilaginous thickness indicating response to corticosteroids therapy.

existing body of literature, particularly a systematic review focusing on SVF therapy for knee osteoarthritis[29,40]. This comprehensive review highlighted noteworthy enhancements in both pain levels, as assessed by the VAS, and functional outcomes, as measured using the WOMAC. Such congruence between our study and the broader scientific consensus further strengthens the case for SVF as a viable treatment option for this debilitating condition.

Our study has employed Patient Reported Outcome Measures (PROMs) extensively, which aligns with the increasing recognition of their importance in assessing therapeutic interventions[41-44]. PROMs provide insights into the patient's perception of their symptoms and the effects of treatment on their quality of life, enabling a more holistic evaluation of therapy effectiveness.

Our study, along with previous works, reveals inconsistencies in the duration of improvements following adipose-derived therapy[13,41,45]. These discrepancies underscore the necessity for a standardized protocol to effectively evaluate the long-term efficacy of these therapies. A significant observation in our research, aligning with Nguyen *et al*[46], is the variability in patient responses to AD-MSCs. This highlights the critical role of individual differences in regenerative medicine, emphasizing the need for a personalized approach to treatment. Factors such as age, overall health status, degree of tissue damage, and genetic factors are posited to significantly influence the therapeutic effectiveness of AD-MSCs and SVF, a theory also supported by findings from Koh *et al*[47].

Our findings are particularly relevant in the context of managing knee OA. Currently, the focus in knee OA treatment is predominantly on symptom control, with limited options for altering disease progression. The potential of adipose-derived therapies, as suggested by our study and others[29,33,38,48], lies in their ability to not only provide symptomatic relief but also possibly modify the disease trajectory. This represents a significant advancement in the current treatment paradigm for knee OA.

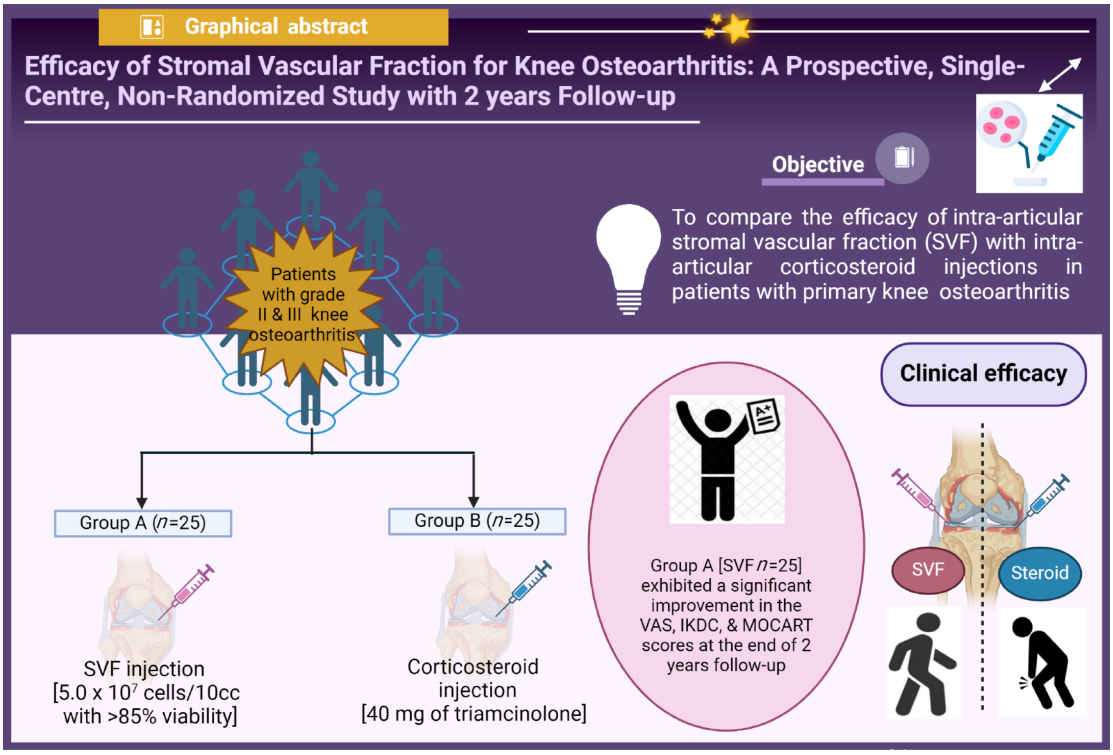


Figure 5 Graphical abstract demonstrating the summary of the study. SVF: Stromal vascular fraction; VAS: Visual analog score; IKDC: International knee documentation committee; MOCART: Magnetic resonance observation of cartilage repair tissue 2.0 knee score.

Moreover, our research substantiates the robust safety profile of adipose-derived therapies, consistent with previous studies[29,38,48-53]. While we observed minimal adverse events, which were transient and self-limiting, it's imperative to note that these findings are based on short-term studies. The long-term safety of these therapies remains an area for future research. In addition, our study offers fresh insights into the safety profiles of AD-MSCs *vs* SVF, an area not extensively explored in existing literature[50,53]. Despite the promising results, there remains a call, echoed by several other studies, for more comprehensive and rigorous research to fully ascertain the efficacy and safety of adipose-derived therapies[22,46,48,51,53,54]. This includes addressing potential risks associated with their extraction, processing, and application[22,53,54]. The emergence of novel approaches, such as nanofat grafting discussed by Jeyaraman *et al*[55], further underscores the potential of adipose-derived therapies, warranting continued exploration and validation.

Our research indicates that adipose-derived therapies show promise for treating knee OA, but further studies are needed to address unanswered questions and challenges. Future research should focus on standardizing treatment protocols, defining patient selection criteria, examining factors that influence individual responses, and ensuring safety to establish their clinical relevance. A balanced perspective is essential as we explore the potential of these therapies in regenerative medicine. Emphasizing rigorous study designs, comprehensive outcome measures, and standardized assessment methods will enhance the comparability of study results and improve clinical decision-making. Additionally, considering patient-specific factors, such as age and comorbidities, is crucial in choosing the most appropriate therapy, like AD-MSCs or SVF[54,56]. Hence, future research should strive to elucidate these factors' role in influencing treatment outcomes, unravel the complexities around dosing, and ascertain the long-term safety and efficacy of these therapies. Through such comprehensive research efforts, we can harness the full potential of these promising therapies, opening new horizons in the management of knee OA, and solidifying the potential of adipose-derived therapies as a key player in regenerative medicine.

Despite the promising findings from our study and others, it is crucial to acknowledge the limitations inherent in the existing body of evidence. The selection of patients who might benefit most from adipose-derived therapies requires clarification. It is plausible that the degree of OA severity could influence treatment outcomes. For example, patients with less advanced OA may have a better potential for tissue regeneration and could, therefore, show greater benefits from adipose-derived therapies than those with more advanced diseases. Studies exploring this possibility could provide essential guidance for clinicians when considering patient eligibility for these therapies. As Schmitz astutely pointed out, there are substantial methodological inconsistencies and flaws in many published studies on this topic[57]. Many investigations, including ours, have been limited by factors such as the lack of a control group, small sample sizes, and short follow-up durations. Such limitations could potentially introduce bias and confound the results, limiting the generalizability of the findings. The preliminary findings are promising but require cautious interpretation, emphasizing the need for rigorous, large-scale, and longer-term randomized controlled trials. These studies are essential for generating high-quality evidence to guide clinical practice. Additionally, further research is necessary to understand the mechanistic pathways underlying the therapeutic effects of AD-MSCs and SVF, which can improve the therapies' effectiveness and safety. The clinical application of adipose-derived therapies faces challenges, including regulatory obstacles, lack of

standardized protocols, and high costs, hindering their widespread adoption. To facilitate the translation of research into clinical use, concerted efforts should address these barriers. Collaborative efforts from researchers, clinicians, and policy-makers are essential to advance the field of adipose-derived therapies for knee OA. This study represents a step in this direction and encourages further investigations to build upon its findings.

CONCLUSION

Our study demonstrates that SVF therapy provides notable functional and pain improvement for patients with mild to moderate knee OA. In comparison to the short-term benefits offered by intra-articular corticosteroid injections, SVF shows the potential for longer-lasting results. However, to ensure the widespread integration of SVF therapy into routine clinical practice, larger randomized controlled studies involving a larger cohort are necessary to validate the efficacy and safety of SVF therapy and provide more comprehensive evidence for its adoption in the management of knee OA.

FOOTNOTES

Author contributions: Jeyaraman M and Jha SK contributed to conceptualization; Jeyaraman M, Jeyaraman N, and Ranjan R contributed to patient screening, acquired clinical data, performed the desired investigation and follow-up; Jeyaraman M, Jayakumar T, and Ramasubramanian S contributed to manuscript writing; Gupta A contributed to manuscript revision; Jeyaraman M, Gupta A, and Jha SK contributed to proofreading; Jha SK contributed to administration. All the authors have read and approved the final manuscript. Jeyaraman M and Jha SK have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. The collaboration between Jeyaraman M and Jha SK is crucial for the publication of this manuscript and other manuscripts still in preparation.

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Country/Territory of origin: India

ORCID number: Madhan Jeyaraman 0000-0002-9045-9493; Naveen Jeyaraman 0000-0002-4362-3326; Tarun Jayakumar 0000-0002-4305-1022; Swaminathan Ramasubramanian 0000-0001-8845-8427; Rajni Ranjan 0000-0003-2324-6970; Saurabh Kumar Jha 0000-0002-7437-0755; Ashim Gupta 0000-0003-1224-2755.

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