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ORIGINAL ARTICLE

Randomized Controlled Trial

Comparative outcome analyses of stromal vascular fraction *vs* nanofat in primary osteoarthritis knee: A double-blinded randomized controlled trial protocol

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Abstract

BACKGROUND

Osteoarthritis (OA) of the knee is a prevalent degenerative joint disease that significantly impairs quality of life and functional mobility. Emerging regenerative therapies, such as stromal vascular fraction (SVF) and nanofat, have demonstrated potential in cartilage repair and symptom alleviation. However, comparative clinical evidence evaluating their efficacy and safety remains limited.

AIM
To compare the clinical outcomes of SVF *vs* nanofat therapy in patients with primary knee OA.

METHODS
Conducted at Mother Cell Regenerative Centre, Trichy, over 18 months (June 2025 to December 2026), the study will enroll 30 patients, randomly assigned to two groups of 15 each. Both interventions will be administered as a single intra-articular injection under sterile conditions, with cell viability (> 85%) confirmed by a standardized assay. Group A will receive autologous SVF injections, while Group B will receive autologous nanofat injections. The primary outcome measure is the change in pain scores at 12 months using the visual analog scale (VAS). Secondary outcomes include functional improvement assessed by Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities (WOMAC), and International Knee Documentation Committee (IKDC) scores, cartilage regeneration evaluated *via* magnetic resonance imaging with colour coded mapping of the cartilage volume (MR cartigram), and monitoring of adverse events.

RESULTS
This study aims to evaluate pain reduction at 12 months post-injection, using the VAS as the primary outcome. Secondary outcomes include functional improvement (KOOS, WOMAC, IKDC), cartilage regeneration (T2 cartigram), adverse event incidence, patient satisfaction (standardized questionnaires, Likert scale), and quality of life (EQ-5D). Ethical considerations follow the Declaration of Helsinki and Good Clinical Practice, with IRB approval and participant informed consent ensured. Confidentiality and data security comply with regulations, and a Data Safety Monitoring Board oversees trial safety. Results will be shared *via* peer-reviewed journals, presentations at international orthopedic conferences, and detailed summaries for stakeholders and participants. The trial is registered under CTRI/2024/03/064076. Findings emphasize patient-centered advancements in knee osteoarthritis management.

CONCLUSION
This trial evaluates the efficacy and safety of SVF and nanofat therapies in knee OA, addressing a significant evidence gap. It employs robust methods to enhance cartilage repair and patient quality of life. Future research should standardize dosages, protocols, and injection techniques, explore autologous/allogenic preparations, and advance radiological tools, broadening accessibility and clinical applications.

Key Words: Osteoarthritis; Stromal vascular fraction; Nanofat; Regenerative therapy; Cartilage regeneration; Randomized controlled trial

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Core Tip: The double-blinded, randomized controlled trial at Mother Cell Regenerative Centre, Trichy, compares the efficacy and safety of stromal vascular fraction (SVF) *vs* nanofat in treating primary knee osteoarthritis. Over 18 months, 30 patients will receive either autologous SVF or nanofat injections. Primary outcome is pain reduction at 12 months, while secondary outcomes include functional improvement, cartilage regeneration, and monitoring adverse events. This study aims to provide clinical evidence for these regenerative therapies.

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INTRODUCTION

Osteoarthritis (OA) of the knee is a leading cause of disability worldwide, affecting millions of individuals and contributing to substantial healthcare burdens[1-4]. Characterized by the degeneration of articular cartilage, subchondral bone changes, and synovial inflammation, OA results in chronic pain, reduced joint function, and diminished quality of life[5-8]. Further, the disease by itself is not limited to cartilage or subchondral matrix but extends to involve meniscus, collateral ligaments and other joint tissue, hence called as a whole joint disease[9,10]. Traditional management strategies, including pharmacological interventions and surgical procedures, often provide symptomatic relief but fail to address the underlying cartilage damage and joint degeneration[11-14].

Recent advancements in regenerative medicine have introduced novel therapeutic approaches aimed at restoring joint integrity and function. Among these, stromal vascular fraction (SVF) and nanofat therapies have garnered significant

attention due to their regenerative and anti-inflammatory properties[15-17]. SVF, derived from adipose tissue, comprises a heterogeneous population of cells, including adipose-derived mesenchymal stem cells (AD-MSCs), endothelial cells, and immune cells, which collectively contribute to tissue repair and modulation of inflammatory responses[18]. Nanofat, on the other hand, is a mechanically emulsified form of adipose tissue that retains the stromal and vascular components essential for regenerative processes[19].

Preclinical and clinical studies have demonstrated the potential of both SVF and nanofat in promoting cartilage regeneration and reducing inflammation in OA knee[17,20-27]. However, direct comparative studies evaluating the efficacy and safety of SVF *vs* nanofat in human patients with primary knee OA are scarce[28,29]. Establishing a comparative analysis is crucial for determining the optimal regenerative therapy, considering factors such as treatment efficacy, safety profile, preparation protocols, and cost-effectiveness. The study aims to compare the efficacy and functional outcome of stromal vascular fraction and nanofat in primary osteoarthritis knees. The objectives of the study are (1) To compare the effectiveness of stromal vascular fraction and nanofat in knee osteoarthritis; (2) To assess the functional outcome of stromal vascular fraction and nanofat in knee osteoarthritis; and (3) To study the quantitative & qualitative imaging of cartilage regeneration following the therapy.

MATERIALS AND METHODS

Study design

This study is an unicentric, double-blinded, randomized controlled trial designed to compare the clinical outcomes of SVF *vs* nanofat therapy in patients with primary knee OA. The study will be conducted and reported in adherence to the Consolidated Standards of Reporting Trials guidelines[30]. Participants will be allocated to either the SVF group or the nanofat group in a 1:1 ratio using a computer-generated randomization sequence generated *via* a secure web-based system (randomization.com). Blinding will be maintained for patients, assessors, and statisticians to minimize bias.

Study setting

The trial will be conducted at Mother Cell Regenerative Centre, Trichy, within the Department of Orthopaedics. The center is equipped with advanced facilities for adipose tissue-derived therapies and imaging modalities necessary for comprehensive outcome assessments.

Sample size calculation

The sample size was calculated using the formula: $n = d2Z\alpha/22 \times P \times (1\text{-}P)$, where: $Z\alpha/2 = 1.96$ (95%CI).

P = Prevalence of early OA knee grade II and III = 3.5% (0.035)[31].

d = Desired margin of error = 7% (0.07).

Calculating: $n = (0.07)2(1.96)2 \times 0.035 \times (1 - 0.035) = 0.00493.8416 \times 0.035 \times 0.965 \approx 26.47$.

This estimate was based on previously reported prevalence data of early knee OA and preliminary pilot observations at our center, assuming a 95% confidence level and 80% power to detect clinically meaningful differences in pain and function. Considering a dropout rate of 15%, the total required sample size is 30 patients, divided equally into two groups of 15 each.

Randomization and blinding

Participants will be randomly assigned to either the SVF or nanofat group using a web-based randomization system. Randomization will use a permuted block design (block size of four) generated *via* a secure web-based system (randomization.com), ensuring balance between the two groups. A study coordinator not involved in recruitment or assessment will maintain the allocation sequence and prepare identical 10 mL syringes (containing approximately 5-6 mL of injectate), making certain that labeling is neutral and does not disclose the treatment arm. The injecting physician and outcome assessors will remain blinded to allocation throughout the trial. In the event of an adverse event requiring unblinding, the study coordinator will break the code in a controlled manner, with appropriate documentation. Allocation concealment will be ensured by employing sealed opaque envelopes. Blinding will be maintained for patients, outcome assessors, and statisticians to prevent bias in outcome evaluation.

Eligibility criteria

Inclusion criteria: Patients with age between 30-80 years of both sex; Patients with radiological primary osteoarthritis of knees (Kellgren Lawrence grade 2 & 3 based on X-ray findings); Patients with severe pain and under anti-inflammatory treatment without improvement > 3 months; Patients who have given consent for treatment as per our protocol; Regular visits in the out-patient department; Ability to comply with the home-based exercise regimen and scheduled follow-up visits.

Exclusion criteria: Patients with ages less than 30 and more than 80 years of both sex; Patients with advanced primary osteoarthritis of knees (Kellgren Lawrence grade 1 & 4 based on X-ray findings) and secondary osteoarthritis of knees; Patients with h/o prior corticosteroid injection at a treatment site within 3 months of duration; Patients with rheumatoid arthritis, inflammatory arthritis or polyarticular arthritis, and autoimmune diseases; Patients with hemoglobin < 10 gm/dL and platelet count < 10^5/μL; Patients with local infection at the site of the procedure, HIV, Hepatitis B or C, septicemia, other systemic metabolic disorders, bleeding, and other coagulation disorders.

After obtaining informed written consent from the patients enrolled in our study, they will be subjected to a thorough clinical examination to rule out the other causes of stiff and painful knee syndrome. The baseline investigations such as complete hemogram, erythrocyte sedimentation rate, C-reactive protein, renal function tests, random blood glucose, serological testing for HIV 1 & 2 and HbsAg, and radiographic analysis and MR cartigram of affected knee joint in a standing position will be done.

Preparation of stromal vascular fraction: After explaining the procedure to the patients in vernacular language, 300 mL of lipoaspirate will be aspirated from the lower part of the abdomen and rinsed with normal saline. The resultant adipose tissue will be converted into microfat by intrasynringing through the Leur Lok connector (30 passages) and filtration will be done to obtain nanofat. The resultant nanofat will be subjected to centrifugation at a rate of 1200 rpm for 5 minutes. The resultant column will contain an SVF pellet at the bottom of conical tubes as shown in Figure 1. A total of 5–6 mL of stromal vascular fraction (containing AD-MSCs) will be yielded with 300 mL of adipose tissue. Cell viability (> 85%) is confirmed *via* a trypan blue exclusion test on a small aliquot of the final pellet before intra-articular injection.

Preparation of nanofat: After explaining the procedure to the patients in vernacular language, 300 mL of lipoaspirate will be aspirated from the lower part of the abdomen and rinsed with normal saline. The resultant adipose tissue will be converted into microfat by intrasynringing through the Leur Lok connector (30 passages) and filtration will be done to obtain nanofat as shown in Figure 1. A total of 5-6 mL of nanofat (containing AD-MSCs) will be yielded with 300 mL of adipose tissue. We will likewise evaluate cell viability (> 85%) using the same trypan blue assay, confirming an adequate regenerative cell population in the final nanofat product. Further, flow cytometry of both nanofat and SVF will be done to quantify specific cellular populations present in SVF and confirm the absence of significant cellular content in nanofat.

Pre-procedural protocol: After obtaining a radiograph and magnetic resonance (MR) cartigram of the affected knee joint, the patient will be informed regarding the procedure, informed and written consent will be obtained and the patient will be taught active quadriceps exercises.

Intra-procedural protocol: Group A (n = 15) – One dose of 5-6 mL (cellular dosage of 5.0×10^7 cells with the viability of > 85%) of SVF injectate will be injected on each knee joint on day 0 under sterile conditions. The injection will be performed *via* a superolateral or anterolateral approach under ultrasound guidance with a 20-gauge needle, ensuring precise intra-articular placement.

Group B (n = 15) – One dose of 5-6 mL of nano fat injectate will be injected on each knee joint on day 0 under sterile conditions. The same ultrasound-guided superolateral or anterolateral approach with a 20-gauge needle will be used for nanofat injection.

All syringes will be covered by a non-transparent sleeve or label to obscure any differences in color or consistency. The same caliber needle will be used for both interventions. Neither the patient nor the injector will see the final contents prior to injection. After the procedure, containing dressing and crepe bandage will be applied. After 10 minutes of post-procedure, gentle knee mobilization exercises will be done for equal distribution of injected solution into the joint space. The patients will be trained for home-based active quadriceps and knee strengthening programs. All the patients will be advised to bear weight on a sequential weight bearing protocol after SVF or nano fat injection and the pain will be combated with ice pack application. NSAIDs and painkillers will be avoided in all patients.

Post-procedural protocol: Once SVF/Nanofat is injected into knee joints for osteoarthritis, the patients are advised to take adequate rest and ice fomentation therapy.Patients are advised to avoid full weight bearing for 48 to 72 hours and to perform active range of motion of knees along with active quadriceps exercises. Patients are advised to perform partial weight bearing from 3rd day to 7th post-op day and full weight bearing at the end of 1st week. Regular follow-up radiographs are performed at the end of 1, 3, 6, and 12 months. Functional scoring will be performed pre-procedurally and post-procedurally at the end of 1, 3, 6, and 12 months with visual analog scale (VAS), Knee injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities (WOMAC), and International Knee Documentation Committee (IKDC) scores[32-35]. Patients will be subjected for MR cartigram of the knee to check the cartilage thickness after 1 year as shown in Figure 2.

The standardized MR cartigram protocol will include T2 mapping and proton density sequences to assess cartilage thickness and integrity. Cartilage repair will be analyzed by two blinded musculoskeletal radiologists using a semi-quantitative grading system.

Statistical analysis

The statistical analysis will be done with Statistical Package for Social Sciences software Version 26, IBM Corp, Chicago, Illinois, United States. Both an intention-to-treat analysis and a per-protocol analysis will be performed to account for any missing data or dropouts, preserving the benefits of randomization while also examining treatment efficacy in those who fully adhere. To determine the effect of the intervention on the outcome variables, a paired t-test will be done to compare pre-procedure and post-procedure scores at the end of 1st, 2nd, 6th, and 12th-month follow-up scores for the VAS, KOOS, WOMAC, and IKDC scores for each group. Numerical variables will be compared by using the Kruskal-Wallis test. On the other hand, intra-group comparisons will be performed by using the Friedman test. If data are normally distributed, repeated-measures ANOVA with post-hoc Bonferroni corrections will be applied. If data deviate from normality, the Friedman test with pairwise Wilcoxon signed-rank tests will be employed. Categorical variables were compared by using Fisher's exact test. An alpha level of $P < 0.05$ will be used to determine statistical significance.

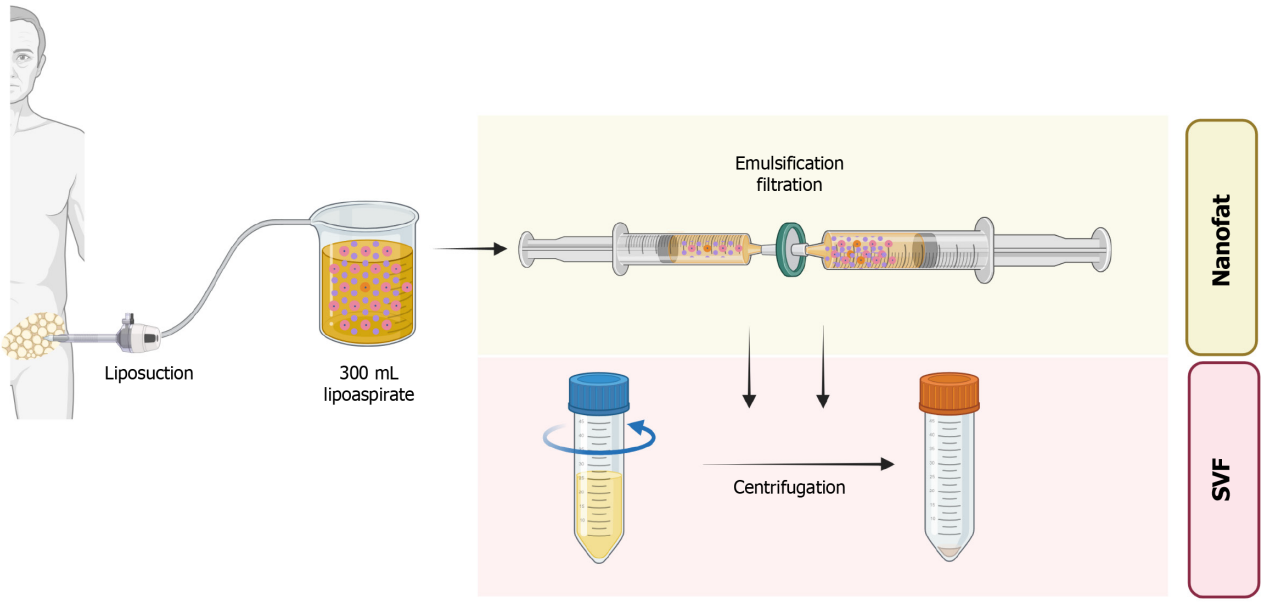

Figure 1 Isolation of stromal vascular fraction and nanofat from adipose tissue. SVF: Stromal vascular fraction.

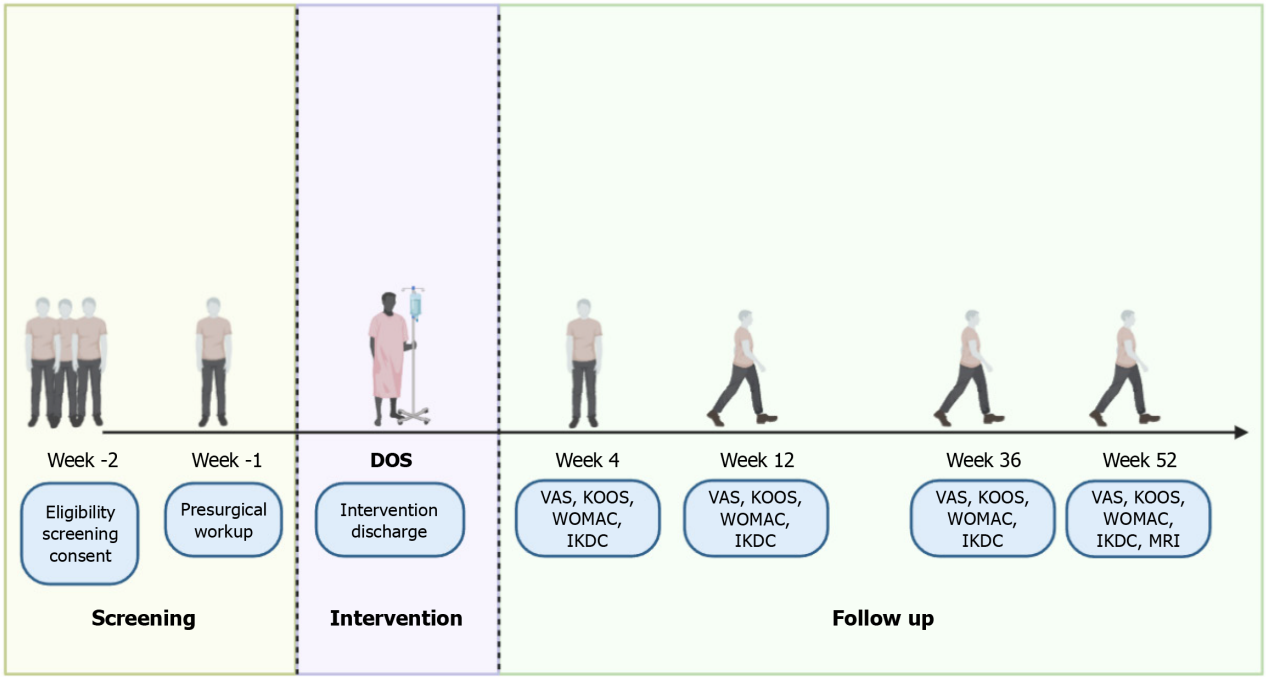

Figure 2 Timeframe of events in the proposed randomized controlled trial. VAS: Visual analog scale; KOOS: Osteoarthritis Outcome Score; WOMAC: Western Ontario and McMaster Universities; IKDC: International Knee Documentation Committee.

RESULTS

Outcome measures

Primary outcome: Change in pain scores at 12 months post-injection, measured using the VAS.

Secondary outcomes: (1) Functional improvement assessment by KOOS, WOMAC, and IKDC scores at various intervals; (2) Cartilage regeneration evaluation *via* MR carigram at 12 months; (3) Incidence of adverse events related to the treatments; (4) Patient satisfaction measurement through standardized questionnaires; (5) Quality of life improvements assessment using the EQ-5D scores; and (6) Patient satisfaction will be quantified using a 5-point Likert scale (ranging from 'very unsatisfied' to 'very satisfied'), documented at each follow-up interval.

Cartilage integrity will be assessed using T2 cartigram, a well-established MRI technique that provides a quantitative evaluation of cartilage health[36]. This method measures the T2 relaxation time of cartilage tissue, offering insights into the biochemical composition, particularly the hydration status and collagen fiber organization. The choice of a T2

cartigram is based on its ability to detect early degenerative changes in cartilage, which are critical in the context of knee osteoarthritis.

Ethical considerations

This study will adhere to the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval has been obtained from the institutional review board (IRB No. Plasmaart Resto Ethics Committee PR23NJS016 dated 28.10.2023). The clinical trial is registered under Clinical Trial Registry of India (CTRI) number CTRI/2024/03/064076 dated 13.03.2024. All participants will provide informed consent before enrollment. Confidentiality of participant data will be maintained, and data will be stored securely in compliance with relevant data protection regulations. Any serious adverse events will be reported to the institutional review board within 24 hours, and a Data Safety Monitoring Board will oversee ongoing trial safety.

Dissemination

The results of this trial will be disseminated through publication in peer-reviewed medical journals and presentations at international orthopedic and regenerative medicine conferences. Additionally, findings will be shared with healthcare stakeholders and participants through detailed reports and summaries.

DISCUSSION

OA of the knee remains a significant public health concern, contributing to substantial morbidity and decreased quality of life among the aging population[2,37-42]. Current therapeutic approaches, including pharmacological interventions and surgical procedures, primarily offer symptomatic relief without addressing the underlying degenerative changes in the joint[11,43-46]. This study aims to compare the efficacy and functional outcomes of two promising regenerative therapies—SVF and nanofat—in the treatment of primary knee OA. The discussion herein contextualizes our study within the existing body of literature, explores the potential implications of our findings, and delineates the strengths and limitations of our research design.

Our literature review underscores the therapeutic potential of both SVF and nanofat in cartilage regeneration and symptom alleviation in OA. Various studies have consistently demonstrated that SVF, rich in AD-MSCs, possesses regenerative and anti-inflammatory properties that facilitate cartilage repair and modulate the inflammatory milieu within the joint[47-49]. Similarly, nanofat therapy, characterized by its mechanically emulsified adipose tissue, has shown promise in enhancing chondrocyte viability and promoting anabolic processes while reducing catabolic markers in OA models[25,50-52].

In addition to their regenerative potential, both SVF and nanofat harness significant immunomodulatory capabilities [53,54]. Adipose tissue serves as a reservoir of diverse cell types—including mesenchymal stromal cells, endothelial progenitor cells, and various immune cells—that collectively secrete a broad array of cytokines and growth factors[18]. These secretions, notably interleukin-10 and transforming growth factor-β, help modulate the local inflammatory environment. By tempering inflammatory cascades and encouraging anabolic activity, these factors not only alleviate pain but also create conditions conducive to cartilage repair. Moreover, the heterogeneous cell composition inherent to adipose-derived preparations facilitates a dynamic immunoregulatory response[55,56]. The interplay between pro-inflammatory and anti-inflammatory mediators, along with a shift from M1 to M2 macrophage phenotypes and enhanced regulatory T-cell activity, contributes to a reduction in synovial inflammation[57-62]. This coordinated immunomodulation may play a pivotal role in mitigating joint degradation and slowing osteoarthritic progression, thereby augmenting the overall efficacy of both SVF and nanofat therapies.

Notably, comparative studies are limited, making our randomized controlled trial a crucial addition to the literature. Previous research indicates that both SVF and nanofat can significantly improve pain and functional outcomes in OA patients. For instance, SVF therapy has been associated with sustained pain relief and functional improvement over extended follow-up periods, with minimal adverse events reported[20-24]. On the other hand, nanofat injections have demonstrated significant improvements in pain scores and delayed the need for total knee arthroplasty in OA patients[17,25-27,52]. However, direct comparisons between these two therapies are sparse, necessitating studies like ours to establish their relative efficacy and safety profiles.

The outcomes of this study hold significant implications for clinical practice. Should SVF demonstrate superior efficacy in pain reduction and cartilage regeneration compared to nanofat, it could position SVF as the preferred regenerative therapy for primary knee OA. Conversely, if nanofat shows comparable or enhanced outcomes, it may offer a more cost-effective and easily prepared alternative, particularly beneficial in resource-constrained settings. Furthermore, understanding the differential effects on cartilage morphology *via* MRI could inform personalized treatment strategies, optimizing therapeutic outcomes based on individual patient profiles.

Strengths of the study

Several strengths underpin the robustness of our study design:

Randomized controlled design: The double-blind, randomized allocation minimizes selection bias and confounding, enhancing the internal validity of the findings.

Comprehensive outcome measures: By evaluating primary outcomes (pain scores *via* VAS) and multiple secondary outcomes (functional scores, cartilage regeneration on MRI, adverse events), the study provides a holistic assessment of therapeutic efficacy and safety.

Standardized protocols: Detailed intervention protocols for both SVF and nanofat ensure consistency in treatment administration, facilitating reproducibility and reliability of results. We have followed the standardized methods of preparation of SVF and nanofat as detailed earlier[19,21,63,64].

Ethical considerations: Adherence to ethical guidelines, including informed consent and data confidentiality, ensures the protection of participant rights and the integrity of the research process.

An essential strength lies in the double-blind structure, which reduces both observer and participant bias in subjective outcome measures such as VAS pain scores. By incorporating a robust randomization scheme—using a permuted block algorithm and neutral syringe labeling—we minimize the potential for allocation imbalances and ensure that neither patients nor clinical staff can predict group assignments. This meticulous approach is especially critical when evaluating treatments like SVF and nanofat, whose differences might be visually evident. Through careful masking of the injectate and strict allocation concealment, the current design offers a high level of internal validity.

Limitations of the study

Despite its strengths, the study is subject to certain limitations:

Sample size: With a total of 30 patients, the study may lack sufficient power to detect smaller effect sizes and generalize findings across diverse populations. Future studies with larger cohorts are warranted to validate our results.

Short follow-up duration: An 18-month study period may not capture long-term outcomes and potential delayed adverse events. Extending follow-up durations in subsequent research could provide more comprehensive insights into the durability of treatment effects.

Single-center design: Conducting the trial at a single center may limit the generalizability of the findings to other clinical settings with different patient demographics and treatment practices.

Variability in SVF and Nanofat preparations: Although standardized protocols are employed, inherent variability in adipose tissue-derived cell preparations may influence therapeutic outcomes. Inherent differences in the liposuction technique or adipose tissue microenvironment among participants may influence cell yields. Although standardized protocols are employed, such variability could affect the regenerative potential in each group, which may in turn limit the generalizability of our findings.

Blinding challenges: While efforts are made to maintain blinding, the distinct nature of SVF and nanofat preparations may inadvertently unblind participants or clinicians, potentially introducing bias.

Another notable limitation concerns the inherent challenge of masking treatments that may differ in appearance, consistency, or color. Despite using opaque syringe covers and a standardized injection protocol, subtle visual or tactile differences might inadvertently unblind the clinician or participant. Although the randomization technique reduces selection bias, larger multi-center trials would offer stronger external validity and better capture the nuances of real-world patient populations.

Future directions

Building on the findings of this study, future research should consider the following avenues:

Larger, multi-center trials: Expanding the sample size and involving multiple centers can enhance the generalizability and robustness of the findings, providing a more comprehensive understanding of SVF and nanofat efficacy across varied populations.

Long-term follow-up: Extending the follow-up period beyond 18 months will allow for the assessment of long-term benefits and potential late-onset adverse events, ensuring the sustained efficacy and safety of the therapies.

Mechanistic studies: Investigating the molecular and cellular mechanisms underlying the regenerative effects of SVF and nanofat can elucidate their pathways of action, optimizing therapeutic strategies and potentially enhancing efficacy.

Comparative effectiveness research: Direct comparisons with other regenerative therapies, such as platelet-rich plasma or cultured MSCs, can position SVF and nanofat within the broader landscape of regenerative medicine, guiding clinical decision-making. Further research should also explore the use of objective biomarkers (*e.g.*, serum or synovial fluid inflammatory markers) to correlate clinical improvement with local tissue changes, refining our understanding of the mechanisms behind SVF and nanofat efficacy.

Standardization of preparation protocols: Developing universally accepted protocols for SVF and nanofat preparation can reduce variability, ensuring consistent therapeutic outcomes and facilitating widespread clinical adoption.

CONCLUSION

This randomized controlled trial addresses a critical gap in the comparative clinical evidence for the efficacy and safety of SVF and nanofat therapies in the management of primary knee OA. As a condition associated with significant morbidity and diminished functional quality of life in the adult population, knee OA demands innovative treatment approaches. Regenerative therapies, particularly SVF and nanofat, hold significant promise in promoting cartilage repair and alleviating symptoms. By employing a robust study design, comprehensive outcome measures, and stringent adherence to ethical standards, this trial seeks to inform optimal regenerative treatment strategies and improve patient outcomes and quality of life.

The findings of this study will contribute meaningfully to the field of regenerative medicine in orthopedics. However, there remains considerable scope for further research to advance the field. Future studies should focus on the standardization of dosage and injection frequency for both SVF and nanofat therapies, alongside the development of universal protocols for preparation methods and injection techniques. Comparative investigations into autologous *vs* allogenic preparations are needed to optimize therapeutic efficacy. Additionally, the integration of advanced radiological tools to document cartilage regeneration comprehensively will enhance evidence-based practices. Exploration of allogenic formulations may further improve the accessibility and scalability of these promising therapies, ultimately broadening their clinical application.

FOOTNOTES

Author contributions: Jeyaraman N designed the research; Jeyaraman N and Nallakumarasamy A analyzed the articles for performing review and wrote the manuscript; Shrivastava S, Ravi VR, Ramasubramanian S, Muthu S, and Jeyaraman M finalized the manuscript.

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Informed consent statement: All authors consented in publishing the protocol.

Conflict-of-interest statement: No conflicts of interests in publishing the protocol.

Data sharing statement: Data is contained within the manuscript.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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