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Ultrasound-Guided PRP and SVF Therapy Shows Sustained Improvement in Severe Knee Osteoarthritis: A 12-Month Retrospective Study

Authors' Contribution:
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Statistical Analysis C
Data Interpretation D
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Background: Knee osteoarthritis (OA) is a chronic disease caused by cartilage degeneration in the joint accompanied by joint deformities, pain, and stiffness. This study assessed the changes over time in the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) and Visual Analog Scale (VAS) values of patients after the combined application of stromal vascular fraction (SVF) and platelet-rich plasma (PRP).

Material/Methods: A retrospective clinical study was designed. Thirty-four patients (8 males, 26 females, mean age 65.21±10.71, range 30-83 years) with pain due to knee osteoarthritis received SVF and PRP between 2019 and 2020. During and after the procedure, ultrasound-guided intra-articular spread was checked.

Results: PRP+SVF injection provided significant improvement in the clinical symptoms of the patients measured according to their VAS and WOMAC scores, and this improvement continued until the twelfth month. The change in VAS scores of the patients was 1.76±1.18 (P=0.000) in the first month, 1.50±1.46 (P=0.000) in the sixth month, and 1.53±1.41 (P=0.000) in the twelfth month. VAS scores decreased 6.6 to 1.6 point at the end of the twelfth month. The WOMAC scores of the patients were 23.20±12.12 (P=0.000) in the first month, 19.48±12.0 (P=0.000) in the sixth month, and 20.01±10.48 (P=0.000) in the twelfth month. WOMAC scores decreased 51.99 to 20.48 point at the end of the twelfth month.

Conclusions: Applying ultrasound-guided PRP+SVF injection into the knee joint once in OA patients improved VAS and WOMAC scores.

Keywords: Osteoarthritis • Pain • Stromal Cells • Treatment Outcome

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Introduction

Osteoarthritis (OA) of the knee is a chronic inflammatory disease that leads to cartilage degeneration in the joint, often accompanied by persistent pain, joint deformity, and stiffness [1]. The combination of these symptoms can lead to reduced mobility and quality of life [1,2]. OA remains the most common degenerative and progressive joint disease and is a major cause of pain and disability in adults, affecting approximately 7% of the world's population [3]. The increase in OA cases is likely due to factors such as aging and the emergence of poor metabolic health, particularly obesity [4]. Currently, widely used techniques for treatment of OA provide symptomatic relief but are not effective in regenerating damaged tissue, including repairing cartilage damage. No drug treatment will stop the progression of OA and modify the disease. Although physical therapy modalities and exercise provide partial cartilage recovery, they cannot stop the progression of the disease [5,6]. Although joint arthroplasty is an effective option for the last stage of the disease, it is considered the last option due to its high cost, long recovery period, and adverse effects [7]. The lack of an effective treatment option that changes the course of the disease for patients diagnosed with OA requires further research in regenerative medicine, which can improve the disease course by preventing and healing cartilage damage [8,9]. Regenerative medicine applications have become an option in the treatment of knee OA due to their fast recovery time and low cost compared to traditional methods consisting of pharmacological treatments, including analgesics and anti-inflammatory drugs, physical therapy, exercise, and surgical treatments such as arthroplasty. Stromal vascular fraction (SVF) is obtained by liposuction from adipose tissue via enzymatic or mechanical methods and has been widely used in the treatment of OA in recent years. Studies have shown that this treatment protects against joint degeneration, reduces pain, and increases cartilage volume and function [10-15]. Adipose-derived stem cells in the stromal vascular fraction obtained are multipotent stromal cells with regenerative capacities found in adipose tissue as progenitor cells (supra-adventitial cells and pericytes) [16,17]. In our study, the SVF was prepared by the enzymatic method in a certified laboratory and therefore contained a higher number of progenitor and nucleated cells per volume of lipoaspirate [18,19]. Platelet-rich plasma (PRP) is used in regenerative medicine in treatment of osteoarthritis of the knee. PRP can be easily obtained from centrifuged whole blood and is defined as a portion of the plasma fraction of autologous blood with a platelet concentration increase of 2 to 2.5, preferably above baseline [15]. PRP has been shown to slow the catabolic processes in the tissue or joint caused by the primary disease and to help restore an anabolic environment. In addition, many studies have been published showing that PRP is effective in the treatment of knee OA [20-25].

Therefore, this study was designed with the assumption that the combination of leukocyte-poor PRP and SVF prepared by an enzymatic method injected intra-articulary under ultrasound guidance would be a more effective treatment option in the treatment of knee OA and that this improvement would continue in the long term.

Material and Methods

Ethical Approval

Before the study, ethics approval was received from the Ethics Committee of Demiroglu Science University, Republic of Türkiye (date: 05.27.2020; meeting number 9; decision number 8: (2020/9-8)). Informed consent forms were obtained from all patients by face-to-face interview and approval of the written form. Patients were informed about potential adverse effects, such as bleeding, pain, skin bruising, and infection, as well as the fluid accumulation that can occur in the joint, related to the liposuction and intra-articular injection procedure. The study was conducted according to the Declaration of Helsinki, and patient data protection and privacy regulations were followed for all patient data accessed.

Participants and Design

In the retrospective clinical study, we included 46 patients who were admitted to our department between 2019 and 2020 with pain due to knee osteoarthritis, who received SVF+PRP injections in both knee joints. Among 46 patients who underwent SVF+PRP, 34 patients who met the inclusion criteria were selected for the study. Inclusion criteria were patients with diagnosed Grade 3-4 osteoarthritis, male and female, with pain in both knee joints, who did not respond to previous treatments, including physical therapy and medical treatments. Exclusion criteria were patients with severe uncontrolled disease, previous major knee trauma or surgery, mechanical pain due to severe meniscal damage, autoimmune or inflammatory arthritis, intra-articular injection of hyaluronic acid or corticosteroids in the previous 3 months, hormonal or hematologic disease, cancer, sepsis, antiaggregant therapy in the medical history, and patients who cannot come to follow-ups. Two patients could not be included because of diabetes mellitus and previous hemiplegia, 1 patient was diagnosed with cancer-associated lymphoma, 2 underwent intra-articular intervention within 3 months before the intervention, 3 of 7 did not give consent, and 4 could not be included because they did not regularly attend follow-up appointments for up to 12 months.

OA of the knee was defined according to the Kellgrene–Lawrence (KL) grading system and was confirmed by MRI and/or radiography. VAS and WOMAC scores obtained from the

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evaluation forms completed at baseline, 1 month, 6 months, and 12 months, as well as the patient's general health status, primary disease, and intervention-related adverse events, were reviewed and recorded. Demographic and other descriptive data from patient files were used for the study. The study outcome was the change in VAS and WOMAC scores over time in patients who underwent ultrasound-guided SVF+ leukocyte-poor PRP injection into both knee joints.

Adipose Tissue Harvesting

Adipose tissue harvesting and subsequent processing of SVF cells followed the International Guidelines and Protocols of the International Federation for Adipose Therapeutics and Science (IFATS) and International Society for Cellular Therapy (ISCT) [15,19,26].

The procedure was performed under conscious sedation in the operating room. On the day of the SVF injection, subcutaneous adipose tissue was harvested from the abdomen by tumescent liposuction [24].

Through a small incision (3.7 mm), a solution prepared with 10 ml 2% lidocaine and 0.1% adrenaline in 200 ml saline was infiltrated into the area to be liposuctioned with a blunt-tipped cannula. After waiting 10 minutes, the material collected with a blunt-tip liposuction cannula was centrifuged under sterile conditions, and the underlying fluid was discarded.

Tulip brand reusable infiltration and liposuction cannulas were used. Liposuction was performed on 34 patients included in the study. The liposuction time was approximately 20 minutes, including a 10-minute waiting period after infiltration. The liposuction procedure was performed by an experienced anesthesia and reanimation specialist trained in the field of pain management. We collected 100 cc of liposuction material and placed it in the transport container prepared by the certified laboratory. The final SVF product was sent to the laboratory for processing. Compression bandages were applied around the abdomen for 48 hours after the procedure.

Preparation of SVF Cells

Liposuction material (adipose tissue) was processed in a certified tissue laboratory (Florence Nightingale Tissue Laboratory-Florence Cell). This certification is known as good manufacturing practices., which issues a quality license after being inspected by the Ministries of Health of the countries included in the Pharmaceutical Inspection Co-operation Scheme. As described in previous studies and international standards, washing, collagenase treatment, stopping of collagenase activity, resaturation, isolation filtration, and the dilution of the pellet in a closed glass vial were performed.

In the certified laboratory, 100 ml of adipose tissue was mixed with collagenase NB4 in 50-ml falcon tubes in laminar flow cabinets. It is incubated for 1 hour at 37°C with shaking, then centrifuged at 400 g for 15 minutes. Shredded adipocytes and extracellular matrix were discarded along with the supernatant, and the pellet was collected. The collected pellet was suspended with phosphate buffer saline and centrifuged again at 400 g. The resulting pellet was prepared for use after contamination and cell viability tests.

The necessary tests for infection of the final product and the necessary certificate for the end user were prepared by the laboratory. A sample of the final product was stored in the appropriate laboratory for quality testing. A total of 6 ml of SVF solution for both knees of the patients was delivered to the clinic, where the application was performed in a sterile container in a glass vial.

PRP Preparation

We collected 40 cc of blood from each patient; 10 mL of blood was sent to a certified tissue laboratory for other control and quality testing, and 30 mL of blood was manually prepared in a sterile syringe for a total of 6 mL of leukocyte-depleted PRP (3 mL for each knee).

We centrifuged 30 ml of blood in Na citrate tubes at 400 g for 10 minutes. Plasma was collected and erythrocytes were discarded. The plasma was centrifuged again at 800 g for 15 minutes. The supernatant was discarded, and the pellet was prepared in the desired volume.

SVF+PRP Application

The patient was placed supine on the operating table. The injection site was sterilized with a povidone-iodine solution. Before treatment, a subcutaneous local anesthetic was applied to the suprapatellar lateral region of the knee joint. After the final evaluation of the knee joint under ultrasound guidance, the injection was performed through suprapatellar access.

The SVP+PRP injection was performed via in-plane intervention using the 15-20 high-frequency linear probe of the Fujifilm sonoside EDGE II ultrasound device. It was visualized that the needle was in the joint and that the injected PRP+SVF solution was spread throughout the joint with small manipulations in the position of the ultrasound probe. All applications were performed by an anesthesiology and reanimation specialist with 15 years of experience who was trained in the use of ultrasound and pain management interventions.

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Table 1. Descriptive characteristics of patients (n=34).

Characteristics		n	%
Age (M±SD) (Min-Max)		(65.21±10.71) (30-83)	
BMI	Underweight	1	2.94
	Normal	6	17.64
	Pre-obesity	13	38.24
	Class I	12	35.30
	Class II	2	5.88
	Class III	–	0.00
Gender	Male	8	23.50
	Female	26	76.50
Comorbidities	Yes	30	88.23
	No	4	11.77
Grade of arthritis (for each knee)	Grade	36	52.94
	Grade 4	32	47.05
SVF final product containing cells (M±SD) (Min-Max) (10^6)		(29.68±20.75) (8.63-87)	
The viability rate of the cells (M±SD) (Min-Max)		(89.94±3.91) (83.73-99)	
Sterility status		34	100.00
Pyrogenicity test	<0.25 EU/ml	18	52.94
	Not detected	16	47.06

SVF – stromal vascular fraction.

The viability rate of the cell populations of the SVF final product containing $29.68\times10^6\pm20.75\times10^6$ cells with nuclei was measured as (89.94±3.91)% (**Table 1**).

Delivered in a 6-ml glass vial, the product was divided in half, and 3 ml of cell suspension and 4 ml of leukocyte-poor PRP were injected slowly into the joint one after the other. During the intervention, an 18-gauge 1.5-inch needle was used. During and after the procedure, ultrasound-guided intra-articular spread was checked. The injection site was covered with a sterile bandage for 48 hours. After the injection, patients were discharged after 1 hour of rest. Patients were warned to avoid overloading their knees for 48 hours.

Statistics

The SPSS 22.0 Windows package program was used for data analysis. To evaluate the research data, frequency distributions (number, percentage) were used for categorical variables, and descriptive statistics (mean, standard deviation) were used for numerical variables. Changes in measurements over time were evaluated using repeated measures analysis of variance (ANOVA). The one-way ANOVA test, which is an extension of the dependent *t* test for repeated measurements, was used for repeated measurements. The Bonferroni test for post hoc analysis was used to compare the mean scores. The study accepted P=0.05 as the significance level.

Results

The patients' characteristics are presented in **Table 1**. Thirty-four patients were enrolled in the study (8 males, 26 female). The mean age of the patients was 65.21±10.71 years, 76.5% were female, 38.24% were pre-obese and 88.23% had comorbidities (30 of them had hypertension and 4 had hypercholesterolemia). A total of 68 joints were injected. According to the KL system, 36 knees had Grade 3 OA (52.94%) and 32 knees had Grade 4 OA (47.05%), while the SVF final product contained $29.68\times10^6\pm20.75\times10^6$ cells, the cell viability rate was 89.94±3.91, the pyrogenicity test was 52.94% <0.25 EU/ml, and 47.06% were not detected (**Table 1**).

The WOMAC and VAS scores of the patients before the intervention were 51.24±12.62 and 6.52±1.30, respectively. The results obtained based on ANOVA in repeated measurements

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Table 2. Comparison of baseline values over time.

	Baseline[a]	1st month[b]	6th month[c]	12th month[d]	*P***
VAS P*	6.52±1.30	1.76±1.18 **0.000** **a>b**	1.50±1.46 **0.000** **a>c**	1.53±1.41 **0.000** **a>d**	**0.000**
Pain P*	9.32±3.60	3.79±2.29 **0.000**	2.94±2.49 0.000	2.24±2.17 **0.000**	**0.000**
Stiffness P*	3.35±1.79	1.58±0.25 **0.000**	0.94±0.18 **0.000**	0.85±0.19 **0.000**	**0.000**
Physical function P*	36.23±8.82	16.97±9.20 **0.000**	14.97±9.13 **0.000**	16.32±8.11 **0.000**	**0.000**
WOMAC P*	51.24±12.62	23.20±12.12 **0.000** **a>b**	19.48±12.06 **0.000** **a>c**	20.01±10.48 **0.000** **a>d**	**0.000**

* Post hoc test: Bonferoni; ** repeated measures one-way ANOVA. VAS – visual analog scale; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index.

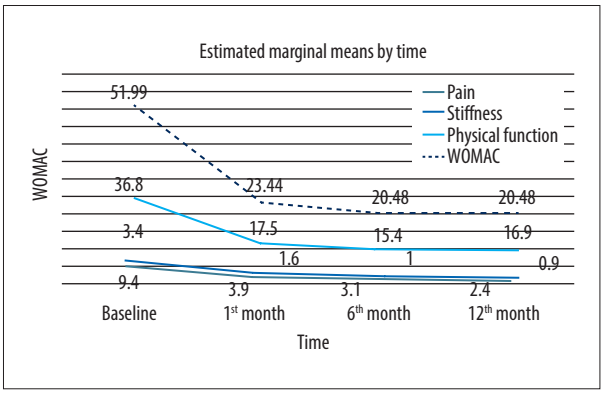

Figure 1. WOMAC and subgroups estimated means by time. WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index. *The Microsoft 365 Office program was used to create Figure.*

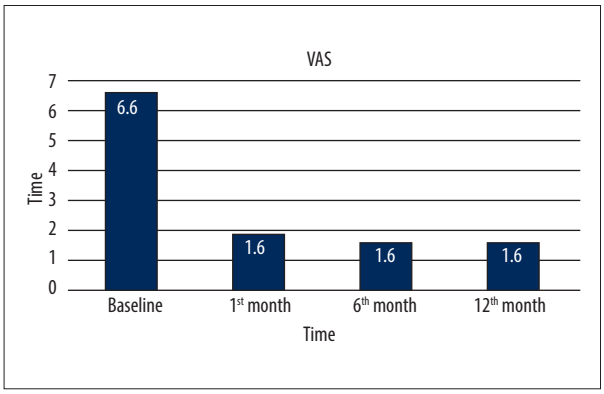

Figure 2. Graph of estimated marginal means of VAS over time. VAS – visual analog scale. *The Microsoft 365 Office program was used to create Figure.*

of changes in measured values over time showed that the change in VAS scores was 1.76±1.18 (*P*=0.000) in the first month, 1.50±1.46 (*P*=0.000) in the sixth month, and 1.53±1.41 (*P*=0.000) in the twelfth month, and that the highly significant change that started with the first month measurement continued in the sixth and twelfth months (**Table 2**).

The WOMAC scores of the patients were 23.20±12.12 (*P*=0.000) in the first month, 19.48±12.0 (*P*=0.000) in the sixth month, and 20.01±10.48 (*P*=0.000) in the twelfth month, and the change, which was also highly significant at the first month and continued at the sixth and twelfth months. The WOMAC subscales of pain were 3.79±2.29 (*P*=0.000) in the first month, 2.94±2.49 (*P*=0.000) sixth month, and 2.24±2.17 (*P*=0.000) in the twelfth month, and the highly significant change that started with the first month measurement continued in the sixth and twelfth months. The WOMAC subscales of stiffness were 1.58±0.25 (*P*=0.000) in the first month, 0.94±0.18 (*P*=0.000) sixth month, and 0.85±0.19 (*P*=0.000) in the twelfth month, and the highly significant change that started with the first-month measurement continue in the sixth and twelfth months. The WOMAC subscales of the physical function were 16.97±9.20 (*P*=0.000) in the first month, 14.97±9.13 (*P*=0.000) sixth month, and 16.32±8.11 (*P*=0.000) in the twelfth month, and the highly significant change that started with first-month measurement continue in the sixth and twelfth months. In the post hoc analysis, a significant difference was found in the first-month (*P*=0.000), sixth-month (*P*=0.000), and twelfth-month (*P*=0.000) values compared to VAS and WOMAC baseline values (**Table 2**).

When the estimated marginal means of WOMAC and subgroups were examined over time, it was found that they decreased

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significantly in the first month compared to the baseline, and these effects continued in the sixth and twelfth months compared to the baseline. WOMAC scores decreased from 51.99 to 20.48 points at the end of the twelfth month (**Figure 1**).

The graph of VAS estimated marginal means over time showed that they decreased significantly in the first month compared to the baseline, and these effects continued in the sixth and twelfth months compared to the baseline (**Figure 2**).

Swelling was observed at the injection site for 10 of the 34 patients for several days, and swelling and bruising was also observed at the liposuction site for 15 of the 34 patients; this was resolved within 2 weeks. Concerning other potential treatment-emergent adverse events, there were no adverse events, such as decreased knee range of motion, fat embolism, deep vein thrombosis, sepsis due to intra-articular infection, infection at the injection sites, or intra-articular bleeding. Two patients had fluid accumulation in both knees at different levels during the first week, which was drained under ultrasound guidance, and they did not require additional treatment in subsequent periods.

Discussion

This study demonstrated that a single injection of PRP+SVF into bilateral knee joints for Grade 3-4 OA resulted in a significant improvement in the clinical problems of these patients, as measured by VAS and WOMAC scores, from the first month, and this improvement was sustained for at least 12 months. Ultrasound-guided intervention not only ensured a safe procedure but also eliminated the risk of intra-articular access. To our knowledge, there are few similar studies in which high-quality SVF and PRP prepared by enzymatic method in a certified laboratory were applied to the knee joint under ultrasound guidance in cases of advanced OA (Grade 3-4) [20-22].

Ultrasound-guided knee injections are more accurate at the anatomical injection site compared with blinded/anatomically described injections [27]. Knee OA is typically the result of wear and progressive loss of articular cartilage. It has been proposed that progression of OA is associated with development of low-grade inflammation (LGI) in the joint. In support of this, LGI is also recognized as an important mechanism contributing to the pathogenesis of obesity, aging, and metabolic syndrome, which have been documented as major risk factors for development of OA. A better understanding of the pathological mechanism initiated by LGI in the joint is a critical step in the discovery of therapeutic strategies for the treatment of OA [28]. From this perspective, studies have shown that SVF exerts anti-inflammatory effects on chondrocytes and synoviocytes. SVF has been shown to exhibit immunosuppressive properties and release anti-inflammatory molecules such as IL-10, IL-1, receptor antagonist (IL-1ra), indoleamine 2,3-dioxygenase, transforming growth factor (TGF) β, and prostaglandin E2. Cells in the SVF appear to be able to sense and respond to the local environment in OA knees, which contributes to healing by stimulating angiogenesis, immunomodulation, and cell differentiation and proliferation [29,30].

A systematic review by Boada-Pladellorens et al concluded that SVF treatment is a promising treatment for OA in terms of improving pain, functionality, and anatomical structure, albeit with a low level of evidence. Their systematic review also demonstrated that SVF is a safe treatment for OA. However, they mentioned the lack of standardization of SVF products and the inability to conduct and compare high-quality studies as an important problem [31]. Although we used the products of a certified laboratory (Florence Nightingale Tissue Laboratory-Florence) that follows International Guidelines and Protocols International Federation for Adipose Therapeutics and Science (IFATS) and International Society for Cellular Therapy (ISCT) [15,19,26], optimizing dose frequency of injection and cell dose need to be standardized.

Lapuente et al found similar results to our study in terms of clinical outcomes at the end of a 1-year follow-up of injection of enzymatically produced SVF alone into 100 joints in 50 patients [32]. WOMAC and VAS scores showed significant improvement after 1-year follow-up, which is consistent with our study.

PRP, one of the regenerative medicine treatments, is used in the treatment of OA of the knee. It can be easily obtained from centrifuged whole blood and is defined as a portion of the plasma fraction of autologous blood with a platelet concentration increase of 2 to 2.5, preferably above baseline [15]. PRP has been shown to slow the catabolic processes in the tissue or joint caused by the primary disease and to help restore an anabolic environment [20-22]. Growth factors in PRP, such as hepatocyte growth factor, platelet-derived growth factor, IGF, and TGF-β1, inhibit the NFκβ signaling pathway, potentially reducing catabolic and antianabolic effects [33]. Numerous preclinical and clinical studies have shown variable results of PRP or SVF as OA treatment. However, there has been increasing interest in the combination of PRP and SVF [30,34,35].

In our study, we preferred to use PRP and SVF together. Our patients were diagnosed with Grade 3-4 osteoarthritis, and we felt that in these advanced cases we needed the synergistic effect of the 2 effective regenerative options available to us. In addition, the mechanisms discussed in detail in the sections above and the publications based on them support the use of SVF and PRP together.

Similar to our study, Pak et al, one of the first publications on this subject, applied SVF and enzymatically prepared PRP to 100 joints in many orthopedic conditions with similar results

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to ours; however, our study was limited to the knee joint only [28]. We believe that the use of leukocyte-poor PRP and the application of the injections under ultrasound guidance reduced the patients' symptoms related to local inflammation after the procedure, which positively influenced the recovery scores.

In their case series, Stevens et al used a combination of PRP+SVF, which they called "platelet-rich stroma," in the treatment of knee OA and demonstrated that a single injection of PRP into the knee with OA improved the physical and socio-emotional well-being of these patients up to 12 months after injection. However, in their MRI controls, they were unable to demonstrate the improvement in cartilage tissue that corresponded to this clinical improvement, which may be due to not using proper analysis of cartilage tissue [29].

The present study has 2 limitations. There was no control group, the sample size was small, and the placebo effect and the effect of intra-articular injection cannot be neglected in assessments. The strengths of our study are the significant improvement in symptoms of OA patients starting from the first month, and the increased safety by performing the procedure under ultrasound guidance.

0SVF combined with PRP has great potential as a therapeutic agent in regenerative medicine, especially in musculoskeletal diseases. The high number of MSCs in SVF makes it a suitable source for regenerative medicine. Preliminary studies suggest that this is a safe and effective method for the treatment of OA. The ultrasound-guided intervention not only ensured a safer procedure but also eliminated the risk of intra-articular access. Additional studies with more patients and control subjects are needed to confirm the above results. The results of this study suggest that combined intra-articular injection of SVF and PRP in the knee is a promising minimally invasive treatment for OA patients in whom other therapies have failed and before surgical treatment.

Conclusions

A single injection of PRP+SVF into bilateral knee joints for OA resulted in a highly significant improvement in the symptoms of these patients, as measured by VAS and WOMAC scores starting from the first month, and this improvement was sustained for at least 12 months. Further controlled trials with larger samples are required to determine the optimal dose, timing, and treatment regimen.

The authors confirm that all graphics are original, were created by the authors, and have not been published elsewhere.

Institution Where Work Was Done

This study was done at Gayrettepe Florence Nightingale Hospital, Besiktas, Istanbul, Türkiye.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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