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A modified protocol for mechanical extraction of stromal-vascular fraction in combination with platelet-rich plasma for osteochondral defects of the knee joint

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Abstracts

Introduction Mechanical isolation of the stromal vascular fraction (SVF) from autologous adipose tissue represents a promising approach in regenerative treatment of osteochondral defects of the knee joint. However, intra-articular SVF administration may be associated with a post-injection synovial reaction, which decreases the tolerability of the procedure and complicates early clinical assessment. Therefore, optimization of the cell preparation protocol aimed at improving biological purity and reducing reactive intra-articular changes remains clinically relevant.

Purpose To evaluate the impact of a modified mechanical SVF isolation protocol combined with highly concentrated platelet-rich plasma (P-PRP) on the severity and duration of post-injection synovial reaction in patients with osteochondral knee defects.

Materials and Methods A retrospective-and-prospective comparative non-randomized study included 62 patients. Group I consisted of 41 patients treated using the standard mechanical SVF protocol. Group II included 21 patients treated with a modified protocol incorporating liposaspirate washing, mechanical emulsification through a 0.6 mm filter, and P-PRP preparation using double centrifugation with ACD-A anticoagulant. Comparative analysis was performed based on the severity and duration of post-injection synovial reaction using clinical and instrumental stratification and ultrasound assessment.

Results In the standard protocol group, mild synovial reaction was observed in 4 (9.8 %) patients, moderate in 16 (39.0 %), and severe in 21 (51.2 %). In the modified protocol group, mild reaction was recorded in 11 (52.4 %) patients, moderate in 7 (33.3 %), and severe in 3 (14.3 %). The median duration of synovial reaction was 11 (9–12) days in the standard protocol and 5 (3–7) days in the modified protocol ($p < 0.001$).

Discussion The addition of liposaspirate washing and mechanical purification through a 0.6 mm filter in the protocol, along with double centrifugation using ACD-A, reduced the final injection volume and increased platelet concentration in PRP (> 1 × 10^6/μL), which was associated with decreased severity and shorter duration of synovial reaction.

Conclusion The modified mechanical SVF isolation protocol improves early post-injection tolerability by reducing the severity and duration of post-injection synovial reaction. The proposed technique is reproducible and may represent a promising approach for optimizing regenerative therapy in patients with osteochondral knee defects.

Keywords: stromal vascular fraction, chondromalacia, adipose-derived mesenchymal stromal cells

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INTRODUCTION

Currently, the problem of treating patients with osteochondral defects with adipose tissue-derived mesenchymal stromal cells (ADSCs) remains highly relevant, and therefore an important task is to find an optimal technique for performing the procedure that meets safety and efficacy criteria.

Degenerative diseases of the knee joint cartilage, including chondromalacia and patellofemoral osteoarthritis (PFOA), are among the most common causes of chronic anterior knee pain, especially in young and middle-aged individuals having active lifestyles [1–5]. In the individuals over 60 years of age, the incidence of isolated PFOA reaches 60–79% [3, 6, 7].

PFOA is characterized by progressive thinning of the articular cartilage at the contact area of the patella and femur, accompanied by pain, limited motion, and impaired support function of the limb. Key factors in its pathogenesis include impaired biomechanics, muscle imbalance, excess weight, post-traumatic changes, and anatomical features of the patellofemoral joint [3–5].

Current clinical guidelines recommend primarily conservative treatment, including kinesitherapy, weight loss, nonsteroidal anti-inflammatory drugs (NSAIDs), chondroprotectors, and intra-articular injections of hyaluronate or glucocorticosteroids [8]. However, the effectiveness of these approaches is limited, as they are primarily aimed at relieving symptoms and do not have a significant effect on the biological mechanisms of cartilage regeneration [9]. This is especially relevant for patients with chronic chondropathy, in whom degenerative changes are associated with subchondral sclerosis. The lack of timely diagnosis and adequate treatment results in the progression of degenerative changes and osteoarthritis of the patellofemoral joint.

In this regard, the development and implementation of effective conservative and minimally invasive treatment methods is particularly relevant. Among modern approaches, the most promising, according to some researchers, is the use of mesenchymal stromal cells, which have the potential to modulate inflammation and regenerate cartilage tissue [2, 10]. Thus, according to the literature, the use of autologous products, platelet-derived plasma (PRP) and stromal vascular fraction (SVF) of adipose tissue, demonstrate regenerative potential in degenerative joint lesions [2, 11–14].

However, despite the potential of biological methods, an important task remains to develop an optimal method for performing the procedure that combines high biological activity, safety and technological accessibility.

Purpose To evaluate the impact of a modified mechanical SVF isolation protocol combined with highly concentrated platelet-rich plasma (P-PRP) on the severity and duration of post-injection synovial reaction in patients with osteochondral knee defects.

MATERIAL AND METHODS

Our study investigated a modification of the existing protocol for intra-articular administration of autologous adipose tissue SVF in combination with platelet-rich plasma aimed to optimize the clinical tolerability of the procedure. A retrospective and prospective non-randomized comparative study of 62 patients with osteochondral defects of the knee joint treated with SVF was performed. The results of treatment according to the standard protocol (n = 41) were analyzed retrospectively, while patients treated with the modified technology (n = 21) were followed prospectively.

The study was conducted in accordance with the ethical principles set forth in the World Medical Association's Declaration of Helsinki (2013 edition, with subsequent amendments), as well as with the requirements of the Rules of Good Clinical Practice (GCP) and the Rules of Clinical Practice

in the Russian Federation, approved by Order of the Ministry of Health of Russia dated April 1, 2016, No. 200n. All study participants signed informed consent to participate and to publish anonymous data obtained during the study.

The sample was selected based on predetermined inclusion and exclusion criteria. The study included patients aged 25 to 65 years with diagnosed osteochondral defects of the knee joint in various locations, grades I–III according to the International Cartilage Repair Society (ICRS) classification. Clinical indications included knee pain, limited range of motion, occasional swelling, and evidence of chondromalacia or degenerative changes in the articular cartilage confirmed by magnetic resonance imaging.

A mandatory inclusion condition was the lack of a positive effect from standard conservative therapy, as evidenced by persistent pain and functional limitations. Conservative therapy was administered for at least three months and included kinesitherapy, nonsteroidal anti-inflammatory drugs, chondroprotectors, and intra-articular injections of hyaluronic acid or glucocorticosteroids. Patients participated in the study only after providing written informed consent for SVF therapy and subsequent follow-up.

Patients with inflammatory and autoimmune joint diseases (rheumatoid arthritis, gout, etc.), active infection, or signs of local inflammation in the knee joint were excluded from the study. Patients with severe somatic pathologies, including cancer, decompensated diabetes mellitus, and chronic heart failure of functional classes III-IV, were also excluded. Patients with hemostatic disorders, as well as patients receiving anticoagulant therapy and patients who had previously received intra-articular injections of biological agents (AOT, PRP, SVF, BMAC) earlier than six months prior to inclusion, were excluded. Pregnant and lactating women were also ineligible.

Statistical data processing was performed using descriptive and comparative statistics methods in the R version 3.2.4 software environment. Pearson's χ^2 test was used to compare independent groups by categorical characteristics. Comparison of synovial reaction duration between the groups was performed using the nonparametric Mann-Whitney test. Differences were considered statistically significant at $p < 0.05$.

All patients were divided into two groups (Table 1). Group I ($n = 41$) included patients who received therapy using the standard protocol of mechanical SVF isolation combined with autologous conditioned plasma using a double-syringe system. Group II ($n = 21$) included patients who received treatment using a modified protocol of mechanical SVF isolation followed by its combination with platelet-rich plasma, also applying a closed double-syringe system.

Table 1

Characteristics of patients in the groups

earlier		Group I (SVF standard), $n = 41$		Group II (SVF, modification), $n = 21$	
		абс.	%	абс.	%
Age, years	< 44	21	51,2	11	52,4
	45–59	16	39,0	8	38,1
	> 60	4	9,8	2	9,5
Gender	Males	28	68,3	12	57,1
	Females	13	31,7	9	42,9
BMI, kg/m²	< 25 (norma)	14	34,1	5	23,8
	25–29,9 (excessive)	19	46,3	12	57,1
	⩾ 30 (obesity)	8	19,5	4	19,0
Chondromalacia grade (ICRS)	I	3	7,3	3	14,3
	II	25	61,0	11	52,4
	III	13	31,7	7	33,3

A comparative assessment was conducted based on the severity and duration of the post-injection synovial reaction in the early post-injection period, which in this study we considered not as an inflammatory complication, but as a transient reaction of the intra-articular environment to SVF administration. Its severity was assessed on the second day after SVF therapy. Synovitis diagnosis was based on a combined assessment of clinical data, visual examination, ultrasound, and functional tests. The duration of the synovial reaction was determined based on follow-up examinations with ultrasound confirmation of normalization of the synovial fluid volume. Follow-up examinations were performed at intervals of two to three days until the ultrasound criterion for reaction completion was reached. The ultrasound criterion for synovial reaction completion was defined as a decrease in the thickness of the fluid layer in the suprapatellar (upper) recess to physiological values (0–3 mm).

For a comprehensive assessment of the impact of post-injection synovitis, a modified patient satisfaction scale (mPSS) was additionally used. It reflects the patient's subjective assessment of the general condition and quality of life in the early post-injection period. The scale included a five-point gradation from –2 to +2, where: –2 is a significant deterioration in condition and a sharp decline in quality of life; –1 is a moderate deterioration; 0 represents no significant changes; +1 is a moderate improvement; +2 is a significant improvement in well-being and functional activity. The mPSS scale was used exclusively to assess the subjective impact of the post-injection synovial reaction on quality of life and was not used to determine the severity of synovitis. The patient conducted a self-assessment based on their general well-being, pain intensity, range of motion, and daily activity on the second day after the procedure.

Mild synovitis was defined as a combination of the following clinical and instrumental signs: no visually detectable swelling of the knee joint; negative patellar ballottement sign; fluid layer thickness in the suprapatellar recess area according to ultrasound data of 0–5 mm (values of 0–3 mm corresponded to the physiological norm and were considered as part of the mild grade for standardized assessment); no restriction of range of motion or its minor limitation (extension deficit up to 5°, flexion up to 120°).

Moderate synovitis was recorded with a combination of the following clinical and instrumental signs: minor visually detectable swelling of the knee joint; negative ballottement sign; fluid layer thickness of 5–10 mm; limited range of motion (extension deficit 5–10°, flexion 110–120°).

Severe synovitis was characterized by a combination of the following clinical and instrumental signs: pronounced visually detectable swelling of the knee joint; positive ballottement symptom; fluid layer thickness of more than 10 mm; limited range of motion (extension deficit of 10–15°, flexion of 100–110°).

Note: The mPSS scale was used to assess the subjective impact of post-injection synovial reaction on quality of life and was not used to determine its severity. Range of motion is evaluated in degrees; extension values reflect extension deficit, while flexion values represent maximum active flexion.

The SVF collection system was a closed, dual-syringe design. The main syringe had a nominal volume of 20 ml, while the inner syringe held 8 ml. The piston base with the second syringe was equipped with a connector, allowing for the connection of 10 and 20 ml LUER LOCK syringes; this feature was utilized for the flushing step.

The modification of the protocol began with the inclusion of a lipoaspirate wash procedure after the primary centrifugation (2500 rpm, 1100 g, 4 minutes, Liston C2202). After removal of Klein's solution and the oil fraction, a fat fraction of approximately 10 ml was left. Ten ml of sterile saline

was added to the system, followed by mechanical mixing and repeated short-term centrifugation (2500 rpm, 1100 g, 1 minute, Liston C2202). The sediment containing residual cellular debris and erythrocytes was removed. Washing was performed one to three times until a homogeneous yellow fat mass free of blood was obtained (Fig. 1).

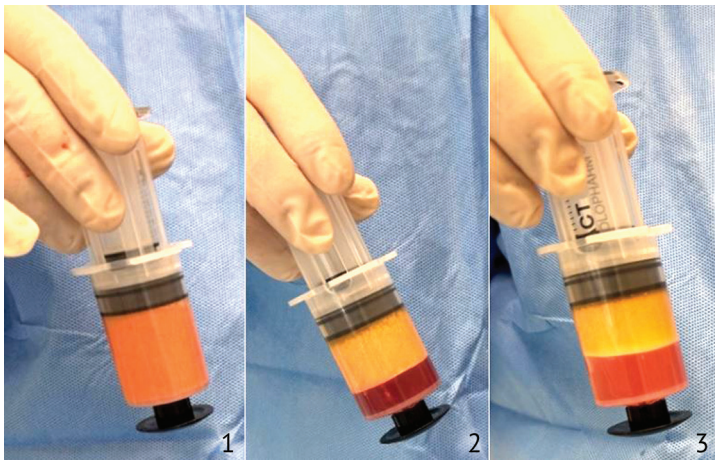

Fig. 1 Washing of adipose tissue with isotonic solution: 1 — syringe with lipoaspirate; 2 — lipoaspirate after the first centrifugation; 3 — final appearance of the fraction after washing

Next, the obtained fraction was mechanically processed through an emulsifier with a 0.6 mm diameter mesh, which ensured the removal of most of the connective tissue structures while maintaining the viability of the mesenchymal cells. The use of meshes of a smaller diameter led to increased pressure on the cells and an increased risk of their damage. A gentler mechanical processing of adipose tissue allows for minimizing damage to cellular structures and preserving the viability of the SVF cell populations [15]. After emulsification, repeated centrifugation was performed (2500 rpm, 1100 g, 4 minutes, Liston C2202), resulting in 2–3 ml of purified SVF, practically free of connective tissue fibers and excessive cellular substrate (Fig. 2). The time that took to obtain the SVF fraction was approximately 50 minutes from the start of subcutaneous fat infiltration.

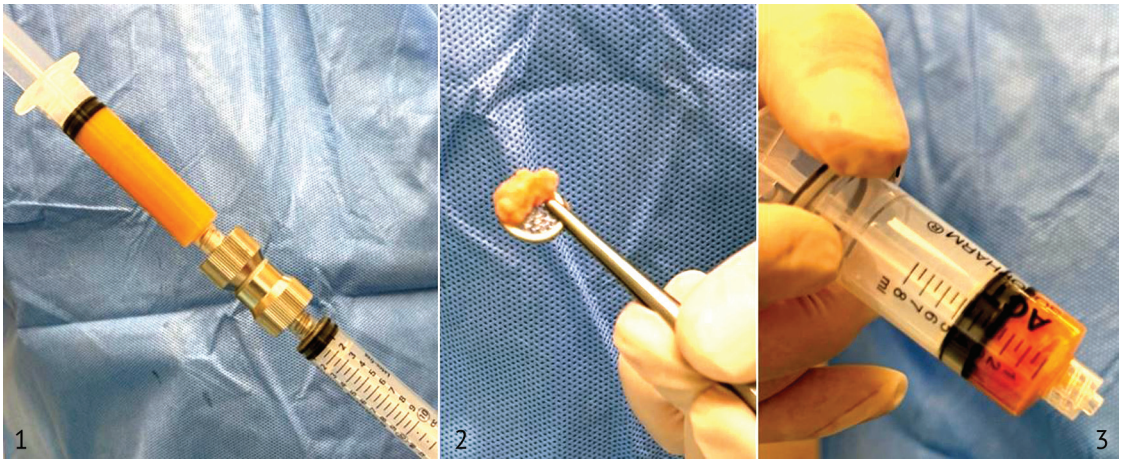

Fig. 2 The moment of mechanical cleaning from connective tissue fibers: 1 — general view of the syringe and emulsifier with a 0.6 mm filter; 2 — connective tissue fibers on the filter; 3 — final view of the SVF after washing

The next and technologically most complex stage of modification was the production of platelet-rich plasma (P-PRP) with the aim of reducing the final volume of the drug while simultaneously achieving a therapeutically significant platelet concentration (> 1 × 10^6/μl) with a low leukocyte content.

When using a double-syringe system with single centrifugation, the platelet concentration, according to the literature, is (583 ± 75) × 10^9/L (≈ 0.58 × 10^6/μL) [16], which is below the generally accepted therapeutically significant level of > 1 × 10^6/μL and limits the possibility of obtaining highly concentrated PRP in small volumes. The use of double centrifugation with 4 % sodium citrate did not ensure stable targeted platelet concentration.

For optimization, a double centrifugation method was used with the anticoagulant ACD-A (citrate-phosphate-dextrose), recommended for obtaining highly concentrated PRP [17].

The first centrifugation was performed at 1164 rpm (250 g) for eight minutes (CM-6MT). The upper two-thirds of the plasma were then collected, avoiding the buffy coat, which could reduce the effectiveness of platelet concentration. The resulting plasma was transferred to the main syringe of the system.

The second centrifugation was performed at 2350 rpm (1000 g) for 10 minutes (Liston C2202), resulting in the formation of a platelet pellet. For resuspension, the upper portion of the platelet-poor plasma was removed, leaving approximately 2 ml of supernatant plasma. Resuspension was performed in a double-syringe system by slowly moving the plasma between the syringes repeatedly, which prevented foaming and mechanical damage to the cellular elements. This resulted in P-PRP with a volume of approximately 2 ml with a platelet concentration exceeding 1 × 10^6/μl (Fig. 3). The time required to obtain P-PRP was 20 minutes; however, since this process was parallel with the SVF isolation process, this did not significantly increase the overall procedure time.

The final step involved mixing P-PRP with SVF, resulting in a final graft volume of 4–5 ml, allowing for easy injection through a 21G needle. The total time required to obtain the substance ready for injection was 60 minutes.

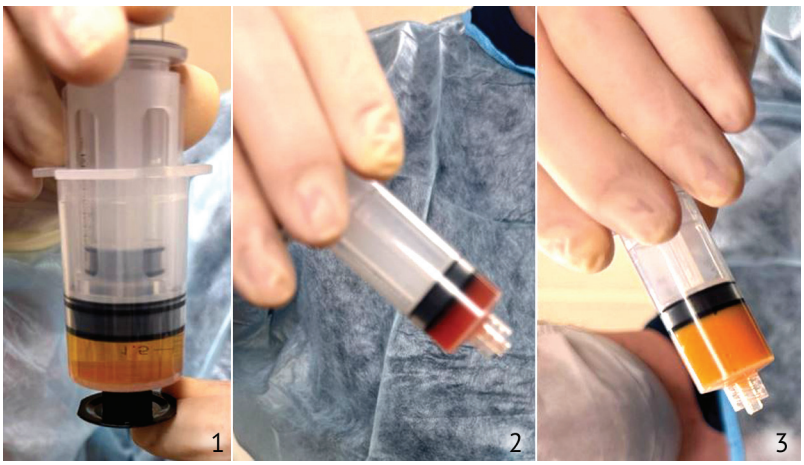

Fig. 3 The moment of obtaining platelet-rich plasma (1 — general appearance of plasma after the second centrifugation, a pellet with platelets is visible at the bottom of the syringe; 2 — appearance of plasma after resuspension; 3 — final appearance of SVF combined with platelet-rich plasma)

RESULTS

The distribution of the severity of post-injection synovial reaction differed significantly between the groups (χ^2 = 15.44; p < 0.001). In Group I of the standard SVF protocol (n = 41), the predominant degree of reaction was severe in 21 patients (51.2 %), moderate in 16 (39.0 %), mild in four (9.8 %) patients. In Group II of the modified protocol (n = 21), mild in 11 patients (52.4 %), moderate in seven (33.3 %), severe in only three (14.3 %). Thus, the use of the modified technology was accompanied by a significant decrease in the proportion of severe synovial reaction and an increase in the number of mild forms (Table 2).

Table 2

Comparison of synovitis severity by application of the standard and modified methods

Synovitis severity	Group I (SVF standard), *n* = 41		Group II (SVF, modification), *n* = 21	
	абс.	%	абс.	%
Mild synovitis	4	9.8	11	52.4
Moderate synovitis	16	39.0	7	33.3
Severe synovitis	21	51.2	3	14.3

Analysis of the duration of post-injection synovial reaction also revealed statistically significant differences between the groups. In the standard protocol group, the median duration was 11 days (Q1–Q3: 9–12; min–max: 7–15), whereas when using the modified technology it was five days (Q1–Q3: 3–7; min–max: 2–14). The differences were significant (Mann – Whitney test, $p < 0.001$). The values were (10.83 ± 2.07) days in Group I of the standard protocol and (5.43 ± 3.04) days in Group II of the modified technique, which reflects a more than twofold reduction in the duration of the reaction (Table 3).

Table 3

Duration of post-injection synovial reaction in the groups

Parameter	Group I (SVF standard), *n* = 41	Group II (SVF, modification), *n* = 21
Mean ± SD (days)	10.83 ± 2.07	5.43 ± 3.04
Median (Q1–Q3), days	11 (9–12)	5 (3–7)
Minimum – maximum, days	7–15	2–14

DISCUSSION

A comprehensive analysis of the obtained data demonstrates a statistically significant and clinically validated advantage of the modified protocol for mechanical SVF production. Its use is accompanied by a significant redistribution of the severity of post-injection synovial reactions toward milder forms, a reduction in the proportion of severe reactions, and a more than twofold reduction in their duration. The identified differences indicate decreased synovial membrane reactivity and a more physiological response of the intra-articular environment to the introduction of the cellular graft.

In the present study, we used a standard mechanical protocol for obtaining SVF in a closed system without the use of enzymatic agents as a control. This protocol involved mechanical disruption of adipose tissue through adapters of varying diameters. The resulting material was then mixed with autologous plasma. This approach is widely used in clinical practice and is characterized by its technological simplicity and safety [18].

Despite these advantages, the standard technique has several limitations. Specifically, the lack of a preliminary lipoaspirate wash hinders the removal of cellular debris, residual blood, and dissolved lipolysis products. Furthermore, the standard protocol does not include a filtration step, resulting in the final product retaining a significant amount of connective tissue structures. PRP preparation using the original technology is performed using a standard single-centrifugation protocol, which prevents achieving the maximum possible concentration of platelets and growth factors necessary to stimulate reparative processes in joint tissue. This results in a relatively large volume of injectable preparation (2–3 ml of SVF and 7–9 ml of AOT, a total of 9–12 ml), which may be considered excessive even for the knee joint. One of the key goals of this modification was to reduce the final volume of the injected preparation.

An additional clinical problem with standard SVF therapy protocols is the development of post-injection synovitis of the knee joint. An analysis of the causes suggests that the inflammatory reaction may be due to the presence of cellular debris, residual blood, connective tissue fibers, and the significant volume of the final product. These factors served as the basis for the development of a modified protocol for mechanical SVF production.

An important aspect of interpreting the obtained data is the understanding of the nature of post-injection synovitis. In this study, we viewed this condition not as an inflammatory complication, but as a transient reaction of the intra-articular environment to the introduction of biologically active autologous material. The clinical manifestations were reversible, unaccompanied by signs of infectious or systemic inflammation, and regressed spontaneously within a limited time. Given current understanding of the mechanisms of SVF action, this condition may reflect the adaptation of the synovial membrane to the altered cellular and molecular composition of the intra-articular environment. In this context, the reduction in its severity and duration with the modified protocol should be interpreted as a result of higher purification and optimization of the graft volume, rather than the prevention of an inflammatory complication.

The data obtained in the present study are comparable with published results of the use of mechanically isolated SVF and microfragmented adipose tissue in degenerative lesions of the knee joint. In a systematic review by Goncharov et al. [19], it was shown that intra-articular SVF administration is characterized by a favorable safety profile, and post-injection reactive phenomena are generally transient and regress within the first days after the procedure. Similar conclusions are presented in the review by Bora and Majumdar [20], which emphasizes the low incidence of serious inflammatory complications when using autologous SVF. In a clinical study by Russo et al. [21], devoted to the use of microfragmented adipose tissue in knee osteoarthritis, transient reactive phenomena were noted in the early post-injection period without persistent inflammatory complications. Similar data are presented by Totlis et al. [22]. In their work, a modified method of mechanical SVF isolation provided a high yield of viable cells and a favorable safety profile.

A number of studies noted that the intra-articular use of biological agents may be accompanied by a transient local reaction, while severe inflammatory complications are extremely rare [2, 11, 23, 24]. In our study, the use of a modified protocol was accompanied by a decrease in the proportion of pronounced synovial reaction to 14.3 % and a median duration of five days, which is within the range described in the literature [11, 20–23] and demonstrates a trend towards improved tolerability compared to the standard technique. This is consistent with published data and confirms the reproducibility of the identified trend. It should be noted that in most published studies, tolerability assessment is limited to subjective clinical symptoms, without standardized ultrasound gradation of effusion volume. In the present study, a comprehensive clinical and instrumental stratification of post-injection synovial reaction was used, which increases the objectivity of the assessment and allows for a more accurate comparison of various graft preparation protocols.

Unlike most described methods for mechanical SVF production, the presented protocol combines several steps aimed at standardizing and purifying the final cellular product. Key distinguishing features of the developed technology include the inclusion of a lipoaspirate washing step, which ensures the removal of cellular debris, red blood cells, and lipolysis products, as well as the use of an emulsifier with a 0.6 mm diameter filter mesh, which reduces the content of connective tissue fibers and produces a more homogeneous cell suspension. An additional advantage is the use of double centrifugation with the ACD-A anticoagulant, which ensures a higher platelet concentration in the plasma and simultaneously reduces its volume.

Despite the relatively limited sample size, the differences identified are statistically significant and clinically relevant. These results are promising and warrant further research with larger groups and a more in-depth assessment of long-term clinical outcomes.

CONCLUSION

The developed modified protocol for mechanical SVF production, including the steps of lipoaspirate washing, emulsification through a 0.6 mm diameter filter mesh, and production of highly concentrated platelet-rich plasma (P-PRP) by double centrifugation using the ACD-A anticoagulant in a closed system, demonstrated a statistically and clinically significant advantage over the standard method.

The use of the modified technology was accompanied by a significant redistribution of post-injection synovial reaction towards milder forms and a significant reduction in the proportion of severe reactions (14.3 % versus 51.2 %; $p < 0.001$). At the same time, a more than twofold reduction in the duration of reactive changes in the joint was noted: the median duration was 5 (3–7) days versus 11 (9–12) days with the use of the standard protocol ($p < 0.001$).

The results obtained indicate a decrease in the reactivity of the intra-articular environment and an increase in the biological tolerability of the graft if the modified protocol is used. The probable mechanism for these differences is the increased purification and standardization of the final cell product, as well as the reduced volume of injected material, which leads to a more physiological local tissue response.

The presented technology is reproducible, technologically feasible, and clinically valid. The statistically significant differences identified suggest that the modified protocol could be considered a promising approach to optimizing SVF therapy for osteochondral lesions of the knee and a basis for further prospective studies with a larger sample size and evaluation of long-term clinical outcomes.

Conflict of interests *None.*

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