Evaluation of the effect of injectable platelet-rich fibrin (I-PRF) in reducing the resorption of fat graft during facial lipostructure: A randomized clinical trial

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Abstract

Background. Fat graft is considered to be the ideal material for soft tissue augmentation. However, its disadvantage are unpredictable outcomes due to variable resorption.

Objectives. This study is the first clinical trial to evaluate the efficacy of adding injectable platelet-rich fibrin (I-PRF) to fat graft and to compare it with the conventional fat graft in terms of absorption rate.

Material and methods. The study was designed as a double-blind, randomized, controlled clinical trial. Twenty patients were randomly assigned with regard to the right or left nasolabial folds into 2 groups ($n = 10$ in each group): group A (fat graft only); and group B (fat graft with I-PRF). Surgical lipostructure was performed in accordance with the protocols described by Coleman. The adipose tissue was extracted from the umbilical region. Then, for the I-PRF preparation, peripheral venous blood was collected into plastic tubes. The follow-up recall visits took place after 1 and 12 months. Five investigators evaluated the pre- and post-surgical intervention photographs based on the Modified Fitzpatrick Wrinkle Scale (MFWS).

Results. The nasolabial fold depth scores were recorded at each of the study phases: before the intervention (1); after 1 month (2); and after 12 months (3). There were statistically significant differences between the scores at various study phases in each group. The Mann–Whitney *U* test was used to detect differences between the 2 groups. There was no statistically significant difference between the 2 groups regarding nasolabial fold depth 1 month after the intervention ($p = 0.360$). After 12 months, however, the patients in group A showed higher nasolabial fold depth scores as compared to group B; this difference was statistically significant ($p = 0.000$).

Conclusions. The study demonstrated the efficacy of I-PRF in reducing the resorption of fat graft, following facial lipostructure.

Keywords: injectable platelet-rich fibrin, fat graft, lipostructure

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Introduction

Autologous fat grafting has proven to be an excellent choice of treatment for the correction of acquired and congenital facial deformities.[1] Fat graft is considered to be the ideal material for soft tissue augmentation, since fat occurs in abundance, can be easily harvested from different body parts, has host compatibility, and is non-immunogenic.[2,3] Despite these merits, fat grafting techniques have a major disadvantage, namely a high resorption rate due to their failure to stimulate neoangiogenesis. Therefore, multiple attempts are often needed to correct facial defects with fat grafting.[4]

Since post-transplant revascularization is crucial for the retention of fat graft, several methods have been suggested to stimulate neoangiogenesis. Many strategies to induce revascularization have been proposed, including the use of growth factors. Basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF) have shown promising results in promoting angiogenesis and increasing vessel density, thus enhancing graft quality and survival.[5,6] Other growth factors, such as insulin-like growth factor (IGF), erythropoietin, and platelet-derived growth factor (PDGF), have also been demonstrated to have a positive effect on the survival of fat graft.[7,8] Unfortunately, the direct use of growth factors is of limited clinical utility due to their short half-lives and the risk of tissue hyperplasia.[9]

Platelet-rich plasma (PRP) was the first plasma concentrate developed in 1998.[10] When platelets are activated, they release various bioactive proteins, which are condensed in alpha granules along with other growth factors to increase the process of tissue repair and regeneration.[11] Platelet-rich plasma requires the addition of bovine thrombin or calcium ions upon initial blood collection to activate PDGFs, which is followed by the use of anticoagulants to generate a fluid concentrate after centrifugation.[12] The drawback of using PRP is that the growth factors are released excessively after adding coagulants such that they reach their peak concentration at the first hour and decrease significantly thereafter.[13,14]

Despite the fact that PRP has shown some improvement in facial skin appearance and texture, the clinical use of PRP is limited due to the heterogeneity of the employed preparation and administration techniques, and the lack of standardization of outcome measures.[15] Moreover, there are concerns over the use of thrombin and anticoagulants, as it may interfere with wound healing by inhibiting the clotting process.[16] To overcome these challenges, a second-generation platelet concentrate, platelet-rich fibrin (PRF), was introduced.[17]

The use of PRF is a totally autologous technique that involves a one-step centrifugation process and does not require any exogenous material. Platelet-rich fibrin has demonstrated advantages when used for the soft and bony tissue healing process, and in enhancing the survival rate of fat graft.[18] In 2014, an injectable fluid form of PRF (I-PRF) was developed by reducing the force of centrifugation. The use of a lower centrifugation speed selectively augments growth factors, platelets and leukocytes within the PRF fluid matrix.[19,20] Platelets and cytokines are hitched in the I-PRF fibrin matrix after injection, resulting in the slow and gradual release of growth factors over time.[21] Injectable PRF has reportedly been used in various oral and maxillofacial procedures, such as root surface biomodification and gingival augmentation.[22,23]

To the best of our knowledge, this study is the first clinical trial to evaluate the efficacy of adding I-PRF to fat graft and to compare it with the conventional fat graft in terms of absorption rate.

Material and methods

The Ethics Committee of the Faculty of Dentistry of Damascus University, Syria, provided ethical approval for this study. Informed written consent forms that described the purpose and scope of the study were signed by the participants. The study was designed as a double-blind, randomized, controlled clinical trial. It was recorded in the German Clinical Trials Register (DRKS – Deutschen Register Klinischer Studien) (ID: DRKS00023758). The CONSORT (Consolidated Standards of Reporting Trials) statement was used; the CONSORT flow diagram illustrating the research process is presented in Fig. 1.

Sample size determination

The sample size was calculated using the G*Power software, v. 3.1 (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower). The significance level was set at 0.05 and the power of the study was set at 95%. The sample size was determined to be a total of 20 patients randomized for treatment group A or B (10 patients in each arm).

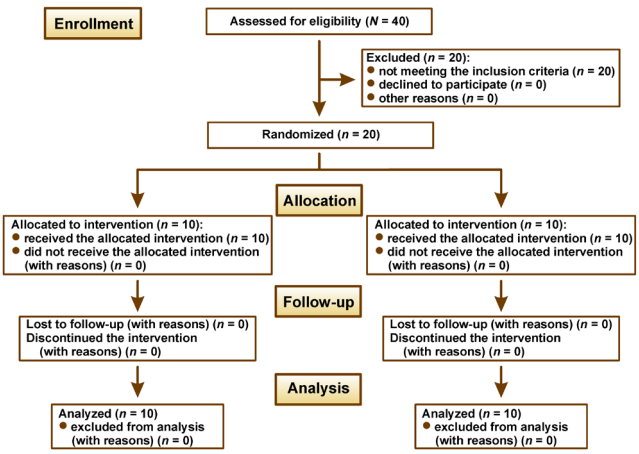

Fig. 1. Flow diagram of the study design according to the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement

Selection of participants

Twenty participants were selected from the patients attending the Department of Oral and Maxillofacial Surgery at the Faculty of Dentistry, Damascus University, according to the following inclusion and exclusion criteria as assessed by an experienced investigator:

– inclusion criteria: patients aged 18 years or older; and patients with a visible wrinkle score of 2 or 3 based on the Modified Fitzpatrick Wrinkle Scale (MFWS)[24] (moderate to deep wrinkles);
– exclusion criteria: patients under 18 years of age; patients with any systemic disease that affects the inflammatory response; patients who have previously underwent facial reconstruction surgery with the use of fat or any other filler; and patients with bleeding disorders (hemophilia, von Willebrand disease).

Allocation method

The participants were blinded to the kind of treatment applied. The units for randomization were treatment A or treatment B. An opaque envelope was used in the allocation process and each participant drew a lot from the envelope. The 2 kinds of treatment were as follows:

– treatment A (n = 10) – the injection of fat graft into the nasolabial fold; and
– treatment B (n = 10) – the injection of fat graft with I-PRF into the nasolabial fold.

Outcome measurement

The follow-up recalls were conducted after 1 and 12 months. Five investigators evaluated the pre- and post-surgical intervention photographs based on MFWS. All examiners were blinded as to which side received treatment A or B, as well as to other reviewers' responses. They were asked to provide the corresponding score from 0 to 3 based on MFWS (Table 1).

Table 1. Modified Fitzpatrick Wrinkle Scale (MFWS) (the evaluation of wrinkle depth is based on the assessors' estimation rather than a physical measurement)

Score	Discretion
0	no wrinkle; no visible wrinkle, a continuous skin line
0.5	very shallow yet visible wrinkle
1	fine wrinkle; visible wrinkle and slight indentation
1.5	visible wrinkle and clear indentation (wrinkle depth <1 mm)
2	moderate wrinkle; clearly visible wrinkle (wrinkle depth of 1–2 mm)
2.5	prominent and visible wrinkle (wrinkle depth >2 mm and <3 mm)
3	deep wrinkle; deep and furrow wrinkle (wrinkle depth >3 mm)

Fat preparation

Surgical lipostructure was performed in accordance with the protocols described by Coleman.[25] The adipose tissue was extracted from the umbilical region. The extraction was carried by means of a special aspiration nozzle with a diameter of 3 mm and a length of 15 cm, with foam ends and openings on both sides. Approximately 60 mL of fat was extracted; there were variations between the patients depending on the indication and the amount required for re-injection. The next step in the preparation process was the centrifugation of the extracted tissue. The 10-milliliter syringes were sealed and centrifugation was performed for 3 min at a speed of 3,000 rpm. Once centrifuged, the syringe contents were divided into 3 layers. The upper layer included triglycerides from the damaged adipocytes; this part is usually eliminated. The middle layer contained adipocytes, which were grafted. The bottom layer contained primarily blood debris, which was eliminated when the syringe was withdrawn.

I-PRF preparation

At the start of each treatment session, 40 mL of peripheral venous blood was collected into a sterile 10-milliliter plastic PRF tube without an anticoagulant and centrifuged immediately at room temperature, using a low relative centrifugal force of 700 rpm for 3 min.[26]

Combination of I-PRF and fat

The activation of coagulation and central forces formed 2 layers in the tube – a liquid top layer that represented I-PRF, which was drawn into a new sterile tube for use, and a lower layer that contained red blood cells, which was removed. According to Coleman's technique,[27] the resulting I-PRF was mixed with fat graft material and injected into the face. The harvested tissue was added gradually. Cannulas of various lengths and shapes were used to reduce the risk of hematoma formation, and lateral injection apertures were used to avoid injection into blood vessels.

Statistical analysis

The level of significance (p-value) and the power of the study were set at 0.05 and 90%, respectively. The Friedman test was applied to study differences in the depth of the nasolabial folds between the study phases in each group. The post hoc Wilcoxon test was used to show differences more precisely. In addition, the Mann–Whitney U test was carried out to study differences between the 2 groups. The IBM SPSS Statistics for Windows software, v. 23.0 (IBM Corp., Armonk, USA), was used to perform the statistical analysis.

Results

The sample consisted of 20 patients. Each patient was randomly assigned into one of the 2 groups: group A (fat graft only); or group B (fat graft with I-PRF). The gender and age of the participants are summarized in Table 2.

Follow-up evaluations were conducted after 1 and 12 months to record the changes in nasolabial fold depth caused by the interventions according to MFWS. The scores of the nasolabial fold depth were recorded for each of the 3 study phases. The study phases corresponded to the assessments made before the intervention (1), 1 month after the intervention (2) and 12 months after the intervention (3). The frequencies of each score for nasolabial fold depth within each group through the study phases are recorded in Table 3.

In order to study differences in nasolabial fold depth between the study phases in each group, the Friedman test was applied. It revealed that there were statistically significant differences between the study phases for each group. Table 4 presents the mean ranks for nasolabial fold depth and the Friedman test results. Pairwise comparisons with the use of the Wilcoxon test revealed that the differences between all the particular phases of the study for both treatment groups were statistically significant (Table 5). When analyzing the mean ranks for nasolabial fold depth shown in Table 4, it can be noticed that the lowest nasolabial fold depth values were recorded in study phase 2. The values were higher 1 year after the intervention, but still lower than those recorded before the intervention.

The Mann–Whitney *U* test was carried out to study differences between the 2 groups. The test showed that 1 year after the intervention, the patients in group A had higher scores for nasolabial fold depth than those in group B; this difference was statistically significant (p = 0.000). This means that the resorption rate of the fat injected was higher in group A in comparison with group B. Conversely, there was no statistically significant difference between the 2 groups regarding nasolabial fold depth 1 month after the intervention (p = 0.360) (Table 6).

Table 2. Gender and age of the study participants

Characteristics	*N* = 20
Male *n* (%)	2 (10)
Female *n* (%)	18 (90)
Mean age [years]	39.4

Table 4. Mean ranks for nasolabial fold depth and the Friedman test results

Treatment group	Mean ranks for nasolabial fold depth			χ^2 value	*p*-value
	study phase 1	study phase 2	study phase 3		
A (*n* = 10)	2.85	1.00	2.15	18.865	0.000*
B (*n* = 10)	3.00	1.05	1.95	19.538	0.000*

* statistically significant.

Table 5. Wilcoxon test results showing statistically significant differences in nasolabial fold depth between every 2 study phases for both treatment groups

Treatment group	Pairwise comparison of the study phases	*p*-value
A	phase 1 vs. phase 2	0.004*
	phase 1 vs. phase 3	0.011*
	phase 2 vs. phase 3	0.004*
B	phase 1 vs. phase 2	0.004*
	phase 1 vs. phase 3	0.005*
	phase 2 vs. phase 3	0.007*

* statistically significant.

Table 6. Differences in nasolabial fold depth between the 2 treatment groups for all study phases

Study phase	Treatment group		*p*-value
	A	B	
1	2.85	3.00	0.110
2	1.00	1.05	0.360
3	2.15	1.95	0.000*

* statistically significant.

Table 3. Frequencies of the particular scores assigned to nasolabial fold depth within each treatment group through the study phases

Study phase	Treatment group	Nasolabial depth scores							Total
		0	0.5	1	1.5	2	2.5	3	
1	A	0	0	0	0	3	4	3	10
	B	0	0	0	0	2	4	4	10
2	A	1	6	3	0	0	0	0	10
	B	5	5	0	0	0	0	0	10
3	A	0	0	0	2	4	4	0	10
	B	0	2	5	3	0	0	0	10

Study phases: 1 – before the intervention; 2 – 1 month after the intervention; 3 – 12 months after the intervention. Treatment groups: A – fat graft only; B – fat graft with injectable platelet-rich fibrin (I-PRF).

Discussion

In this study, the efficacy of I-PRF added to fat graft for nasolabial augmentation was assessed and compared with the conventional fat graft without I-PRF. After 1 month, great enhancement was noted in both groups. However, this improvement was more significant at 1 year after treatment with I-PRF.

Although there are many donor sites from which fat can be obtained, the optimal area has not yet been determined. In this study, the abdomen was selected for fat extraction. This is because it can be considered a safe and easy-to-reach site with abundant fat. Coleman's protocol of fat aspiration was implemented in this study.[27] A special aspiration nozzle with a diameter of 3 mm and a length of 15 cm, with foam ends and openings on both sides was used. According to Simonacci et al., this method has many advantages; it causes the least trauma to the donor site and preserves the viability of the adipose cells.[28]

There are many techniques that can be used for fat preparation. Coleman's protocol is the most common method, according to many studies.[29] The fat syringes were centrifuged for 3 min at a speed of 3,000 rpm. This technique is the easiest one and it aids in preserving the adipose cells.

The fan injection technique was used to inject the fatty tissue. This technique can increase the fat graft surface area and help in providing more blood supply to the graft. Cook et al. noted that injecting fat into a blood-rich area can protect the adipose tissue from subsequent necrosis.[30] A 16-gauge cannula connected to a 1-cubic centimeter syringe was used to inject the graft. This was recommended by Coleman in order to prevent the development of hematoma after injection.[3]

Platelet-rich fibrin is the effect of the progressive development of platelet-rich matrices, advantageous in terms of positive outcomes of PDGFs on tissue rejuvenation. It varies from other platelet-rich aggregates, such as PRP and plasma rich in growth factors (PRGF) in numerous aspects.[31] The PRF preparation does not necessitate any additives to prevent blood coagulation or activate the platelets. Moreover, the PRF preparation requires a very low centrifugation speed to ensure the successful apprehension of both platelets and regenerative cells, which leads to an increased concentration and a prolonged effect of growth factors. Furthermore, it has been shown that PRF has higher amounts of platelets, fibrin, growth factors, and leukocytes in comparison with PRP and PRGF, leading to a more enhanced growth factor-mediated functional outcome.[32]

The clinical use of I-PRF for facial rejuvenation has been previously reported in a few studies,[21,33,34] but the efficacy of I-PRF added to fat graft in nasolabial augmentation has not yet been studied. Hassan et al. recently reported the efficacy of I-PRF for facial rejuvenation.[35] The injectable form of PRF employed in their study was prepared using short-time and low-speed centrifugation (3 min at 700 rpm), which is similar to the preparation method used in this study. They demonstrated significant improvement in several skin characteristics, which was mirrored by significant improvement in patient satisfaction, thereby suggesting a benefit for the use of I-PRF for facial skin rejuvenation.[35]

Twelve months after the intervention, the degree of wrinkle relapse on the I-PRF side was lesser as compared to the other side in all patients. This can be attributed to the enrichment of I-PRF with growth factors, especially PDGF, which is considered to be the primary factor in wound healing and angiogenesis in the injected area.[36] Vascular endothelial growth factor is another factor that contributes to angiogenesis by encouraging the development of the basal cell layers of the endothelial tissue.[37] The effect of these growth factors on preserving blood supply to the graft could be the main reason for reducing the resorption of the graft in the treatment B group. This is in accordance with the findings of Chasan and Rahban, who reported that the most common reason for the resorption of autogenous fat graft is the impaired blood supply.[38]

Limitations

One limitation of this study is that the literature lacks research on this topic. Another limitation is that it was a single-center trial with a single ethnic group, so the results cannot be generalized until further multicenter trials with different ethnic groups are available. Finally, the limited treatment area (the nasolabial fold) could be considered yet another limitation.

Conclusions

In summary, this study demonstrated the efficacy of I-PRF in reducing the resorption of fat graft, following facial lipostructure.

Trial registration

The trial was recorded in the German Clinical Trials Register (DRKS – Deutschen Register Klinischer Studien) (ID: DRKS00023758).

Ethics approval and consent to participate

The study was approved by the institutional ethics committee at the Faculty of Dentistry of Damascus University, Syria. The participants provided informed written consent prior to the investigations.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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