

The Addition of Platelet-Rich Plasma to Facial Lipofilling: A Double-Blind, Placebo-Controlled, Randomized Trial

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Background: Lipofilling is a treatment modality to restore tissue volume, but it may also rejuvenate the aging skin. Platelet-rich plasma has been reported to augment the efficacy of lipofilling, both on graft take and rejuvenation, by altering the adipose-derived stem cells. The authors hypothesized that addition of platelet-rich plasma would increase the rejuvenating effect and shorten recovery time.

Methods: The study conducted was a single-center, double-blind, placebo-controlled, randomized trial (2012 to 2015). In total, a well-defined cohort of 32 healthy female patients enrolled in the study, with 25 completing the follow-up. All patients underwent aesthetic facial lipofilling with either saline or platelet-rich plasma added. Outcome was determined by changes in skin elasticity, volumetric changes of the nasolabial fold, recovery time, and patient satisfaction during follow-up (1 year).

Results: Platelet-rich plasma did not improve the outcome of facial lipofilling when looking at skin elasticity improvement, graft volume maintenance in the nasolabial fold. Reversal of the correlation between age and elasticity, however, might suggest a small effect size, and thus might not be significant with our small study population.

Conclusions: This randomized, double-blind, placebo-controlled study clearly has shown that platelet-rich plasma significantly reduces postoperative recovery time but does not improve patient outcome when looking at skin elasticity, improvement of the nasolabial fold, or patient satisfaction. The reversal of the correlation between age and elasticity might indicate some effect on skin but requires more power in future studies. (*Plast. Reconstr. Surg.* 141: 331, 2018.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Lipofilling (i.e., autologous fat transplantation or fat grafting) has become an important treatment modality in facial rejuvenation procedures: it is a safe procedure that requires only limited additional operating time. The presence of adipose-derived stem cells in the lipograft¹ could result in tissue regeneration.²⁻⁴ This has resulted in a paradigm shift toward the combination of facial rejuvenation by using both surgical lifting techniques and lipofilling procedures to

restore both volume^{5,6} and tissue damage at the cellular level. By this combination of both surgical lifting and lipofilling, effects of gravity, loss of skin elasticity because of elastin degradation, loss of

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volume because of fat atrophy, and bone resorption^{7,8} are all well addressed.

Fat grafting not only restores volume but also contributes to regeneration processes that become apparent by improved surface structure and tissue elasticity.⁹ Nature's own regenerative source of wound healing is clot formation after platelet aggregation, homing of the cells involved in repair, and fibrinogenesis. Another reliable manner to produce injectable clots is the generation of platelet-rich plasma and to use that to augment wound healing. Platelet-rich plasma both serves as an instant scaffold for regeneration and is a rich source of proregenerative growth factors.¹⁰

With extensive experience with the use of platelet-rich plasma as an additive to facial lipofilling procedures in our clinic dating back to 2005, retrospective analysis revealed several significant beneficial effects when adding platelet-rich plasma to the lipograft.¹¹ We hypothesized that the addition of platelet-rich plasma to lipografts would augment tissue regeneration. This hypothesis was subsequently tested in this double-blind, randomized, placebo-controlled clinical trial for facial lipofilling.

PATIENTS AND METHODS

Study Overview

The study conducted was a single-center, patient- and investigator-blinded, placebo-controlled trial undertaken at Bergman Clinics, The Hague, The Netherlands. A flowchart overview of the study is shown in Figure 1. Patient follow-up was 12 months so that long-term, lasting results could be obtained.

The study protocol complied with the Declaration of Helsinki and was approved by local medical ethics committee Zuid-West Holland (National legislator trial code, NL35142.098.11; local METC code, 12-014). All patients provided written informed consent.

Patient Population and Randomization

Before inclusion, a power calculation was performed based on the limited available published data at that time. After this calculation, the aim was to include 32 subjects that would receive facial lipofilling in this study, with one half of the population receiving platelet-rich plasma and the other half receiving a placebo (sterile saline) and serving as the control group. A detailed description of the randomization process is available online. (See **Figure, Supplemental**

Digital Content 1, which shows a description of the randomization process, <http://links.lww.com/PRS/C548>.) Inclusion and exclusion criteria were strict, and are listed in Figure 1.

The primary outcome of the study was skin elasticity improvement [R7 parameter measured by the Cutometer MPA 580 device (C&K Electronic, Cologne, Germany)] on predetermined fixed measurement locations (Fig. 2) overlying the area of intervention. Secondary outcome parameters of the study were as follows: other changes in skin characteristics (R5 and R6 parameters, using the Cutometer MPA 850 device, in the same locations), graft take (nasolabial fold decrease), and patient questionnaires regarding recovery time and satisfaction.

Patient enrollment in the study started in 2012 and ended in mid 2015. During enrollment in this study, patients were prohibited from undergoing further subsequent facial rejuvenating procedures. If a patient still did, the patient was excluded from the study.

Procedures

On the day of surgery, but before intervention, measurements were performed by the blinded investigator (J.C.N.W.) to determine baseline values. All measurements were performed by the same investigator (J.C.N.W.) throughout the whole study, for every patient, at every follow-up time point (1 week, 3 months, and 1 year postoperatively) (Fig. 1). Clear patient instruction was given to not use any skin products on the day of the operation or during the different follow-up moments.

In the operating room, with the patient sedated mildly, 30 cc of whole blood was drawn from the patient, with an additional 2 cc was drawn for platelet analysis. After the pretrial randomization, opening of the envelope determined whether the whole blood was either discarded or introduced into the Biomet GPSIII device (Biomet Biologics, Warsaw, Ind.) for platelet-rich plasma isolation (3 cc of platelet-rich plasma output) following the manufacturer's protocol; 3 cc of sterile saline was used as placebo control.

Lipoharvesting, processing, and lipofilling were performed following the standard Coleman method; however, both the lipoharvesting and lipofilling cannulas were significantly smaller (harvester, 2.4 × 22 cm; injector, 0.9 × 5 cm). The upper legs served as the donor site in all patients. Location and applied lipofilling volume are presented in Figure 3. All procedures were

Inclusion criteria:

- Female, age 35-65 years
- Stable normal BMI (20-25, 1-year stable)

Exclusion criteria:

- Smoking
- Pregnancy or active child wish
- Prior operations in the mid-face
- Active or previous use of hormone replacement therapy.
- A known systemic disease that will impair wound healing (e.g. diabetes mellitus, known atherosclerosis with an event that required hospitalization, collagen diseases, diseases of the skin)
- A known psychiatric condition
- History of cancer

Pre-trial randomization

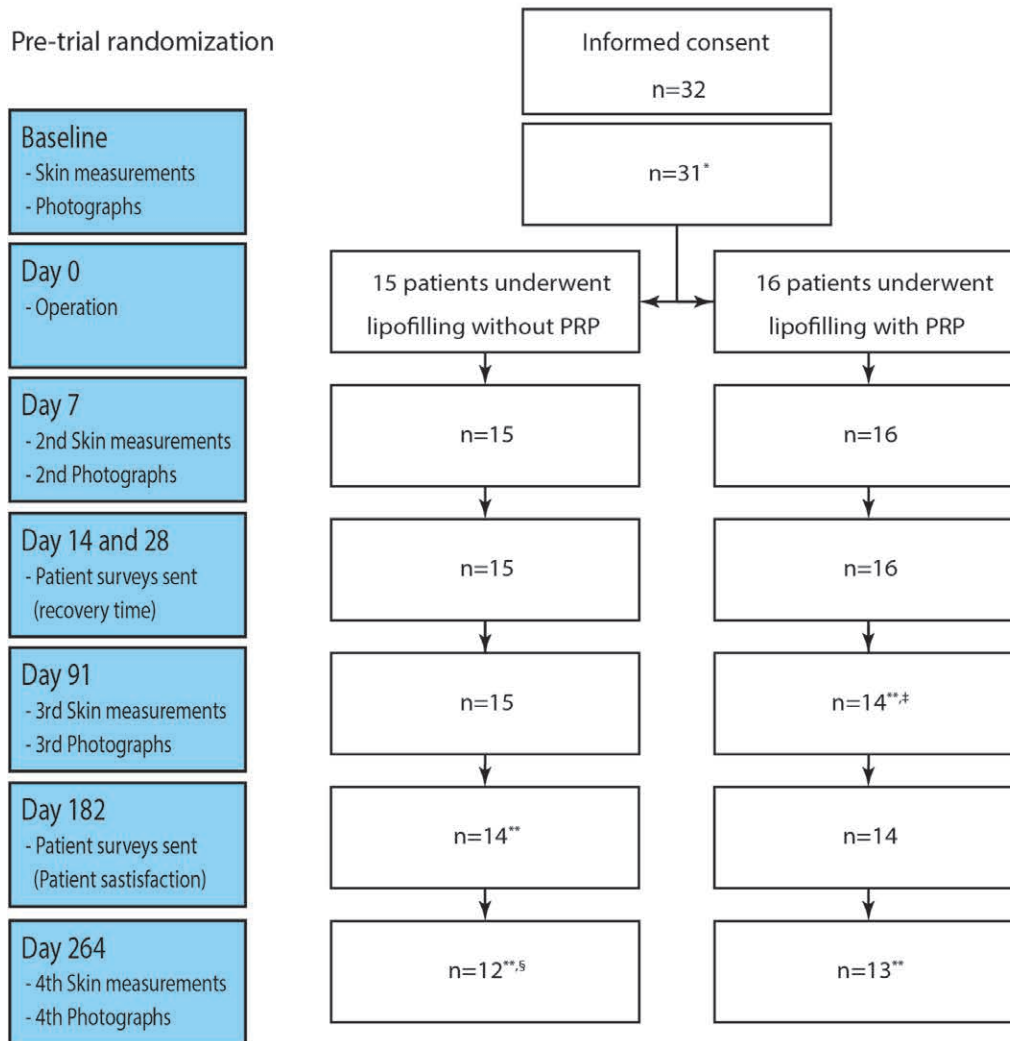


Fig. 1. Study design with a breakdown of enrolled subjects that completed the study, and inclusion/exclusion criteria. Several patients were excluded for the following reasons. *A patient was diagnosed with a gastrointestinal oncologic disease; **patients failed to complete all follow-up time points by not showing up; ‡patient chose to leave the study because of personal circumstances; §patient underwent aesthetic facial surgery during the follow-up. BMI, body mass index; PRP, platelet-rich plasma.

performed by the same surgeon (H.P.S.), who at that time already had experience with more than 2000 lipofilling procedures. A detailed, step-by-step description of the lipofilling procedure is

available online.⁵ [See Video, Supplemental Digital Content 2, which demonstrates how the processed lipoaspirate was injected with the tip of the curved cannulas pointed upward. Superficial

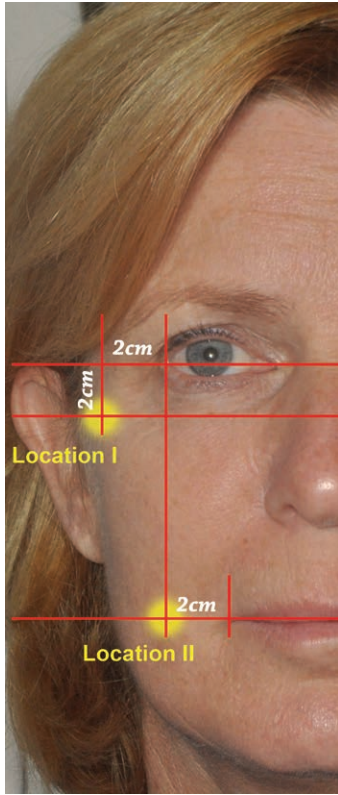


Fig. 2. Locations of skin measurements, marked before each measurement. Patients lay down on an examination table to enable correct Cutometer probe placement. *Location I*: 2 cm lateral and 2 cm caudal from the lateral canthus. *Locations II*: 2 cm lateral from the lateral commissure.

lipofilling was performed against the inside of the skin in the entire face. Additional deep lipofilling was performed with the tip of the curved cannulas pointed downward if increased volume was desired (midface, cheek bones, skin folds) into the deep subcutaneous plane of each side of the face. Micro fat grafting was performed of the lower lid/tear trough region in the supraperiosteal/submuscular plane and the temporal area superficial from the superficial fascia of the temporal muscle. Subsequently, platelet-rich plasma or saline as placebo was dispersed evenly into these planes by transcutaneous injection using a 22-gauge needle. All patients were operated on by the same surgeon (H.P.S.), available in the “Related Videos” section of the full-text article on PRSJournal.com, or, for Ovid users, at <http://links.lww.com/PRS/C549>.]

Skin Measurements

Local skin quality was measured with the Multi Probe Adapter system (C&K Electronic) containing the Cutometer MPA 580 (elasticity) probe. The Cutometer is a valid method of objectifying elasticity

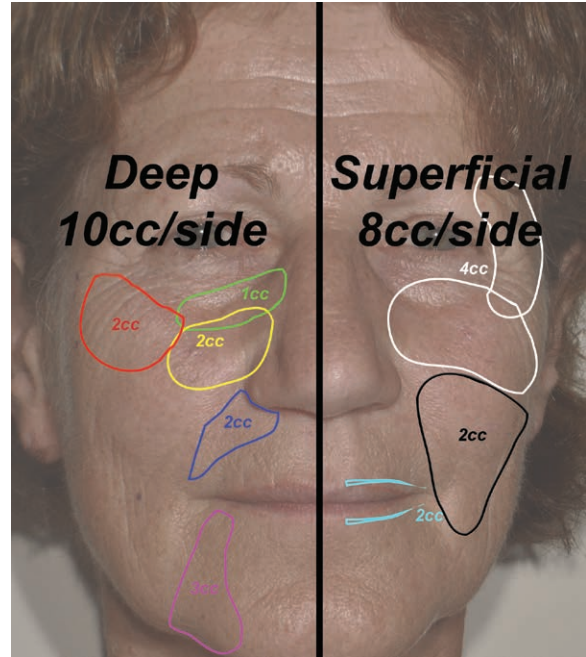


Fig. 3. Lipofilling locations and applied volume. Both superficial and deep lipofilling was performed on both sides of the face (18 cc per side; 36 cc in total). Within the platelet-rich plasma group, 3 cc of platelet-rich plasma was added to the lipofilling planes. (Left) Deep: temporal projection (red), nasojugal groove (green), central midface (yellow), nasolabial fold (blue), marionette line, and prejowling area and chin (pink). (Right) Superficial: temporal and central midface area (white), lower midface-cheek area (black), and white rolls (cyan).

of the skin.^{12–16} Measurements were performed on fixed locations for every patient (Fig. 2) at every follow-up time point. Before each measurement, the probes were calibrated and tested for correct function. Also, local temperature and humidity were logged. True skin elasticity was defined by the Cutometer MPA 850 R7 output parameter (the ratio of elastic recovery to the total deformation), elaborated by the R5 (the net elasticity) and R6 (the ratio of viscoelastic to elastic extension) parameters.

Volumetric Changes of the Nasolabial Fold

Standardized photographs were captured in three views with a professional three-dimensional camera system (anteroposterior, three-quarters left and right) at every follow-up time point. Primarily, three-dimensional reconstructions were used to determine volumetric facial changes over time but were abandoned because of data inconsistency, variation, and reproducibility of the measured area. Instead, the preoperative, 3-month, and 1-year postoperative anteroposterior views were used to determine changes in the nasolabial



Video. Supplemental Digital Content 2 demonstrates how the processed lipoaspirate was injected with the tip of the curved cannulas pointed upward. Superficial lipofilling was performed against the inside of the skin in the entire face. Additional deep lipofilling was performed with the tip of the curved cannulas pointed downward if increased volume was desired (midface, cheek bones, skin folds) into the deep subcutaneous plane of each side of the face. Micro fat grafting was performed of the lower lid/tear trough region in the supraperiosteal/submuscular plane and the temporal area superficial from the superficial fascia of the temporal muscle. Subsequently, platelet-rich plasma or saline as placebo was dispersed evenly into these planes by transcutaneous injection using a 22-gauge needle. All patients were operated on by the same surgeon (H.P.S.), available in the “Related Videos” section of the full-text article on PRSJournal.com, or, for Ovid users, at <http://links.lww.com/PRS/C549>.

fold depth using a validated grading method (Merz scale),^{17–20} that consists of five options, where I indicates the minimal fold expression and V indicates the most prominent fold expression. In total, four independent plastic surgeons served as the expert panel. The nasolabial fold was chosen because alteration in depth would implicate relevant external changes of facial appearance.

Patient-Reported Recovery Time and Satisfaction

Recovery after the procedure was assessed by means of two patient questionnaires sent at 2 and 4 weeks after the operation. Questions included the number of days required to return to work and/or resume social activities without using camouflaging agents, and notable changes in facial volume and skin expressed on a visual analogue scale (1 = no changes and 10 = most significant changes). Patient-reported satisfaction was recorded by means of a questionnaire sent 6 months after surgery: questions included overall satisfaction, changes in volume effect, skin changes, and whether or not they would

recommend the procedure to a peer (visual analogue scale ranging from 1 to 10).

Statistical Analysis

Statistical analyses were performed by an independent statistician that received all blinded data by the principal investigator, along with the original randomization from the surgeon. All analyses were performed using IBM SPSS Version 20 (IBM Corp., Armonk, N.Y.). Data figures were generated using Prism 6 (GraphPad Software, Inc., La Jolla, Calif.). The paired samples *t* test, analysis of covariance, and standard linear regression were used. All data fulfilled the requirements for normality and equal variances. A two-sided values of $p < 0.05$ were considered statistically significant.

RESULTS

In total, 32 patients that met inclusion criteria were enrolled in this study, with 25 patients completing the study. Seven patients were excluded from the study: four patients failed to complete all follow-up appointments by not showing up, one patient was diagnosed with a gastrointestinal oncologic disease (ruled as undiagnosed preexistent, and unconnected with the study ruled by the independent physician), one patient underwent aesthetic facial surgery during the follow-up period, and one patient chose to leave the study because of personal circumstances. Excluded patients, unfortunately, could not be replaced because of limited study duration as allowed by the ethical board.

Of all patients that completed the study, 13 underwent lipofilling with platelet-rich plasma (platelet-rich plasma–positive) and 12 underwent lipofilling with saline (placebo, platelet-rich plasma–negative). Average photographic results are presented in Figure 4. Mean patient age at the time of surgery was 52 ± 6.75 years (range, 38 to 63 years), with no significant age difference between the groups. Whole blood platelet counts were within the normal range for all patients (Table 1).

Lipofilling with or without Platelet-Rich Plasma Does Not Significantly Change Overlying Skin Elasticity in This Study

Analyzed R7 parameter data (representing true elasticity) from both groups showed no significant difference before intervention (Fig. 5). The platelet-rich plasma–positive group did not differ significantly from the placebo group at any time point. Data correction for age, room temperature, humidity conditions, and baseline (preoperative) measurements resulted in similar findings.



Fig. 4. Average results. Anteroposterior photographs obtained preoperatively (left), 1 week postoperatively (center), and 1 year postoperatively (right). (Above) Platelet-rich plasma–positive (PRP+). (Below) Platelet-rich plasma–negative (PRP–).

Table 1. Descriptive Statistics for Both Groups*

	Group I (No PRP, n = 12)			Group II (PRP, n = 13)			p†	Overall (n = 25)		
	Mean	SD	Range	Mean	SD	Range		Mean	SD	Range
Age at the time of surgery, yr	52.5	7.1	42–63	51.73	6.7	38–62	NS	52.10	6.8	38–63
Platelet count at the time of surgery	234.2	47.9	153–299	250.1	37.5	168–312	NS	242.8	42.9	153–312
Recorded complications (major or minor)	0			0			—	0		

PRP, platelet-rich plasma; NS, not significant.

*No significant differences were found. No complications occurred during the study.

†t test.

Analyzed R5 and R6 Data Showed Comparable Values in Both Groups, at Every Follow-Up Time Point

Regression analysis of the preoperative R7 parameter as a function of age showed a negative correlation in both groups, comparable to the result shown by Ezure and Amano.²¹ However, after

intervention, the correlation reverses (Fig. 6), which could be a sign of facial rejuvenation. Changes were most noticeable in the platelet-rich plasma–positive group: the high prediction value of the regression line ($R = 0.542$, $p = 0.055$) could suggest that the sample size in this study was not adequate. Interestingly, this reversal was only

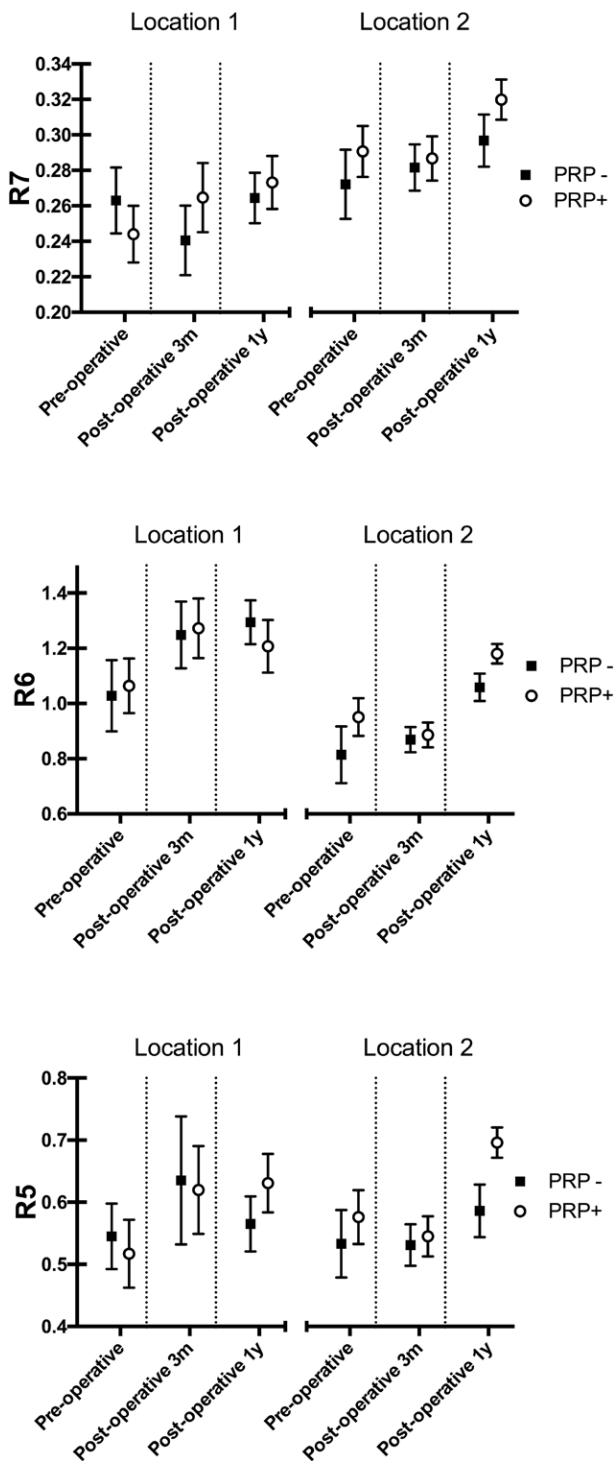


Fig. 5. Changes in average true skin elasticity (R7) and R5 and R6 parameters for both groups preoperatively and during follow-up measured with the Cutometer MPA 850 at both locations. Data represent group means with SEM. (Above) R7 parameter at locations 1 and 2, showing true skin elasticity. Higher values represent an increase in skin elasticity and a positive effect. There is a marginal increase in both groups, with no significance. (Center) R6 parameter locations 1 and 2, showing the ratio of viscoelastic to elastic extension. Lower values represent a positive

notable on the location 1 R7 parameter, not on location 2 or with the R5 and R6 parameters.

Changes of the Nasolabial Fold

Summarized data from both groups at every follow-up time point are presented in Figure 7; lower scores represent a less prominent nasolabial fold. Grading scores showed a high level of agreement between each expert (Spearman intraclass correlation coefficient for all: $r > 0.576$, $p < 0.001$).

Preoperative scores were comparable in both groups (mean \pm SD for platelet-rich plasma-negative, 2.359 ± 0.1531 ; platelet-rich plasma-positive, 2.622 ± 0.2388 ; $p > 0.05$). Data after 3 months and 1 year also showed comparable results, with no significant differences between both groups at any time point. Furthermore, no changes between preoperative and postoperative scores within each group were found.

Addition of Platelet-Rich Plasma Speeds Up Recovery but Does Not Increase Patient Satisfaction

Patient questionnaire-reported recovery time, derived from the number of days until return to work/social activities with or without camouflaging agents, showed a significantly faster recovery in the platelet-rich plasma-positive group (Table 2). Mean \pm SD number of days until return to work/social activities with camouflaging agents was 9 days (9.133 ± 3.701 days; $p < 0.01$) in the platelet-rich plasma-positive group and 15 days in the control group (15.43 ± 4.949 days). Return to work/social activities without camouflaging agents supported this finding (platelet-rich plasma-positive group, 14.87 ± 4.604 days; platelet-rich plasma-negative group, 20.57 ± 6.61 days; $p < 0.05$). Questions regarding noticeable differences in facial volume and skin quality after 2 and 4 weeks showed no differences ($p > 0.05$).

Patient satisfaction and changes in volume and skin quality, reported after 6 months, proved to be similar in both groups (data not presented). Overall satisfaction was reported as “moderate.” Positive skin changes were reported by several patients in both groups, contradicted by patients that did not notice any skin changes at all. Overall, the level of recommendation of the procedure

Fig. 5. (Continued). effect. (Below) R5 parameter at locations 1 and 2, showing the net elasticity. Higher values represent a positive effect. Again, a minimal gain in both groups, with no significant differences, between both groups or within each group at every follow-up time point. PRP+, platelet-rich plasma-positive; PRP-, platelet-rich plasma-negative.

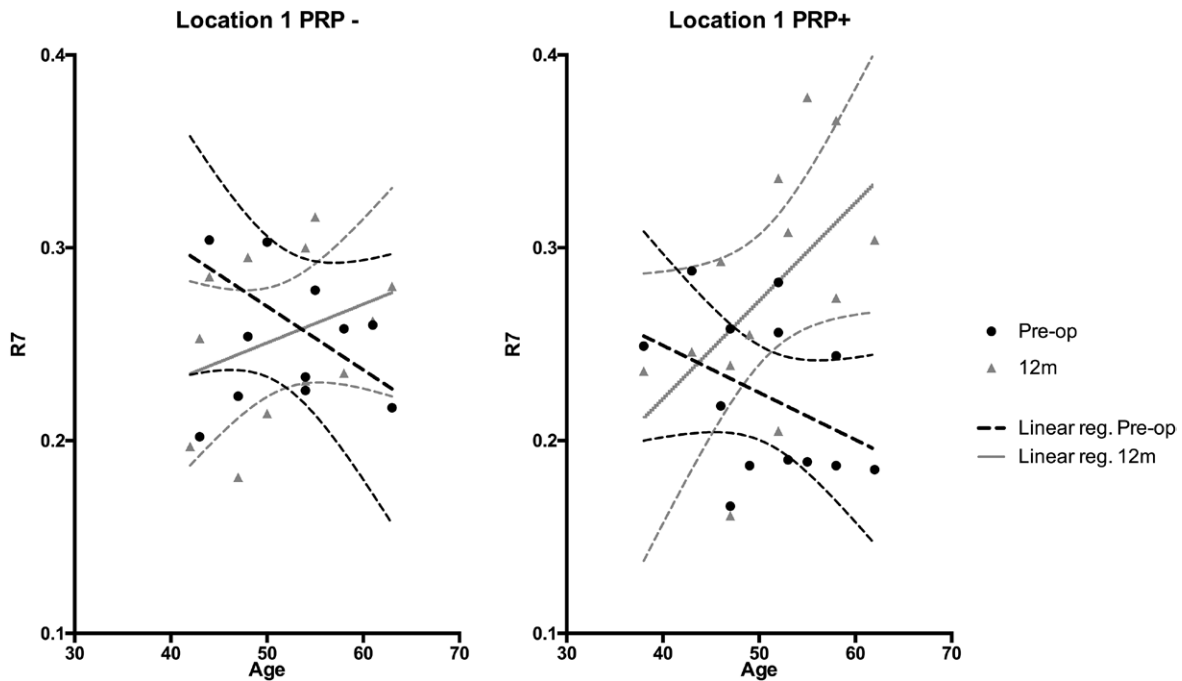


Fig. 6. Regression analysis of true skin elasticity as a function of age, before and 12 months after intervention. All measurements and the calculated regression curve with 95 percent confidence intervals are presented. (*Left*) Platelet-rich plasma–negative (PRP–). Preoperatively, age correlates negatively with true elasticity ($y = -0.003293 * x + 0.4343$, $r = 0.402$, $p = 0.195$), but this correlation reverses 12 months postoperatively ($y = 0.002005 * x + 0.1507$; $r = 0.326$, $p = 0.299$). (*Right*) Platelet-rich plasma–positive (PRP+). Again, a negative correlation before operation ($y = -0.002444 * x + 0.3471$; $r = 0.392$; $p = 0.184$), with a stronger reversal after intervention ($y = 0.005078 * x + 0.01921$; $r = 0.542$, $p = 0.055$) compared with the platelet-rich plasma–negative group.

to peers was negative for both groups, mainly because of higher expectations of the effect of the procedure.

DISCUSSION

This randomized, placebo-controlled, double-blind study was undertaken to investigate the possible beneficial effects of adding platelet-rich plasma to aesthetic facial lipofilling in a well-defined healthy patient cohort. The results clearly demonstrate that the addition of platelet-rich plasma to the lipograft significantly reduces the patient's reported recovery time. However, the addition of platelet-rich plasma to the lipograft does not significantly improve skin elasticity, produce changes in nasolabial fold depth, or change overall patient satisfaction compared with lipofilling alone. The reversal in the correlation of net elasticity as a function of patient age could suggest some form of rejuvenation by lipofilling that is enhanced by platelet-rich plasma, but lacked significance with the number of patients in this study.

Reported in vitro effects of platelet-rich plasma^{10,22–24} thus could not be reproduced in our

clinical study setting, possibly because of uncontrollable patient-related confounding factors combined with a small therapeutic window for effect. Moreover, reported effects of “normal” (not stromal vascular fraction/adipose-derived stem cell enriched) lipofilling on skin rejuvenation, as has been reported and suggested to be seen in clinical studies when used in combination with face-lift surgery,^{2,9} could also not be addressed; this forces us to question what the additional effect (other than some volume enhancement) of normal lipofilling is when used during face-lift surgery.

Lipofilling Does Not Increase Skin Elasticity in the Aging Face, Even with Added Platelet-Rich Plasma

Since the comeback of lipofilling, suggestions have been made that it is “more than a filler”² and may induce rejuvenation of the skin. However, this adipose-derived stem cell–induced effect is only well studied after deep dermal injury (e.g., thermal radiation damage, excessive scarring^{4,25–27}). Surprisingly, skin rejuvenation of the normal aging skin has been described and studied histologically only by Charles-de-Sá et al.⁹ In this study, an

Nasolabial fold grading scores

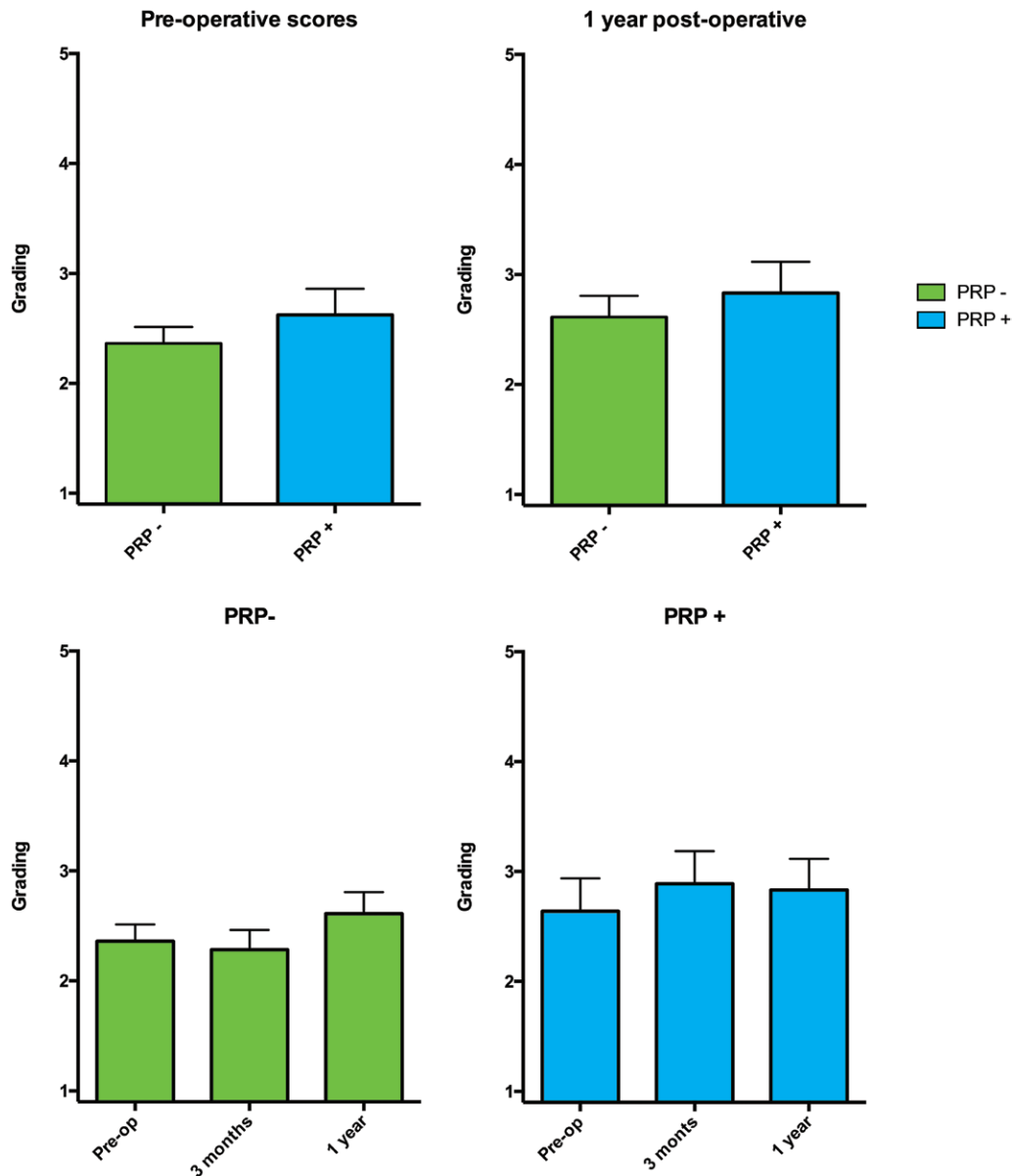


Fig. 7. Result of nasolabial fold grading preoperatively and at follow-up. Data represent group means with SEM from grading by four experts. Lower scores represent a less prominent nasolabial fold. No significant differences, between both groups or within each group at every follow-up time point, could be calculated. (Above, left) Preoperative scores for both groups. (Above, right) Postoperative scores for both groups. (Below) Changes in grading during follow-up for both groups. No effect was observed during follow-up. PRP-, platelet-rich plasma-negative; PRP+, platelet-rich plasma-positive.

increase in dermal elastin deposition was reported in biopsy specimens after normal lipofilling of the aging skin. However, to date, no controlled studies have been conducted to verify the clinical relevance of their finding. In our study, skin elasticity was determined with the Cutometer because it is a reliable and validated method of measuring skin age, and the mostly likely candidate to show

changes, supported by the findings of Charles-de-Sá et al. Nevertheless, there remains minor controversy regarding the reliability of the Cutometer. A study by Nedelec et al. presented low intraclass correlation coefficients of skin elasticity measurements of dermal scars. The intraclass correlation coefficients found for normal skin elasticity measurements were, however, acceptable for the R0

Table 2. Patient-Reported Recovery Time after Intervention Extracted from Surveys*

Facial Lipofilling	Group I (No PRP, n = 12)		Group II (PRP, n = 13)		p†
	Mean	SD	Mean	SD	
Return to work/ social activities with camouflaging agents, days	15.4	9.1	9.1	3.7	0.0101
Return to work/ social activities without camouflaging agents, days	20.6	6.6	14.9	4.6	0.0112

PRP, platelet-rich plasma.

*Data represent group means \pm SD. The addition of platelet-rich plasma has a significant impact on patient-reported number of days to return to work. Recovery time was defined as the patient-reported number of days after surgery until returning to work/social activities. †Independent samples *t* test.

(0.81), R6 (0.81), and R7 (0.78) parameters.²⁸ We found that normal (not stromal vascular fraction/adipose-derived stem cell boosted) lipofilling with or without platelet-rich plasma did not alter skin elasticity. Reversal of the correlation between age and elasticity, however, might suggest a small effect size, and thus might not be significant with our small study population. Nevertheless, the small effect size raises questions of whether normal lipofilling is “just a filler” in aesthetic procedures in the aging face that involve only lipofilling. Improvement in outcome when lipofilling is combined with lifting procedures could be explained by the large wound surface created and adipose-derived stem cell modulation during healing, down-regulating fibrosis pathways. Recent publications on stromal vascular fraction–boosted/adipose-derived stem cell–expanded lipofilling, however, do show a significant clinical effect^{29,30} and indicate that it seems the way forward.

In theory, adding platelet-rich plasma could affect overlying skin through several pathways and cell lines. Angiopoietin-1 and angiopoietin-2, abundantly present in platelets,^{31,32} have been shown to stimulate endothelial cell growth, migration, and differentiation in cultured human dermal microvascular endothelial cells in vitro.^{22,23} Also, platelet-rich plasma lysate is a strong proliferator for adipose-derived stem cells,^{10,33} is essential for graft take,³⁴ and is a proven down-regulator of fibrosis.^{26,35}

Effects of Lipofilling with or without Platelet-Rich Plasma on Nasolabial Fold Depth

Grading of the nasolabial fold during follow-up showed no noticeable lasting effect of

lipofilling or lipofilling with platelet-rich plasma on the depth of the nasolabial fold. Even though the Merz scale used in this study has been shown to successfully differentiate small-volume changes (e.g., filler injection),³⁶ we could not determine these differences, probably because lipofilling increased the overall facial volume, not altering relative differences between facial zones. In our opinion, only in combination with a face lift may lipofilling also demonstrate its effect on the nasolabial fold: lifting probably is definitely needed as such. Furthermore, changes in facial volume are minimal because of the limited amount of lipograft that is injected, with uncertainty about the clinical impact of these minor changes if not combined with a lifting procedure. To date, only one study has been published that reported facial graft retention determined with external three-dimensional photographic reconstruction³⁷ after aesthetic facial lipofilling. In this study, an overall retention of 32 percent was reported; however, the range and variation of reported data question its scientific merit. Moreover, the vast number of patients in this study also received some form of lifting procedure that most likely changed the distribution of facial volume and by this means influenced facial volume attributed to lipofilling, again suggesting that lipofilling should be combined with a lifting procedure in aesthetic facial rejuvenation. Even though lipograft survival in the face has been documented with magnetic resonance imaging,³⁸ the clinical relevance of aesthetic facial lipofilling procedures without lifting procedures on facial fold depth remains to be determined.

With ongoing uncertainty about lipograft survival, several fundamental studies explored addition of platelet-rich plasma^{39–41} and found positive effects. Graft take might improve by platelet-rich plasma effects on adipose-derived stem cell proliferation,³⁹ blockage of apoptosis pathways,⁴² and differentiation into adipocytes.⁴³ Moreover, platelet-rich plasma lysate stimulates proliferation, migration, and tube formation of human umbilical vein endothelial cells both in vitro and in a nude mouse model.³⁹ Platelet-rich plasma induces changes on endothelial cells that can contribute to (neo)angiogenesis of the fat graft and thereby enhance fat graft survival.⁴⁴ These findings, however, fail to make a significant impact in the majority of available clinical platelet-rich plasma lipofilling studies,^{45,46} thus casting doubt on the clinical use of addition of platelet-rich plasma to lipofilling for this reason.

Platelet-Rich Plasma Speeds Up Patient Recovery

Patient-reported recovery time was significantly reduced by the addition of platelet-rich plasma in this study. This finding is in line with previous data from our retrospective study¹¹ and current literature on aesthetic procedures such as fractional carbon dioxide laser resurfacing treatment.^{47,48}

Dermal and wound closure effects observed after platelet-rich plasma injection might be explained by the effect of platelet-rich plasma on fibroblasts. An *in vitro* study by Ramos-Torrecillas et al.⁴⁹ showed that PRP increases fibroblasts proliferation rate and induces their differentiation into myofibroblasts, thus playing a key part in wound contracture.²² Collagen I and extracellular matrix remodeling by fibroblasts is also affected by platelet-rich plasma. Fibroblasts exposed to platelet-rich plasma lysate *in vitro* up-regulate the expression of matrix metalloproteinase-1,²⁴ which in turn plays a key role in collagen remodeling. Also, type I collagen expression is increased under these circumstances.⁵⁰ Increased fibroblast activity, along with changes in collagen production and a potentially stronger inflammation response,⁵¹ could also play a role in our observed reduced recovery time after surgery when the lipograft was combined with platelet-rich plasma.

The Concentration Paradox: Less Is More?

A potential pitfall in evaluating the effect of platelet-rich plasma is the lack of uniform concentrations of created platelet-rich plasma. The studies of Yamaguchi et al.^{52,53} were the first publications that showed that a higher concentration of platelet-rich plasma (or more platelets) may produce counterproductive effects, possibly by unwanted cell differentiation. Most commercially available platelet-rich plasma kits capture a percentage of available platelets from whole blood, not a certain quantitative number of platelets. Considering the fact that normal human platelet counts are defined within a wide range and show large daily variations, the cumulative amount of growth factors in kit-isolated platelet-rich plasma is inconsistent.⁵⁴ This variation can inadvertently influence its effect in a way as is observed *in vitro* on different cell types.²² Regarding cells present in the lipograft, platelet-rich plasma concentration alters adipose-derived stem cell proliferation, function, and behavior. High platelet-rich plasma concentrations increase proliferation but also change adipose-derived stem cells into a fibroblast-like phenotype, with increased collagen RNA expression and altered paracrine signaling

that negatively influences endothelial vessel formation.^{55,56}

Although platelet counts were normal within our well-defined healthy patient cohort, combined with comparable fat-graft, platelet-rich plasma, or placebo mixture ratios, our study is potentially biased and weakened by this concentration-dependent effect. Moreover, this phenomenon could explain the failure of clinical studies.

Local growth factor conditions after lipofilling are also issues that remain unclear; in a healthy patient, the release of platelets and pro-inflammatory factors because of damage caused by the lipofilling procedure itself could be of such an extent that the addition of platelet-rich plasma actually is insignificant and/or redundant or even too high.

CONCLUSIONS

This randomized, double-blind, placebo-controlled study clearly has shown that platelet-rich plasma significantly reduces postoperative recovery time but does not improve patient outcome when looking at skin elasticity, improvement of the nasolabial fold, or patient satisfaction. The reversal of the correlation between age and elasticity might indicate some effect on skin but requires more power in future studies. Thus far, the use of platelet-rich plasma as an additive in lipofilling has shown great promise *in vitro*. These beneficial effects, however, have only partially been reproduced in a clinical setting. A growing number of studies report a concentration-dependent effect of platelet-rich plasma *in vitro*, making optimal use in a clinical setting delicate and complex. Further studies of platelet-rich plasma interactions on both the lipograft and the receptor host site-involved cells seem to be of paramount importance to determine the optimal use and concentrations of platelet-rich plasma in a clinical setting.

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PATIENT CONSENT

Patients provided written informed consent for the use of their images.

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