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Review

Comparison of Conventional and Platelet-Rich Plasma-Assisted Fat Grafting: A Systematic Review and Meta-analysis

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KEYWORDS
Fat grafting, Plate-rich plasma, Fat survival rate, Patient satisfaction, Recovery time;
Meta-analysis

Abstract *Background:* Autologous fat grafting (FG) is a popular technique for soft-tissue augmentation, but the fat survival rate is unpredictable. Platelet-rich plasma (PRP) has emerged as an adjuvant to enhance fat graft survival.
Objectives: This literature review and meta-analysis aimed to investigate the effect of PRP on the survival rate of fat grafting.
Methods: A comprehensive systematic literature search was done to identify clinical studies on PRP and fat cotransplantation in PubMed, Cochrane Library, Web of Science, and EMBASE databases up to May 2020. The reference lists of selected articles were reviewed to identify any additional related articles. A meta-analysis was conducted to compare PRP + FG and conventional FG in terms of fat graft survival rate, patient satisfaction rate, and recovery time after surgery.
Results: Eleven studies consisting of 1125 patients were analyzed. Patients were followed up from 3 to 24 months post-FG. The fat survival rate varied from 20.5% to 54.8% in FG alone and from 24.1% to 89.2% in the PRP + FG groups. The survival rate was significantly higher and recovery time was significantly lower in the PRP + FG group than in the FG alone group. However, there was no significant difference in the patient satisfaction rate between the groups.

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Conclusions: This study demonstrates that PRP-enhanced fat transplantation has better efficacy than conventional fat grafting. Further studies are required to provide the optimum concentration of PRP and the long-term efficacy of the technique. There is not enough evidence to compare the rate of complications with PRP and fat cotransplantation and conventional fat grafting.

Contents

Introduction

Autologous fat grafting (FG) is a popular procedure in plastic and cosmetic surgery employed both for soft tissue reconstruction as well as augmentation. Among its advantages are an abundant source, ease of accessibility and harvesting, versatility, and nonimmunogenicity.[1,2] Studies have highlighted the widespread use of fat grafting,[2] including for tissue defect contouring, scar softening,[3-5] and improving fibrosis.[6]

Despite its versatility and other advantages, the most challenging issue limiting autologous FG is its unpredictable survival rate.[7] Long-term graft resorption rates have been reported as high as 90%. Hypoxia and the consequent build-up of reactive oxygen species (ROS) have been reported as the most common causes of fat necrosis and subsequent volume loss of grafted fat tissue.[8,9]

Although passive diffusion and perfusion of nutrients from the surrounding tissue appears to be the initial source of nutrition for grafted fat,[10] adequate neovascularization may be an equally important prognostic factor in graft survival.[11,12] Fat grafts that are well vascularized have been shown to display higher retention rates.[13-15] Given this background, strategies that interfere with the detrimental effects of ROS and improve neovascularization can augment fat grafting.

In a clinical setting, these effects can be controlled with an adjuvant using various methods proposed to improve fat graft survival. Several products, which include platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and stromal vascular fraction, have been tested in combination with fat to improve the retention rate through enhanced neovascularization.[16,17] The optimal technique, however, remains controversial.[18-21]

PRP and PRF are autologous sources of concentrated platelets, growth factors, and cytokines used widely in regenerative medicine.[22-24] More recently, autologous PRP and PRF have been reported to significantly enhance angiogenesis and thus survival of grafted fat.[25-28] Numerous studies have been performed to evaluate the effect of these adjuvants, but results have differed and are, hence, inconclusive.[29,30] Therefore, there is a lack of consensus on the overall clinical efficacy of these modalities.

To date, no meta-analysis has sought to investigate the clinical studies that utilize FG adjunct with PRP. We, therefore, performed this meta-analysis to investigate the clinical efficacy of cotransplanting PRP for improving fat graft survival. Patient satisfaction and recovery time, defined as the number of days that passed before patients considered themselves able to return to work or to restart social activities, were also evaluated.

Methods

Search Strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines for the conduct of meta-analysis of intervention trials[31] (PRISMA Checklist, available as **Supplementary material 1** at www.aestheticsurgeryjournal.com). A review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020185632). The Cochrane, PUBMED, Web of Science, and EMBASE electronic databases were screened from their inception to May 2020. Both "free-text terms" and "MeSH term" searches were run sequentially to capture all papers in which PRP was coadministered with fat. Search terms included various combinations of the following keywords as detailed in the **Supplementary material 2**: "platelet-rich plasma," "PRP," "platelet concentrate(s)," "platelet-rich fibrin," "PRF," "fat graft(s)," "fat transfer," "fat injection(s)," "mixed," "method(s)," "extraction," "preparation," "activated," "human," and "autologous." Only English language studies were considered for review. The reference lists of selected articles from databases were reviewed as well to identify any additional related articles that may have not been found through the database searches.

Inclusion and Exclusion Criteria

The inclusion criteria were cohort studies, case series, randomized controlled trials, and case-controlled studies in which: (a) the study subjects were human patients who had undergone soft tissue augmentation or filling with autologous fat grafting, (b) a control group was included in which patients were treated with FG alone, and (c) primary outcomes, including fat graft survival and/or patient satisfaction rate and/or recovery time were reported.

Our exclusion criteria were as follows: (a) studies in which the outcomes, including fat graft survival, patient satisfaction, and recovery time were not provided or could not be calculated or (b) studies that did not provide original data such as reviews, letters, and conference abstracts. If a single study sample was used in more than one study, the latest reference was selected for the meta-analysis.

After excluding duplicates, all identified studies underwent a two-stage article selection process independently completed by two reviewers (MW and MK). Data were imported into Microsoft Excel 2020 (Microsoft, Redmond, WA). Titles and abstracts were first screened to identify potentially relevant studies. The full manuscripts of articles that passed through the first stage were then evaluated according to the inclusion and exclusion criteria. Any inconsistencies between the two reviewers were resolved by consensus or consultation with a third reviewer (ACP).

Assessment of Risk of Bias of Included Studies

Two authors (MW and MK) independently assessed the included studies using the Cochrane risk of bias tool, [32] which includes Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. Disagreement between the two reviewers was resolved by consensus or by a third review author.

Statistical Analysis

This meta-analysis was performed using RevMan (Review manager V5.3) and Stata 15.1 software (Stata Corporation, College Station, TX). Fat graft survival rates and recovery time were transformed into estimates of weighted mean difference (WMD) with its 95% confidence interval (95% CI). Patient satisfaction was transformed into estimates of odds ratio (OR) with its 95% CI. Cochran's Q statistic and I^2 test were used to analyze heterogeneity among individual studies.[33] If significant heterogeneity was identified ($P < 0.05$ or $I^2 > 50\%$), a random effects model was used to calculate the combined effect value. Otherwise, a fixed effects model was used to combine the data. Recovery time was defined as the number of days that passed before patients considered themselves capable to return to work or to restart social activities.

Subgroup Analysis

Subgroup analysis was performed by stratifying fat graft survival rates according to the recipient sites.

Sensitivity Analysis

A leave-one-out sensitivity analysis was performed by iteratively removing 1 study at a time and calculating the WMD or summary OR for the remaining studies, to confirm that our findings were not driven by any single study.

Results

Primary Studies Included in the Literature Review

A flow chart of the literature search is shown in Fig. 1. A total of 895 articles were originally identified in PubMed (n = 166), EMBASE (n = 260), Web of Science (n = 449), and the Cochrane library (n = 18). After removing duplicate articles (n = 854), 41 articles were left of which 12 articles were found to be irrelevant and excluded upon reviewing the titles and abstracts. After the full text was reviewed, 18 more articles were excluded. No article was included upon manual search. Finally, 11 articles were included in the meta-analysis.

Main study characteristics and risk of bias in included studies

The baseline characteristics of the included studies are shown in Table 1. Among the included articles, there were

Table 1 Baseline characteristics of the included studies

Study, year, country	Type, LOE	Application	FU, months	VMM	Group	No. of cases	Age (years)	Gender (M/F)	FSR(M ± SD%)	PS	RT (M ± SD days)	Comp.
Cervelli, 2009, Italy	P, 2	Facial soft tissue defects & low extremity ulcers	18	Photo	PRP + FG	35	NR	NR	70 ± 5	NR	NR	0
					FG	10	NR	NR	30 ± 3	NR	NR	0
Cervelli, 2013, Italy	R, 2	Different soft tissue defects & lower extremity ulcers	12	MRI and Ultrasound	PRP (different concentra-tions) + FG	40	36.6 (18-75)	NR	62.5 ± 9.04	NR	NR	NR
					FG	10			30 ± 3	NR	NR	NR
Chandarana, 2009, Canada	P, 2	Facial soft tissue defects	6	MRI	PRP + FG	6	52	2/4	69 ± 12	NR	NR	0
					FG	6	52	4/2	43 ± 17			3 fat liquefaction
Gentile, 2012, Italy	P, 2	Breast reconstruction	12	MRI and Ultrasound	PRP + FG	13	19-60	0/100	69 ± 5	NR	NR	NR
					FG	10			39 ± 3	NR	NR	NR
Gentile, 2013, Italy	P, 2	Breast reconstruction	12	MRI and Ultrasound	PRP + FG	50	19-60	0/100	69 ± 5	NR	NR	NR
					FG	50			39 ± 3	NR	NR	NR
Gentile, 2014, Italy	P, 2	Facial scars	12	MRI and Ultrasound	PRP + FG	10	21-69	5/5	69 ± 3	NR	NR	NR
					FG	10	NR	NR	39 ± 3	NR	NR	NR

(*continued on next page*)

Table 1 (*continued*)

Study, year, country	Type, LOE	Application	FU, months	VMM	Group	No. of cases	Age (years)	Gender (M/F)	FSR(M ± SD%)	PS	RT (M ± SD days)	Comp.
Sasaki, 2015, USA	C, 3	Facial soft tissue defects	12	3D Vectra Analysis	PRP + FG	105	62.1 (19-77)	5/105	68.5 ± 39.5	NR	NR	0
					FG	82	60.5 (58-63)	3/89		NR	NR	0
Sasaki, 2019, USA	C, 3	Facial fat grafting	12	3D Vectra Analysis	PRP + FG	10 (self-control)	54.4	0/10	24.1 ± 10.3	NR	NR	0
					FG				20.5 ± 0.8	NR	NR	0
		Hand fat grafting	12	3D Vectra Analysis	PRP + FG	10 (self-control)			89.2 ± 87.2	NR	NR	0
					FG				54.8 ± 53.8	NR	NR	0
Study, year, country	**Type, LOE**	**Application**	**FU, months**	**VMM**	**Group**	**No. of cases**	**Age, years**	**Gender (m/f)**	**FSR (M ± SD%)**	**PS**	**RT (M ± SD days)**	**Comp.**
Sadati, 2006, USA^	R, 2	Breast, face, trunk, and extremity fat grafting	6-12	NR	PRP + FG	448	NR	NR	NR	403	NR	NR
					FG	132	NR	NR	NR	66	NR	NR
Salgarello, 2011, Italy^	R, 2	Breast fat grafting	9 (3-16)	NR	PRP + FG	17	NR	0/17	NR	4	NR	7 fat necrosis
			9 (3-24)		FG	25	NR	0/25	NR	7	NR	2 fat necrosis
Willemsen, 2014, Netherlands*	R, 2	Facial fat grafting	3	NR	PRP + FG	18	35-65	0/18	NR	NR	13.2 ± 6.4	NR
					FG	25		0/25	NR	NR	18.9 ± 8.5	NR
Willemsen, 2018, Netherlands*	RCT, 2	Facial fat grafting	12	NR	PRP + FG	13	51.73 (38-62)	0/13	NR	NR	14.87 ± 4.604	0
					FG	12	52.5 (42-63)	0/12	NR	NR	20.57 ± 6.61	0

^ Studies included in the patient satisfaction analysis.

* Studies included in the recovery time after surgery analysis.LOE: level of evidence; FU: follow-up; VMM: volumetric measurement method; MRI: magnetic resonance imaging; PRP platelet-rich plasma; FG: fat grafting; BMI: Body mass index; M: male; F: female; FSR: fat survival rate; PS.: Patients satisfaction rate; RT: recovery time; Comp.: complications; R: retrospective cohort; P: prospective cohort; C: case-controlled study; RCT: randomized controlled trials; and NR: none reported.

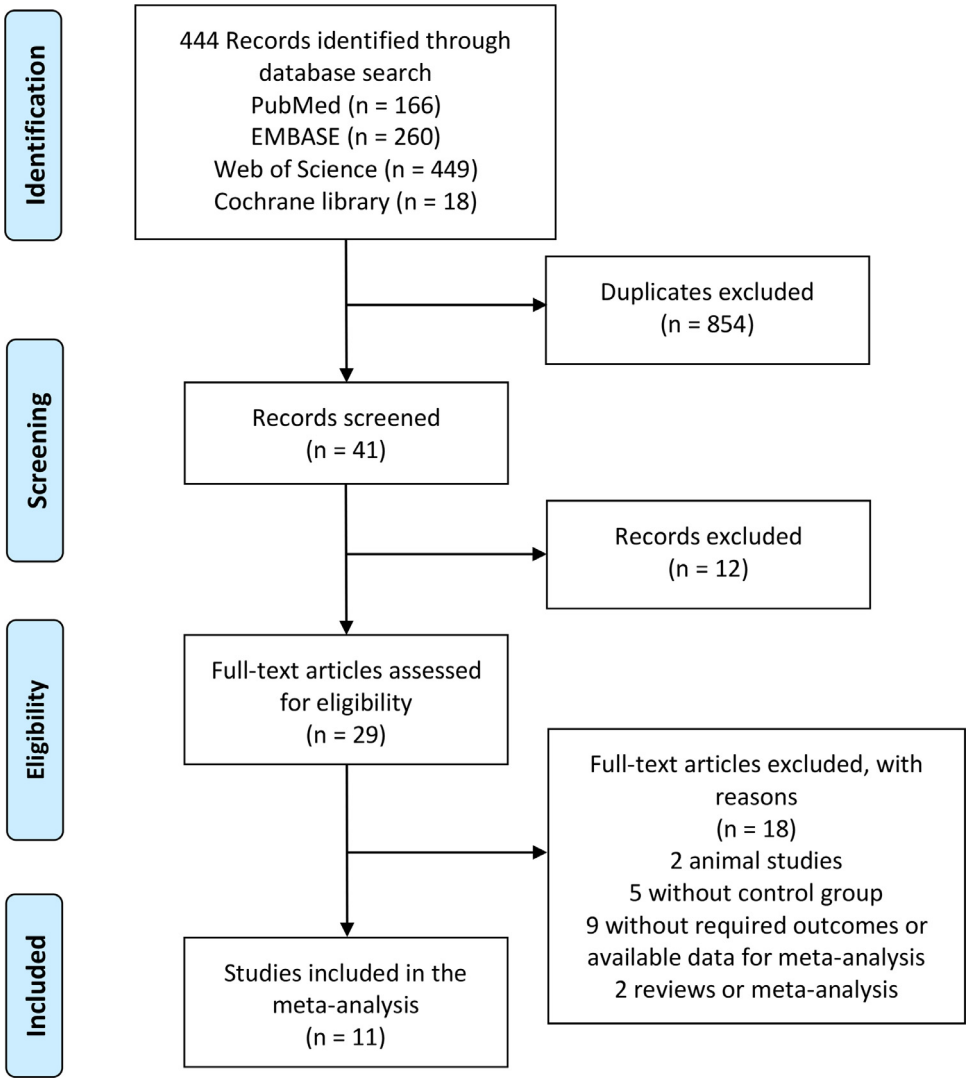

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart, depicting study selection.

four prospective studies,[34-37] two case-controlled studies,[38,39] four retrospective studies,[40-43] and one randomized controlled trial[44] with a total of 1125 patients. Face and breast were the two main recipient sites that were included in the meta-analysis. Patients were followed up from 3 to 24 months post-FG. A risk-of-bias graph and a summary in **Supplementary material 3** were prepared to depict the Cochrane bias parameters against which the studies were assessed.

Meta-analysis of fat graft survival and patient satisfaction rates

The fat graft survival rate was reported in seven studies (Figure 2A). Fat survival rate varied from 20.5% to 54.8% in FG alone and 24.1% to 89.2% in PRP + FG groups. Significant heterogeneity in this variable was observed among individual studies ($I^2 = 94\%$, $P < 0.001$); hence, the random effects model was used to pool estimates of fat survival rate. The fat survival rate in the PRP group was significantly higher than that of control group by 29% (WMD = 0.29, 95% CI 0.23 to 0.34; $P < 0.001$). When analyzing only the higher quality papers (the papers with low risk of bias as assessed with the Cochrane tool) in the sensitivity analysis, the conclusion remained unchanged, suggesting the stability of the meta-analysis (Figure 2B).

Patient satisfaction was reported in two studies (Figure 3A). Sadati *et al.*[41] presented the results using a categorical rating system consisting of five categories based on the degree of satisfaction with the outcome (i.e., excellent, better than expected, as expected, less than expected, and no change). Another study by Salgallero *et al.*[42] used a scoring scale consisting of five ascending grades from 1 to 5 (grade 1, no result obtained; grade 2, poor improvement; grade 3, fair visible result; grade 4, good result that almost satisfies the volume and result expected; and grade 5, excellent result). As a cut-off point between the positive and negative categories was easily identifiable in both of these studies, to standardize the scales, scores were divided into two distinct categories: satisfied and dissatisfied. These two categories were defined as follows: "Excellent," "Better than expected," and "As expected" categories in the study of Sadati *et al.*[41] and grades 4 and 5 in the study done by Sal-

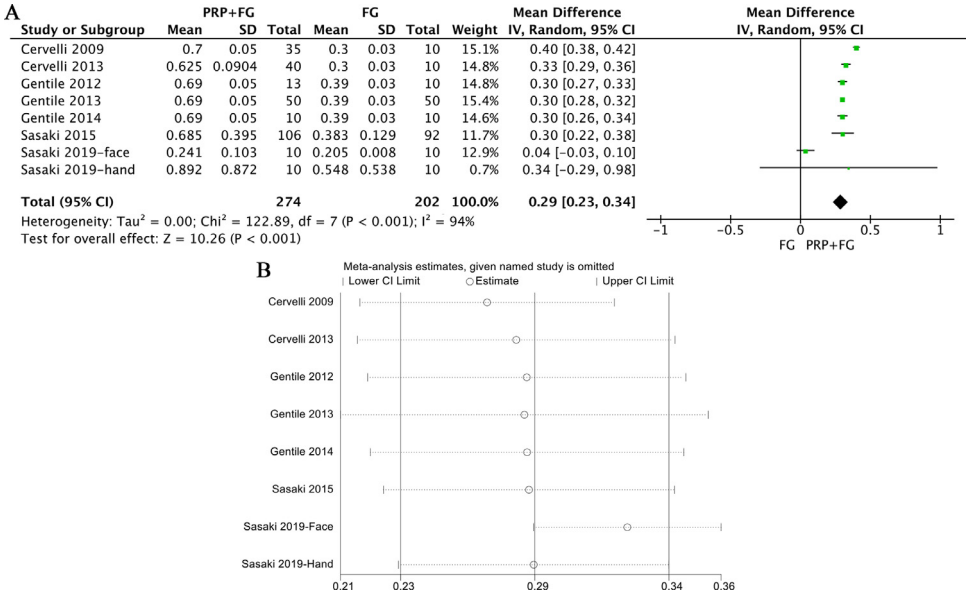

Figure 2 Fat survival rate after PRP-assisted fat grafting (PRP + FG) and conventional fat grafting (FG). (A) Forest plots of the analysis of the retention rate in PRP + FG when compared with FG alone and (B) Sensitivity analysis.

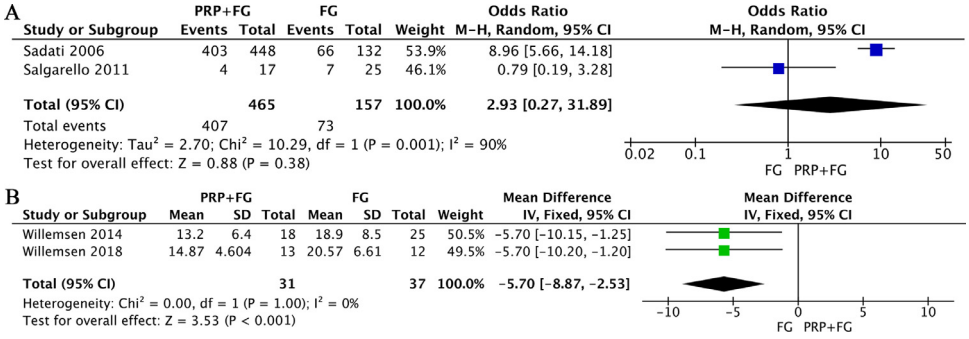

Figure 3 Forest plots of the analysis of (A) patient satisfaction and (B) recovery time after surgery in PRP + FG when compared with FG alone.

garello *et al.*[42] were considered as satisfied and remainder of categories in both studies were deemed as dissatisfied. Heterogeneity among individual studies was statistically significant ($I^2 = 90.0\%$ and $P = 0.001$), and the random effects model was used to pool data on patient satisfaction. There was no significant difference between the PRP+FG and control groups in patient satisfaction (OR = 2.93, 95% CI 0.27, to 31.89; $P = 0.38$).

Recovery time after surgery was reported in two studies (Figure 3B). Heterogeneity among individual studies was similar ($I^2 = 0.0\%$, $P = 1.00$), and the fixed effects model was used to pool data on recovery time. Recovery time was significantly lower in the PRP as compared to the control group by 5.07 days (WMD = -5.07, 95% CI -8.87 to -2.53; $P < 0.001$).

Subgroup analysis

Subgroup analysis for fat retention rate was performed by stratifying according to the recipient site (Table 2 and Figure 4). A significant difference was found between the PRP and control groups in terms of recipient sites which include the breast (WMD = 0.30, 95% CI from 0.29 to 0.31, and $P < 0.001$), face (WMD = 0.26, 95% CI from 0.13 to 0.40, and $P < 0.001$), and other parts of the body (WMD = 0.33, 95% CI from 0.29 to 0.36, and $P < 0.001$).

Table 2 Subgroup analysis for fat survival rate

Subgroup	N	WMD (95% CI)	*P*a	*P*h	I^2 (%)
Breast	2	0.30 [0.29, 0.31]	<0.001	1.00	0
Face	4	0.26 [0.13, 0.40]	<0.001	<0.001	97
Others	2	0.33 [0.29, 0.36]	<0.001	0.95	0

Discussion

Cotransplantation of autologous PRP and fat has become an interesting technique in soft tissue reconstruction. Clinical effectiveness and safety of this combination, however, remain controversial.[28,35,36,42,45-47] This study attempted to

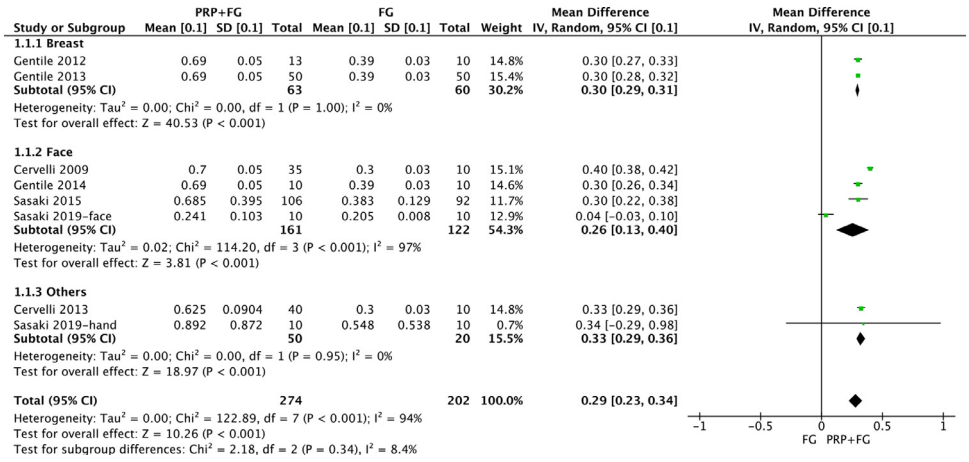

Figure 4 The subgroup analysis based on the recipient site. Forest plots of fat graft (FG) survival rates in PRP + FG when compared with FG alone according to the recipient site.

systematically investigate the clinical efficacy of cotransplantation of PRP and fat in comparison to conventional FG in soft tissue reconstruction. In total, 11 articles were included in this meta-analysis, which demonstrated that as compared to the traditional FG technique, cotransplantation of PRP and fat had a significantly higher fat graft survival rate. Moreover, the recovery time after surgery was significantly lower in these patients. However, no significant difference between the PRP + FG and control groups in terms of patient satisfaction was identified.

PRP is a concentration of platelets in blood plasma that is typically derived from whole blood through centrifugation.[48] PRP contains substantial amounts of growth factors, most importantly angiogenic factors, and its cotransplantation with fat grafts may enhance neovascularization in the recipient site, which ultimately improves fat graft survival. In addition, PRP can act as a source of nutrients at the early stages of fat transplantation when passive diffusion of materials from the surrounding tissue is the primary source of nutrition for the grafted tissue. PRP is autologous and biocompatible and can be utilized immediately without the requirement of complex preconditioning procedures.[21,46,49,50] In addition, PRP has been shown to be anti-inflammatory, optimizing fat graft retention by minimizing inflammation and edema, both of which have been shown to increase resorption of fat grafts.[51] PRP's anti-inflammatory properties are believed to be largely due to two of its constituent factors: hepatocyte growth factor and tumor necrosis factor α both of which are known to downregulate the proinflammatory transcription factor NF-kB,[52] an effect that may contribute to the significantly increased fat graft survival identified in this study.

Although both animal experiments and clinical studies have highlighted the promising effect of PRP in fat grafting, the methodologies used in such studies vary significantly. This inconsistency in the methodology is important, particularly because the current evidence suggests that methodological factors are critical determinants of PRP quality and FG outcomes.[53-56] Further evidence from high quality studies is warranted to address these methodological disparities in the context of fat grafting. The results of our meta-analysis are in agreement with those of a recent meta-analysis focusing on animal studies showing that PRF combined with FG may improve the survival rate and microvessel density of the grafted tissue. In their study, no statistically significant difference was seen between the effects of PRF and PRP on fat graft survival rate.[57]

Strengths and Limitations

Our study, as other reviews and meta-analyses, carries limitations. First, there are currently very few high-quality clinical studies examine the efficacy of PRP-enhanced fat and thus, only a small number of studies was included. In addition, these studies used different methods of fat graft survival measurement (including MRI, ultrasound, or 3D Vectra Analysis), PRP extraction, activation as well as concentration. All included studies used Coleman fat grafting; however, some used purified SVF and ADSCs. We extracted data only from PRP + FG groups when performing the meta-analysis. This methodological heterogeneity was not taken into consideration when this meta-analysis was performed because of the lack of adequate data.

Inclusion of only English language studies increased our study's publication bias as potential studies published in other languages may have been excluded. Finally, as identified in other meta-analyses, the quality of a meta-analysis cannot supersede the quality of the studies it includes.[58,59] Therefore, given that four included studies were retrospective nonrandomized case-control studies, and only one was a randomized-controlled study; the included studies carry inherent bias, such as selection bias.

Despite these limitations, this study is, to the best of our knowledge, the first to summarize and analyze the clinical evidence on the efficacy of PRP-enhanced fat grafting, in terms of fat graft survival, length of recovery postsurgery, and satisfaction rate. We analyzed recent studies, including one study from 2018 and one from 2019. In addition, our research followed the PRISMA guidelines.[31] Finally, we utilized the Cochrane risk of bias tool to assess the quality of

the studies, and to perform a sensitivity analysis to verify our results.

Conclusion

Numerous methods have been proposed to enhance the clinical outcomes of autologous fat grafting, but there currently exists no consensus on the optimum technique. PRP has offered new potential for the optimization of fat graft survival. In summary, this study suggests that PRP-enhanced FG is superior to conventional FG as it not only improves fat graft survival rate, but also lowers recovery time. To the best of our knowledge, this is the first meta-analysis on the effect of PRP on fat graft survival in clinical settings. Nonetheless, our results must be verified through future well-designed, randomized controlled studies that evaluate PRP's optimal concentration and combination ratio, safety profile, and long-term clinical efficacy.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethical approval

Not required.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2021.05.046.

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