Autologous Platelet Concentrates as Clinical Substitutes for Connective Tissue Graft in the Treatment of Miller Class I and II Gingival Recessions: An Updated Meta-Analysis

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This meta-analysis aimed to evaluate the clinical effectiveness of autologous platelet concentrates (APC) + coronally advanced flap (CAF) (Group A) compared with connective tissue graft (CTG) + CAF (Group B), and CAF alone (Group C), in patients with Miller Class I or II gingival recessions. Relevant articles published before December 2018 were retrieved electronically without date or language restriction and screened according to inclusion criteria. Quantitative meta-analysis was conducted comparing the groups. The inverse variance method was applied in fixed or random effects models according to heterogeneity. Sixteen randomized controlled trials were included. Root coverage (RC), clinical attachment level (CAL), gingival thickness (GT), and probing depth (PD) did not differ significantly between Groups A and B. The keratinized gingival width (KGW) of Group A was significantly less than that of Group B. The RC and GT of Group A were significantly greater than that in Group C. CAL and PD for Group A were lower than for Group C. KGW for Group A did not differ significantly from that of Group C. The results suggested that APC + CAF represents a promising alternative for root coverage for Miller Class I and II gingival recession defects. Nevertheless, CTG + CAF exhibits superior outcomes in terms of KGW. Hence, in scenarios lacking keratinized gingiva (Miller Class II), APC + CAF might not be the most suitable therapeutic choice.


Gingival recession is characterized by the apical migration of the marginal gingiva away from the cementoenamel junction as well as the exposure of root surface to the oral environment.1 The main causes of gingival recession are widely known to be chronic trauma, periodontal disease, occlusal trauma, and decreased alveolar bone crest thickness.2

Connective tissue graft (CTG) combined with coronally advanced flap (CAF) is the gold standard treatment for single or multiple gingival recessions.3 Nevertheless, disadvantages of the CTG technique are the need to harvest the subepithelial graft at the donor site, and pain after surgery is often reported. Consequently, alternative biomaterials and autologous grafts, such as autologous platelet concentrates (APCs; as well as platelet-rich fibrin [PRF] and concentrated growth factor [CGF]), enamel matrix derivatives, and amniotic membrane, have gradually emerged as alternative and adjuvant treatment options.4,5

In recent decades, numerous studies have reported satisfactory application of PRF or CGF in the treatment of Miller Class I or II gingival recessions.4,6,7 However, robust evidence concerning the extent to which this kind of promising autologous graft can substitute for the gold standard technique (CTG)
is lacking, with few large-scale randomized controlled trials (RCTs) comparing the outcome of APC and CTG applications.

The objective of this meta-analysis was to compare the effects of APC + CAF with CTG + CAF and CAF alone, to evaluate whether APCs can be used as clinical substitutes for CTG in the treatment of gingival recession.

Materials and Methods

Search Strategy

According to the standard guidelines for meta-analyses, a comprehensive literature search was independently performed by two investigators (P.Y. and T.W.). The Cochrane Library, PubMed, EMBASE, and Wiley Online databases were searched without language or date restrictions. Search terms included Medical Subject Heading (MeSH) and free text words: “gingival recession” and “periodontal surgery,” in combination with “platelet-rich plasma,” “platelet-rich fibrin,” or “concentrated growth factors.”

Study Selection

Articles that satisfied the following criteria were included: (1) RCTs and prospective controlled trials published in peer-reviewed journals comparing the effectiveness of APC + CAF and CTG + CAF or APC + CAF and CAF alone; (2) all cases diagnosed as Miller Class I or II gingival recession; and (3) mean follow-up period of no less than 6 months. Animal studies, retrospective cohort studies, case reports, case series, or studies comparing the performance of APC + CAF with other biomaterials were excluded.

Data Extraction and Outcomes

Following the authentic checklist of Meta-analysis of Observational Studies in Epidemiology,8 two investigators reviewed and extracted all the data from eligible studies carefully and independently. For each study, the following details were collected: first author’s name, year of publication, study design, number of patients or teeth, grouping method, percentage of root coverage (RC), clinical attachment level (CAL), probing depth (PD), keratinized gingival width (KGW), gingival thickness (GT), and duration of follow-up. Discrepancies were resolved by a third arbitrator Y.W.).

Methodologic Quality Evaluation

Two investigators (P.Y. and T.W.) separately evaluated the methodologic quality of included RCTs according to the Cochrane Collaboration’s tool for assessing risk of bias,9 which includes seven domains: random sequence generation, allocation of concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, incomplete outcome data, and other sources of bias. For each domain, the risk was rated as low, high, or unclear. Consensus was obtained when discrepancies were encountered.

Statistical Analysis

The mean values and standard deviations (SDs) of RC, CAL, PD, KGW, and GT at the time of the latest follow-up were acquired from cases and controls directly from the original research. Meta-analyses were performed using RevMan 5.3 software (Cochrane). The pooled standard mean differences (SMDs) with 95% confidence intervals (CIs) were calculated by a fixed effects model if the heterogeneity was not significant. Otherwise, a random effects model was used. Higgins’ I-squared (I²) statistic was applied to offer evidence of heterogeneity, with I² > 50% suggesting significant heterogeneity. Publication bias was evaluated by funnel plot. Paired t test was used to compare the difference in RC between Group A (APC + CAF) and Group B (CTG + CAF) or Group A and Group C (CAF alone), using SPSS version 20.0 (IBM) rather than RevMan 5.3, as RC values in more than half the eligible studies lacked SDs. P < .05 was considered statistically significant.

Results

Study Selection and Characteristics of Eligible Studies

The initial comprehensive search yielded 440 articles. According to the inclusion and exclusion criteria,
16 of these articles were selected for further analysis. A detailed flow diagram of literature retrieval and screening is shown in Fig 1.

Among the 16 studies, 7 were split-mouth RCTs and 9 were conventional RCTs, with a total of 353 cases and 360 controls enrolled. Of the included studies, 7 studies (nearly half) gave the mean value for RC without SD, 9 studies compared the effectiveness of Group A (APC + CAF) with Group B, and 8 studies compared the performance of Group A (APC + CAF) with Group C. The general characteristics of the eligible studies are outlined in Table 1.

**Quality Assessment**

The results of assessment of the risk of bias for the eligible studies are described in Table 2. Three articles were characterized by a high risk of bias, and moderate risk bias was detected in the other 13 articles.

**Meta-Analysis**

**Group A vs Group B**

Figure 2 shows the results of meta-analysis for the outcomes of Group A and Group B. The tests for heterogeneity were significant (CAL: $\tau^2 = 86\%$, $P$ for heterogeneity $< .0001$; KGW: $\tau^2 = 74\%$, $P$ for heterogeneity $< .0001$; GT: $\tau^2 = 89\%$, $P$ for heterogeneity $< .0001$; PD: $\tau^2 = 65\%$, $P$ for heterogeneity $= .003$), therefore a random effects model was used to calculate the pooled SMDs. The results did not demonstrate any statistically significant difference in CAL (SMD: $-0.05$, $P = .84$, 95% CI: $-0.58$ to $0.47$), GT (SMD: $-0.57$, $P = .1$, 95% CI: $-1.24$ to $0.1$), and PD (SMD: $-0.2$, $P = .24$, 95% CI: $-0.53$ to $0.13$). However, a statistically significant difference was detected for KGW (SMD: $-0.5$, $P = .01$, 95% CI: $-0.88$ to $-0.12$).

![Flow diagram of study screening and selection.](image-url)
Table 1 Characteristics of Eligible Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Author, y</th>
<th>Study design</th>
<th>Case/ control n</th>
<th>Group</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
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<td>Araca et al, 2009</td>
<td>Split-mouth RCT</td>
<td>20/20</td>
<td>(CAF+PRF) vs CAF</td>
<td>80.7 ± 14.7 vs 91.5 ± 11.4</td>
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<tr>
<td>Aroca et al, 2018</td>
<td>Split-mouth RCT</td>
<td>15/15</td>
<td>(CAF+PRF) vs CAF</td>
<td>88.68 ± 10.65 vs 91.96 ± 15.46</td>
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<tr>
<td>Padma et al, 2013</td>
<td>Split-mouth RCT</td>
<td>15/15</td>
<td>(CAF+PRF) vs CAF</td>
<td>100 ± 0.00 vs 68.44 ± 17.42</td>
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<tr>
<td>Bozkurt Doğan et al, 2015</td>
<td>Split-mouth RCT</td>
<td>60/59</td>
<td>(CAF+PRF) vs CAF</td>
<td>86.67 ± 15.59 vs 82.06 ± 17.49</td>
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<tr>
<td>Gupta et al, 2015</td>
<td>RCT</td>
<td>15/15</td>
<td>(CAF+PRF) vs CAF</td>
<td>91.00 ± 19.98 vs 86.60 ± 23.83</td>
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<tr>
<td>Tunali et al, 2018</td>
<td>Split-mouth RCT</td>
<td>22/22</td>
<td>(CAF+PRF) vs CAF</td>
<td>76.63 ± 77.36 vs 86.60 ± 23.83</td>
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<td>Thamaraiselvan et al, 2017</td>
<td>RCT</td>
<td>10/10</td>
<td>(CAF+PRF) vs CAF</td>
<td>74.16 ± 28.98 vs 65.00 ± 44.47</td>
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<td>92.7 ± 94.2 vs 1.59 ± 0.65</td>
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<td>RCT</td>
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<td>86.67 ± 15.59 vs 82.06 ± 17.49</td>
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<td>Split-mouth RCT</td>
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<td>(CAF+PRF) vs CAF</td>
<td>77.12 ± 84 vs 74.63 ± 80</td>
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<td>Kuka et al, 2018</td>
<td>Split-mouth RCT</td>
<td>15/15</td>
<td>(CAF+PRF) vs CAF</td>
<td>88.36 ± 15.45 vs 80.13 ± 18.93</td>
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<td>Culaeoglu et al, 2018</td>
<td>Split-mouth RCT</td>
<td>21/21</td>
<td>(CAF+PRF) vs CAF</td>
<td>56.34 ± 14.51 vs 60.00 ± 20</td>
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<td>Split-mouth RCT</td>
<td>63/51</td>
<td>(CAF+PRF) vs CAF</td>
<td>93.29 ± 93.22 vs 91.96 ± 15.46</td>
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RC = root coverage; CAL = clinical attachment level; KGW = keratinized gingiva width; PD = probing depth; GT = gingival thickness; SD = standard deviation; RCT = randomized control trial; CAF = coronally advanced flap; PRF = platelet-rich fibrin; CTG = connective tissue graft; CGF = concentrated growth factor; NA = not available.

Group A vs Group C

Figure 3 shows the results of the meta-analysis for outcomes of Group A and Group C. No statistically significant difference could be found for KGW (SMD: 0.13, P = 0.46, 95% CI: –0.22 to 0.48, I² = 59%, P for heterogeneity = 0.2, random effects model), but a significant difference was found for CAL gain (SMD: –0.38, P = 0.001, 95% CI: –0.6 to –0.15, I² = 47%, P for heterogeneity = 0.08, fixed effects model), GT gain (SMD: 1.6, P = 0.007, 95% CI: 0.43 to 2.76, I² = 94%, P for heterogeneity < 0.0001, random effects model), and PD reduction (SMD: –0.27, P = 0.03, 95% CI: –0.51 to –0.03, I² = 43%, P for heterogeneity = 0.13, fixed effects model).
Root Coverage

RC was not included in the present meta-analysis, as seven articles did not report SDs and one article reported nothing about RC. Thus, paired t test was used to compare the difference in RC (mean value) between different groups using SPSS (IBM). No difference in RC was found between Group A and Group B (P = .777), and RC for Group A was significantly higher than for Group C (P = .037).

Publication Bias

Figures 4 and 5 show eight funnel plots for comparison. The funnel plots show relative symmetry, indicating that there was no publication bias among the included studies.

Discussion

In contrast with CTG, APCs have several specific characteristics: (1) invasive surgery is not required; (2) they are rich in growth factors, inflammatory cytokines, and immune host cells; and (3) they have the ability to accelerate the healing process of soft tissue.23 Periodontal plastic surgery is regarded as regenerative surgery, attempting to achieve periodontal tissue rehabilitation. Regenerative engineering requires three key factors: scaffolds, signaling molecules, and cells.24 As autologous biomaterials, APCs contain all these ingredients: fibrin (scaffolds), growth factors (signaling molecules), and platelets and white blood cells (cells).25 These merits, along with APC’s biocompatibility and activity, make APCs promising biomaterials in periodontal plastic surgery.

To the authors’ knowledge, this study is the largest population-based meta-analysis evaluating the effectiveness of APCs in the treatment of Miller Class I and II gingival recessions. Previous case reports, RCTs, or systemic reviews had reported inconsistent results, leaving controversy over whether APC was able to replace CTG as the preferred technique.5,16,26,27 By comparing APC with CTG + CAF (the gold standard treatment) and CAF alone, the advantages and disadvantages of APCs were comprehensively assessed.

<table>
<thead>
<tr>
<th>Author, y</th>
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+ = low risk; − = high risk; ? = unknown risk.
Fig 2 Forest plots comparing Group A and Group B for (a) CAL, (b) KGW, (c) GT, and (d) PD.
Fig 3 Forest plots comparing Group A and Group C for (a) CAL, (b) KGW, (c) GT, and (d) PD.
After a comprehensive search, 16 eligible articles with a total of 353 cases and 360 controls enrolled were selected for this meta-analysis. The effectiveness of APC + CAF (Group A) was compared with that of CTG + CAF (Group B). KGW of Group B was found to be significantly greater than that of Group A, but no significant differences were found between Groups A and B for other parameters (RC, CAL, GT, and PD). Similarly, Moraschini and Barboza Edos reported in their systematic review that RC and CAL did not differ significantly between APC + CAF and CTG + CAF, but KGW gain was significantly greater in the CTG + CAF group. In another systematic review conducted by Castro et al., KG, PD, and CAL showed no significant differences between APC + CAF and CTG + CAF. However, each of these two systematic reviews only included three articles and fewer patients than in the present, updated meta-analysis. Hence, the relatively small study size limited the power of their results.

Fig 4 Funnel plots comparing Group A and Group B for (a) CAL, (b) KGW, (c) GT, and (d) PD.
According to the current findings on KGW, APCs appeared unable to induce keratinization of the overlying gingiva in the same way that CTG combined with CAF resulted in widening of the keratinized gingiva in periodontal plastic surgery. This phenomenon was proven by the subsequent comparison of KGW between Groups A and C. In contrast with CAF alone, the application of APC did not increase KGW after surgery ($P = .46; \text{SD: 0.13}; 95\% \text{ CI: } -0.22 \text{ to } 0.48$). The same findings were reported by Moraschini and Barboza Edos and Castro et al., respectively, in their systematic reviews.

KGW is widely recognized as an important factor in maintaining long-term periodontal tissue health, especially for thin-scalloped gingiva. The findings of the present study show that APCs were not a completely satisfactory substitution for CTG in gingival recession therapy, in particular when KG was lacking (Miller Class II). Although unable to improve KGW, application of APCs achieved the same degree of
PD, CAL, and GT as CTG. To further evaluate the potential benefits of APCs in this type of surgery, Group A was compared with Group C for all parameters. There was no significant difference in KGW, but the other parameters were significantly better in Group A, with the use of APC leading to greater RC and GT gain and less CAL and PD. These results were similar to those of Agarwal et al, who found that the use of PRF enhanced RC and GT compared with CAF alone. 17

Some limitations of the present meta-analysis should be noted. Firstly, the biologic features of APCs vary, and the preparations used in each study may not have been consistent. This may have led to APCs performing differently in the healing process across the studies. Secondly, not all of the included studies reported every parameter of interest to the authors (RC, CAL, KGW, GT, and PD), affecting the integrity of the overall data analysis. Thirdly, most follow-up periods of the included studies were only 6 months, which was not long enough, as postoperative recovery and stabilization of periodontal soft tissue is a longer process. Fourthly, since included studies showed moderate or high risk of bias, the results should be interpreted with caution. Finally, significant heterogeneity was observed in some parameters among the included studies, thus the conclusions drawn must be conservative.

Conclusions

Based on the present meta-analysis, a conclusion can be drawn that APCs + CAF represent a promising alternative for root coverage for Miller Class I and II gingival recession defects, in particular when compared to CAF alone. Nevertheless, CTG + CAF exhibits superior outcomes in terms of KGW. Hence, in scenarios where keratinized gingiva is lacking (Miller Class II), APCs + CAF might not be the most suitable therapeutic choice.

Acknowledgments

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References


