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Review Article

Efficacy of autologous platelet concentrates for root coverage of Miller's Class I and II gingival recession defects: A systematic review and meta-analysis

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ABSTRACT

Background: This systematic review and meta-analysis aimed to assess the efficacy of autologous platelet concentrate (APCs) in comparison with coronally-advanced flap alone or in combination with connective tissue graft or other biomaterials or bioactive agents for root coverage (RC) of Miller's Class I and II gingival recession defects by measuring the keratinized mucosa width (KMW).
Materials and Methods: This systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis guidelines. An electronic search of the literature was conducted in PubMed, EMBASE, Scopus, Cochrane, Web of Science, Magiran, Scientific Information Database, and Irandoc for randomized clinical trials (RCTs) that used APCs for RC in their intervention group. Eligible articles were retrieved by assessment of titles and abstracts and then the full texts. The risk of bias was assessed by the Cochrane Library Risk of Bias Assessment Tool. Meta-analysis was carried out by RevMan 5.3 software. In the case of homogeneity, variables were reported as weighted mean difference (WMD) with 95% confidence interval (CI) for each group.
Results: The search yielded 689 articles; out of which, 32 were eligible for study inclusion. Meta-analysis did not show any additional effect for RC and KMW with APCs. Clinical parameters were as follows: RC: WMD = −1.57 mm (95% CI: −2.49, −0.659; P = 0.001) and KMW: −0.106 mm (95% CI: −0.3222, 0.110; P = 0.337).
Conclusion: The application of APCs for RC of Miller's Class I and II gingival recession defects does not seem to improve the clinical parameters.

Key Words: Gingival recession, mucogingival surgery, periodontal plastic surgery, platelet-rich fibrin, root resorption

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INTRODUCTION

Gingival recession refers to apical displacement of the gingival margin and exposure of the cementoenamel junction and root surface to the oral cavity.[1] Several factors are responsible for gingival recession and denuding of root surfaces, such as periodontal disease, mechanical forces applied by incorrect toothbrushing,

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iatrogenic factors, faulty restorations and crowns in contact with the gingival margin, and anatomical factors such as tooth malposition and abnormal frenal attachments.[2-4]

Following the gingival recession, denuded root surfaces are exposed to the oral environment, which makes them highly susceptible to erosion and caries, hypersensitivity, and esthetic problems.[5]

A systematic review indicated that gingival recession defects that were left untreated progressed in the long term in patients with good oral hygiene.[6] Complete root coverage (RC) for the treatment of gingival recession provides a homogenous appearance and decreases the probing depth.[7] However, several factors need to be considered for the selection of surgical techniques. Among different surgical techniques, coronally advanced flap (CAF) is a commonly adopted method for RC in case of the presence of adequate keratinized mucosa width (KMW). CAF in combination with connective tissue graft (CTG) is the gold standard for RC and brings about the most favorable results in patients without proximal attachment loss.[8-11]

The alternative treatment options for CTG include different biomaterials and bioactive agents that were introduced over the past years aiming to minimize patient morbidity. For instance, several types of collagen-based membranes and dermal tissue derivatives with allograft or xenograft origin were introduced for RC. Despite the fact that such alternative materials provide an excellent 3D network for the migration and proliferation of fibroblasts, they have drawbacks such as limited regenerative potential and lack of long-term tissue keratinization.[12] Recently, different types of membranes derived from placental tissue were suggested for enhanced bioactivity; however, information regarding their long-term application is scarce.[13,14] Another strategy is to use regenerative growth factors alone or in combination with CTG or collagen membranes to induce the regenerative potential of fibroblasts at the defect site. Enamel matrix derivative (EMD) is among such materials. Animal and human studies have reported positive clinical and histological results for EMD in combination with CAF.[15,16]

Researchers have recently focused on the development of regenerative treatments with an autologous origin that decrease the risk of cross-contamination and are cost-effective. These investigations led to the development of autologous platelet concentrates (APCs) by Choukroun *et al*.[17] Attempts are ongoing to find alternatives to CTG. The use of biomaterials such as acellular dermal matrix, collagen membranes, or EMD has some limitations due to the high cost and clinical conditions of patients.[18] APC is a new biomaterial, the efficacy of which needs to be investigated in prospective trials with long follow-up periods. The predictability of RC with APC, its effects on healing, and the molecular mechanisms of its function have yet to be fully elucidated.[19] Furthermore, the effects of APC are often compared with CTG, and other alternatives have not been assessed. Considering the diversity of APC products and the controversial results regarding their efficacy, this systematic review and meta-analysis were conducted to assess the efficacy of APCs for RC in Miller's Class I and II gingival recession defects by measuring the clinical parameters such as RC and KMW, in comparison with other therapeutic modalities. Using these materials, there will be no need for autogenous intraoral soft-tissue grafts, thereby reducing patient discomfort and morbidity, leading to increasing quality of their lives. On the other side, concentrated growth factors in APCs are promising in long-term outcome stability and comparable results with conventional methods.

MATERIALS AND METHODS

Population, intervention, comparisons, and outcome protocol

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist.[20] The study was approved by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.RESEARCH.REC.1400.398).

The study question was designed according to the population, intervention, comparisons, and outcomes as follows:

Population (P): Patients with Miller's Class I and II gingival recession defects. Intervention (I): Use of APCs. Comparison (C): CAF alone or in combination with CTG, or other biomaterials and bioactive agents. Outcomes (O): RC and KMW. Study design (S): Randomized clinical trials (RCTs).

Focused question

The focused question of the study was that "whether APCs, in comparison with CAF alone or

in combination with CTG, or other biomaterials and bioactive agents can improve RC and KMW in patients with Miller's Class I and II gingival recession defects."

Search strategy

An electronic search was conducted in PubMed, EMBASE, Scopus, Cochrane, Web of Science, Magiran, Scientific Information Database (SID), and Irandoc. Furthermore, the bibliography of previous systematic reviews was searched [Supplementary File 1 and Supplementary Table 1].

Eligibility criteria

Inclusion criteria

Teeth with Miller's Class I and II gingival recession defects confirmed by radiography and clinical examination. Studies in which the test group received APC (all types of APCs) + CAF and the control group received CAF alone or in combination with CTG or biomaterial and Articles in English or Farsi.

Exclusion criteria

Animal or *in vitro* studies, case reports, and case series, follow-up <6 months, and patients under orthodontic treatment.

Data extraction

The eligibility of the articles retrieved from the electronic search was evaluated by two independent examiners (J.Y. and A.M.). The titles and abstracts were evaluated to eliminate irrelevant articles. Next, the full texts were independently assessed by the two examiners. Disagreements were resolved by discussion. Concordance between the two examiners was evaluated by the Cohen's kappa coefficient. Data were extracted according to predesigned forms. In case of missing data, correspondence was performed with the corresponding author. Table 1 presents the extracted data items. The outcomes included RC and KMW after treatment compared with baseline.

Risk of bias assessment

Assessment of the risk of bias was conducted according to the Revised Cochrane Risk of Bias Tool for Randomized Trials. Based on the risk of bias in all six items, each article was categorized as having a low risk of bias if it had a low risk of bias in all six items, high risk of bias if it had a high risk of bias in at least one item, or unclear risk of bias if at least one item had unclear risk of bias.

To assess the publication bias, the funnel plots were drawn to assess the symmetry of each variable according to the Cochrane Handbook for Systematic Reviews of Interventions.[21]

Assessment of treatment effect

The weighted mean difference (WMD; change score) and 95% confidence interval (95% CI) were calculated for each variable in each treatment group. Data were reported in millimeters for all four variables.

Statistical analysis

The random effect model was used for pooling data using RevMan 5.3 software. Data from split-mouth and parallel design RCTs were analyzed separately and also in combination.

RESULTS

Selection of studies

A total of 788 articles were retrieved from the eight databases as follows: PubMed (167 articles), ISI (Web of Science) (152 articles), Scopus (157 articles), EMBASE (141 articles), Cochrane (130 articles), SID (15 articles), Magiran (22 articles), and Irandoc (2 articles). A manual search also yielded one thesis. Of all, 540 were duplicates and excluded. Assessment of title and abstract of articles yielded 42 relevant articles. After reading the full text of the articles, 7 were excluded since they were case reports or case series, 2 were excluded due to language other than English and Farsi, and one was excluded due to the absence of a control group. Finally, 32 articles underwent qualitative and quantitative analysis [Figure 1]. Studies with more than 1 control group were included as separate records in the meta-analysis.

Descriptive findings

This meta-analysis on the efficacy of APCs for RC evaluated 32 studies on RC and 31 studies on KMW. Table 1 presents the characteristics of the included studies.

Analytical findings

Root coverage

A total of 32 articles regarding RC underwent meta-analysis. Considering the I^2 statistics and Cochrane test which were significant for heterogeneity ($P < 0.001$), the random-effect model was applied to pool the results of studies. Studies with a control group (CTG + CAF, CAF, modified coronally-advanced flap [MCAF], and amniotic membrane + CAF) and an intervention group (platelet-rich fibrin [PRF] + MCAF,

Table 1: General characteristics of included studies in the meta-analysis

Code/first author (year)/country	Study design/ duration (months)	Subjects (*n*)/gender/ mean age (years)/ smoking (yes/no)	Surgical sites (*n*)/recession type/Miller's classification	Test group(s)	Control group(s)	Presurgical procedure	Postsurgical care	PRF preparation: Centrifugation speed (rpm)/time (min)/ blood volume (mL)/ machine
1. Jain (2017)[47] India	*RCT* parallel, 6	30, (female=15, male=15), 29.37, no	-, -, I and II	PRF + CAF	Amniotic M + CAF	SRP	Dressing- CHX- analgesics	3000, 10, 10, -
2. Bozkurt Doğan (2015)[48] Turkey	RCT split mouth, 6	20, (female=13, male=7), 37.1, no	119, multiple, I and II	PRF + CAF	CAF	SRP	Naproxen- CHX	Medifuge
3. Tunalı (2015)[49] Turkey	RCT split-mouth, 12	10, (female=6, male=4), 34.2, no	44, multiple, I and II	PRF + CAF	CTG + CAF	SRP	Dressing-amoxicillin-naproxen-CHX	2700, 12, 10, Hettich Zentrifugen
4. Agarwal (2016)[22] India	RCT, parallel, 6	23, (female=5, male=18), >18, no	30, multiple, I and II	PRF + CAF	I: amniotic M + CAF II: CAF	SRP + PRF fluid rinse	Dressing-amoxicillin-ibuprofen-CHX	2700, 12, 10, REMI
5. Aroca (2009)[50] Hungary	RCT split-mouth, 6	20, (female=15, male=18), 31.7, yes	67, multiple, I and II	PRF + MCAF	MCAF	Betamethasone + alprazolam + SRP	Niflumic acid + clindamycin + CHX	3000, 10, 10, REMI
6. Kuka (2018)[51] Turkey	RCT parallel, 12	24, (female=13, male=11), 32.35, no	52, multiple, I	PRF + CAF	CAF	SRP	Co-amoxiclav-naproxen- CHX	3000, 10, 10
7. Cheung (2004)[52] USA	RCT split-mouth, 8	15, (female=6, male=8), 36.1, no	54, single or multiple, I and II	PRP + CAF	CTG + CAF	SRP + tetracycline solution	Dressing-CHX-penicillin VK	-, -, 54, PCCS
8. Gautam (2020)[53] India	RCT parallel, 6	28, -, -, -	30, single, I and II	PRF + CAF	CAF	-	Dressing-antibiotic-analgesic-CHX	3000, 10, 10
9. Akcan (2020)[54] Turkey	RCT split-mouth, 6	19, (female=8, male=11), -, no	74, single or multiple, I	PRF + CAF	CTG + CAF	Phase I therapy	dressing-NSAID-CHX-Augmentin	-, - ,-, Medifuge
10. Öncü (2017)[55] Turkey	RCT split-mouth, 6	20, (female=11, male=9), 40, no	60, multiple I and II	PRF + MCAF	CTG + MCAF	SRP	Analgesic-CHX	2700, 12, 9, PC-O2
11. Jankovic (2012)[56] Serbia	RCT split-mouth, 6	15, (female=10, male=5), -, -	-, single or multiple, I and II	PRF + CAF	CTG + CAF	SRP	Dressing-CHX	3000, 10, 10, -
12. Dixit (2018)[57] India	RCT split mouth, 6	12, (female=5, male=7), 37.5, No	24, -, I and II	PRF + CAF	MCAF	SRP	Dressing-CHX-ibuprofen	2700, 12, 5, -
13. Joshi (2020)[58] India	RCT split-mouth, 6	15, -, -, no	30, -, I	PRF + CAF	CTG + CAF	SRP	Diclomol-CHX	3000, 10, 5, REMI R8C
14. Gupta (2015)[59] India	RCT parallel, 6	26, (female=10, male=16), 37.17, no	30, single, I and II	PRF + MCAF	MCAF	-	Dressing-antibiotic-analgesic-anti-inflammatory-CHX	2700, 12, 10, REMI
15. Padma (2013)[60] India	RCT split-mouth, 6	15, -, -, no	30, single, I and II	PRF + CAF	CAF	-	Dressing-ibuprofen-amoxicillin-CHX	3000, 10, 5,-
16. Kumar (2017)[61] India	RCT parallel, 6	36, (female=2, male=34), 32.1, No	26, single, I and II	PRF + CAF	I: CTG + CAF II: CAF	-	Dressing-amoxicillin-ibuprofen paracetamol-CHX	2700, 12, 10, -
17. Mufti (2017)[62] India	RCT parallel, 6	32, (female=14, male=18), 36.97, no	32, single, I	PRF + CAF	CTG + CAF	SRP	Dressing-antibiotic-analgesic-CHX	3000, 10, 10, anterior-premolar
18. Ramireddy (2018)[63] India	RCT split-mouth, 6	20, (female=2, male=18), -, -	78, single or multiple, I and II	PRF + CAF	RMGI + CAF	Curette-finishing bur	Dressing	2700, 12, 10, -
19. Thamaraiselvan (2015)[64] India	RCT parallel, 6	20, (female=11, male=9), -, No	-, single, I and II	PRF + CAF	CAF	SRP-tetracycline conditioning	Dressing-antibiotic-analgesic	3000, 10, 10, -

Contd...

Table 1: Contd...

Code/first author (year)/country	Study design/ duration (months)	Subjects (*n*)/gender/ mean age (years)/ smoking (yes/no)	Surgical sites (*n*)/recession type/Miller's classification	Test group(s)	Control group(s)	Presurgical procedure	Postsurgical care	PRF preparation: Centrifugation speed (rpm)/time (min)/ blood volume (mL)/ machine
20. Uraz (2015)[65] Turkey	RCT split mouth, 6	15, (female=5, male=10), 33.7, no	106, multiple, I and II	PRF + CAF	e-MCTG + CAF	SRP	Analgesic-CHX	2700, 12, 10, -
21. Rehan (2018)[66] India	RCT parallel, 18	10, (female=0, male=10), -, no	20, -, I	PRF + CAF	Amniotic M + CAF	-	Analgesic-anti-inflammatory-MW	3000, 10, 10, -
22. Al-Qershi (2019)[67] Syria	RCT split mouth, 12	20, (female=10, male=10), 30.5, -, no	40, -, I and II	PRF + CAF	CTG + CAF	-	Augmentin-diclofenac-CHX	2700, 12, 10, Hettich Zentrifugen
23. Culhaoglu (2018)[68] Turkey	RCT parallel, 6	22, (female=12, male=10), 34.6, no	42, multiple, I	I: 2 layer PRF + CAF II: 4 layer PRF + CAF	CTG + CAF	Root planning	Dressing- flurbiprofen -chx	2700, 12, 20, PC-O2
24. Jankovic (2010)[69] Serbia	RCT split mouth, 12	20, (female=12 male=8), -, no	-, Single, I and II	PRF + CAF	EMD + CAF	Root planning/24%EDTA, 2 min (EMD)	Dressing-penicillin VK-CHX-ibuprofen	3000, 10, 10, -
25. Eren (2014)[70] Turkey	RCT split mouth, 6	22, (female=13, male=9), 33.8, no	44, -, I and II	PRF + CAF	CTG + CAF	-	NSAID	2700, 12, 10, -
26. Shivakumar (2016)[71] India	RCT split mouth, 6	10, (female=2, male=8), 28.4, no	20, single, I and II	PRF + CAF	CAF	-	Dressing-antibiotic-analgesic	2700, 12, 5, -
27. Dandekar (2019)[72] India	RCT parallel, 6	20, (female=7, male=13), 36.13, no	30, multiple, I and II	PRF + CAF	Chorion M + CAF	Root planing	Dressing-antibiotic-analgesic-CHX	2700, 12, 10, -
28. Potey (2019)[73] India	RCT split mouth, 6	20, (female=4, male=16), 32.6, no	75, multiple I and II	PRF + CAF	CAF	-	Ibuprofen-amoxicillin-CHX	2700, 12, 10, -
29. Shashikumar (2020)[74] India	RCT parallel, 60	36, (female=19, male=17), 34.15, no	-, -, I and II	PRF + CAF	Collagen M + CAF	Root planing	Dressing-amoxicillin-acetaminophen-CHX	3000, 10, 10, -
30. Huang (2005)[75] USA	RCT parallel, 6	23, (female=17, male=6), 43.8, no	-, multiple, I	PRF + CAF	CAF	Root planning (curette + carbide and diamond bur)/T group: PRP	NSAID-CHX NSAID-CHX	1300/2000, 20, 30, REMI R8C
31. Yaghini (2020)[76] Iran	RCT parallel, 6	24, (female=14, male=10), 41.89, -	-, -, I and II	PRF + CAF	CTG + CAF	SRP	-	2700, 12, 20, general-Purposo centrifuge

RCT: Randomized clinical trial; PRF: Platelet-rich fibrin; CAF: Coronally advanced flap; Amniotic/collagen/chorion M: Amniotic/collagen/chorion membrane; SRP: Scaling and root planning; CTG: Connective tissue graft; CHX: Chlorhexidine; NSAID: Nonsteroidal anti-inflammatory drug; EMD: Emdogain; MCAF: Modified coronally advanced flap; RMGI: Resin modified glass ionomer; PRP: platelet-rich plasma; MW: mouth wash; EDTA: Ethylenediamine tetraacetic acid

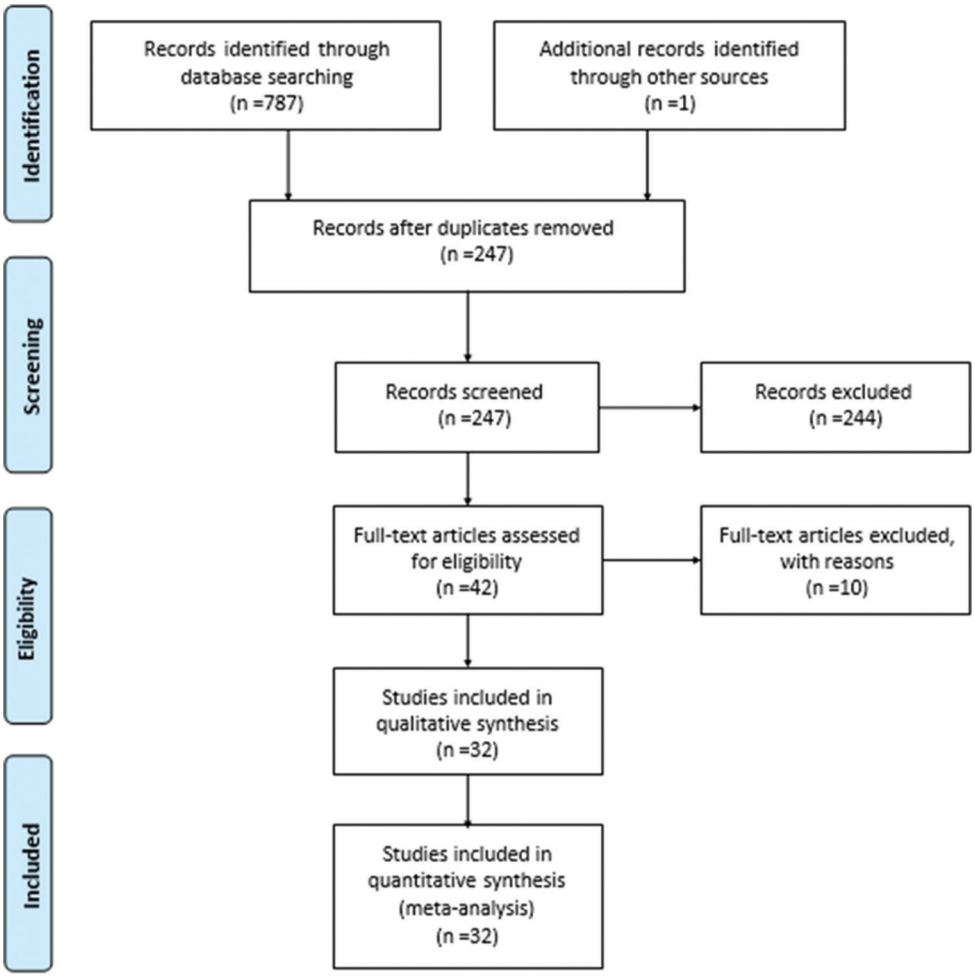

Figure 1: Selection of studies.

PRF + CAF, PRF + ammonitic membrane) were compared regarding RC. The results showed no significant difference between the intervention and control groups in RC [Figure 2; WMD = 0.023 mm, 95% CI: −0.118, −0.15; I^2 = 99.3%, Z = 0.32, P = 0.751].

Publication bias of articles regarding RC was evaluated by the funnel plot and Begg and Egger's test. Although the results showed no significant difference ($P > 0.05$) and confirmed the absence of publication bias, the funnel plot was not symmetrical. Thus, to control for the negative effect of publication bias on the results, the Trim and Fill technique was applied, which changed the results, and revealed a significant difference between the intervention and control groups regarding RC in favor of the control group (WMD = −1.57 mm, 95% CI: −2.49, −0.659; Z = −3.371, P = 0.001; P for Egger's test = 0.376 and P for Begg's test = 0.858).

To control for the negative effect of duration of follow-up, age, number of surgical sites, and blood volume obtained for centrifugation as confounders on the difference in RC between the intervention and control groups, meta-regression analysis was performed, which showed no significant difference between the two groups after this adjustment (F [3,13] = 0.90, P = 0.4899). Accordingly, none of the abovementioned variables had a confounding effect on the difference between the two groups regarding RC.

A detailed subgroup analysis was conducted to assess the impact of various qualitative variables on the differences in RC between the intervention and control groups. The results of this analysis, including additional statistical details and findings, are provided in the Supplementary File 1. Sensitivity analysis revealed that none of the studies had a significant effect on the pooled standardized mean difference (SMD).

Keratinized mucosa width

Thirty-one studies regarding KMW underwent meta-analysis. The I2 statistic and Cochrane test

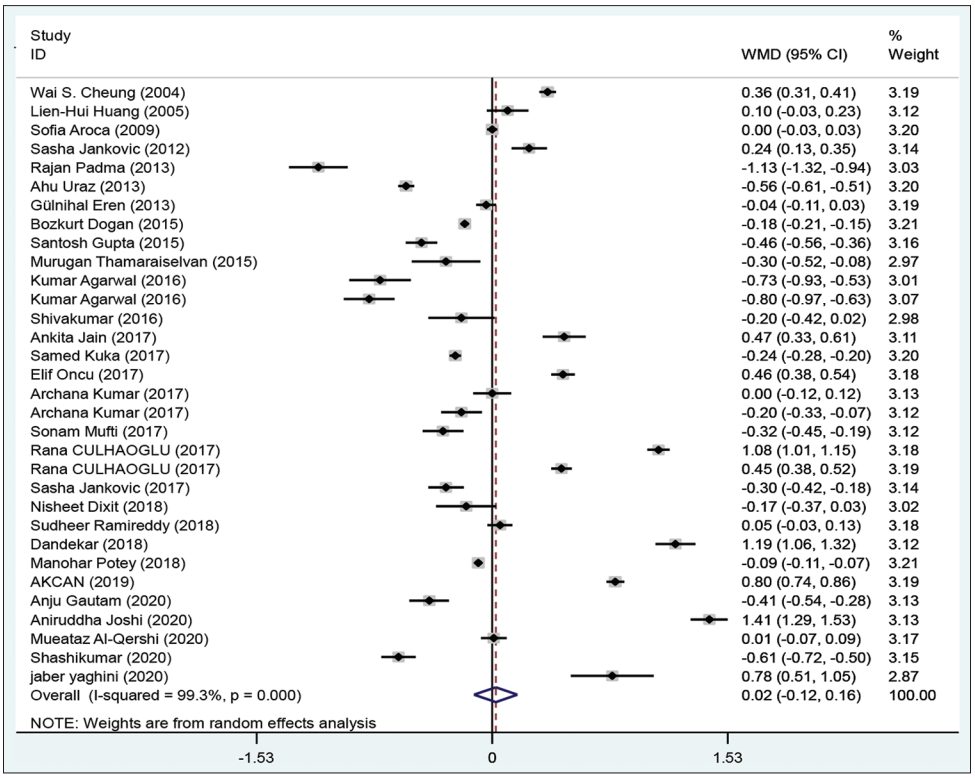

Figure 2: Comparison of the intervention and control groups regarding root coverage.

results were significant for heterogeneity ($P < 0.001$). Thus, the random-effect model was applied to pool the results of studies. Studies with the control groups of CAF, CTG + CAF, amniotic membrane + CAF, and MCAF and the intervention groups of PRF + MCAF, amniotic membrane + PRF, and PRF + CAF underwent meta-analysis. The results revealed no significant difference in KMW between the intervention and control groups [Figure 3, WMD = −0.106 mm, 95% CI: −0.322, 0.110; I^2 = 99.7%, Z = 0.96, P = 0.337].

Publication bias regarding KMW was evaluated by the funnel plot and Begg and Egger's test. Although the results showed no significant difference ($P > 0.05$) and confirmed the absence of publication bias, the funnel plot was not symmetrical. Thus, to control for the negative effect of publication bias on the results, the Trim and Fill technique was applied, which changed the results, and showed a significant difference between the control and intervention groups regarding KMW in favor of the control group (WMD = −0.418 mm, 95% CI: −0.704, 0.132; I^2 = 99.7%, Z = −2.867, P = 0.004; P for Egger's test = 0.145 and P for Begg's test = 0.760).

To control for the negative effect of duration of follow-up, age, number of surgical sites, and blood volume obtained for centrifugation as confounders on the difference in KMW between the intervention and control groups, meta-regression analysis was performed, which showed no significant effect of these variables on the results (F [4,13] = 1.01, P = 0.4399). Accordingly, none of the abovementioned confounding variables had a significant effect on the observed difference in KMW between the two groups.

Details on the subgroup analysis of KMW differences between intervention and control groups are available in the Supplementary File 2. Sensitivity analysis showed that none of the studies had a significant effect on pooled SMD.

Qualitative assessment

Table 2 presents the risk of bias in the reviewed studies.

DISCUSSION

It has been reported that CAF in combination with APC may show a higher success rate compared with other techniques that include the application of APC.[22-25] The focused question of this systematic review and meta-analysis was that whether APCs, in comparison with CAF alone or in combination with CTG, or other biomaterials and bioactive agents

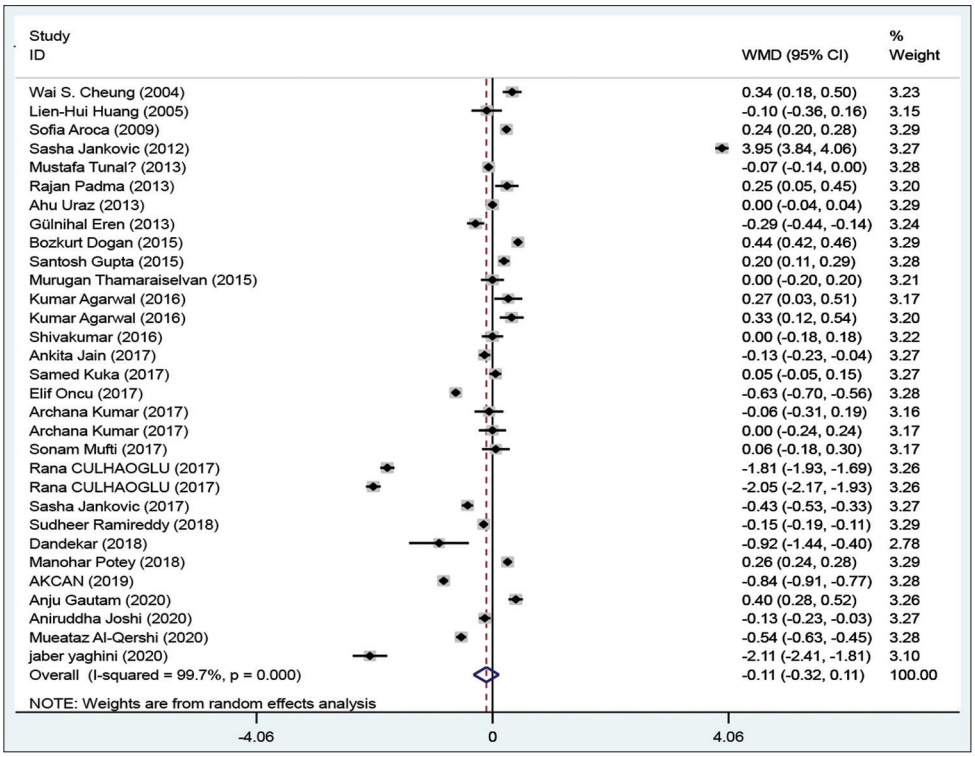

Figure 3: Comparison of the intervention and control groups regarding keratinized mucosa width.

can improve RCand KMW in patients with Miller's Class I and II gingival recession defects. The search yielded 689 articles; out of which, 32 were eligible for study inclusion. Meta-analysis did not show any additional effect for RC and KMW with APCs. Clinical parameters were as follows: RC: WMD = −1.57 mm (95% CI: −2.49, −0.659; P = 0.001) and KMW: −0.106 mm (95% CI: −0.3222, 0.110; P = 0.337).

The current meta-analysis included all types of APCs used as biomaterial in the intervention group and all different types of treatments performed for the control groups without the use of APC, making it a comprehensive systematic review. Subgroup analyses were also carried out for a more in-depth assessment. However, only one RCT had a low risk of bias, and the rest of them had an unclear risk of bias. Thus, the results should be interpreted with caution. This is a common challenge because blinding of personnel in the process of preparation of APC is not possible. However, the CONSORT guideline should be precisely followed in RCTs to increase the quality and transparency of the studies.

RCTs included in this systematic review used different APC products including PRF membrane, platelet-rich plasma (PRP) along with collagen sponge as a drug carrier, and PRP gel for the intervention group. None of the studies assessed the quality or quantity of platelet products regarding the level of growth factors, cytokines, or other biomolecular components. Due to different preparation methods, the APC products may not have the same level of quality and characteristics; this issue can limit accurate interpretation of results especially since subgroup analysis based on the type of product was not performed.

The present study evaluated the effects of APC products with four techniques of MCAF, CAF, amniotic membrane + CAF, and CTG + CAF on RC and KMW. Except for two studies that used PRP, the remaining studies used PRF, which has optimal properties such as low cost, relatively simple preparation process, no need for a donor site, high concentration of cytokines, immune cells, and growth factors, and stability of sutures. The potential of these products in the reduction of postoperative symptoms and enhancement of tissue healing through induction of angiogenesis and matrix biosynthesis has been previously discussed.[26] However, relatively fast degradation and subsequently decreased release of biomolecules can interfere with the primary stability of periodontal tissue unlike CTG.[27] CAF + CTG is the gold standard for RC.[28,29]

Table 2: Risk of bias in the reviewed studies

Code/first author (year)/Country	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Free of other sources of bias	Overall
1. Jain (2017)[47] India	+	?	?	?	+	+	+	?
2. Bozkurt Doğan (2015)[48] Turkey	+	+	?	+	+	+	+	?
3. Tunalı (2015)[49] Turkey	+	+	?	+	+	+	+	?
4. Agarwal (2016)[22] India	+	?	?	?	+	+	+	?
5. Aroca (2009)[50]	+	+	?	–	+	+	+	–
6. Kuka (2018)[51] Turkey	+	?	?	+	+	+	+	?
7. Cheung (2004)[52] USA	+	+	?	+	+	+	+	?
8. Gautam (2020)[53] India	?	?	?	?	?	+	+	?
9. Akcan (2020)[54] Turkey	+	+	?	?	+	+	+	?
10. Öncü (2017)[55] Turkey	+	+	?	?	+	–	+	–
11. Jankovic (2012)[56] Serbia	+	+	?	+	?	+	+	?
12. Dixit (2018)[57] India	+	+	–	+	+	+	+	–
13. Joshi (2020)[58] India	+	+	?	?	+	+	+	?
14. Gupta (2015)[59] India	+	+	+	+	?	+	+	+
15. Padma (2013)[60] India	+	+	?	?	+	–	+	–
16. Kumar (2017)[61] India	+	+	?	?	+	+	+	?
17. Mufti (2017)[62] India	+	?	?	+	?	+	+	?
18. Ramireddy (2018)[63] India	+	+	?	+	?	+	+	?
19. Thamaraiselvan (2015)[64] India	+	+	?	+	+	+	+	?
20. Uraz (2015)[65] Turkey	+	+	?	+	+	?	+	?
21. Rehan (2018)[66] India	+	?	+	?	+	+	+	?
22. Al-Qershi (2019)[67] Syria	+	+	?	?	+	+	+	?
23. Culhaoglu (2018)[68] Turkey	+	+	?	?	+	+	+	?
24. Jankovic (2010)[69] Serbia	+	+	?	?	?	+	+	?
25. Eren (2014)[70] Turkey	+	?	?	?	+	+	+	?
26. Shivakumar (2016)[71] India	+	+	–	+	+	+	+	–
27. Dandekar (2019)[72] India	+	+	–	+	+	+	+	–
28. Potey (2019)[73] India	+	+	?	?	+	+	+	?
29. Shashikumar (2020)[74] India	+	+	?	+	+	+	+	?
30. Huang (2005)[75] USA	+	+	?	+	+	+	+	?
31. Yaghini (2020)[76] Iran	+	?	?	–	+	+	+	–

+: Low risk of bias; –: High risk of bias; ?: Unclear risk of bias

With respect to the effect of APC on RC, the results showed statistically superior outcomes in the control groups that did not use APC; although the clinical significance of this finding is questionable. This result was in contrast to the findings of previous systematic reviews. Li *et al*.[30] compared three types of APCs with CAF; out of which, PRF and concentrated growth factors showed higher efficacy, and PRP was not superior to CAF in any parameter. This result may be due to the long and sensitive preparation process and the need for the addition of artificial thrombin for the preparation of PRP since the fibrin network obtained as such is not perfectly suitable for attachment of cytokines or cell proliferation, compared with PRF. In PRP, growth factors are mainly released in the first few days and this process continues for only 7 days. Furthermore, the 3D fibrin network of PRF improves cell proliferation and migration and protects the growth factors against proteolysis for a longer period of time. Release of growth factors continues for 21 days. Moreover, it contains a higher number of white blood cells. Such structural superiorities of PRF over PRP are probably responsible for superior results regarding RC.[31-33] However, high heterogeneity, type of teeth, APC preparation protocol, duration of follow-up, and a limited number of reviewed studies are the drawbacks of the study by Li *et al*.[30] Miron *et al*.,[34] only compared PRF + CAF with CAF alone, Li *et al*.[30] compared CAF alone and in combination with APC, and Panda *et al*.[35] compared L-PRF and CAF; however, no comparison was made between CTG as the gold standard with PRF, and single and multiple recession defects were analyzed all in one group.

Mancini *et al*.[19] compared L-PRF and CAF alone and reported improvement of RC by APC. However, Del Fabbro *et al*.[36] reported no improvement in any parameter with APC. Platelet-derived growth factors have a short half-life. Thus, it appears that APCs only affect the very early stages of bone and soft-tissue healing and can enhance tissue regeneration and healing only in the very 1st weeks after surgery. Thus, studies with a shorter follow-up probably report better results for APC compared with those with longer follow-ups. However, in the present study, the follow-up time had no significant effect on any parameter. Tooth position, baseline KMW and gingival thickness (GT), and papillary dimensions can also affect the results.[37,38] Moreover, the success of CAF depends on the postoperative position of the displaced flap margin. More coronal suturing of the gingival margin increases the possibility of achieving a complete RC.[39] Most studies did not report the magnitude of coronal displacement of gingival margin postoperatively. Panda *et al*.[35] found no significant difference between CAF and L-PRF + CAF in complete RC but mentioned high heterogeneity of the results. It appears that the magnitude of coronal displacement of the gingival margin should be taken into account in future studies.

Subgroup analysis showed similar results between the control and intervention groups regarding study design (split-mouth versus parallel) and centrifugation protocol (speed and time). RC was greater in the control group in studies on single recession defects in the maxilla and maxillary anterior region. RC was greater in CAF alone compared with CAF + APC. However, RC was greater in CAF + APC compared with CAF + CTG. In the present study, subgroup analysis on different APC products was not performed, which may explain the difference between the present results and the findings of previous systematic reviews. Also, no significant difference was noted between the intervention and control groups in RC in studies with high and unclear risk of bias, and there was only one study with low risk of bias.

Regarding the effect of APCs on KMW, the findings showed inferior results in APC groups compared with the control groups. Furthermore, the control group showed superior results in multiple recession defects. This result was in contrast to the findings of Mancini *et al*.,[19] who reported higher KMW in multiple recession defects in the APC group compared with CAF alone. They discussed that superior results in the CAF + CTG group compared with the intervention group in KMW were due to the fact that CTG serves as a scaffold, and increases the blood clot stability and GT, resulting in stability of the outcome in the long term. Moreover, induction of keratinization of the superficial epithelium by CTG explains higher KMW.[38-40] However, the present study found no significant difference between CAF + CTG and CAF + PRF. Furthermore, superior results were obtained in the control group regarding KMW in the anterior and maxillary canine/premolar regions and 2700 rpm/12 min centrifugation protocol. However, a previous study showed that a lower speed of centrifugation was associated with higher content of cells and growth factors.[41] In contrast, superior results were noted in the intervention group in the maxilla and maxillary anterior region. In comparison of CAF and MCAF alone or along with PRF, greater KMW was noted in the PRF group, which was in line with the results of Li *et al*.,[30] Akhtar *et al*.,[42] and Moraschini *et al*.,[43] and different from the results of Miron *et al*.,[34] Panda *et al*.,[35] Del Fabbro *et al*.,[36] and Rodas *et al*.[44] On the other hand, the effect of PRF on the proliferation of keratinocytes has been confirmed *in vitro,*[45] but the present study found no significant difference in this parameter. No consensus exists regarding the KMW required for periodontal health. Furthermore, KMW affects the selection of surgical technique, which may also explain the variations in the results. It appears that the presence of the small amount of KMW in the use of biomaterials plus CAF brings about better results.[46]

A high number of studies with unclear and high risk of bias, and moderate and high heterogeneity of the studies were among the limitations of this study. Thus, the results should be interpreted with caution. The majority of studies had a 6-month follow-up and only one study had a 5-year follow-up. Some studies did not mention the smoking status of patients, and one study included smokers smoking less than 20 cigarettes a day. The centrifugation protocol and system had not been mentioned in some studies. Furthermore, all types of APC products were assessed in one group, and subgroup analysis was not performed for this parameter.

Future studies should include more studies with low risk of bias and longer follow-ups, if available, and perform subgroup analysis for different types of APC products.

CONCLUSION

The results showed the superiority of the control group in RC and KMW. In total, it appears that the application of APCs for RC of Miller's Class I and II gingival recession defects does not improve the clinical parameters. Although considering the amount of heterogeneity that exists, conclusions should be made with caution.

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Conflicts of interest
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SUPPLEMENTARY FILES

Supplementary File 1: Detailed subgroup analysis on the impact of qualitative variables on root coverage (RC) differences between intervention and control groups.

To assess the effect of qualitative variables on the difference in RC between the intervention and control groups, subgroup analysis was performed, which showed no significant difference in RC between the two groups in parallel design (weighted mean difference [WMD] = 0.000, 95% confidence interval [CI]: −0.294, 0.294, $P = 0.999$) or split-mouth (WMD = 0.046, 95% CI: −0.126, 0.219, $P = 0.600$) randomized clinical trials. Due to high heterogeneity, analysis was performed by random-effect model for both study designs.

Subgroup analysis based on the recession type revealed that in studies with single or multiple gingival recession sites, a significant difference existed in RC between the intervention and control groups in favor of the intervention group (WMD = 0.364, 95% CI: 0.035, 0.692, $P = 0.030$). However, in studies with single recession sites, a significant difference was found between the intervention and control groups in favor of the control group (WMD = −0.375, 95% CI: −0.581, −0.170, $P < 0.001$). In studies with multiple recession sites, the difference in RC was not significant between the intervention and control groups (enamel matrix derivative = 0.058, 95% CI = −0.154, 0.269, $P = 0.593$). Due to high heterogeneity in all three types of single, multiple, and single or multiple defects, the random-effect model was used for the analyses.

Subgroup analysis based on the speed and duration of centrifugation showed no significant difference regarding RC between the control and intervention groups with 3000 rpm/10 min protocol (WMD = −0.105, 95% CI: −0.356, 0.146, $P = 0.412$) and 2700 rpm/12 min protocol (WMD = 0.046, 95% CI: −0.176, 0.268, $P = 0.687$). Due to high heterogeneity, the random-effect model was used for this analysis in both groups.

Subgroup analysis based on the recession site showed no significant difference in RC between the intervention and control groups in studies that evaluated gingival recession in the anterior-premolar (WMD = 0.186, 95% CI: −0.071, 0.443, $P = 0.156$), mandible-maxilla (WMD = −0.280, 95% CI: −0.828, −0.269, $P = 0.318$), anterior region (WMD = 0.622, 95% CI: −0.926, 2.170, $P = 0.431$), and maxillary-canine/premolar region (WMD = 0.050, 95% CI: −0.031, 0.131, $P = 0.226$). However, this difference was significant in favor of the control group in studies that evaluated gingival recession in the maxilla (WMD = −0.180, 95% CI: −0.205, 0.155, $P < 0.001$) and maxillary anterior region (WMD = −0.353, 95% CI: −0.610, −0.097, $P = 0.007$).

Due to high heterogeneity, the random-effect model was used for this analysis in all six regions.

Analysis based on the control groups (amniotic membrane + CAF, CAF, MCAF, and CTG + CAF) revealed no significant difference in RC between the intervention and control groups in studies with amniotic membrane + CAF (WMD = −0.129, 95% CI: −1.302, 1.044, $P = 0.829$) and MCAF (WMD = −0.321, 95% CI: −0.420, −0.223, $P = 0.219$) control groups. However, in studies with the CAF control group (WMD = −0.321, 95% CI: −0.420, −0.223, $P < 0.001$), this difference was significant in favor of the control group. In studies with CTG + CAF control group (WMD = 0.432, 95% CI: 0.160, 0.704, $P = 0.002$), this difference was significant in favor of the intervention group. Due to high heterogeneity, the random-effect model was used for this analysis.

Subgroup analysis based on the risk of bias showed that in studies with unclear (WMD = 0.011, 95% CI: −0.153, 0.175, $P = 0.895$) and high (WMD = 0.134, 95% CI = −0.271, 0.539, $P = 0.517$) risk of bias, the difference in was not significant between the intervention and control groups. However, in a study with a low risk of bias (WMD = −0.460, 95% CI: −0.562, −0.358, $P < 0.001$), this difference was significant in favor of the control group. Due to high heterogeneity, the random-effect model was used for this analysis. Among the studies included in the meta-analysis, only one study had a low risk of bias.

Supplementary Table 1: Search strategy

("gingival recession*" OR "root coverage" OR recession OR "recession defect*" OR "class Ⅰ" OR "class Ⅱ" OR "miller class Ⅰ" OR "miller class Ⅱ" OR "miller" OR "marginal tissue recession" OR "dehiscence-type recession defects") AND ("autologous platelet concentrates" OR "platelet concentrates" OR "platelet-rich fibrin" OR "platelet-rich plasma" OR "leucocyte platelet rich fibrin" OR "blood buffy coat" OR "Advanced Platelet Rich Fibrin") AND ("connective graft" OR "connective tissue" OR "subepithelial connective graft" OR "periodontal plastic surgery" OR "coronally advanced flap" OR "soft tissue substitute*" OR "soft-tissue graft* "OR "soft-tissue augmentation" OR "graft material" OR "collagen matrix" OR "collagen graft" OR "porcine collagen graft" OR mucoderm OR "alloderm" OR mucograft OR allograft OR xenograft OR "xenogenic collagen matrix" OR "acellular dermal matrix" OR "enamel matrix derivate*" OR "biomaterial" OR EMD OR Emdogain OR "guided tissue regeneration" OR "amnion membrane" OR "placental membrane" OR "placental tissue*" OR "fetal membrane" OR "chorion" OR "recombinant human growth factor*" OR rhPDGF OR "growth substance*" OR "mucogingival surgery" OR "mucogingival therapy" OR "mucogingival" OR "periodontal surgery" OR "Periodontal Regeneration")

Supplementary File 2: Subgroup analysis on the impact of qualitative variables on keratinized mucosa width (KMW) differences between intervention and control groups.

Subgroup analysis based on study design revealed no significant difference in KMW between the intervention and control groups in studies with parallel (weighted mean difference [WMD] = −0.389, 95% confidence interval [CI]: −0.851, 0.073; $P = 0.099$) or split-mouth (WMD = 0.149; 95% CI = −0.123, 0.421; $P = 0.284$) design. The random-effect model was applied for this analysis due to high heterogeneity.

Subgroup analysis based on the recession type showed no significant difference in KMW between the intervention and control groups in studies with single or multiple (WMD = 0.825, 95% CI: −0.885, 2.535; $P = 0.345$) and single (WMD = 0.048, 95% CI: −0.188, 0.284; $P = 0.691$) gingival recession defects. However, this difference was significant in favor of the control group in studies on multiple gingival recession defects (WMD = −0.312, 95% CI: −0.566, 0.059; $P = 0.016$). The random-effect model was applied for this analysis due to high heterogeneity.

Subgroup analysis based on the speed and duration of centrifugation showed no significant difference regarding KMW between the control and intervention group with 3000 rpm/10 min protocol (WMD = 0.426, 95% CI: −0.274, 1.127; $P = 0.233$). However, this difference was significant in 2700 rpm/12 min protocol (WMD = −0.437, 95% CI: −0.182, −0.693; $P = 0.001$) and the mean KMW was significantly greater in the control group. Due to high heterogeneity, the random-effect model was used for this analysis in both groups.

Subgroup analysis based on the recession site showed no significant difference in KMW between the intervention and control groups in studies on gingival recession in the mandible-maxilla (WMD = 0.120; 95% CI: −0.115, 0.355; $P = 0.317$) and anterior premolar (WMD = −0.248; 95% CI: −0.910, 0.414; $P = 0.464$) regions. However, this difference was significant in favor of the intervention group in studies on maxilla (WMD = 0.440; 95% CI: 0.416, 0.464; $P < 0.001$) and maxillary anterior (WMD = 0.183; 95% CI: 0.052, 0.314; $P = 0.006$) recession sites, and in favor of the control group in studies on anterior (WMD = −0.130, 95% CI: −0.031, −0.229; $P = 0.010$) and maxillary canine/premolar (WMD = −0.150, 95% CI: −0.106, −0.194; $P < 0.001$) recession sites. Due to high heterogeneity, the random-effect model was used for this analysis in both groups.

Subgroup analysis based on the control groups revealed a significant difference between the intervention and control groups regarding KMW in studies with MCAF (WMD = −0.234, 95% CI: 0.198, 0.269; $P < 0.001$) and CAF (WMD = −0.187, 95% CI: 0.087, 0.288; $P < 0.001$) control groups in favor of the intervention group. However, in studies with amniotic membrane + CAF (WMD = 0.053, 95% CI: −0.341, 0.447; $P = 0.793$) and CTG + CAF (WMD = −0.295, 95% CI: −1.153, 0.563; $P = 0.500$) control groups, this difference was not significant. The random-effect model was applied for this analysis due to high heterogeneity.

Subgroup analysis based on the risk of bias showed no significant difference in KMW between the intervention and control groups in studies with high (WMD = −0.509, 95% CI: −1.033, 0.014; $P = 0.056$) and unclear (WMD = −0.021; 95% CI: −0.281, 0.238; $P = 0.781$) risk of bias. However, in the only study with a low risk of bias (WMD = 0.200; 95% CI: 0.110, 0.290; $P < 0.001$), this difference was significant in favor of the intervention group. The random-effect model was applied for this analysis due to high heterogeneity. Of studies included in the meta-analysis, only one study had a low risk of bias.