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Efficacy of coronally advanced flap in combination with platelet rich fibrin and enamel matrix derivative for root coverage procedures: A systematic review and meta-analysis

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Abstract

Previous systematic reviews have reported that the use of a coronally advanced flap (CAF) combined with a connective tissue graft (CTG) or enamel matrix derivative (EMD) is more likely to achieve complete root coverage (CRC) than other modalities. However, the details of periodontal parameters and comparisons among a variety of combinations of CAF with PRF and/or EMD are left to be investigated. This study aimed to analyze the differences in periodontal parameters between these treatment modalities. A literature search was performed using PubMed, google scholar and Scopus for studies focused on the treatment of gingival recession (Miller Class I and II) with CAF alone or combined with PRF, EMD or both up to March 2021. Randomized controlled clinical trials with a follow-up duration ≥ 12 months were included. The outcome analysis included changes in root coverage, clinical attachment level, and keratinized tissue width (KTW). Five randomized controlled clinical trials, including 124 Miller Class I–II defects were included. In conclusion, with reference to gain in root coverage, clinical attachment level gain and gain in keratinized tissue width, the present results indicate that coronally advanced flap alone or with EMD result in an additionally beneficial clinical outcome, when combining this for root coverage procedures.

Keywords: Coronally advanced flap, Platelet rich fibrin, Enamel matrix derivative, Root coverage, Clinical attachment level, Keratinized tissue width

Introduction

Periodontal diseases are chronic inflammatory processes characterized by the destruction of connective tissue and dental bone support following an inflammatory host response secondary to infection by periodontal bacteria. Clinically these conditions manifest themselves by periodontal pocket formation, gingival enlargement, furcation involvement and at times are associated with gingival recession.[1,2]Gingival recession (GR), is the apical displacement of the gingival margin beyond the cementoenamel junction (CEJ).[3] Histologically, the collapse of gingival tissue results in attachment loss by destruction of the periodontal connective tissue and alveolar bone.[4] Its frequency increases with age, as 50% of people aged 18 to 64 years and 88% of people older than 65 years have at least one GR. It can occur in single or multiple teeth.[5] The primary etiologies of gingival recession are plaque-induced inflammation, mechanical abrasion and trauma.[6] It may be a concern because of esthetic problems, root hypersensitivity or fear of tooth loss.[7] The major aims of GR treatment are full coverage of the exposed surface, gingival dimension increase and optimal esthetic appearance.[8]There are mainly three different types of approaches to achieve root coverage; the free gingival graft, the coronally advanced flap (CAF) and combined procedures involving CAF with tissue/material interposed between the flap and root surface. CAF has been tried with varying degrees of success to cover the recession defects. Histologically, this technique leads to reformation of junctional epithelium and the connective tissue attachment with minimal bone repair. The connective tissue attachment achieved by CAF is not stable over long periods, and various adjunctive agents have been used to promote healing and to further enhance the clinical outcomes which include the use of root biomodification agents, enamel matrix derivatives (EMD), acellular dermal matrix (ADM), and platelet-rich fibrin (PRF).[9]Platelet-rich fibrin (PRF) is a second-generation platelet concentrate.[10] It is composed of a dense three-dimensional fibrin matrix comprising of platelets, leukocytes, growth factors, and circulating stem cells.[11] It slowly releases significant amounts of growth factors and other matrix glycoproteins during a minimum of 7 days. It can also serve as a resorbable interpositional membrane. The structure and composition of PRF supports cell migration, accelerates wound healing, angiogenesis, and tissue regeneration.[12] EMDs are potential regenerative materials and their contents serve as proteins capable of inducing the formation of new periodontal ligament fibres, cementum, and alveolar bone.[13]Amelogenin, the protein responsible for the biological activity of EMDs, accounts for 90% of the total EMD content.[14] It was reported that EMDs have a positive effect on cell proliferation and survival, cell adhesion, spreading and chemotaxis, and the expression of transcription factors, growth factors, cytokines, extracellular matrix components, and other macromolecules.[15] It has been shown to promote periodontal regeneration by mimicking the embryonic development of the periodontal tissues.[16] The present study aims to compare a variety of combinations of CAF with PRF and/or EMD by analyzing three periodontal parameters, including the gain in root coverage, clinical attachment level (CAL) and keratinized tissue width (KTW).

Material And Methods

Search strategy: The electronic databases were searched for the identification of studies: PubMed,

Google scholar and Scopus. The search included "gingival recession" OR "root coverage" OR "platelet rich fibrin" OR "enamel matrix derivative" AND "coronally advanced flap". References from previous systematic reviews focused on root coverage procedures were checked for identification.

Inclusion and exclusion criteria

The studies had to be randomized controlled trials (RCTs) published from January 2010 to March 2021. Only English publications were included. Other inclusion criteria were systemized by the PICO method as following. The patients were diagnosed as class I or II gingival recession. The surgical procedures focused in the present studies were CAF alone or in combination with materials, i.e.,PRF or EMD. Consequently, three kinds of interventions were considered as CAF, CAF + PRF, CAF + EMD. There were three comparisons between interventions which were (i) CAF vs. CAF + PRF, (ii) CAF vs. CAF + EMD, (iii) CAF + PRF vs. CAF +EMD based on the comparisons between surgical interventions (control vs. test). The outcomes included three clinical parameters, including the gain in root coverage, clinical attachment level and keratinized tissue width in millimeters between baseline and follow-up visit. Articles that matched all the inclusion criteria were retrieved and underwent a second-stage evaluation of eligibility by the exclusion criteria: All in-vitro and animal studies, case series, case reports, qualitative studies, all descriptive and analytical studies, studies done on patients with systemic disease, allergic to medication, pregnancy or lactating women and studies done on patients with habit like smoking/alcohol/narcotic drugs. Two reviewers (AK and SVK) screened the articles, and disagreement regarding the exclusion or inclusion of an article was resolved through discussion between reviewers. The following procedures of quality assessment and data collection were also performed by the same reviewers.

The quality assessment was to determine the potential for selection bias [eligibility criteria, sampling strategy, sample size, primary outcome (Gain in root coverage) and secondary outcomes (CAL, KTW). The risk of bias in individual studies were assessed using the RevMan 5.4.1., five main criteria were examined: random sequence generation (adequate, inadequate and unclear), allocation concealment (adequate, inadequate and unclear), blinding of outcome assessment (yes, no and unclear), incomplete outcome data (yes, no and unclear) and selective reporting (yes, no and unclear). The studies were grouped into three categories after quality assessment: low risk of bias if all the criteria were met, moderate risk of bias if three or four criteria were met and high risk of bias if < 3 criteria were met.

Data collection and statistical analysis

The following characteristics of the studies were extracted from the included studies: year of publication, study design, demographic characteristics of participants, numbers of patients and gingival recession defects type of interventions and duration of follow-up. The clinical parameters (gain in root coverage, CAL and KTW) were collected from the included studies for meta-analysis. If the studies did not report the mean difference and standard deviation of treatment effect (difference between follow-up and baseline), a further calculation of mean difference would be necessary.

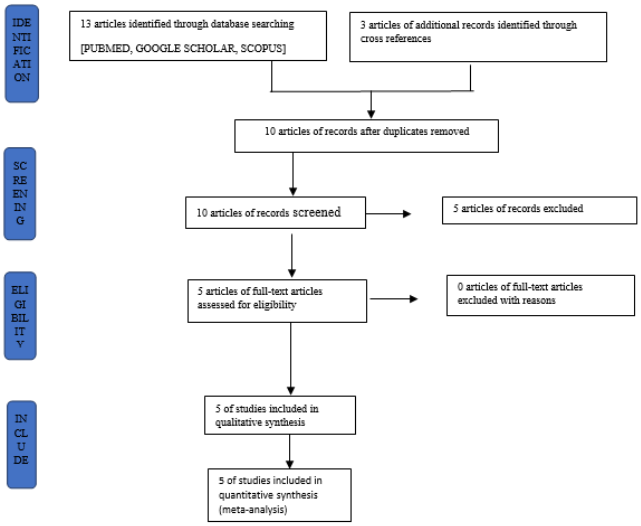
The heterogeneity was assessed by I^2 measurement. The I^2 ranged from 0 to 100%, where 0% meant no heterogeneity and ≥ 75% suggested a high heterogeneity. The result of each meta-analysis was presented by a forest plot showing associated information.

Results

Literature Search and Screening

A total of 13 records were identified through the literature search. After duplication, 10 studies were screened by title and abstract. Consecutively, full-text articles were assessed for eligibility, and, finally, 5 investigations were included. Details of the study selection process are presented in Figure 1.

Figure1



Study and Patient Characteristics

Four studies compared Coronally advanced flap alone with PRF, one investigation compared Coronally advanced flap with PRF and/or EMD.

The number of participants in the included studies ranged from 20 to 30. The age of participants ranged from 18 to 60 years; the mean age or gender ratio could not be calculated due to missing uniform data concerning these variables among certain studies.

Included were studies carried out at university hospitals in India, Turkey and Serbia, where participants were recruited from the departments of periodontology.

Study duration ranged from 6 months to 12 months. Five investigations used a COE pack to ensure the duration of the applied medicament. Details of study characteristics are summarized and presented according to their controls and interventions in Table 1 and 2.

Table 1: Table showing features of the included studies

Sr No.	Author	Year	Study design	Follow up months	Age (Years)	Sample size	Interventional group	Comparison group
1.	R Thakur et al	2018	RCT	BL 6 Months	20 - 40 years	30	Coe pak placed Antibiotics and analgesics	Coe pak placed Antibiotics and analgesics
2.	SJankovic et al	2010	RCT	BL 12 Months	21 - 48 years	20	No. 15c blade Coe pak placed Antibiotics (Penicillin 500mg) and Analgesics (Ibuprofen 800 mg)	No. 15c blade Coe pak placed Antibiotics (Penicillin 500mg) and Analgesics (Ibuprofen 800 mg)
3.	M Thamaraiselvan et al	2015	RCT	BL 6 Months	21-47 years	20	Coe pak placed Antibiotics and analgesics	Coe pak placed Antibiotics and analgesics
4.	S Gupta et al	2015	RCT	BL 3 Months 6 Months	20 – 50 years	30	Coe pak placed Antibiotics and analgesics	Coe pak placed Antibiotics and analgesics
5.	SKuka et al	2017	RCT	BL 12 Months	21 - 41 years	24	Coe pak placed Antibiotics (Amoxicillin clavulanate, 1000 mg) and analgesics (Naproxen sodium, 550 mg)	Coe pak placed Antibiotics (Amoxicillin clavulanate, 1000 mg) and analgesics (Naproxen sodium, 550 mg)

RCT: randomised controlled trial, BL: baseline, M: months

Table 2: Summary of Primary and Secondary outcomes using Coronally advanced flap with Platelet rich fibrin and Enamel matrix derivative for root coverage in Miller's Class I and II gingival recession at Baseline and at 6 months and 12 months follow up :

Slno	Author	Clinical outcomes								
		Primary Outcomes			Secondary Outcomes					
		Gingival recession	Gain in root coverage		CAL gain (in mm)			KTW gain (in mm)		
		BL	6 M	12 M	BL	6 M	12 M	BL	6M	12 M
1	R Thakur et al 2018	2.40 ± 0.63 (CAF+PRF), 2.53 ± 0.52 (CAF)	0.60 ± 0.74 (CAF+PRF), 0.57 ± 0.78 (CAF)	ND	4.07 ± 0.88 (CAF+PRF), 4.40 ± 0.63 (CAF)	2.53 ± 0.74 (CAF+PRF), 2.57 ± 0.73 (CAF)	ND	1.87 ± 0.64 (CAF+PRF), 1.93 ± 0.46 (CAF)	2.37 ± 0.61 (CAF+PRF), 1.90 ± 0.39 (CAF)	ND
2	SJankovic et al 2010	4.10±1.05 (CAF+PRF); 3.90±1.0 (CAF+EMD)	ND	1.05 ± 0.45 (Group 1); 1.15 ± 0.65 (Group 2)	ND	ND	ND	1.45 ± 0.86 (Group 1); 1.30± 0.56 (Group 2)	ND	1.62 ± 0.28 (Group 1); 1.90 ± 0.81 (Group 2)
3	M Thamaraisel	2.30 ± 0.67 (CAF +	1.60 ± 0.51(CAF +	ND	3.70±0.82	2.50 ± 1.17(C	ND	2.30± 0.82(	0.40 ±	ND

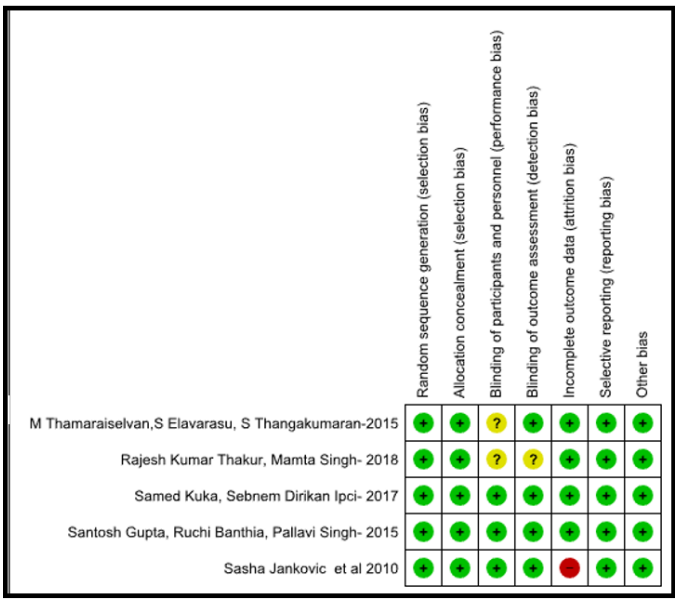
	van et al 2015	PRF);2.20 ± 0.91(Only CAF)	PRF); 1.30 ± 0.91 (Only CAF)		(CAF+ PRF); 3.50 0.97 (Only CAF)	AF+PR F); 1.80 ±0.91 (Only CAF)		CAF =PRF);2.40 ±0.69 (Only CAF)	0.69(CAF= PRF); 0.40 ± 0.69 (Only CAF)	
4	SGupta et al 2015	2.80±0.41(CAF+PRF) ; 2.47±0.64 (CAF)	0.27±0.59(C AF+PRF); 0.40±0.74 (CAF)	ND	4.53±0 .64(C AF+P RF), 3.93±0 .96 (CAF)	1.27±0. 59(CAF +PRF); 1.47±0. 92 (CAF)	N D	5.07± 0.46(CAF +PRF); 5.0±0 .66 (CAF)	6.67± 0.49(CAF+ PRF); 6.40± 0.51 (CAF)	ND
5	S Kuka et al 2017	3.15 ± 0.24 (CAF+PRF); 3.36 ± 0.34(CAF)	ND	0.40 ± 0.52 (CA F+P RF); 0.85 ± 0.24 (CA F)	4.25 ± 0.35(C AF+P RF); 4.54 ± 0.3(C AF)	ND	2. 15 ± 0. 78 (C A F+ PR F); 2. 8 ± 0. 35 (C A F)	2.60 ± 0.77(CAF+ PRF); 2.95 ± 1.01(CAF)	ND	3.3 0 ± 0.9 8 (C AF +P RF;)3.6 0 ± 1.2 9(C AF)

CAL: Clinical attachment level, KTW: Keratinized tissue width, CAF: Coronally advanced flap, PRF: Platelet rich fibrin, BL: baseline, M: months, ND: not determined

Quality Assessment

The possibility of bias in design and analysis was evaluated by RevMan application. Most of the trials were at low risk of bias in many domains we assessed. Summary of the judgements of the risk of bias are shown for each domain in each of the included studies. Overall, the studies included in this review were classified as high-quality study. All studies reported about random sequence generation. Allocation concealment was clear in all the included studies. 4 studies were unclear about the blinding of the participants and personnel. The blinding of outcome assessment was done only in one study R. Thakur et al). Only one study (S. Jankovic et al) did not show attrition bias. None of the included studies showed unclear other bias.

Figure 2: Diagram showing the bias detected in the different domains and overall bias of studies included



For meta-analysis 5 articles were selected as data from them could be ambiguously extracted regarding the changes in the clinical parameters. The forest plots for Gain in root coverage and KTW at 6 and 12 months were recorded in all 5 studies; CAL at 6 and 12 months was recorded in four studies; and are demonstrated in figures (Figure No. 3,4,5). Random-effect model was applied as significant heterogeneity was found in the studies and are shown with the help of forest plots.

Figure 3: Gain in root coverage

The overall reduction of gingival recession was reported in 5 articles which was -0.19, having a precision of -0.63 to -0.25. The result obtained was statistically not significant (p-value =0.2).

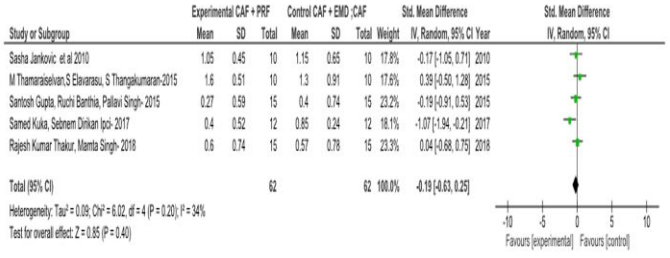


Figure 4: Clinical attachment level gain

The overall gain in Clinical attachment level was reported in 4 articles which was -0.18 having a precision of -0.79 to -0.43 The results obtained was statistically not significant (p-value=0.07).

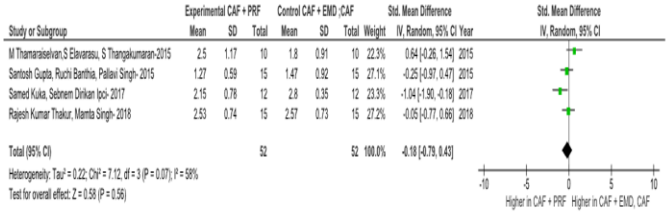
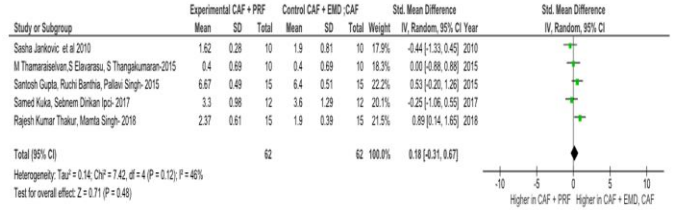


Figure 5: Keratinized tissue width gain

The overall gain in keratinized tissue width was reported in 5 studies which was 0.18 having a precision of -0.31 to 0.67. The result was statistically not significant (p-value=0.12).



However, a considerable heterogeneity (I^2) value ranging from 34% to 58% was observed with respect to gain in root coverage, gain in clinical attachment level and keratinized tissue width gain. This can be attributed to varying sample size, follow up period, different procedures done, different graft materials used, oral hygiene maintenance by the patient.

Discussion

Gingival recession has been a prevalent problem in adults and if left untreated may lead to complications such as hypersensitivity, unesthetic appearance, root caries, resorption, or cervical lesions that are noncarious.[17] It has been associated with many factors such as inflammatory periodontal disease, toothbrush injury, developmental anatomic abnormalities (e.g. aberrant frenal attachment), tooth malposition, and iatrogenic factors.[18]Various surgical techniques have been developed to achieve complete root coverage like , coronally advanced flap (CAF), free gingival grafts, pedicle flaps without tissue grafts, , enamel matrix derivative (EMD) or the application of an acellular dermal matrix (ADM), platelet-rich plasma (PRP) and platelet rich fibrin (PRF) in combination with CAF, and guided tissue regeneration.

Platelet rich fibrin (PRF) is defined as an autologous platelet and leukocyte enriched fibrin biomaterial. The advantages of PRF technique include shorter time of preparation, lack of requiring anticoagulant and bovine thrombin, composed of denser fibrin matrix and easiness of application.[19] The PRF consists of platelets, leukocytes, growth factors and presence of circulating stem cells. The natural polymerized fibrin architecture of PRF seems responsible for releasing high amounts of growth factors and other matrix glycoproteins for approximately 7 days. These biochemical components and fibrin formation of PRF support cell migration, wound healing and tissue regeneration.[20] Enamel matrix derivative (EMD) has been developed as a clinical treatment to promote periodontal regeneration.[21] EMD is an amelogenin derivative of porcine origin having an enhanced potential to regenerate periodontal tissues.[22] Improvement in results occurs, when EMD is combined with CAF may be because of EMD influence on cells, tissue proliferation and angiogenic factors, favoring the healing process.[23]The present systematic review focused on RCTs and CCT in order to assess the effectiveness of coronally advanced flap alone or in combination with Platelet rich fibrin and Enamel matrix derivative for root coverage procedures.5 Randomized controlled studies were found as a result of the focused question. The primary outcome evaluated in this systematic review was gain in root coverage. The secondary outcomes evaluated were CAL and KTW.

The overall improvement in the clinical parameters i.e., gain in root coverage, clinical attachment level, keratinized tissue width of gingiva in PRF and EMD groups were evaluated. On comparison with PRF and EMD, there was an increase in gain in root coverage and KTW in the EMD group when compared to PRF group (study no. 2)

A total of 124 patients between the age of 18-60 years were recruited who required root coverage. The patients were then divided into two groups; the Intervention group – CAF + PRF group and Control group –CAF alone and CAF + EMD. The CAF + PRF and CAF/CAF + EMD received clinical parameters as described in Table No. 1 and 2. Comparison of gain in root coverage and keratinized tissue width of gingiva in all included studies (Study No. 1,2,3,4,5) showed an overall gain in root coverage and increase in keratinized tissue width of gingiva in the control group when compared to the intervention group ($p<0.05$). Whereas, Comparison of clinical attachment level gain in all included studies (Study No. 1,3,4,5) showed an overall gain in clinical attachment level in the control group when compared to the intervention group.

Gain in root coverage

Five studies specifically reported on various techniques and materials for root coverage in Miller's class I and II recession. In all studies, the gain in root coverage was successfully done, due to a large heterogeneity between the studies, and different time-points applying for the root coverage procedures. The selection of the included studies also demonstrates advances and trends in clinical research. The root coverage procedure has several advantages including coverage of the exposed surface, gingival dimension increase and optimal esthetic appearance. Five studies (R Thakur et al, S Jankovic et al, M Thamaraiselvan et al, S Gupta et al, S Kuka et al) have compared the gain in root coverage in PRF and EMD which showed increased gain in root coverage in the EMD group when compared to the control group. Within these five articles Kuka et al have explained briefly recession height in CAF + PRF and CAF + EMD/CAF groups were 3.15 ± 0.24 and 3.36 ± 0.34 mm. RH reduction was 2.75 ± 0.33 and 2.51 ± 0.33 mm. The results were insignificant for CRC reduction ($p> 0.05$).In comparison with EMD; there was an increase in root coverage when compared to the control group. The root coverage success rate with CAF combined with EMD showed significant reduction of treated gingival recession when compared with CAF combined with PRF. It is theorized that EMD provides adequate root coverage.The result was found to be similar in 3 studies (Rajesh Thakur et al, S Gupta et al and Thamaraiselvanet al.) which were statistically significant. ($P<0.05$) The study done by S Jankovic et al; compared PRF and EMD; showed increase in the root coverage in the EMD group which was 2.75 ± 0.45 when compared to the PRF group. S Gupta et al in their study concluded that at 6 months postoperatively, the mean root coverage was 2.20 ± 0.56 mm, with a mean additional increase of 0.13 mm when compared with baseline ($P<0.05$). Statistically significant achievement in recession reduction was reported at both 3 and 6 months. By comparing these two articles, we can conclude increase in root coverage in the EMD group compared to the PRF group.

Gain in Clinical attachment level

Four studies specifically reported on various techniques and materials for gain in clinical attachment level in Miller's class I and II recession. In all studies, the gain in clinical attachment level could be successfully done, due to a large heterogeneity between the studies, and different time-points applying for the gain in clinical attachment level. The selection of the included studies

also demonstrates advances and trends in clinical research. Four studies (R Thakur et al, M Thamaraiselvan et al, S Gupta et al, S Kuka et al) compared the gain in clinical attachment level in PRF with EMD and reported increased gain in CAL in the EMD group when compared to the control group. Within these four articles Kuka et al have explained briefly clinical attachment level in CAF + PRF and EMD/CAF groups was 4.25 ± 0.35 and 4.54 ± 0.30mm. Gain in CAL was 22.15 ± 0.78 and 2.8 ± 0.35mm. The results were significant for gain in CAL ($p < 0.05$). In comparison with EMD; there was gain in clinical attachment level when compared to the control group. The clinical attachment level with CAF combined with EMD showed significant increase of gain in CAL when compared with CAF combined with PRF. It is theorized that EMD provides adequate gain in CAL similar to studies done byS Gupta et al and Thamaraiselvanet al. ($P<0.05$) Study by R Thakur et al; have compared PRF and EMD; the results showed that mean CAL at baseline was 4.31 mm which significantly reduced to 1.31 mm showing attachment gain of 3mm at 6 months in control group. No statistically significant difference between control group and test group was reported at the end of 6 months. By comparing these articles, we can conclude there was increase in clinical attachment level in the EMD group compared to the PRF group.

Gain in Keratinized tissue width

Five studies specifically reported on various techniques and materials for gain in keratinized tissue width in Miller's class I and II recession. In all studies, the gain in keratinized tissue width could be successfully done,due to a large heterogeneity between the studies and different time-points applying for the gain in keratinized tissue width. The selection of the included studies also demonstrates advances and trends in clinical research. Five studies (R Thakur et al, S Jankovic et al, M Thamaraiselvan et al, S Gupta et al, S Kuka et al) compared gain in keratinized tissue width in PRF with EMD and showed increased gain in KTW in the EMD group when compared to the control group. Within these five articles Kuka et al have explained briefly keratinized tissue width in CAF + PRF and EMD/CAF groups was 4.25 ± 0.35 and 4.54 ± 0.30mm. Gain in KTW was 22.15 ± 0.78 and 2.8 ± 0.35mm. The results were significant for gain in KTW ($p < 0.05$). In comparison with EMD; there was gain in keratinized tissue width when compared to the control group. The KTW with CAF combined with EMD showed significant increase of gain in KTW when compared with CAF combined with PRF. It is theorized that EMD provides adequate gain in KTW,as reported in study byS Gupta et al and Thamaraiselvanet al. ($P<0.05$). PRF Versus EMD S Jankovic et al in their study concluded that at 12 months postoperatively, the gain in keratinized tissue width was 0.60 ± 0.26 mm, when compared with baseline ($P<0.05$). No Statistically significant achievement in gain in keratinized tissue width was reported at12 months. By comparing the article, it can be concluded that there was significant gain in keratinized tissue width in the EMD group compared to the PRF group.

Conclusion

In conclusion, with reference to gain in root coverage, clinical attachment level gain and gain in keratinized tissue width, the present results indicate that coronally advanced flap alone or with EMD result in an additionally beneficial clinical

outcome, when combining this for root coverage procedures.

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