Combination of Coronally Advanced Flap and Platelet Rich Fibrin in The Treatment Of Millers Class I & II Gingival Recessions: A Systematic Review

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Abstract: Gingival recession is defined as the displacement of soft tissue margin apical to cement–enamel junction with exposure of root surface. In the last decade, because of the ever increasing esthetic demands from patients, surgical techniques have been further developed to obtain complete root coverage associated with a perfect integration of the grafted tissue with the adjacent soft tissues. Choukroun's platelet rich fibrin (PRF) is a fibrin matrix in which platelet cytokines and cells are trapped which are released after a certain time, and that can serve as a resorbable membrane. PRF production protocol attempts to accumulate platelets and released cytokines in a fibrin clot. This review aims to highlight the outcomes of various studies performed using the combination of coronally advanced flap and platelet rich fibrin in the treatment of Millers Class I and II gingival recession. [Kith J NJIRM 2017; 8(3):135-144]

Key words: Coronally advanced flap, Platelet Rich Fibrin, Gingival recession

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Introduction: Gingival recession is defined as the displacement of soft tissue margin apical to cement–enamel junction with exposure of root surface [1, 2]. It has been associated with mechanical factors such as traumatic tooth brushing impacting on predisposed thin soft tissues [3], even though a recent systematic review [4] concluded that data to support or refute the association between tooth brushing and gingival recession are still inconclusive. A long-term clinical study recently reported that shallow recessions showed a tendency for further apical displacement of the gingival margin in highly motivated patients with high standards of oral hygiene and enrolled in a stringent supportive periodontal care system (4–6 months) over a period ranging from 10 to 27 years [1]. The study concluded that untreated gingival recessions show a negative prognosis over time in spite of good patient motivation, while the prognosis is improved after performing mucogingival procedures.

The ultimate goal of root-coverage procedures is the complete resolution of the recession defect, with minimal probing depths after treatment, along with a nice chromatic and texture integration of the covering tissues with the adjacent resident soft tissues [5, 6, 7, 8].

History: In the 1970s and 1980s, the main treatment goals were achieving recession reduction and increasing keratinized tissue. The proposed surgical techniques were pedicle flaps (laterally or coronally positioned) and free gingival grafts. During the 1980s and 1990s, new approaches, such as bilaminar techniques or regenerative procedures, were proposed to achieve the goal of complete root coverage. In the last decade, because of the ever increasing esthetic demands from patients, surgical techniques have been further developed to obtain complete root coverage associated with a perfect integration of the grafted tissue with the adjacent soft tissues [5, 6]. In broad terms, three different approaches can be identified from the published literature: (i)the free gingival graft(ii)the coronally advanced flap, and (iii) combined procedures.

The latter approaches are based on a coronally advanced flap plus a connective tissue graft (coronally advanced flap with connective tissue graft) , a non-resorbable barrier , a bio-resorbable barrier , enamel matrix derivative , platelet derived factors , acellular dermal matrix , or living tissue-engineered human fibroblast-derived dermal substitute.

Although all the proposed techniques have shown potential for root coverage, meta-analyses from several systematic reviews [5,6,8,9,10] showed the greatest potential for recession reduction and complete root coverage when applying coronally advanced flap or combined procedures.

Over-view: Ideally, a clinician should first discuss with the patient the desired ⁄ expected outcome(s), then select the best option to reach those outcome(s). Most studies have reported surrogate outcomes, such as complete root coverage, amount of root coverage,

per cent root coverage and changes in the amount of keratinized tissue.

Potential prognostic factors: Potential prognostic factors for root coverage can be divided into three different categories: patient-related factors, tooth / site-related factors and technique-related factors.

Patient – related factors: There is weak evidence that poor oral hygiene will negatively influence the success of root coverage [11]. Similarly, there is little information on the influence of traumatic tooth brushing in the recurrence of recession after treatment [12].Some authors report less favorable outcomes in terms of root coverage in smokers [13], whereas other studies did not find differences between smokers and nonsmokers [14].

Tooth/ site-related factors: Cervical dental caries and/or abrasion are often associated with gingival recessions. Root curvature might potentially influence the outcome of root coverage. This hypothesis is based on the size of the avascular area, which is larger in prominent root surfaces. According to the Miller classification, Class I and II type defects, in which the interdental bone support is intact, have the best potential for complete root coverage. Conversely, only partial root coverage is thought to be achievable in Miller Class III and IV type defects: these are associated with some (from mild to severe) loss of interdental bone support. on Miller Class III recessions. The authors reported complete root coverage in 38% of patients treated with a modified tunnel / connective tissue graft technique, with or without the additional use of enamel matrix derivative. Evidence on treating Miller Class III and IV defects is both scarce and weak and does not provide any clear indications on the potential of interproximal bone loss to impact on root coverage[15]. A papilla height of 5 mm was consistently associated with complete coverage of the root using both surgical approaches [16]. Clinicians select a coronally advanced flap or a sliding flap when the residual keratinized tissue is well represented, or place a graft under the flap when keratinized tissue is insufficient in thickness and width[12]. 0.8mm can be considered as the critical flap thickness [10]. A flap thickness of >0.8 mm was associated with complete root coverage, while a flap thickness of < 0.8 mm was associated with partial root coverage. Statistically significant relationship is observed between complete root coverage and the amount of keratinized tissue lateral to the gingival defects: the greater the amount of keratinized tissue, the greater the percentage of root coverage [17].

Technique-related Factors: Root surface: Hand and ultrasonic root instrumentation were equally effective in terms of root coverage and clinical attachment gain at 6 months post surgery [18]. Residual hypersensitivity was experienced only in sites treated with root planing [19]. The presence of a restoration does not necessarily prevent root coverage but also does not improve the outcome [20].

Soft tissue: A clinical study [21] reported that thick gingiva was consistently associated with better outcomes in terms of recession reduction and complete root coverage in sites treated with a coronally advances flap. Sharper and the finer surgical blades, together with finer suture material used in the microsurgical approach, were responsible for the reduced tissue damage [22]. The vascularization of the pedicle flap when performing a coronally advanced flap can be further improved if vertical releasing incisions are avoided. Zucchelli & DeSanctis [23] proposed a surgical technique to treat multiple adjacent recession defects based on an envelope type of flap without vertical releasing incisions. Sutures that are too tight may damage the residual vascular system of the flap: vessel patency is reduced and neo-vascularization is impaired. In addition, the residual tension of the flap could favor a postoperative apical shift of the gingival margin during the early phase of healing [24]. The statistical analysis showed that minimal flap tension (ranging from 0.0 to 0.4 g) favored recession reduction, while higher tension of the flap (ranging from 4 to 7 g) was associated with lower recession reduction. Pini Prato et al. positioned and sutured the gingival margin 2 mm coronal to the cemento– enamel junction, obtaining complete root coverage. Coronal displacement of the flap of ≥2 mm was associated with complete root coverage in 100% of the patients [25].

Surgical procedures:

Coronally advanced Flap: Single recessions: The coronally advanced flap is based on the coronal shift of soft tissues apical to the exposed root surface [26]. The original procedure was described for covering isolated gingival recessions. The design of the flap included 'vertical incisions lateral to the recessed area beginning at a point apical to the papilla tip and

extending well into the alveolar mucosa [26]. A sulcular incision and sharp dissection close to the periosteum allowed a split-thickness flap elevation to be performed, reaching the alveolar mucosa. Epithelium was removed from the papillae adjacent to the recession and the flap was coronally positioned and stabilized with interproximal sutures and apico–coronal interrupted sutures to close the vertical releasing incisions. The area was dressed with a periodontal pack. Pini Prato et al. [27] described a flap with divergent releasing incisions to obtain a broad base that included major gingival vessels. The design of the vertical incisions was a 'golf club design' to achieve enough mesio–distal extension of the coronal part of the flap and obtain perfect adaptation to the cemento–enamel junction and the interproximal vascular recipient bed.

The clinical study of Baldi et al. [21] proved the relevance of gingival thickness, as thick gingiva was consistently associated with improved outcomes. Flap elevation should therefore be performed through a buccal intrasulcular incision to the bone crest followed by a full-thickness flap elevation beyond the mucogingival junction. Then, sharp horizontal dissection of the periosteum reaching the vertical incisions has to be performed for flap mobilization. tension-free flaps have a higher chance of achieving complete root coverage.[24]

Multiple recessions: The coronally advanced flap described above can be extended to treat multiple recession defects. Zucchelli & De Sanctis [23] proposed a modified technique to treat multiple recessions; this technique was based on an envelope flap, aiming to avoid vertical releasing incisions and to better preserve the vascular system and reduce potential scars caused by the vertical incisions .The design of the envelope flap requires the involvement of one extra tooth mesial, and one extra tooth distal, to the treatment area to allow for sufficient flap mobility. A modified oblique papilla incision is performed to obtain proper adaptation of the surgical papilla to the recipient bed. A comparison between the coronally advanced flap, with or without vertical incisions in multiple recessions, demonstrated that both approaches were effective in providing root coverage, but the envelope flap was associated with an increased probability of obtaining complete root coverage and with a better postoperative result [28].

Platelet Rich Fibrin: Regenerative potential of platelets was intorduced in 1974, and Ross et al. [29] were amongst the pioneers who first described a growth factor from platelets. Growth factors released after activation from the platelets trapped within fibrin matrix, and have been shown to stimulate the mitogenic response in the periosteum for bone repair during normal wound healing [30]. Last two decades has seen the better understanding of physiologic properties of platelets in wound healing that led to increased therapeutic applications in the various forms with varying results. However, controversies owing to the complexity of the production protocols for autologous fibrin adhesives or risk of cross infection for commercial adhesives, alongwith legal restrictions on blood handling with concentrated platelet rich plasma (cPRP), a new family of platelet concentrate, an autologous cicatricial matrix, platelet rich fibrin (PRF) appeared in France [31]. Choukroun's platelet rich fibrin (PRF) is a fibrin matrix in which platelet cytokines and cells are trapped which are released after a certain time, [32] and that can serve as a resorbable membrane. More recently, Gassling et al. [30] have shown that PRF is a suitable scaffold for proliferation human periosteal cells in vitro, which may be suitable for bone tissue engineering applications [33].

Autologous platelet rich fibrin (PRF), considered to be a healing biomaterial, was initially used in oral implantology by its promotors, [34] and presently, studies have shown its application in various disciplines of dentistry.

PRF Biology: Platelet-rich fibrin (PRF), classified as a leukocyte- and platelet rich fibrin (L-PRF), often named as Choukroun's PRF after its inventor, to avoid any confusion with other techniques using similar names such as Vivostat PRF (Vivolution, Alleroed, Denmark), a pure platelet rich plasma (PRP) or Fibrinet PRF (Cascade Medical, Wayne, NJ) matrix (without leukocyte), [35,36] belongs to the second generation platelet concentrate, collecting on a single fibrin membrane containing constituents of blood sample favorable for healing and immunity. [37,38]

PRF production protocol attempts to accumulate platelets and released cytokines in a fibrin clot. Granules present in platelet contain many proteins, which may be platelet specific (eg. beta-thromboglobulins) or non platelet specific

(fibronectin, thrombospondin, fibrinogen, and other coagulation, growth promoters, fibrinolysis inhibitors, immunoglobulins etc) calcium and serotonin etc. Also phospholipids double layer of platelet membrane constitute many receptors for other molecules. [39]

Growth factors released by alpha-granules encompass a group of cytokine polypeptides with relatively low molecular weight ranging from 6 to 45 kDa [40]. Activation and degranulation is important to initiate and support aggregation at the healing site and the release of the cytokines (IL-1 beta, IL-6, TNF-alpha) [41] and growth factors (TGF beta 1, PDGF, VEGF, EGF) that stimulates cell migration and proliferation within the fibrin matrix and thus begins the first stage of healing. [39]

Presence of cytokine vascular endotheilial growth factor (VEGF), the most powerful and omnipresent known vascular growth factor, functions to start angiogenesis and combination of its different isoforms will make it possible to direct and redefine the development plan of the network growth. [41]

Fibrinogen is the final substrate of all coagulation reactions which is transformed into an insoluble fibrin by thrombin while the polymerized fibrin gel constitutes the first cicatricial marix of the injured site [43,44]. Characteristic of polymerization naturally and slowly during centrifugation, alongwith physiologic thrombin action on collected autologus fibrinogen is crucial to determine the three dimentional organization of fibrin network that will give great elasticity and very strong PRF membrane. [31]

Method for obtaining PRF: PRF is obtained by centrifuging blood without any additives. A blood sample is taken without anticoagulant in 10 ml tubes and immediately centrifuged at 2700-3000 rpm for 10-12 minutes. The resultant product consists of following three layers: (a) RBC at the bottom, (b) PRF clot in middle and (c) upper most layer consisting of platelet poor plasma (PPP) [31,45] . Driving out the fluids trapped in the fibrin matrix by squeezing the PRF clot between the sterile dry gauze, practitioners will obtain a highly resistant autologous PRF membrane (a highly promising biomaterial) for multiple clinical usage. [46]

Recent introduction of PRF box (Process, Nice, France) devised to produce homogenously thickened hydrated (for several hours) membrane [35] and an exudate rich in platelets, leukocytes, vitronectin and fibronectin expressed from the fibrin clots [47], has improved the issues regarding the handling of the PRF clot, a living biomaterial .[35]

The technique for obtaining PRF over its first generation counter-parts viz. PRP has certain distinct advantages. First, the technique is quite simple involving less armamentarium and less time consuming as well. PRP can be prepared by two techniques whch differ in their technical aspects and are divided into either general purpose cell separators or platelet concentrating cell separators. The first one requires large amount of blood (450 ml) and is done in hospital settings. For platelet concentrating sytems a double spin or single spin technique is utilised, [48] on other hand PRF can be procured by using a table top centrifuged in a matter of 10 minutes. However, the most important advantage of PRF over PRP has been the deletion of any additive constitutent such as bovine thrombin which is mandatory for making PRP.
Recently, increasing interest was focused on the adjunctive use of platelet concentrates as a way to accelerate wound healing and repair.Five major growth factors, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor (TGF)-b and insulin-like growth factor-I, were released from the local application of platelet concentrates which may enable better tissue regeneration and faster healing process. [49, 50, 51]

It is plausible that topically applied platelet concentrates could upregulate cellular activity and subsequently promote periodontal regeneration .[52]

The systematic analysis involves studies that include CAF and PRF in combination to evaluate the effects of PRF in gingival recession treatments.

Methods: This research covered articles published till June 2014. Following electronic databases were searched: PUBMED, Cochrane Central Register of Controlled Trials. These keywords are used as the search terms: PRF,CAF and recession. No language restrictions were applied. An additional hand search was carried out in the major international journals in the field of periodontology.

Inclusion criteria: Trial design: Only randomised controlled trials (RCTs) with a follow-up ≥3 months were included and analysed accordingly.

Type of participants: Patients diagnosed as localised or multiple recession-type defects and only gingival defects sites classified as Miller Class I or II were evaluated. [Miller Class I or II were recessions that extend to or beyond the muco-gingival junction, with no periodontal bone loss in interdental areas].

Outcome Measures:

A. Primary outcome variable was the change in gingival recession depth. Recession depth (RD) was defined as the distance between cement–enamel junction and the gingival margin, which was measured by a Boley gauge at the midbuccal of the tooth.
B. Secondary outcome variables were described as follows:

1. width of keratinised tissue (KTW) was measured at the midbuccal point from the
2. muco-gingival junction to the free gingival margin by a Boley gauge caliper;
3. CAL change was measured from the cemento–enamel junction to the most apical part of the sulcus;
4. wound healing index: healing status including gingival oedema, erythema, suppuration, patient discomfort, or flap dehiscence was recorded after surgery by clinical examiners.

Exclusion criteria: Clinical trials were excluded if they did not meet the above criteria. In addition, following types of studies were excluded as well:

i. studies in which the patients had previous surgical treatment to correct the gingival recession;
ii. studies involving teeth with intrabony defects;
iii. studies failed to provide the mean value and standard deviation which were needed for the analysis of RD, KTW, CAL.

Results: A total of 3 studies [53,54,55] fulfilled the inclusion criteria's and where selected for review. A total of 55 patients with190 defects (95 in test and 95 in control) were treated. In the selected articles , the time of follow up ranged from , 6-9 months, the articles were published between 2009-2014.

Author (year)		Padma et al.(2013)	Jovicic B. et al. (2013)	Aroca et al. (2009)
Methods		RCT, Spilt mouth design ,two treatment groups and 6 months duration	RCT,spilt mouth design, two treatment groups and 9-month duration	RCT, split-mouth design, two treatment groups and 6-month duration
		15 individuals (aged 18-35 years)with bilateral buccal Millers Class I and II recession defects.	20 individuals(aged 18-35 years) with one buccal Millers Class I and II recession defects.	20 individuals (aged 22-47) with atleast 3 bilateral multiple Millers class I and II recession defects.
Intervention	Test	CAF+PRF	CTG+CAF+PRF	MCAF+PRF
	Control	CAF	CTG+CAF	MCAF
Data	RD	3.44±1.99 2.31±1.05		
	KTW	2.44±1.45 2.19±0.81	2.7±0.47 2.3±0.43	-0.24±0.99 -0.48±1.10
	CAL	3.75±1.29 2.69±1.11		2.47±1.36 2.56±1.24
Other Outcomes		RC		RW, PD, GTH

CAF- Coronally advanced flap, CAL-clinical attachment level, CTG- Connective tissue grafts, KTW- Keratinized tissue width, MCAF- Modified coronally advanced flap,

RW- Recession width PD- Probing depth on mid-buccal aspect, PRF- platelet rich fibrin, RC- percentage of root Coverage, RCT- randomized control trail, RD-Recession defect, GTH-gingival/ mucosal thickness.

Recession depth change: In all studies, RD was defined as the distance from cement–enamel junction to the gingival margin. Jovici_c B et al.[54] made a conclusion that platelet concentrates might have

adjunctive effect on gingival recession while no significant difference was found in Aroca et al.'s [55] study.

Keratinised tissue width change: Keratinised tissue width was measured at the midbuccal point from the mucogingival junction to the free gingival margin. The mucogingival junction was determined using the rollover technique. There was a greater effect of platelet concentrates. Platelet concentrates may bring 0-35-mm increase in KTW.

Clinical attachment level change: Clinical attachment level was measured from the cemento-enamel junction to the most apical part of the sulcus. Padma et al. [53] Studies in 2013 and Aroca et al.[55] studies find no evidence supporting PRF adjunctive effect on CAL.

Aroca etal. Study in 2009 which saw a combined approach of modified coronally advanced Flap (MCAF) and PRF to MCAF alone found that combination with PRF was effective procedure to cover denuded roots, the only benefit of PRF was a statistically significsnt increase in the thickness of keratinized marginal gingival.

Several polypeptide growth factors including PDGF, FGF, EGF, TGF-b and insulin-like growth factor alone or in combination are effective in the healing mechanisms [56–58]. PDGF plays a critical role in physiological repair mechanisms as a regulator for the migration, proliferation, survival of mesenchymal cell lineages [59]. Transforming growth factor-b can induce fibrin matrix remodelling as well as secretion of a cicatricial collagen matrix such as collagen I and fibronectin [60].

Discussion: Bayesian network meta- analysis of root coverage procedures by Buti j. et al. concluded that CAF+CTG might be considered the gold standard in root coverage procedures [61]. A systematic review on the efficacy of periontal plastic surgey procedures in the treatment of localized facial gingival recessions by cairo et al. that CAF was associated with higher probability of complete root coverage and higher amount of recession reduction than semilunar coronally positioned flap combination techniques involving CAF and other graft material yielded better results than CAF alone in terms of root coverage and recession reduction.

Pini Prato et al. [19] reported that the gingival margin sutured on average, 1 mm coronal to the cemento–enamel junction remained stable at week 1, but shifted apically from weeks 2 to 4, uncovering the cemento–enamel junction in 60% of the sites with an average shift of 1.5 ± 0.6 mm. From week 4 to week 12 after the procedure, the gingival margin remained stable. Studies by Cortilleni et al. showed that at week 1, the cemento– enamel junction was visible in five (12%) of the patients treated with a coronally advanced flap and in three (7%) of the patients treated with a coronally advanced flap + connective tissue graft. There was a steady increase in the number of patients with a visible cemento–enamel junction over the following 3 weeks[62]. This trend was further confirmed at the 3- and 6-month examination time-points, ending at 6 months with 27 exposed cemento–enamel junctions out of 43 coronally advanced flaps –treated sites. Leknes et al. [63] reported severe recurrence of gingival recession in a 6-year study of sites treated either with coronally advanced flap or with coronally advanced flap + bioresorbable barriers.

Platelet concentrates might stimulate periodontal ligament and osteoblastic proliferation. TGF-b1 could influence early proliferation of gingival fibroblast-like cells, the formation of blood vessels and extracellular matrix remodelling. Platelet concentrates were proved to inhibit Staphylococcus aureus, Escherichia coli, Bacillus megaterium, Pseudomonas aeruginosa, Enterococcus faecalis [64, 65], and it also has immune regulation ability to stimulate defense mechanisms [66]. Wound healing enhancers, such as PRF or EMD, did not provide any additional benefit to the tested techniques (Aroca et al. 2009, 2010, Cordaro et al. 2012). Explanations may be only speculated. Most probably, the techniques to which enhancers are added are already saturating the healing potential of the subjects. Joseph et al [67], Thorat et al [68] and Sharma et al.[69] reported higher gains in clinical attachment levels and radiographic bone fill in infrabony defects when utilizing PRF with open flap debridement. Bajaj et al [70] reported higher gains in vertical clinical attachment levels in mandibular grade II furcation defects treated with PRF and OFD.

PRF have also been used in the treatment of furcation defects and all clinical and radiographic parameters showed statistically significant improvement at both the test sites (PRF with OFD and PRP with OFD)

compared to those with OFD alone. Relative vertical clinical attachment level gain was also greater in PRF (2.87 - 0.85 mm) and PRP (2.71 -1.04 mm) sites as compared to conventional therapy (1.37- 0.58 mm), and relative horizontal clinical attachment level gain was statistically significantly greater in both PRF and PRP than in the control group.[70]

PRF have also been used in treatment of infrabony defects and studies have found that PRF can improve clinical parameters associated with human intrabony periodontal defects, and Bovine Porous Bone Mineral has the ability to augment the effects of PRF in reducing pocket depth, improving clinical attachment levels and promoting defect fill.[71]

Conclusion: Platelet concentrates are easily available, and several polypeptide growth factors alone or in combination contribute to the acceleration of healing. The concept of its utilisation in gingival recessions are really attractive. The addition of platelet concentrates might exert a positive adjunctive effect in the treatment of gingival recession and also wound healing. The result of this systemic analysis highlight the potential benefits of PRF as a supportive intervention in the treatment of gingival defects.

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