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Esthetic- and patient-related outcomes following root coverage procedures: A systematic review and network meta-analysis

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Keywords: aesthetics; gingival recession; meta-analysis; connective tissue graft; coronally advanced flap.

ABSTRACT

BACKGROUND
Aim of this systematic review (SR) of randomized controlled trials (RCTs) was to evaluate effect of different flap designs and graft materials for root coverage, in term of esthetics, patient satisfaction and self-reported morbidity (post-operative pain/discomfort).

MATERIAL AND METHODS:
A comprehensive literature search was performed. A mixed-modeling approach to Network Meta-Analysis was utilized to formulate direct and indirect comparisons among treatments for Root Coverage Esthetic Score (RES), with its individual components, and for subjective patient-reported satisfaction and post-operative pain/discomfort (visual analogue scale (VAS) of 100).

RESULTS:

Twenty-six RCTs with a total of 867 treated patients (1708 recessions) were included. Coronally Advanced Flap (CAF) + Connective Tissue Graft (CTG) (0.74 (95% CI[0.24, 1.26], p=0.005)), Tunnel (TUN) + CTG (0.84 (95% CI[0.15, 1.53]), p=0.01) and CAF + Graft substitutes (GS) (0.55 (95% CI[0.006, 1.094], p=0.04)) were significantly associated with higher RES than CAF. No significant difference between CAF+CTG and TUN+CTG was detected (0.09 (95% CI [-0.54, 0.72], p=0.77)). Addition of CTG resulted in less natural tissue texture (-0.21 (95% CI [-0.34, -0.08]), p=0.003) and gingival color (-0.06 (95% CI [-0.12, -0.03], p=0.03)) than CAF. CTG techniques were associated with increased morbidity.

CONCLUSIONS:

CTG procedures showed highest overall aesthetic performance for root coverage, although graft integration might impair soft tissue color and appearance. Additionally, CTG-based techniques were also correlated with a greater patient satisfaction and morbidity.

Clinical relevance

Scientific rationale for the study:

Although predictability of root coverage procedures has been extensively demonstrated for the treatment of single and multiple gingival recessions, outcomes in term of esthetic outcomes, satisfaction and patient morbidity are still unclear.

Principal findings:

Coronally Advanced Flap (CAF) + Connective Tissue Graft (CTG) or Tunnel (TUN)+CTG showed superior final RES score than CAF alone, Enamel Matrix Derivatives and Xenogeneic Collagen Matrix. CAF achieved more natural soft tissue texture and gingival color scores than CTG. Higher patient satisfaction was observed for CTG and CTG + EMD compared to flap alone, while CTG techniques were associated with increased morbidity.

Practical implications:

Root coverage procedures are generally well-tolerated and improve aesthetic self-perception. Among techniques, CTG procedures showed highest aesthetic performance, although their use increased morbidity and less natural soft tissue texture and gingival color.

1.INTRODUCTION

Predictability of root coverage procedures for treatment of single and multiple gingival recessions (GRs) has been extensively demonstrated (Cairo et al., 2016a, Cairo et al., 2012, Cairo et al., 2014, Graziani et al., 2014). Systematic reviews and meta-analyses have assessed efficacy of different techniques mainly by comparing mean root coverage (mRC) and complete root coverage (CRC) (Cairo et al., 2014, Graziani et al., 2014, Tavelli et al., 2019b). The connective tissue graft (CTG) is widely considered as the gold standard treatment for single/multiple GRs (Cairo et al., 2014, Graziani et al., 2014, Cortellini and Bissada, 2018a), providing excellent stability of the gingival margin over time compared with flap alone or replacement biomaterials (Pini-Prato et al, 2012; Tavelli et al. 2019b). Nonetheless, outcomes of root coverage procedures are not solely dependent upon the final amount root coverage, but final soft tissue quality and related esthetic outcomes with overall patient satisfaction may be considered the most important treatment goal (Cairo, 2017).

In this scenario, esthetic- and patient-reported outcomes are routinely included in modern clinical studies (Barootchi et al., 2019, Stefanini et al., 2016, Tavelli et al., 2019c, Azaripour et al., 2016, Cairo et al., 2020, Tonetti et al., 2018). In particular, while patient morbidity and satisfaction are usually evaluated with a visual analogue scale (VAS), several methods have been proposed for evaluating esthetic outcomes obtained (Kerner et al., 2009, Cairo et al., 2009, Aichelmann-Reidy et al., 2001, Wang et al., 2001, Zucchelli et al., 2012, Salhi et al., 2014). Some of these methods relied on gingival margin position, level of the mucogingival junction, color match, presence/absence of scar/keloid formation, consistency, and contiguity of soft tissue compared to adjacent sites (Aichelmann-Reidy et al., 2001, Cairo et al., 2009, Wang et al., 2001), while others used a VAS or pink aesthetic score (Zucchelli et al., 2012, Salhi et al., 2014). Among them, root coverage esthetic score (RES) introduced by Cairo et al. in 2009 (Cairo et al., 2009) has been shown to be a reliable tool for assessing esthetic outcomes of root coverage procedures, not only among experts (Cairo et al., 2010) but also among operators with different levels of periodontal experience (Isaia et al., 2018). An early network meta-analysis (NMA) suggested that root coverage procedures improved esthetic perceptions by both patient and dentist (Cairo et al., 2016b). Limitations in the available evidence, however, limited the conclusions. In the last years, an increased number of RCTs and a growing interest in surgical techniques and biomaterials development has been noticed worldwide.

Therefore, the aims of the present systematic review were to evaluate which flap design and graft material are associated with the best esthetic outcomes, highest patient satisfaction and the lowest patient morbidity.

2. Material and Methods

2.1 Study Registration and reporting format

The review protocol was registered and allocated the identification number CRD42020142623 in the PROSPERO International Prospective Register of Systematic Reviews hosted by the National Institute for Health Research, University of York, Centre for Reviews and Dissemination. The current systematic review and meta-analysis follows the 27-item Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009) and Cochrane Handbook (Higgins et al., 2011).

2.2 Focused Questions

The goal of conducting this review was to address the following questions:

1) Which root coverage procedure achieves the highest esthetic outcome, based on the proposed classification of root coverage esthetic score (Cairo et al., 2009)?

2) Relative to other treatments, how do different root coverage approaches affect the individual components of RES?
3) Which root coverage procedure is associated with the highest scores for self-reported patient satisfaction, and the lowest patient morbidity (experienced and self-reported post-op pain/discomfort)?

2.3 Patient, Intervention, Comparison, Outcome, Time (PICOT) Question

P: Systemically healthy patients (at least 10 per trial) with clinical diagnosis of localized or generalized gingival recession(s) categorized as RT1 & 2 (Cairo et al., 2011, Cortellini and Bissada, 2018a)

I: Any type of root coverage procedure

C: Comparison between CAF and TUN, either alone, with CTG or with graft substitutes or biologic agents

O: Primary outcomes: Root Coverage Esthetic Score (RES) (Cairo et al., 2009), self-reported patient satisfaction, and patient morbidity. Secondary outcome measures: individual components of RES, to investigate influence of different treatments for root coverage on each individual constituent of the esthetic score.

T: Only RCTs with a minimum 6-month follow-up duration were included.

2.4 Eligibility Criteria

In order to assert transitivity, the following set of inclusion and exclusion criteria were implemented *a priori* for selection of studies, to observe for significant heterogeneity relative to the design-driven differences, selection criteria and overall approach:

Inclusion criteria:

- Randomized clinical trials with a strict protocol
- Treatment of localized or multiple GRs (only RT1 & 2) with either the coronally advanced flap (CAF) or tunnel (TUN) technique, alone or having utilized a soft tissue graft, substitute or biomaterial
- Evaluating and reporting esthetic outcomes according to RES (Cairo et al., 2009)
- Duration of follow-up and reporting of outcomes reaching at least 6 months

Exclusion criteria:

- Non-randomized studies; cohort and case-control studies, case series, retrospective studies, case reports, and animal studies
- Utilization of other techniques for root coverage other than CAF or TUN (such as the laterally positioned flap, double papilla flap and free gingival graft as these tend to have slightly different indications for their treatment).
- Studies with a follow-up period of < 6 months
- Studies including only smokers
- Lack of data regarding the exact number of treated sites in either test or control groups
- Utilizing different measurements or classifications other than RES (Cairo et al., 2009) for the esthetic evaluation
- Utilization of laser treatment
- Utilization of combination therapies (e.g. CAF + CTG + enamel matrix derivative)

2.5 Information Sources and Search Strategy (see supplemental Appendix)

2.6 Study selection (see supplemental Appendix)

2.7 *Data extraction and management (see supplemental Appendix)*

2.8 Synthesis of the Mixed-models Network Meta-analysis (NMA)

For studies published more than once (i.e., duplicates), or those that utilized the same patient population, only one report with the most informative and complete data was included for the analyses. As per our focused questions, all outcomes were investigated within two sub-analyses; one where the different treatment arms were grouped according to flap design and graft materials (CAF, CAF + CTG, CAF + Graft substitutes (GS), Tunnel technique (TUN) + CTG, and TUN + GS) with CAF serving at the reference for the initial comparisons; and a second sub-analysis where the same study arms were grouped according to the type of graft material (Acellular Dermal Matrix (ADM), CTG, EMD (Enamel matrix derivatives), CTG + EMD, Flap, Platelet-rich Fibrin (PRF), tissue engineering constructs (TEC), with XCM) and Flap serving as the initial reference point for the comparisons (Tavelli et al., 2019a). This was done so for all the outcomes of RES (0 – 10), self-reported satisfaction, and patient morbidity (in terms of self-reported post-op pain/discomfort), which were assessed and analyzed based on 0 – 100 on the VAS scale.

We used a mixed-modeling approach to NMA (Barootchi et al., 2020, Tu, 2015) to simultaneously compare all treatment arms regardless of their preexisting direct comparison. The transitivity assumption underlying the NMA was evaluated by checking the distribution of clinical and methodological variables that could potentially act as effect modifiers across treatment comparisons (such as the study design/approach, and baseline measures of the relevant variable) (Salanti, 2012). Our goal was to formulate indirect comparisons between treatments only if all included treatment arms could be interchangeably implemented and performed in all trials and for all the recruited and treated population.

The following mathematical formula presents our utilized model for both sub-group analyses, similar in construct to previous works (Barootchi et al., 2020, Tavelli et al., 2019a):

$$y_{ijt} = \alpha_{q(ij)} + \beta_{q(ij)}{}^{*}T_{ijt} + \theta_i^{p*} P_i + \theta_i^{sm*}(1 - P_i) + \eta_{ij} + \gamma_i{}^{*}T_{ijt} + \lambda' X_{ijt} + \epsilon_{ijt}$$

where i, j, t index studies, study arms, and occasion respectively; $q(i, j)$ is the treatment type administered in arm j of study i, T_{ijt} refers to the actual time of measurement/assessment of RES/patient satisfaction/morbidity.X_{ijt} contains baseline characteristics (REC, KT and GT baseline). The α and β fixed parameters capture the common intercept and common trend for all study arms with a given treatment type; θ, η, $and\, \gamma$ are random effects that capture study, study arm unique intercepts and a study unique time slope; and ϵ reflects all other sources of variation. P_i is 1 for a study of parallel design, and 0 for any split-mouth trial that contributed to the analysis with both treatment arms (Aydinyurt et al., 2019, Jhaveri et al., 2010, Milinkovic et al., 2015, Pietruska et al., 2019, Stefanini et al., 2016). All other model components are random and capture study specific effects.

Additionally, to evaluate the relative extent to which each treatment affects the individual parameters of RES, for both sub-analyses, the 5 constituents of RES (gingival margin, marginal tissue contour, soft tissue texture, alignment of the mucogingival junction, and gingival color) served as an outcome of the NMA. As previously mentioned, these data were mostly obtained through the respective authors of the included trials and coded as a continuous variable representing the average score of each parameter.

The type of treatment approach (single/multiple site treatment) was controlled for in all models (through inclusion of a fixed-effects co-variate and observing its influence). Additionally, the arms were weighted according to the treated sample size. The analyses also accounted for correlations induced by multi-group studies, by using multivariate distributions. The variance of the random-effects distribution (heterogeneity variance) was considered to measure the extent of across-study and within-comparison variability on the treatment effects.

To obtain direct and indirect pairwise comparisons between different treatment arms, different reference levels were specified in the model and the contrasts were recorded along with their standard errors, and *p* values. Confidence intervals were then produced, and a *p* value threshold of 0.05 was set for statistical significance.

The linearity assumption was tested for all models by including quadratic terms, however no evidence of non-linearity was noticed. All analyses were performed by an author with experience in biostatistics (SB) using the lme4 (Bates, 2015), lmerTest (Kuznetsova, 2017), dplyr (Wickham, 2019a), and tidyr (wickham, 2019b), statistical packages in Rstudio (version 1.2.1335). The igraph (Csardi, 2006) and ggplot2 (Wickham, 2016) packages were used to produce the network plots for visual representation of the formulated direct and indirect comparisons.

2.9 Quality and Risk of Bias assessment (see supplemental Appendix)

3. RESULTS

Twenty-six RCTs with a total of 867 treated patients and 1708 recessions were included.

3.1 Search results & Study selection (see supplemental Appendix)

Figure 1 presents the steps involved in the literature search process.

3.2 Study characteristics and type of intervention (see supplemental Appendix)

Table 1 displays the characteristics of the included studies, their design, interventions and outcomes.

3.3 Synthesis of Results from the Network Meta-analysis

3.3.1 Root coverage Esthetic Score:

When investigating the first subset of analyses, grouped by flap design and their graft materials (treatments arms of CAF, CAF + CTG, CAF + GS, TUN + CTG, and TUN + GS), the model revealed that compared to CAF alone, the treatment groups of TUN + CTG (0.84 (95% CI[0.15, 1.53]), p=0.01), and CAF + CTG (0.74 (95% CI[0.24, 1.26], p=0.005)), and CAF + GS (0.55 (95% CI[0.006, 1.094], p=0.04)) were significantly associated with higher RES scores. With CAF + CTG as the reference, the treatment groups of CAF (-0.74 (95% CI[-1.23, -0.25], p=0.004)), and TUN + GS (-0.9 (95% CI[-1.69, -0.11], p=0.02)) showed significantly lower RES scores, while TUN + CTG (0.09 (95% CI[-0.54, 0.72], p=0.77)) did not present a significant difference.

For second subset of analyses, with study arms grouped according to the type of graft material (ADM, CTG, CTG + EMD, EMD, Flap, PRF, TEC, and XCM), the analysis showed a significantly higher estimate for CTG (0.71 (95% CI[0.27, 1.15]), p=0.003), and CTG + EMD (0.97 (95% CI[0.53, 1.41]), p=0.03), and ADM (0.873 (95% CI[0.23, 1.51], p=0.003)) compared to treatment with Flap alone, while other treatment arms failed to present a statistically significant difference with flap alone in the analyses. With CTG as the reference for the network comparisons, the treatment arms of XCM (-1.127 (95% CI[-1.66, -0.58], p=0.001)), EMD (-1.18 (95% CI[-2.15, -0.21], p=0.01)), and flap (-0.711 (95% CI[-1.15, -0.26], p=0.003) showed to be associated with significantly lower RES scores, whereas no significant difference was apparent for treatment arms of ADM (0.161 (95% CI[-0.43, 0.75], p=0.59)), CTG + EMD (0.264 (95% CI[-0.68, 1.21]), p=0.57), PRF (-0.448 (95% CI[-1.67, 0.77]), p=0.467), and TEC (0.077 (95% CI[-1.02, 1.17], p=0.88)). (see Figures 2-4)

Comparative efficacy of different approaches to the individual components of RES:

1) The level of the gingival margin (GM)

In the first sub analysis, the model demonstrated that with CAF as reference, both treatment groups TUN + CTG (1.14 (95% CI[0.21, 2.06]), p=0.02), and CAF + CTG (0.68 (95% CI[0.09, 1.28]), p=0.03), resulted in significantly higher scores for GM (while not showing significant intergroup differences), whereas the treatment arms of CAF + GS (0.45 (95% CI[-0.11, 1.01]), p=0.12), and TUN + GS (-0.399 (95% CI[-1.17, 0.37]), p=0.31) did not present a significant estimate in the model.

In the second sub analysis for the graft materials, with flap serving as reference, the treatment groups PRF (1.24 (95% CI[1.16, 1.32], p=0.001)), TEC (1.03 (95% CI[0.11, 1.94], p=0.03)), CTG (0.95 (95% CI[0.51, 1.39], p<0.001)), EMD (0.941 (95% CI[0.84, 1.04], p=0.003)), and ADM (0.71 (95% CI[0.07, 1.34]), p=0.03) all showed significantly higher scores, except for XCM (0.04 (95% CI[-0.56, 0.64]), p=0.8). While with CTG as reference the treatment arms of Flap alone (-0.95 (95% CI[-1.39, -0.51], p<0.001)) and XCM (-0.91 (95% CI[-1.49, -0.33], p=0.004)) showed a statistically lower GM score.

2) Marginal tissue contour (MTC)

During the first sub analysis, the only treatment arm that showed a statistically higher coefficient was CAF + GS (0.121 (95% CI [0.01, 0.22]), p=0.02), while other treatment arms failed to show a statistically significant difference compared to CAF alone.

Whereas in the second sub analysis, the treatment groups of PRF (-0.41 (95% CI[-0.48, -0.32]), p<0.001), and ADM (0.33 (95% CI[0.21, 0.45]), p=0.007) presented with statistically lower, and higher scores compared to flap alone, respectively.

3) Soft tissue texture (STT)

The only statistically significant result in the model during the first sub analysis was for CAF + CTG (-0.22 (95% CI [-0.34, -0.08]), p=0.002), with a negative coefficient, while other treatment arms did not present any significant difference compared to CAF alone.

Similarly, in the second subgroup analysis, CTG (-0.20 (95% CI[-0.34, -0.05]), p=0.01) again was the only treatment arm with a significant and negative coefficient, demonstrating that treatment with CTG resulted in significantly lower scores for STT compared to CAF, whereas the other treatment arms did not show a statistically significant difference.

4) Alignment of the mucogingival junction (MGJ)

The only statistically significant coefficient in the model was observed for TUN + GS (0.19 (95% CI[0.06, 0.31]), p=0.03), and the other treatment groups did not show a significant difference compared to CAF.

For the second sub analysis, there was no significant differences observed with any of the treatment arms compared to flap alone.

5) Gingival color (GC)

For this parameter of RES, the only significant result in the model was for treatment with TUN + CTG (-0.12 (95% CI[-0.21, -0.03]), p<0.01), that showed a statistically lower coefficient compared with CAF, while the other the other treatment arms failed to present any statistical correlation.

For the second sub analysis similarly, CTG (-0.06 (95% CI[-0.12, -0.03], p=0.03)) was the only treatment group that showed a significant and negative coefficient compared with flap alone.

3.3.2 Patient satisfaction: For the first set of sub-analyses in comparison with CAF alone, treatment with CAF + CTG (5.91 (95% CI[0.87, 10.95], p=0.01) presented significantly higher scores for patient satisfaction, while other treatment groups did not present statistically significant estimates in the model.

In the second subgroup of analysis, both treatment arms of CTG (8.12 (95% CI[2.9, 13.34]), p=0.004), and CTG + EMD (4.31 (95% CI[0.27, 12.35]), p=0.02) showed to be associated with significantly higher VAS scores when compared to flap alone.

3.3.3 Patient morbidity: During the first sub-group analyses, both CAF + CTG (10.41 (95% CI[2.71, 18.11]), p=0.01), and TUN + CTG (10.67 (95% CI[2.03, 19.31]), p=0.02), were the only treatment groups that presented with statistically significant higher patient morbidity compared to CAF alone.

And for the second sub-analyses, CTG-based materials (9.609 (95% CI [2.26, 16.94]), p=0.01) showed significantly higher scores for patient morbidity compared with treatment with Flap alone.

3.5 Risk of bias assessment (see appendix)

The individual and overall assessment of risk of bias is presented in Appendix (Supplementary Table 2 for the overall observed risk). Fifteen of 26 RCTs were rated at low risk of bias.

4. DISCUSSION

The goals of the present NMA were to assess esthetic- and patient-related outcomes following periodontal plastic surgery considering standardized evaluation assessments. An extensive review using 26 RCTs clustering data on 867 patients and 1708 treated recessions was performed. The outcomes confirmed that root coverage is associated with improved patient satisfaction and limited morbidity (Cairo et al. 2016b).

The present results confirmed that CTG provided superior RES than CAF. In addition, the surgical technique, whether TUN or CAF, did not seem to affect the final esthetic outcomes when a CTG was used. Although it has been suggested that TUN can enhance the esthetic outcomes (Zuhr et al., 2014, Santamaria et al., 2017b), our results suggested that most likely the graft material played a bigger role on the esthetic outcomes than the flap design, as also reported comparing CAF and TUN in term of RES score (Tavelli et al., 2018b, Tavelli et al., 2019c). This may be due to the fact that graft acts as biological filler under the surgical gingival margin, thus reducing post-operative shrinkage and promoting final root coverage outcomes (Cairo, 2017).

Apart from CTG-based techniques, other approaches showed a significantly higher RES than flap alone, including CTG + EMD and ADM. This is line with the previous NMA (Cairo et al., 2016b). Similarly, CTG demonstrated higher RES than XCM and EMD. When interpreting these results, it should be taken into account that the overall RES is largely sensitive to the amount of root coverage achieved (up to 6 points out of 10) (Cairo et al., 2009). Therefore, given the evidence supporting CTG as the gold standard treatment in terms of amount of root coverage (Cairo et al., 2014, Graziani et al., 2014, Tavelli et al., 2019b), it is not surprising that CTG achieved significantly higher overall RES and GM compared to XCM, EMD and flap alone. Similarly, other techniques, such as ADM, EMD, PRF and TEC showed superior scores for GM compared with flap, which is due to higher root coverage outcomes that these treatments can achieve when CAF or TUN are combined with a scaffold material or a biologic agent (Cairo et al., 2014, Tavelli et al., 2020a, Tavelli et al., 2020b).

Interestingly, CTG showed lower scores than CAF for some RES parameters, as STT and GC. In line with this finding, a recent article found that CAF alone had better final RES when the gingival thickness at baseline was > 0.82 mm, suggesting caution regarding the excessive use of CTG in patients with a thick gingival phenotype (Cairo et al. 2016; Cairo et al., 2020). Indeed, it is reasonable to assume that adding a CTG in a case with thick phenotype may result in an unnatural appearance of the gingiva compared to the untreated adjacent sites. The selective use of CTG has been also recently advocated by Stefanini et al., who suggested its use only in case with gingival thickness < 1 mm or keratinized tissue width ≤ 1 mm (Stefanini et al., 2018). It has to be mentioned despite taking baseline characteristics (multiple/single recession treatment, initial recession depth, etc) into account in our analyses, not all studies reported gingival thickness, which may have affected our results.

A recent study evaluated the esthetic outcomes from a multicenter randomized clinical trial comparing CAF + CTG vs CAF + XCM (Pelekos et al., 2019). Although CTG achieved an overall higher RES than XCM, the authors reported superior scores with XCM for STT and MTC (Pelekos et al., 2019). In line with this study, we observed that CAF + GS (either XCM or ADM) obtained better MTC than CAF alone. This may be due to the scaffold properties of XCM and ADM that improve the stability of the blood clot promoting cellular migration and proliferation (Tavelli et al., 2020b). We also found that TUN + GS obtained a superior MGJ score than CAF, however the reasons for this finding are open to speculations.

Patient satisfaction and morbidity are also important parameters when evaluating patient-related outcomes in root coverage procedures (McGuire et al., 2014, Mounssif et al., 2018, Rocha Dos Santos et al., 2017, Tonetti et al., 2018). In a commentary discussing the importance of incorporating PROMs into clinical trials, the use of specific questions for evaluating patients' anxiety, discomfort, preference and esthetics was advocated (McGuire et al., 2014). Recent studies have investigated the impact of different treatments not only on patient morbidity but also in condition-specific health-related quality of life (Rocha Dos Santos et al., 2017, Tonetti et al., 2018). Our analysis showed that CAF + CTG obtained higher patient satisfaction scores than CAF and that CTG and CTG + EMD showed higher satisfaction scores than flap alone. This finding is most likely related to the superior recession reduction and complete root coverage that CTG and CTG + EMD can achieve over treatment with flap alone. On the other hand, it has been suggested that the final satisfaction is not able to capture the possible patient post-surgical discomfort (Cairo et al., 2016b). Indeed, CAF + CTG and TUN + CTG were the only treatments that showed significantly higher morbidity than flap alone. Although, it has been suggested that TUN is a less invasive technique than CAF (Gobbato et al., 2016, Santamaria et al., 2017b), it can be speculated that when the procedure also involves the harvesting of a CTG, the difference in morbidity may no longer be remarkable. This aspect should be further investigated by studies comparing TUN vs CAF without graft materials. When CAF and TUN were compared using the graft substitute (ADM), one study reported less post-operative discomfort for TUN + ADM compared to CAF + ADM (Papageorgakopoulos et al., 2008), while another study did not find any differences (Tavelli et al., 2019c). Our results confirm that CTG-based techniques increase patient morbidity compared to flap alone, while adding a GS does not. Among the advantages of using GS compared to CTG, a lower patient self-reported pain score, analgesic consumption and shorter time to recovery have been described (Tonetti et al., 2018). This aspect needs to be kept in mind since emerging evidence suggests that CTG should not be considered as the *panacea* for the treatment of gingival recessions, since similar root coverage outcomes can be obtained with flap alone in the presence of a thick gingival phenotype (Cairo et al., 2020). A cost-effective evaluation should be performed for each patient to decide the best treatment option considering the clinical, esthetic and patient-related outcomes (Pelekos et al., 2019). Patients' psychosocial factors, such as anxiety, depression, stress and well-being, should also be take into account as they can affect the overall perception of the procedure, post-surgical morbidity and medication consumption (Kloostra et al., 2006).

Limitations of this manuscript may be due to the fact that analysis on single RES variables was performed only on 18 RCTs. Furthermore, a certain degree of heterogeneity in RES assessment (visual vs assessment on photographs) exists among studies, and, that our evaluation captures aesthetic outcomes at only short-time follow-up, while possible changes in the long-term should be assessed. Lastly, most of the included RCTs investigated CAF, CTG, ADM or XCM, while fewer publications have investigated the treatment arms of PRF, TEC and EMD.

5. Conclusions

Based on the currently available evidence, and the limitations within this research, the following conclusions can be drawn:

- CTG with either CAF or TUN showed superior final RES than CAF, EMD and XCM
- CAF and TUN associated with CTG showed similar final RES
- CAF achieved higher soft tissue texture and gingival color scores than CTG
- Adding ADM or XCM to CAF improved the marginal tissue contour compared to CAF
- Higher patient satisfaction was observed for CTG and CTG + EMD compared to flap alone
- CAF + CTG and TUN + CTG had higher morbidity than flap alone, while adding ADM or XCM did not increase patient discomfort

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Figures and Tables:

Table 1. Characteristics of the included studies, interventions and outcomes.

Figure 1. PRISMA flowchart displaying the performed search strategy leading to the inclusion of 26 randomized clinical trials. CAF, coronally advanced flap; RES, root coverage esthetic score; TUN, tunneling technique.

Figure 2. Network meta-analysis of eligible comparisons for A) the analysis based on flap designs and their graft materials, and B) analysis by the graft material.

Black solid lines connect treatments that are directly compared in at least 1 trial. Studies contributing with only one arm are not presented. Gray dotted lines display the indirect comparison of the treatments that have not been compared head-to-head previously and formed through the network model. Note that distances are for plot clarity. The node size is proportional to the number of treated sites.

ADM, Acellular dermal matrix; CAF, Coronally advanced flap; CTG, Connective tissue graft; EMD, Enamel matrix derivatives; GS, Graft substitutes; NMA, network meta-analysis; PRF, platelet rich fibrin; TEC, Tissue engineering constructs; TUN, Tunnel technique; XCM, Xenogeneic collagen matrix.

Figure 3. Pairwise comparisons from the Network Meta-Analysis based on flap designs and their graft materials for the outcome of RES. Treatments are reported in alphabetical order. Results are the estimates (95% CIs) from the NMA model in the cell in common between the column-defining treatment (defined-treatment 1), and the row-defining treatment (defined-treatment 2). A superior treatment indicated on the diagonal will have positive values in its row and negative values it its column. Statistically significant results are in bold, with the estimates underlined. *($p<0.05$), **($p<0.01$). *i* denotes model estimate derived from a purely indirect comparison.

CAF, Coronally advanced flap; CI, Confidence interval; CTG, Connective tissue graft; GS, Graft substitutes;

NMA, network meta-analysis; TUN, Tunnel technique.

Figure 4. Pairwise comparisons from the Network Meta-Analysis according to graft materials for the outcome of RES. Treatments are reported in alphabetical order. Results are the estimates (95% CIs) from the NMA model in the cell in common between the column-defining treatment (defined-treatment 1), and the row-defining treatment (defined-treatment 2). A superior treatment indicated on the diagonal will have positive values in its row and negative values it its column. Statistically significant results are in bold, with the estimates underlined. *(p<0.05), **(p<0.01). *i* denotes model estimate derived from a purely indirect comparison.

ADM, Acellular dermal matrix; CI, Confidence interval; CTG, Connective tissue graft; EMD, Enamel matrix derivatives; NMA, network meta-analysis; PRF, platelet rich fibrin; TEC, Tissue engineering constructs; XCM, Xenogeneic collagen matrix.

Table 1. Characteristics of the included studies, interventions and outcomes.

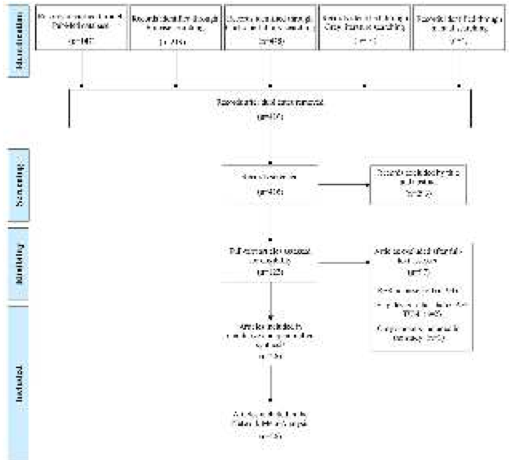
Publication	Country, Setting, Sponsored by companies	Treatment groups*	Patients (n), Sites (n)	Follow-up time (months)	Overall RES outcome (0-10)	Method of RES evaluation	Method of PROMs assessment	
							Satisfaction	Morbidity (reported pain/discomfort)
(Ahmedbeyli et al., 2014)	Turkey, University, No	CAF+ADM CAF	24, 48	12	9.08 ± 1.75 7.58 ± 2.02	Clinical	Three-point rating scale‡	NA
(Ahmedbeyli et al., 2019)	Turkey, University, No	CAF+ADM CAF+ADM	22, 55	12	9.45 ± 1.21 8.91 ± 1.97	Clinical	Three-point rating scale‡	NA
(Aydinyurt et al., 2019)	Turkey, University, No	CAF+CTG+EMD CAF+CTG	19, 38	12	8.93 ± 1.43 8.37 ± 1.85	Clinical	NA	NA
(Azaripour et al., 2016)	Germany, University, No	TUN+CTG CAF+CTG	40, 71	6	9.2 ± 1.1 9.2 ± 1.3	Using photographs	Questionnaire‡	VAS
				12	9.3 ± 1.1 9.2 ± 1.3			
(Bansal et al., 2016)	India, University, NA	CAF	10, 20	6	7.7 ± 1.41	Using photographs	NA	NA
(Barootchi et al., 2019)	USA, University, No	CAF+CTG CAF+CTG CAF	20, 55	6	8.9 ± 1.3 8.4 ± 1.5 8.25 ± 1.7	Clinical	VAS	VAS
(Cairo et al., 2012)	Italy, University, No	CAF CAF+CTG	29, 29	6	6.7 ± 1.5 7.6 ± 1.7	Clinical	VAS	VAS
(Cairo et al., 2015)	Italy, University, No	CAF CAF+CTG	24, 24	36	7.5 ± 1.8 8 ± 1.5	Clinical	VAS	VAS
(Cairo et al., 2016a)	Italy, University, No	CAF CAF+CTG	32, 74	6, 12	7.9 ± 1.4 7.9 ± 1.4	Clinical	VAS	VAS
(Cairo et al., 2020)	Italy, University, No	CAF CAF+CTG	30, 30	6	7.9 ± 4.6 8 ± 4.8	Clinical	VAS	VAS
(Fernandes-Dias et al., 2015)	Brazil, University, No	CAF+CTG	20, 20	6	7.85 ± 0.95	Using photographs	NA	VAS
(Jhaveri et al., 2010)	India, University, No	CAF+ADM+F CAF+CTG	10, 20	6	8.1 ± 2.33 7.9 ± 2.28	Clinical	NA	NA
(Kuka et al., 2018)	Turkey, University, No	CAF CAF+PRF	24, 52	12	7 ± 0 7.8 ± 1.32	Using photographs	Three-point rating scale‡	NA
(Milinkovic et al., 2015)	Serbia, University, No	CAF+CTG CAF+XCM+F	18, 36	12	8.61 ± 1.28 8.67 ± 1.41	Clinical	NA	NA
(Ozcelik et al., 2011)	Turkey, University, No	CAF CAF	41, 155	6	7.43 ± 1.56 8.65 ± 1.47	Clinical	VAS	VAS
(Ozenci et al., 2015)	Turkey, University, No	TUN+ADM CAF+ADM	20, 58	12	7.3 ± 1.25 8.9 ± 1.6	Clinical	Three-point rating scale‡	NA
(Pelekos et al., 2019)	Italy, Private practice/University, Yes	CAF+CTG CAF+XCM	155, 393	6	7.9 ± 2.4 6.4 ± 3.7	Using photographs	NA	VAS (retrieved from: Tonetti et al., 2018)
(Pietruska et al.,	Poland,	TUN+CTG	29, 91	12	8.36 ± 1.78	Using	NA	NA

2019)	University, Yes	TUN+XCM			7.11 ± 1.95	photographs		
(Roman et al., 2013)	Romania, University, No	CAF+CTG CAF+CTG+EMD	42, 57	12	9 ± 1.09 8.58 ± 1.54	Clinical	VAS	NA
(Sangiorgio et al., 2017)	Brazil, University, No	CAF CAF+XCM CAF+EMD	68, 68	6	7.71 ± 2.02 8.29 ± 2.54 7.82 ± 3	Clinical	VAS (retrieved from: Rocha Dos Santos et al., 2017)	VAS (retrieved from: Rocha Dos Santos et al., 2017)
(Santamaria et al., 2017a)	Brazil, University, No	CTG	20, 20	6, 12, 24	7.85 ± 0.95 8.83 ± 0.85 8.68 ± 0.97	Using photographs	NA	NA
(Santamaria et al., 2017b)	Brazil, University, No	CAF+CTG TUN+CTG	42, 42	6	8.4 ± 1.5 7.8 ± 1.9	Clinical	NA	VAS
(Neves et al., 2019)	Brazil, University, No	CAF+CTG TUN+CTG	39, 39	12	8.3 ± 1.5 7.5 ± 1.8	Clinical	NA	NA
				24	8.7 ± 1.2 8.4 ± 1.6			
(Stefanini et al., 2016)	Italy, Spain, Germany	CAF CAF+XCM	41, 82	12	7.34 ± 2.9 7.85 ± 2.42	Using photographs	VAS (retrieved from: Jepsen et al. 2013)	VAS (retrieved from: Jepsen et al. 2013)
(Tavelli et al., 2019c)	USA, University, No	CAF+ADM TUN+ADM	24, 84	6	8.01 ± 1.23 8.12 ± 1.9	Clinical	VAS	VAS
(Zuhr et al., 2014)	Germany, Private practice, No	CAF+EMD TUN+CTG	24, 47	6, 12	6.92 ± 2.32 9.06 ± 0.83	Using photographs	VAS	VAS

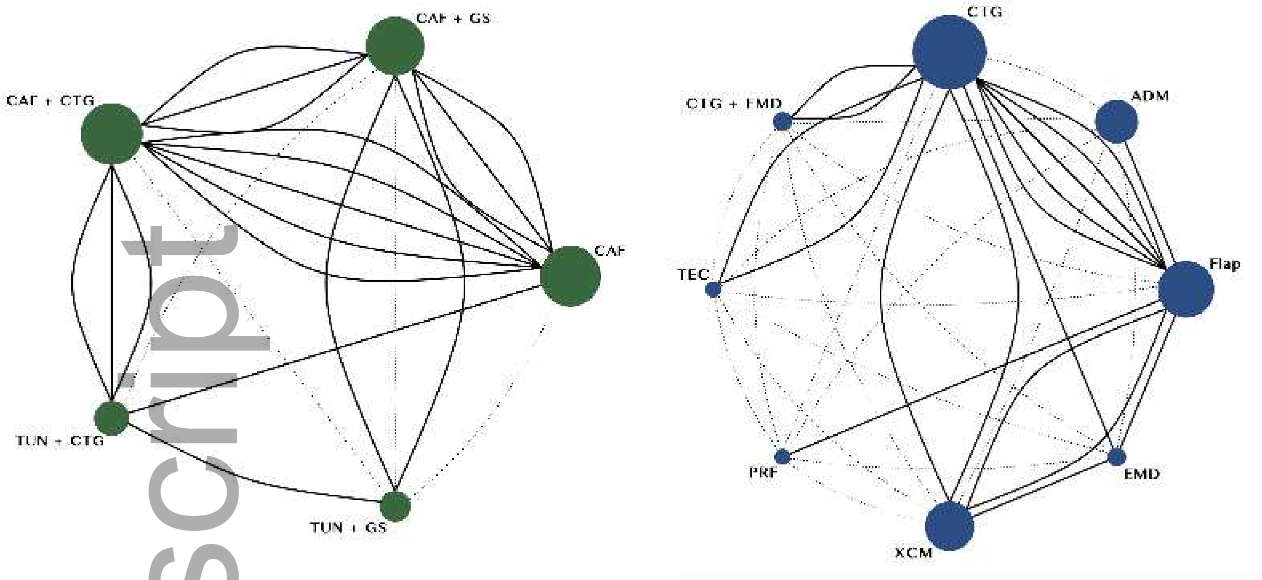
Legend. ADM: Acellular dermal matrix. CAF: coronally advanced flap. CTG: connective tissue graft. EMD: enamel matrix derivative. F: cultured fibroblasts. NA: Not available PRF: platelet-rich fibrin. TUN: tunnel technique. XCM: xenogeneic cellular matrix.

* Note that only those study arms which were included in the network model and the analyses are presented in this table.

‡ Not included in the analysis



jcpe_13346_f1.tif



jcpe_13346_f2.tif

RES (95% CI) | Treatment arm

CAF				
0.78** (0.3, 1.26)	**CAF + CTG**			
0.53* (0.006, 1.09)	-0.24 (-0.77, 0.27)	**CAF + GS**		
0.82* (0.18, 1.45)[i]	0.03 (-0.56, 0.63)	0.28 (-0.39, 0.95)[i]	**TUN + CTG**	
-0.21 (-0.96, 0.54)[i]	-0.99* (-1.74, -0.24)[i]	-0.74* (-1.46, -0.02)	-1.03* (-1.88, -0.17)	**TUN + GS**

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RES (95% CI) | Treatment arm

ADM								
-0.17 (-0.78, 0.43)[I]	CTG							
0.06 (-0.94, 1.08)[I]	0.24 (-0.63, 1.11)[I]	CTG + EMD						
-1.44* (-2.52, -0.36)[I]	-1.27* (-2.22, -0.31)[I]	-1.51* (-2.77, -0.24)[I]	EMD					
-0.88** (-1.52, -0.24)	-0.71** (-1.12, -0.29)	-0.95* (-1.87, -0.02)[I]	0.56 (-0.42, 1.54)	Flap				
-0.53 (-1.83, 0.76)[I]	-0.36 (-1.57, 0.84)[I]	-0.60 (-2.05, 0.85)[I]	0.91 (-0.59, 2.41)[I]	0.34 (-0.84, 1.54)	PRF			
-0.08 (-1.11, 1.01)[I]	0.08 (-0.91, 1.07)	-0.15 (-1.43, 1.12)[I]	1.35* (0.02, 2.69)[I]	0.79 (-0.22, 1.81)[I]	0.44 (-1.07, 1.96)[I]	TEC		
-1.31** (-2.01, -0.61)[I]	-1.13** (-1.60, -0.66)[I]	-1.37** (-2.32, -0.42)[I]	0.13 (-0.86, 1.14)[I]	-0.42 (-0.97, 0.12)	-0.77 (-2.03, 0.48)[I]	-1.22* (-2.26, -0.17)[I]	XCM	

jcpe_13346_f4.tiff