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Autologous connective tissue graft or xenogenic collagen matrix with coronally advanced flaps for coverage of multiple adjacent gingival recession. 36-month follow-up of a randomized multicentre trial

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Abstract

Aim: To report the 36-month follow-up of a trial comparing the adjunct of a xenogenic collagen matrix (CMX) or connective tissue graft (CTG) to coronally advanced flaps (CAF) for coverage of multiple adjacent recessions.

Material and methods: 125 subjects (61 CMX) with 307 recessions in 8 centres from the parent trial were followed-up for 36 months. Primary outcome was change in position of the gingival margin. Multilevel analysis used centre, subject and tooth as levels and baseline parameters as covariates.

Results: No differences were observed between the randomized and the follow-up population. Average baseline recession was 2.6 ± 1.0 mm. 3-year root coverage was 1.5 ± 1.5 mm for CMX and 2.0 ± 1.0 mm for CTG (difference of 0.32 mm, 95% CI from −0.02 to 0.65 mm). The upper limit of the confidence interval was over the non-inferiority margin of 0.25 mm. No treatment differences in position of the gingival margin were observed between 6- and 36-month follow-up (difference 0.06 mm, 95% CI −0.17 to 0.29 mm).

Conclusion: CMX was not non-inferior with respect to CTG in multiple adjacent recessions. No differences in stability of root coverage were observed between groups and in changes from 6 to 36 months. Previously reported shorter time to recovery, lower morbidity and more natural appearance of tissue texture and contour observed for CMX in this trial are also relevant in clinical decision-making.

KEYWORDS
collagen matrix, coronally advanced flap, gingival recession, human, randomized controlled clinical trial, root coverage

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Clinical Relevance

Scientific rationale for the study: Stability of root coverage outcomes is critical to decision-making. CTG is considered to be the standard to obtain stability of outcomes. Little is known about multiple recession sites.

Principal findings: The results of this trial indicated that CMX was not non-inferior to CTG at 36 months. No differences between test and control, however, were observed in terms of stability of outcomes between 6 and 36 months. In this trial, the benefit of CTG was due mostly to improved early outcomes.

Practical implications: The clinical indications for the use of first-generation CMX are primarily as follows: (i) cases with contraindication to autologous CTG harvesting from the palate and (ii) cases where the patient and clinician are seeking to limit morbidity, shorten surgery and time to recovery, obtain a more natural tissue texture and contour but are willing to accept a higher chance of a less than optimal outcome in terms of root coverage.

1 | INTRODUCTION

Stability of outcome after gingival recession coverage procedures is a key component in clinical decision-making. Recent systematic reviews have highlighted the predictability of root coverage for single tooth recession (Cairo et al., 2014; Chambrone et al., 2019) and the emerging evidence pointing to effective coverage of multiple adjacent recessions (Graziani et al., 2014; Chambrone et al., 2019). The short-term benefits, however, need to be substantiated by robust prospective medium- to long-term evaluations. While several reports have described long-term outcomes, many of these studies are retrospective. A recent systematic review has addressed the differential outcomes in terms of stability of position of the gingival margin after different types of root coverage procedures in single-rooted teeth (Dai et al., 2019). The results point to greater stability, defined as lack of significant difference between early- and medium-term results, for procedures involving an increase in thickness of the gingiva, such as those associated with the placement of autologous connective tissue grafts (CTG) compared with coronal displacement of the flap alone. Such understanding, which has long been an important component in clinical practice, has led to greater emphasis on marginal tissue thickness and not only on the position of the gingival margin as a component of success of root coverage procedures. A recent network meta-analysis has shown an association between post-operative gingival thickness, obtained with different biomaterials or grafts, and root coverage outcomes and their stability over time (Tavelli et al., 2019; Barootchi et al., 2020).

In recent years, a lot of emphasis has been placed on biomaterials and biological agents to enhance root coverage outcomes and avoid autologous tissue grafting from the palate. Among them, collagen matrices (CMX) have been extensively investigated.

Preclinical studies have indicated that the collagen matrix is replaced with the subject own connective tissue with the desired histologic and functional characteristics (Thoma et al., 2012) and leads to an augmentation in both the width and the thickness of the band of keratinized tissue (Thoma et al., 2010; Thoma et al., 2011; Vignoletti et al., 2011).

An initial study on isolated recession indicated that combining CMX with a coronally advanced flap (CAF) led to good clinical outcomes that compared favourably with those obtained with the use of autologous connective tissue grafts (McGuire & Scheyer, 2010).

The clinical performance of CMX in a multicentre trial on single tooth recessions (Jepsen et al., 2013) seems to enhance healing outcomes of coronally advanced flaps and accumulating evidence points to benefits in medium-term root coverage outcomes (Jepsen et al., 2017). A possible mechanism for the medium-term benefit of CMX may be the observed increase in tissue thickness when added to coronally advanced flaps in single tooth recessions (Stefanini et al., 2016). No additional benefit, however, has been observed adding CMX to CAF in multiple adjacent recessions (Rotundo et al., 2019).

Results of a non-inferiority trial comparing CMX with autologous grafting from the palate in multiple adjacent recessions indicated that subjects treated with CMX had a quicker recovery after surgery, but the trial failed to demonstrate non-inferiority of CMX with respect to CTG (Tonetti et al., 2018). A follow-up analysis focussing on professional assessment of aesthetic outcomes at 6 months showed that CTG gave better results for the root coverage component of the root coverage aesthetic score while CMX was better for marginal tissue contour and tissue texture (Pelekos et al., 2019).

The aim of this 3-year follow-up study was to compare the root coverage outcomes of CTG and CMX and assess their stability between 6 and 36 months.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This study reports root coverage outcomes at the 36-month follow-up of a non-inferiority, randomized, controlled, parallel arm, standard of care-controlled, assessor-blind, multicentre, multinational and practice-based trial (clincialtrial.gov registration NCT01440426). Ethical approval was obtained by the Freiburg Ethics Committee International (FEKI code 011/1546 and 015/832) and by the competent local authority

for each centre. Subjects provided informed consent, and the study was performed according to the Declaration of Helsinki on experimentation involving human subjects. Details of the inclusion and exclusion criteria, randomization and allocation concealment have been previously reported (Tonetti et al., 2018). In brief, subjects with the presence of a minimum of two adjacent recessions of the gingival margin requiring surgical correction, no prior experience of root coverage surgery, ability to achieve and maintain good oral hygiene and control gingivitis in the whole of the dentition (FMPS <25% and FMBS <25%) were invited to participate. Subjects presenting with (i) untreated periodontitis, (ii) persistence of uncorrected gingival trauma from tooth brushing, (iii) Interdental attachment loss greater than 1 mm or furcation involvement in the teeth to be treated, (iv) Presence of severe tooth malposition, rotation or clinically significant super-eruption, (v) self-reported current smoking exceeding 20 cigarettes/day or pipe or cigar smoking and (vi) rheumatoid arthritis or known sensitization to collagen-based medical products, and/or presence of medical contraindications to elective surgery were excluded. Indications for surgical intervention and required prior therapy have been described in the parent trial. Eight of the original 13 study centres participated in this medium-term follow-up. Methods to control study bias have been described in the original report. To ensure consistency over time in measurements, examiners performed calibration exercises in the clinical measurement of the primary outcome (position of the gingival margin with regards to the cement–enamel junction and the incisal edge of the tooth) and had to achieve an intra-examiner re-producibility >98% within 1 mm (Cairo et al., 2016).

2.2 | Interventions

Surgical interventions, study devices and methods have been described in detail (Tonetti et al., 2018). In brief, both groups received coronally advanced flaps with either autologous connective tissue graft (standard of care control) or a xenogenic collagen matrix (CMX, Geistlich Mucograft®, Geistlich Pharma AG). Based on the local anatomy and the location and distribution of the recessions, coronally advanced flaps included either rotated papillae flap or trapezoidal flap designs with or without vertical releasing incisions (Zucchelli & De Sanctis, 2000; Cortellini et al., 2009; Cairo et al., 2016). The randomization envelope was opened after completion of the preparation of the recipient bed of the graft. Grafts and dried CMX were positioned and sutured 1 mm apical to the cement–enamel junction with 6–0 braided resorbable polylactic sutures. Flaps were sutured with interrupted (Seralene, Serag and Wiessner, Germany) and/or sling (e-PTFE, W.L. Gore) 6–0 and 7–0 monofilament sutures attempting to fully cover both CTG and CMX. Post-operative procedures and instructions have been previously described in detail (Tonetti et al., 2018).

2.3 | Clinical measures

The position of the gingival margin was measured to the nearest mm with a UNC15 periodontal probe (PCP-UNC 15, Hu-Friedy) using both the incisal edge and the natural or composite filling reconstructed cement–enamel junction (CEJ) as the reference point. Outcomes were assessed using changes in recession from the incisal edge as the reference; recessions were characterized using the CEJ as the reference. Depth of the gingival sulcus (PD) and width of the keratinized tissue (KT) were assessed clinically with a UNC15 probe. The location of the mucogingival junction was assessed with the visual and functional method and supplemented by the histochemical method in areas of unclear demarcation (Guglielmoni et al., 2001). Oral hygiene levels were assessed with the plaque control record (O'Leary et al., 1972), while gingival inflammation was assessed as percentage of sites with bleeding on probing (Tonetti et al., 1993).

2.4 | Sample size

The detailed sample size calculation to detect a 0.25 mm non-inferiority margin in recession reduction with CMX has been reported in the 6-month trial. The size of this 36-month follow-up was limited to 8 centre who were available for the medium-term follow-up.

2.5 | Statistical analysis

Data were entered into a database and proofed for entry errors. Descriptive statistics were summarized as means and standard deviations for quantitative data and frequencies and percentages for qualitative data. Multilevel analyses were performed with the treatment (CMX versus CTG) as explicative variable. For the site outcome variables (for example root coverage), the three levels of the models were centre, patient and tooth. Baseline values were used as a covariate. For complete root coverage, a three-level logistical model was tested using CEJ-GM at baseline as a covariate. The intra-class correlation coefficients were calculated to estimate the variability among centres and the variability between measurements using the incisal edge and the CEJ as reference points to detect changes in position of the gingival margin. Estimates for the treatment effect, standard errors and 95% confidence intervals were provided. The statistical software was MLwiN 2.21 (Centre for Multilevel Modelling, University of Bristol, UK), Stata 14 and JMP 13.0.0 (SAS Institute Inc.).

3 | RESULTS

3.1 | Study population and external validity

The CONSORT patient accountability diagram is displayed in Figure 1. 187 subjects with recession at 485 teeth were randomized and received the allocated intervention in 13 centres. 8 centres were available to participate into the 36-month follow-up. These had recruited 125 patients (64 allocated to CTG) for a total of 307 recessions (158 CTG). All subjects completed the 6-month follow-up. Over the

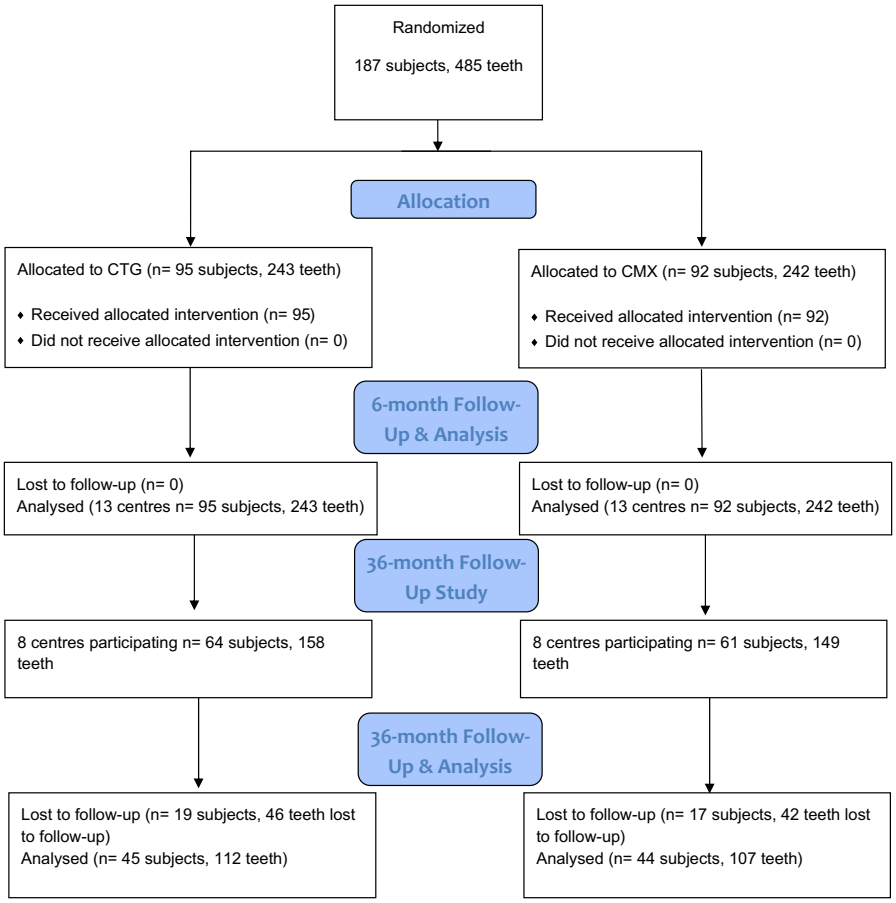

FIGURE 1 CONSORT patient accountability diagram

TABLE 1 Study population

	CTG *N* = 64	CMX *N* = 61
Age (years)	39.1 ± 10.5	41.2 ± 10.0
Females	37 (58%)	37 (61%)
Smokers	12 (19%)	13 (21%)
Baseline OHIP14 values	9.0 ± 6.2	9.1 ± 6.5
Full Mouth Plaque Scores	13.3 ± 7.8	13.2 ± 7.6
Full Mouth Bleeding Score	7.6 ± 7.4	6.2 ± 5.6
Dentine sensitivity Air Test positive	43 (67%)	40 (66%)
Dentine sensitivity Yeaple Test positive	23 (36%)	31 (51%)

Note: Patient-level baseline characteristics (mean ± SD or frequency and percentage). Means ± SD.

Abbreviations: FMBS, full mouth bleeding score; FMPS, Full mouth plaque score.

TABLE 2 Location of treated teeth

Tooth type	CTG *N* = 158	CMX *N* = 149
Maxillary incisors	21 (13)	29 (19)
Maxillary canines	39 (25)	41 (28)
Maxillary pre-molars	58 (37)	44 (30)
Maxillary molars	11 (7)	4 (3)
Mandibular incisors	9 (6)	5 (3)
Mandibular canines	8 (5)	8 (5)
Mandibular pre-molars	12 (8)	17 (11)
Mandibular molars	0 (0)	1 (1)

Note: Frequency (percentage).

36 months, 19 patients allocated to CTG and 17 allocated to CMX were lost to follow-up due to lack of availability for the examination, relocation to distant areas or inability of the study team to contact them. No subject was lost due to known study-related reasons. Subjects gave initial consent for the 6-month trial and were later asked to consent to an extension to 36-month, this may have contributed to the loss of some subjects. At 36 months, 45 subjects in the CTG group (70%, 112 teeth) and 44 subjects in the CMX group (72%, 107 teeth) were available for follow-up. The patient characteristics, the position of the treated teeth and the local condition at teeth with recession that were included are shown in Tables 1–3, respectively. No differences were observed comparing the parent population (6-month trial) and the current population (data not shown).

3.2 | Root coverage and sensitivity at 36 months

Table 4 shows the adjusted comparisons in root coverage outcomes at 36 months between test and control arising from the multilevel

TABLE 3 Baseline characteristics of teeth with recessions

Variable	CTG *N* = 158	CMX *N* = 149
Distance from CEJ-GM (gingival margin) mm	2.6 ± 1.0	2.6 ± 1.0
Distance from incisal edge to-GM mm	11.8 ± 1.6	12.2 ± 1.9
Probing depth mm	1.4 ± 0.5	1.4 ± 0.6
Width of keratinized tissue mm	2.8 ± 1.3	2.6 ± 1.2
Max inter-dental clinical attachment loss mm	0.2 ± 0.4	0.3 ± 0.6
Presence of inter-dental clinical attachment loss	29 (18%)	32 (21%)
Local plaque score	0 (0%)	3 (2%)
Local bleeding on probing	0 (0%)	0 (0%)
Cervical filling	0 (0%)	15 (10%)
Cervical filling removed, if present	0 (0%)	11 (73%)
Cervical caries	2 (1%)	0 (0%)
Cervical caries treated, if caries present	2 (100%)	0 (0%)
Cervical caries filled, if caries present	2 (100%)	0 (0%)
Presence of CEJ abrasion	66 (42%)	63 (42%)
CEJ abrasion re-constructed with adhesive re-construction, if present	56 (85%)	50 (79%)

Note: Means ±SD or frequency (percentage).

models. The main non-inferiority analysis indicates that CMX fails to reach the stipulated margin of 0.25 mm with respect to CTG. A post hoc superiority interpretation of the data was also done due to the loss of power resulting from the reduced sample size. In this context, CTG would have resulted in significantly greater estimated changes in positions of the gingival margin with respect to the incisal edge of the tooth (0.56 more coronal than CTX, 95% CI 0.25–0.88 mm, $p < .001$) and bigger increases in KT width (0.56 mm more than CTX, 95% CI 0.23–0.89 mm, $p < .001$). No significant differences were observed comparing test and control treatments in terms of changes in the position of the gingival margin with respect of the CEJ ($p = .067$, NS) or changes in PD ($p = .084$, NS). No difference in odds ratios of complete root coverage at 36 months was observed ($p = .061$).

The different results obtained using the incisal edge of the tooth or the CEJ (Table 4) was further explored. Firstly, the results of the model using the CEJ as the reference were confirmed with a sensitivity analysis using a multiple imputation method for missing values that assigned 20 different values for every missing observation. The results confirmed those of the main analysis (0.31 mm in favour of CTG, with a 95% CI of −0.01 to 0.62, superiority $p = .055$). With both the main and the sensitivity analysis, the non-inferiority hypothesis cannot be rejected and the superiority of CTG over CMX cannot be excluded. Secondly, the intra-class correlation between the results obtained with the incisal edge and the CEJ as references for determining changes in the position of the gingival margin were calculated as follows: 0.73 (95% CI 0.64 to 0.77).

No differences in the frequency of dentine sensitivity were observed among groups (Table 5).

3.3 | Stability of root coverage between 6 and 36 months

Table 6 shows the tooth-based differences in root coverage parameters between 6 and 36 months. This analysis was based on the 89 subjects available for both the 6-month and 36-month follow-up. No differences were observed between the ITT and this population both in terms of baseline characteristics and oral hygiene and gingival inflammation parameters (data not shown). An increase in recession was observed for both groups. A multilevel model comparing test and control treatments showed 0.06 mm (95% CI −0.17 to 0.29 mm, superiority $p = .63$) greater recession in the CMX group.

TABLE 4 A36-month clinical outcomes

Variable	CTG *N* = 112	CMX *N* = 107	Estimated difference (Odds ratio*)	95% CI
Changes in CEJ-GM (mm)	2.0 ± 1.0	1.5 ± 1.5	0.32	−0.02; 0.65
Changes in IE-GM (mm)	1.8 ± 1.3	1.5 ± 1.3	0.56	0.25; 0.88
Changes in PD (mm)	−0.3 ± 0.7	0.0 ± 0.8	−0.17	−0.37; 0.02
Changes in KT (mm)	0.5 ± 1.0	0.0 ± 1.2	0.56	0.23; 0.89
Complete root coverage *N* (%)	66 (59%)	47 (44%)	2.17*	0.96; 4.91

Note: Multilevel model: Centre, patient, tooth.

Multilevel model estimating clinical outcomes taking into account clustering of multiple teeth in a single patient (surgery) and patients within a specific study centre. Changes in CEJ-GM = changes in the distance from the cement–enamel junction to the gingival margin. Changes in IE-GM (mm) = changes in the distance between the incisal edge of the tooth and the gingival margin. They are estimates of root coverage. PD = probing depth, KT = width of keratinised tissue. Data are expressed as means (SD) in mm.

TABLE 5 Patient-based tooth sensitivity at 36 months

Variable	CTG *N* = 45	CMX *N* = 43	Odds Ratio	95% CI	*p*-value
Air Test (positive)	8 (18%)	10 (23%)	1.38	0.27; 5.13	.6308
Yeaple Test (positive)	6 (13%)	5 (12%)	0.92	0.42; 2.04	.8380

Note: Odds ratios are calculated using baseline sensitivity as a covariate.

TABLE 6 Stability of outcomes in the test and control groups between 6 and 36 months (tooth-based analysis)

Variables	CTG *N* = 112	CMX *N* = 107
Increase in recession from CEJ mm (SD)	0.2 ± 0.6	0.3 ± 0.9
Increase in recession from incisal edge mm (SD)	0.3 ± 0.7	0.2 ± 0.6
Difference in PPD mm	0.0 ± 0.6	−0.1 ± 0.6
Changes in inter-dental CAL mm	0.0 ± 0.2[a]	0.3 ± 1.2
Changes in KT mm	0.0 ± 0.7[a]	0.0 ± 0.8
CRC at 6 and 36 months (%)	63 (56)	44 (41)
CRC not 6 and not 36 months (%)	34 (30)	44 (41)
CRC 6 but not at 36 months (%)	12 (11)	16 (15)
CRC not 6 but yes at 36 months (%)	3 (3)	3 (3)

[a]N = 110, please see text for multilevel model reporting significance of treatment effect.

3.4 | Adverse events

Investigators reported no study-related adverse events during the follow-up period of the study indicating that both treatments were safe and well tolerated.

4 | DISCUSSION

The results of the present report together with the previous ones (Tonetti et al., 2018; Pelekos et al., 2019) of this trial show improved root coverage outcomes for both test and control treatments. Interpretation of the inter-group difference is affected by the loss of power arising from the fact that only 8 study centres were available for the 3-year follow-up. The original non-inferiority hypothesis, therefore, cannot be properly assessed; results, however, point to the fact that CMX was not non-inferior with respect to CTG. An exploratory superiority analysis showed divergent effects with respect to different root coverage parameters: At 36 months, the position of the gingival margin with respect to the incisal edge of the tooth was statistically significantly more coronal in the CTG group than in the CMX group. The size of the effect was just above the clinically significant difference stipulated for the definition of the non-inferiority margin of this study (0.5 mm). The results, however, were not confirmed with measurements that used the CEJ as the reference point to assess variation in the position of the gingival margin. This observation is potentially important. In this trial, reconstruction of the CEJ was performed at sites with cervical abrasion; it is possible that difficulties in recognition of a clearly demarcated CEJ within the composite filling might have led to uncertainty about this location and increased measurement errors in particular in cases with more exposure of the cervical reconstruction. Difficulties in the detection of the CEJ in root coverage procedures have been well recognized and may be even more significant at sites where composite reconstruction is performed (Cairo et al., 2020). This anticipated issue was the rationale for introduction of the incisal edge of the tooth (rather than only the CEJ) as the reference point for assessing changes in position of the gingival margin. The divergent results were further explored by assessing the intra-class correlation of measurements using the incisal margin or the CEJ as the reference point to assess changes in position of the gingival margin. This analysis revealed only moderate agreement between the two measurements (ICC 95% CI range of 0.64 to 0.77). More research is needed to improve accuracy of measurements of root coverage outcomes, in particular for trials incorporating re-construction of the CEJ.

Both test and control cases showed a degree of relapse between 6 and 36 months, but the inter-group difference was small and not significant. This observation raises interesting hypotheses. CTG is generally considered to be the gold standard for the combination of two advantages: (i) better early healing thanks to superior potential arising from improved vascularization and survival of soft tissues on the root surface and (ii) greater stability over time due to enhanced resistance to relapse due to increased tissue thickness (Tavelli et al., 2019). The observations from the parent trial at 6 months (Tonetti et al., 2018) are in broad agreement with the expected early benefits in root coverage outcomes of CTG in multiple recession. The lack of an intergroup difference between 6 and 36 months in terms of position of the gingival margin reported in this study may be interpreted as an indication that CMX and CTG might have similar effect on relapse. The low power of the present study, however, does not allow drawing of firm conclusions.

CTG was statistically significantly better than CMX in terms of increase in KT width, the clinical relevance, if any, of the observed 0.5 mm difference needs to be better understood. Indeed, in recent years, the interest in KT width in periodontal plastic surgery procedures has been questioned and greater attention has been drawn to thickness of the soft tissue margin, or periodontal phenotype (Jepsen et al., 2018; Barootchi et al., 2020). A limitation of the present study is the lack of measurement of tissue thickness and its variations over time.

Comparing outcomes of the present trial with previous studies shows somehow lower frequency of complete root coverage.

Interpretation of this finding needs to take into account at least 5 aspects: (i) the focus on multiple adjacent recessions; (ii) the inclusion of initial RT2 recessions in the population (interdental CAL of 1 mm accepted); (iii) the inclusion of areas with non-carious cervical lesions, cervical fillings and caries; (iv) the re-storative approach to the management of the CEJ defects; and (v) the stringent multicentre design.

The present observations, together with the results of the parent trial (Tonetti et al., 2018), assist in clinical decision-making for multiple recession coverage (Tonetti et al., 2014). They confirm that application of CTG combined with a specifically designed CAF is probably the best approach for root coverage at multiple adjacent recessions (Tonetti et al., 2018). Use of a CMX, and avoidance of a CTG donor site, results in shorter time to recovery, less post-operative morbidity (Tonetti et al., 2018) and more natural tissue texture and contour (Pelekos et al., 2019). CTG or CMX results in similar stability of outcomes between 6 and 36 months. Care must also be exerted when using CMX or collagen-based products in subjects with auto-immune diseases such as rheumatoid arthritis or known sensitization to collagen-based medical products. At this point, however, a full cost-benefit assessment cannot be done as the relative weights of clinically assessed root coverage, aesthetic scores, decreased morbidity, faster recovery, surgery duration and monetary cost of the CMX device remain unclear. More research is necessary in this area.

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CONFLICT OF INTEREST

Authors report no conflict of interest related to this study.

AUTHOR CONTRIBUTIONS

MT and PC conceived the study, wrote the protocol, supervised quality control, analysed and interpreted the data and wrote the manuscript. KD and DB assisted in data collection and analysis and monitored the quality of the data. FC, MA, GC, FG, AG, JH, JM, GR, HT contributed to final study design, were the centre PIs and surgeons, commented and approved manuscript.

DATA AVAILABILITY STATEMENT

Data for this study are not available.

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