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REVIEW ARTICLE

Clinical efficacy of xenogeneic collagen matrix in the treatment of gingival recession: a systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this systematic review (SR) was to evaluate the effects of xenogenic collagen matrix (XCM) on the outcomes of clinical treatments of patients with Miller class-I or -II gingival recessions.

Materials and methods: Articles that were published before March 2018 were electronically searched in four databases without any date or language restrictions and manually searched in regular journals and gray literature. The eligibility criteria comprised randomized controlled trials (RCTs) and prospective controlled trials with follow-up periods of 6 months or more that compared the performance of XCM in the treatment of Miller class-I or -II gingival recessions. This SR was registered in PROSPERO under number CRD42018106118.

Results: Nine RCTs published between 2010 and 2018 were included in this SR. The percentage of root coverage (RC) was significantly higher ($p = .0003$) when gingival recessions were treated with XCM when compared to coronally advanced flap (CAF) alone. In addition, the parameters of keratinized mucosa width (KMW) ($p = .006$) and gingival thickness (GT) ($p = .0003$) were also improved when the XCM was used in comparison to the CAF alone. There was not a statistically significant difference ($p = .22$) between the clinical attachment level (CAL) achieved with the use of XCM and that achieved with CAF alone. RC with the use of XCM, when compared to connective tissue grafts (CTGs) ($p = .09$) and enamel matrix derivative (EMD) ($p = .62$), there was no significant difference; however, XCM yielded lower RC than CTG in the treatment of Miller class-I or -II gingival recessions.

Conclusions: Based on both the individual studies' outcomes and the pooled estimates, it can be concluded that the use of XCM improves the RC, KMW and GT in the treatment of gingival recessions when compared to CAF alone and may be a viable alternative to use of CTG.

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KEYWORDS
Gingival recession; xenogenic collagen matrix; periodontal plastic surgery; graft

Introduction

The literature presents different treatment approaches to increase the soft tissue volume in gingival recessions [1]. For many years, the use of connective tissue graft (CTG) associated with coronally advanced flap (CAF) was considered the gold standard for root coverage (RC) in Miller gingival recessions, improving parameters such as clinical attachment level (CAL), keratinized tissue gain, pocket reduction, and tissue colour and texture [2–4].

However, in instances where the roots of multiple adjacent recessions need to be covered, gingival recessions around implants, or anatomical limitations at the donor site, the collection of CTG carries additional burdens for the patient [5]. The postoperative morbidity associated with soft tissue harvest from the palate, the difficult-to-control bleeding at some cases, second operating fields, pain, and the limited availability of donor areas for autogenous CTG collection justify the application of an adjuvant technique [3,6]. To overcome the issues associated with autogenous grafting, a series of techniques and biomaterials of allogenic and xenogeneic origin were investigated in clinical studies. These techniques and materials were found to improve the width of keratinized tissue [7,8], helping to avoid donor site morbidities, and to have a potential to increase healing rates when compared to autologous tissues.

Recently, an randomized controlled trial (RCT) proposed that an xenogenic collagen matrix (XCM) might be as effective and predictable as a free gingival graft around teeth recessions, replacing the connective tissue from the palate [1,4] and increasing the thickness of peri-implant keratinized tissue [9,10]. This 3D-matrix consists of resorbable pure type I and type III collagen obtained by a controlled-standardized manufacturing procedure without chemical treatment [11]. It has two functional layers, one that is more compact and allows for suturing and protection, and one that is porous, which stabilizes the clot, promoting cell ingrowth and accelerating soft tissue healing [12].

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So far, the use of the XCM presents favourable outcomes in tissue integration. Surgery requires less time than a free gingival graft. The texture and colour of the soft tissue in the regenerated regions are aesthetically satisfying [11], and the tissue has sufficient long-term stability [7] to be considered suitable for the regeneration of the peri-implant keratinized mucosa.

In this context, the aim of this systematic review (SR) was to evaluate the effects of XCM on the outcomes of clinical treatments of patients with gingival recession.

Materials and methods

Protocol registration

The protocol of this SR was based primarily on the PRISMA-P [13], and was registered in PROSPERO under number CRD42018106118. There was no deviation from the originally specified protocol. This SR methodology followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [14]. The PRISMA [15] checklist was followed in order to increase the quality and transparency of the study. Clinical questionnaires were separated and organized using the PICOS strategy [16].

Clinical significance: The use of substitute grafting materials aiming to avoid donor site morbidities, provides comfort, and improves patient acceptance.

Focused question (based on PICO strategy)

What are the clinical effects of XCM (I) on the treatment of single or multiple Miller class I or II gingival recessions (P) when compared to other techniques for root coverage (C) for the outcomes: RC, CAL, KMW, probing depth, GT, and participants' aesthetic satisfaction (O)?

Search strategy

An electronic search without date or language restrictions was performed in PubMed/MEDLINE, Cochrane Library (CENTRAL), Scopus and Lilacs until August 2018. As well, searches were performed on the following journals' websites: *Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research, The International Journal of Periodontics and Restorative Dentistry,* and *Clinical Oral Investigations.* A search of the Grey Literature Report [17] and OpenGrey databases [18] revealed unpublished studies (grey literature). Finally, the reference lists/bibliographies of all candidate full-text articles (cross-referencing) and the ClinicalTrials.gov database were searched. The search strategy for each database can be followed in Table 1.

Eligibility criteria

The present SR included studies that analysed the effect of XCM on the outcomes of the clinical treatments of single or multiple Miller class I or II gingival recessions.

Population: Adults presenting single or multiple Miller class I or II gingival recessions.

Intervention: Treatment of single or multiple Miller class I or II gingival recessions through periodontal plastic surgery involving the use of XCM, with at least 6 months of follow-up.

Table 1. Electronic databases and search strategies.

Databases	Keywords
PubMed	#1 gingival recession[MeSH Terms] OR gingival recessions[MeSH Terms] OR marginal tissue recession[Title/Abstract] OR dehiscence-type recession defects[Title/Abstract] OR keratinized gingiva[Title/Abstract] OR keratinized mucosa width[Title/Abstract] OR gingival thickness[Title/Abstract] OR gingival biotype[Title/Abstract] OR periodontal biotype[Title/Abstract] OR periodontal attachment loss[MeSH Terms] OR Miller class I[Title/Abstract] OR Miller class II[Title/Abstract] AND root coverage[Title/Abstract] OR coronally advanced flap[Title/Abstract] OR Coronally advanced tunnel[Title/Abstract] OR periodontal plastic surgery [Title/Abstract] OR periodontal surgery[Title/Abstract] OR mucogingival surgery[Title/Abstract] OR mucogingival[Title/Abstract] OR mucogingival therapy[Title/Abstract] OR xenogeneic collagen matrix[Title/Abstract] OR collagen matrix[Title/Abstract] OR collagen graft[Title/Abstract] OR porcine collagen matrix[Title/Abstract] OR Mucograft[Title/Abstract] OR Mucoderm[Title/Abstract] #1 AND #2
Scopus	#1 'gingival recession' OR 'gingival recessions' OR 'marginal tissue recession' OR 'dehiscence-type recession defects' OR 'keratinized gingiva' OR 'keratinized mucosa width' OR 'gingival thickness' OR 'gingival biotype' OR 'periodontal biotype' OR 'periodontal attachment loss' OR 'Miller class I' OR 'Miller class II' #2 'root coverage' OR 'coronally advanced flap' OR 'Coronally advanced tunnel' OR 'periodontal plastic surgery' OR 'periodontal surgery' OR 'mucogingival surgery' OR 'mucogingival' OR 'mucogingival therapy' OR 'xenogeneic collagen matrix' OR 'collagen matrix' OR 'collagen graft' OR 'porcine collagen matrix' OR 'Mucograft' OR 'Mucoderm' #1 AND #2
Cochrane Library (CENTRAL)	#1 gingival recession OR keratinized gingiva OR keratinized mucosa width OR gingival thickness OR gingival biotype OR Miller class I OR Miller class II #2 root coverage OR coronally advanced flap OR Coronally advanced tunnel OR periodontal plastic surgery OR mucogingival surgery OR xenogeneic collagen matrix OR porcine collagen matrix #1 AND #2
Lilacs	#1 Abstract: 'gingival recession' OR 'keratinized gingiva' OR 'keratinized mucosa width' OR 'gingival thickness' OR 'gingival biotype' OR 'Miller class I' OR 'Miller class II' #2 Abstract: 'root coverage' OR 'coronally advanced flap' OR 'Coronally advanced tunnel' OR 'periodontal plastic surgery' OR 'mucogingival surgery' OR 'xenogeneic collagen matrix' OR 'collagen matrix' OR 'porcine collagen matrix' #1 AND #2
Grey Literature Report OpenGrey	#1 gingival recession OR keratinized gingiva OR keratinized mucosa width OR gingival thickness OR gingival biotype OR Miller class I OR Miller class II #2 root coverage OR coronally advanced flap OR Coronally advanced tunnel OR periodontal plastic surgery OR mucogingival surgery OR xenogeneic collagen matrix OR porcine collagen matrix #1 AND #2

Comparison: Periodontal plastic surgery using XCM was compared to periodontal plastic surgery without biomaterial or with the use of different biomaterials.

Outcomes: The primary outcome variable was the change in percentage of RC. The secondary outcome variables were CAL, keratinized mucosa width (KMW), probing depth (PD), gingival thickness (GT) and participants' aesthetic satisfaction.

Study design: RCTs and prospective clinical trials.

The exclusion criteria included animal studies, retrospective cohort studies, *in vitro* studies, case series, case reports and reviews. In addition, studies of participants with decompensated metabolic disorders or active periodontal disease were excluded.

Screening process

The search and screening process were conducted by two independent reviewers (V.M. and D.A.), starting with an analysis of titles and abstracts. Next, full papers were selected for careful reading and analysed according to eligibility criteria (inclusion/exclusion) to determine their suitability for future data extraction. Disagreements between the reviewing authors were resolved through careful discussion. When necessary, the authors of the included studies were contacted by email for clarification.

Data extraction

Data were extracted by V.M. and D.A., who used a form to record the following: authors, study design, follow-up, number of treated recessions, number of participants, number of smokers, Miller class, site of recessions, surgical technique, brand of XMC used, mean difference (MD) in RC between baseline and final follow-up, CAL, KMW, PD and GT.

Assessments of the risk of bias

The assessments of the risks of bias of the clinical studies that were included were performed independently by two authors (M. D. C. M. and S.S.), who used the Cochrane Collaboration's tool [19]. The analysis of each study was based on the following six criteria: sequence generation (was the allocation sequence adequately generated?), allocation concealment (was the allocation adequately concealed?), blinding (was the knowledge of the allocated intervention adequately prevented during the study?), incomplete outcome data (were the incomplete outcome data adequately addressed?), selective outcome reporting (were the study reports free of suggestions of selective outcome reporting?) and other sources of bias (was the study apparently free of other problems that could put it at a high risk of bias?). The studies that met all of the criteria were classified as having a low risk of bias, while those that did not meet a criterion were classified as having moderate risk. When two or more criteria were not met, the studies were considered to have a high risk of bias.

Statistical analysis

For direct comparisons, only studies that had the same outcome with heterogeneous methodologies were included in the pairwise meta-analysis. For continuous outcomes, the estimation of intervention effects was expressed as MD, with a confidence interval (CI) of 95%. The inverse variance method was used for the random effect or fixed effect models. Heterogeneity was assessed using chi-squared tests, and possible impact on the meta-analysis was quantified via I^2. Values $\leq$25% were deemed less heterogeneous, while values up to 50% and $\geq$70% were classified as moderately and highly heterogeneous, respectively [20]. When significant heterogeneity was found ($p<$ .10), the results of the random effect model were validated. When less heterogeneity was found, the fixed effect model was considered. The statistical significance level was determined to be $p<$ .05.

Data were analysed using the Review Manager statistical software (version 5.2.8) produced by The Nordic Cochrane Centre and The Cochrane Collaboration (Copenhagen, Denmark, 2014).

Results

Literature search

The initial search produced 3396 titles from MEDLINE/PubMed, 1169 from the Cochrane Library, 1282 from the Scopus, and 52 from Lilacs, for a total of 5889. After the first evaluation (title and abstract assessment), 5882 articles were excluded. Of the 17 potential articles, eight studies [8, 21–27] were excluded after careful reading because they did not meet the inclusion criteria. Consequently, nine studies [4,6,27–33], which were published between 2010 and 2018, were included in this SR. The reasons for the exclusion of potential studies and the search and selection processes are presented in Figure 1.

The *k* values of agreement between the two authors/reviewers for potential article inclusion (titles and abstracts) and for the selected studies were 0.79 and 0.85, respectively, which indicated excellent agreement [14].

Study characteristics

The characteristics of the included studies are presented in Table 2. Four studies [4,27,30,33] present a split-mouth design, while five [6,28,29,31,32] have a parallel design. A total of 1113 gingival recessions were treated in 482 research participants. The follow-up periods ranged from 6 [6,30–32] to 12 [4,27–29,33] months (mean of 9.3 months). The surgical techniques used for the treatment of recessions were CAF [4,6,28–33] and coronally advanced tunnel (CAT) [27]. The control groups used for comparison with the CAF + XCM were CAF alone, CAF + CTG, and CAF + enamel matrix derivative (EMD).

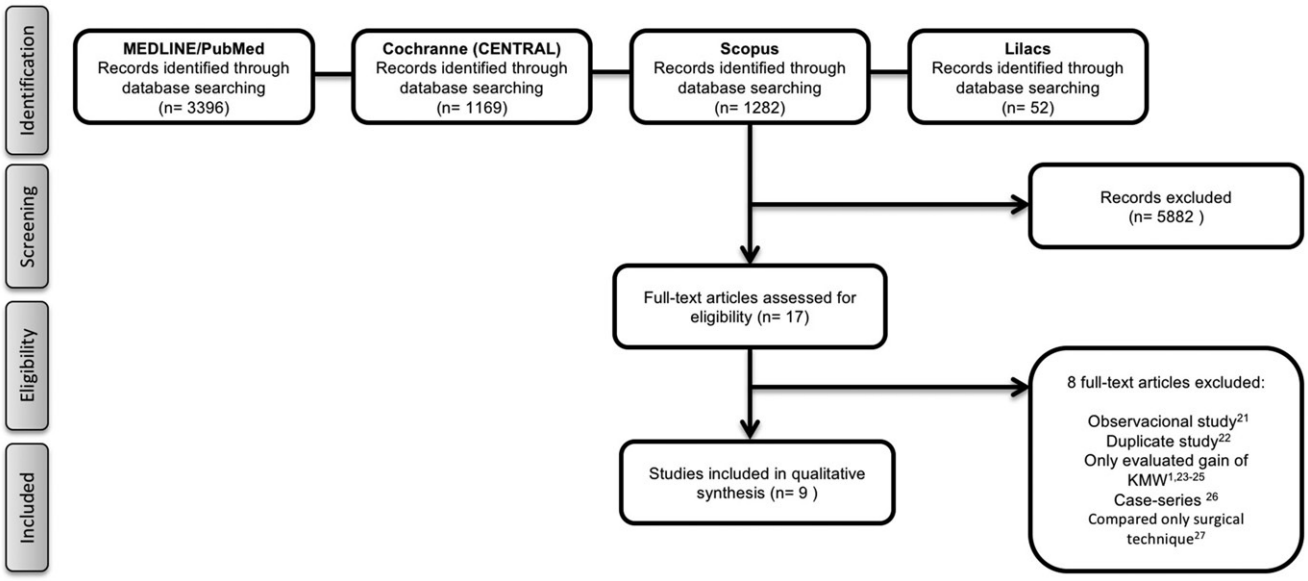

Figure 1. Flow diagram (PRISMA format) of the screening and selection process.

Findings based on previous focused questions

Only one study [27] cannot be included in the meta-analysis because it used a surgical technique (CAT) different from the other included studies. This study observed a lower rate of RC in the test group (CAT + XCM) (42%) when compared to the control group (CAT + CTG) (85%), $p < .05$. Other parameters, such as CAL, KMW, PD and GT, were also significantly ($p < .05$) higher in the control group.

Root coverage

The random effects model was used to evaluate the RC due to the high heterogeneity level of the subgroups ($p < .0001$; $I^2 = 79\%$). RC with the use of XCM differs significantly ($p = .003$) from that achieved with CAF alone, with an MD of 7.12 (95% CI: 2.35–11.8). However, when compared to CTG ($p = .09$) and EMD ($p = .62$), there was no significant difference, with an MD of –6.95 (95% CI: –14.9 to 1.07) and 2.80 (95% CI: –8.30 to 13.9), respectively (Figure 2).

Clinical attachment level

The random effects model was used to evaluate the CAL due to the high heterogeneity level of the analysed subgroups ($p = .010$; $I^2 = 60\%$). There was not a statistically significant difference between the CAL achieved with the use of XCM and that achieved with CAF alone ($p = .22$), CTG ($p = .19$) and EMD ($p = .95$), with an MD of 0.17 (95% CI: –0.10 to 0.45), –0.32 (95% CI: –0.78 to 0.15) and –0.02 (95% CI: –0.61 to 0.57), respectively (Figure 3).

Keratinized mucosa width

The fixed effect model was used to evaluate KMW because of the lack of heterogeneity among the studies ($p = .74$; $I^2 = 0\%$). Only the comparison between XCM and CAF showed a statistically significant difference in favour of XCM ($p = .006$), with an MD of 0.32 (95% CI: 0.09–0.55). The comparison of XCM and CTG ($p = .51$) and EMD ($p = .95$) showed no significant difference, with MDs of 0.07 (95% CI: –0.14 to 0.27) and –0.02 (95% CI: –0.61 to 0.57), respectively (Figure 4).

Probing Depth. The fixed effect model was used in the PD analysis because of the lack of heterogeneity among the studies ($p = .48$; $I^2 = 0\%$). The PD parameter showed no difference in the comparison between XCM and CAF ($p = .25$), CTG ($p = .66$), and EMD ($p = 1.00$). The MD for the comparison of XCM vs. CAF was –0.06 (95% CI: –0.16 to 0.04), XCM vs. CTG: 0.02 (95% CI: –0.07 to 0.11), and XCM vs. EMD: 0.00 (95% CI: –0.43 to 0.43) (Figure 5).

Gingival thickness

The random effect model was used for the GT analysis because of the high heterogeneity of the analysed subgroups ($p < .00001$; $I^2 = 90\%$). GT was considerably higher with XCM than CAF ($p = .003$), with an MD of 0.38 (95% CI: 0.13–0.63). On the other hand, there was no significant difference between XCM vs. CTG ($p = .18$) and XCM vs. EMD ($p = .07$), which had MDs of –0.23.95 (95% CI: –0.57 to 0.11) and 0.18 (95% CI: –0.02 to 0.38), respectively (Figure 6).

Participants' aesthetic satisfaction

Four studies [27,30–32] analysed participants' aesthetic satisfaction through the visual analogue scale (VAS). One study [27] performed a comparison between CAT + XCM vs. CAT + CTG, and the other three [30–32] performed comparisons between CAF + XCM vs. CAF alone. The meta-analysis can only be conducted for the three studies [30–32] that performed the same surgical technique (CAF). The fixed effect model was used because of the homogeneity of the studies ($p = .94$; $I^2 = 0\%$). There was not a considerable difference ($p = .10$) in the participants' aesthetic satisfaction with the techniques, with an MD of 0.19 (95% CI: –0.04 to 0.42) (Figure 7).

Table 2. Main characteristics of selected studies.

Author (year)	Study design	Follow-up period	No. of treated recessions/ no. of participants	Type of defects	Graft used (no.) Surgical technique	Site of recessions No. of smokers	Aesthetic satisfaction (VAS)
Aroca et al. 2013 [27]	RCT (split-mouth)	12 months	156/22	Miller class I/II	CAT + CTG (78) vs. CAT + XCM (78) CAT	Maxillary and mandibular 0	CAT + CTG: 9.06 ± 7.9 CAT + XMC: 9.29 ± 8.4
Cardaropoli et al. 2012 [28]	RCT (parallel)	12 months	22/18	Miller class I/II	CAF + CTG (11) vs. CAF + XCM (11) CAF	Maxillary and mandibular 0	NP
Cardarapoli et al. 2014 [29]	RCT (parallel)	12 months	112/32	Miller class I/II	CAF (54) vs. CAF + XCM (58) CAF	NR 0	NP
Jepsen et al. 2013 [30]	RCT (split-mouth)	6 months	90/45	Miller class I/II	CAF (45) vs. CAF + XCM (45) CAF	Maxillary and mandibular NR	CAF: 9.57 ± 0.63 CAF + XMC: 9.75 ± 0.49
McGuire et al. 2010 [4]	RCT (split-mouth)	12 months	50/25	Miller class I/II	CAF + CTG (25) vs. CAF + XCM (25) CAF	Maxillary and mandibular NR	NP
Moreira et al., 2016 [31]	RCT (parallel)	6 months	40/40	Miller class I/II	CAF (20) vs. CAF + XCM (20) CAF	Maxillary and mandibular NR	CAF: 9.35 ± 7.45 CAF + XMC: 9.4 ± 10.4
Sangiorgio et al. 2017 [32]	RCT (parallel)	6 months	68/68	Miller class I/II	CAF (17) vs. CAF + XCM (17) vs. CAF + EMD (17) vs. CAF + XCM + EMD (17) CAF	Maxillary NR	CAF: 8.29 ± 1.36 CAF + XMC: 8.65 ± 1.58
Stefanini et al. 2016 [33]	RCT (split-mouth)	12 months	90/45	Miller class I/II	CAF (45) vs. CAF + XCM (45) CAF	NR NR	NP
Tonetti et al. 2018 [6]	RCT (parallel)	6 months	485/187	Miller class I/II	CAF + CTG (243) vs. CAF + XCM (242) CAF	NR 31	NP

Author (year)	XMC used	Mean difference in RC between baseline and final follow-up (%)	Mean difference in CAL between baseline and final follow-up (mm)	Mean difference in KMW between baseline and final follow-up (mm)	Mean difference in PD between baseline and final follow-up (mm)	Mean difference in GT between baseline and final follow-up (mm)
Aroca et al., 2013 [27]	Mucograft	CAT + CTG: 90 ± 18 CAT + XMC: 71 ± 21	CTG: 1.3 ± 0.6 XMC: 1.7 ± 0.45	CTG: 0.7 ± 0.75 XMC: 0.3 ± 0.8	CTG: 0.0 ± 0.25 XMC: 0.0 ± 0.25	CTG: 0.5 ± 0.35 XMC: 0.2 ± 0.25
Cardaropoli et al., 2012 [28]	Mucograft	CAF + CTG: 96.9 ± 6.74 CAF + XMC: 94.3 ± 11.6	CAF + CTG: 2.95 ± 0.82 CAF + XMC: 2.41 ± 0.83	CAF + CTG: 1.27 ± 0.65 CAF + XMC: 1.23 ± 0.61	CAF + CTG: 0.23 ± 0.26 CAF + XMC: 0.27 ± 0.41	CAF + CTG: 1.23 ± 0.47 CAF + XMC: 1.00 ± 0.32
Cardarapoli et al., 2014 [29]	Mucograft	CAF: 81.4 ± 23.4 CAF + XMC: 93.2 ± 10	CAF: 1.88 ± 0.94 CAF + XMC: 2.23 ± 0.78	CAF: 0.7 ± 1.04 CAF + XMC: 1.07 ± 0.87	CAF: 0.03 ± 0.44 CAF + XMC: 0.06 ± 0.44	CAF: 0.13 ± 0.36 CAF + XMC: 0.97 ± 0.42
Jepsen et al., 2013 [30]	Mucograft	CAF: 72.6 ± 26.1 CAF + XMC: 75.2 ± 26.6	CAF: 2.47 ± 1.14 CAF + XMC: 2.67 ± 1.04	CAF: 0.51 ± 1.23 CAF + XMC: 1.05 ± 1.89	CAF: 0.11 ± 0.54 CAF + XMC: 0.03 ± 0.57	CAF: 0.36 ± 0.40 CAF + XMC: 0.67 ± 0.38
McGuire et al., 2010 [4]	Mucograft	CAF + CTG: 99.3 ± 2.1 CAF + XMC: 88.5 ± 17.4	CAF + CTG: 2.85 ± 0.52 CAF + XMC: 2.26 ± 1.0	CAF + CTG: 1.09 ± 1.32 CAF + XMC: 1.11 ± 0.68	CAF + CTG: 0.24 ± 0.62 CAF + XMC: 0.50 ± 0.68	NR
Moreira et al., 2016 [31]	Mucograft	CAF: 72 ± 0.14 CAF + XMC: 77 ± 0.21	CAF: 2.09 ± 0.70 CAF + XMC: 1.85 ± 0.73	CAF: 2.75 ± 0.97 CAF + XMC: 2.8 ± 0.83	CAF: 1.20 ± 0.41 CAF + XMC: 1.1 ± 0.31	CAF: 0.14 ± 0.29 CAF + XMC: 0.4 ± 0.19
Sangiorgio et al., 2017 [32]	Mucograft	CAF: 68 ± 24.1 CAF + XMC: 87.2 ± 15 CAF + EMD: 88.7 ± 20.6 CAF + XMC + EMD: 91.5 ± 11	CAF: 2.18 ± 1.11 CAF + XMC: 2.87 ± 0.75 CAF + EMD: 2.70 ± 0.84 CAF + XMC + EMD: 2.91 ± 0.87	CAF: 0.30 ± 1.4 CAF + XMC: 0.35 ± 1.04 CAF + EMD: 0.36 ± 0.9 CAF + XMC + EMD: 0.34 ± 0.86	CAF: 0.03 ± 0.74 CAF + XMC: 0.18 ± 0.50 CAF + EMD: 0.03 ± 0.67 CAF + XMC + EMD: 0.03 ± 0.60	CAF: 0.13 ± 0.32 CAF + XMC: 0.36 ± 0.47 CAF + EMD: 0.12 ± 0.27 CAF + XMC + EMD: 0.30 ± 0.31
Stefanini et al., 2016 [33]	Mucograft	CAF: 75 ± 26.2 CAF + XMC: 76.2 ± 28	CAF: 2.71 ± 1.16 CAF + XMC: 2.7 ± 1.05	CAF: 0.64 ± 1.16 CAF + XMC: 1.05 ± 1.19	CAF: 0.3 ± 0.57 CAF + XMC: 0.07 ± 0.54	CAF: 0.27 ± 0.35 CAF + XMC: 0.52 ± 0.37
Tonetti et al., 2018 [6]	Mucograft	NR	CAF + CTG: 0.3 ± 0.5 CAF + XMC: 0.3 ± 0.6	CAF + CTG: 2.9 ± 1.3 CAF + XMC: 3.0 ± 1.4	CAF + CTG: 1.5 ± 0.5 CAF + XMC: 1.5 ± 0.6	NR

RCT: randomized clinical trial; NR: not reported; NP: not performed; XMC: xenogeneic collagen matrix; CAF: coronally advanced flap; CTG: connective tissue graft; RC: root coverage; CAL: clinical attachment level; KMW: keratinized mucosa width; PD: probing depth; GT: gingival thickness; CAT: Coronally advanced tunnel; EMD: enamel matrix derivative; GT: gingival thickness; VAS: visual analogue scale.

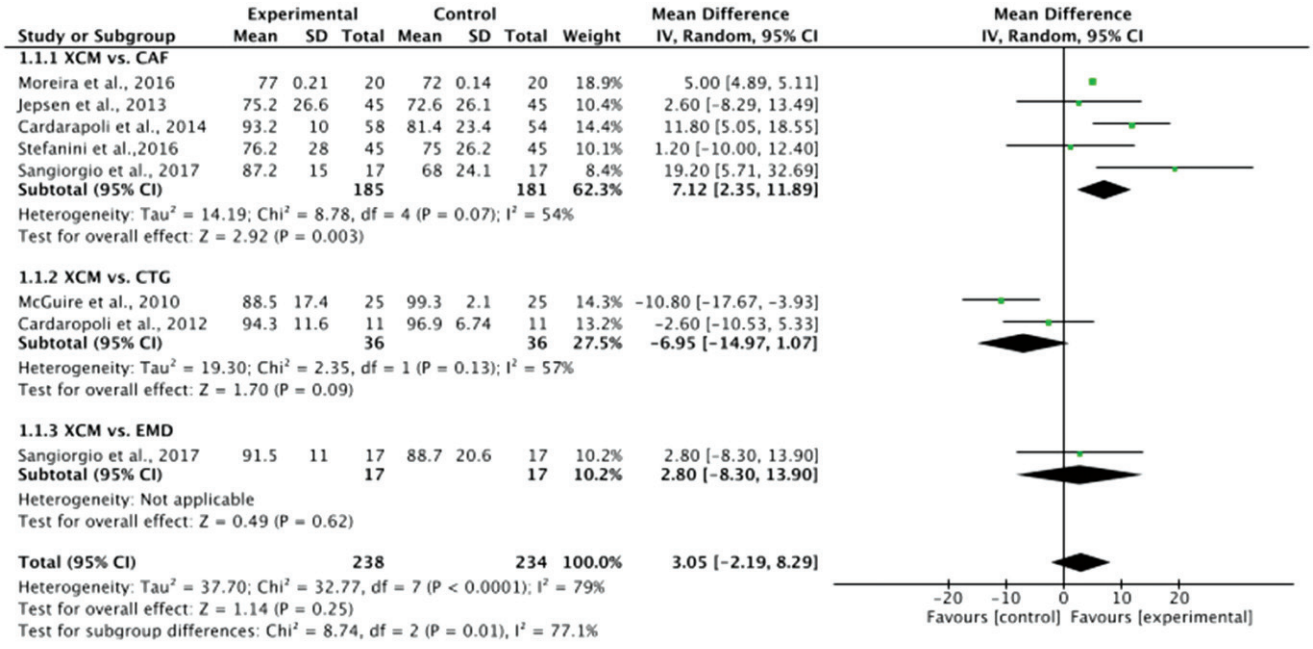

Figure 2. Forest plot for the root coverage parameter.

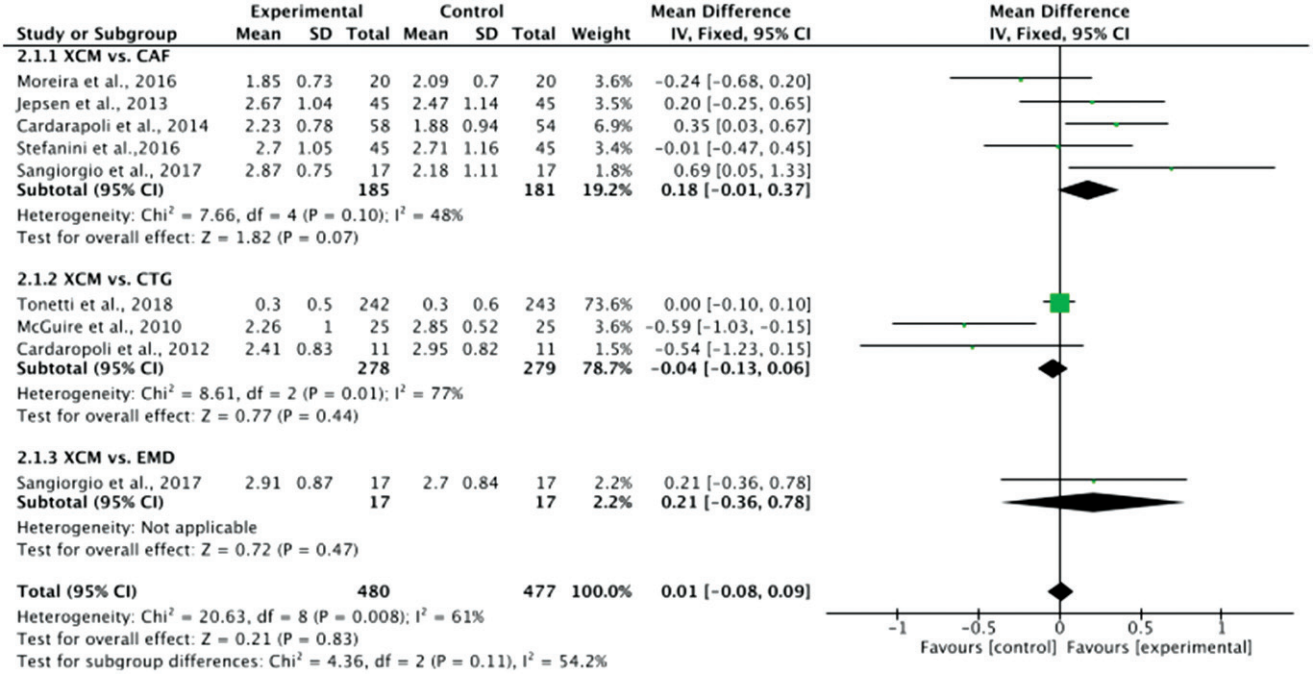

Figure 3. Forest plot for the clinical attachment level parameter.

Assessments of the risk of bias

All studies included all the items in the risk of bias tool developed by Cochrane. Thus, all the studies included in this SR present a low risk of bias (Table 3).

Discussion

Summary of evidence

Only studies evaluating the treatment of gingival recessions were included in this SR. After a comprehensive search that electronic databases, regular journals and the grey literature, nine RCTs were selected. In order to avoid publication bias, there were no restrictions on language or publication date. Only studies with at least 6 months of follow-up were selected for this review. This period was previously reported as sufficient for tissue stability after periodontal plastic surgery [34].

Only RCTs were included in this SR. This is because bias is more likely to exist in nonrandomized studies than in RCTs [35]. In addition, all studies included scored all the requirements of the bias risk analysis tool used. Four of the included studies [4,27–29] did not report adherence to the CONSORT-statement [36]. Adherence to these guidelines is

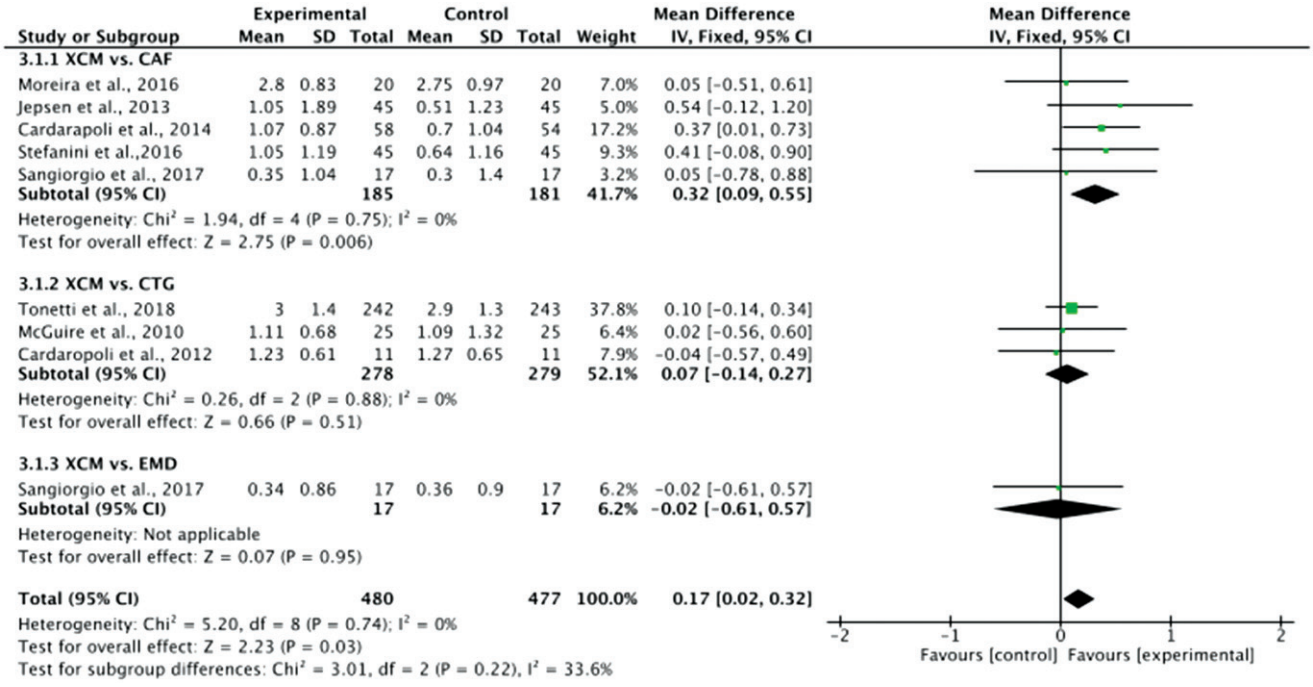

Figure 4. Forest plot for the keratinized mucosa width parameter.

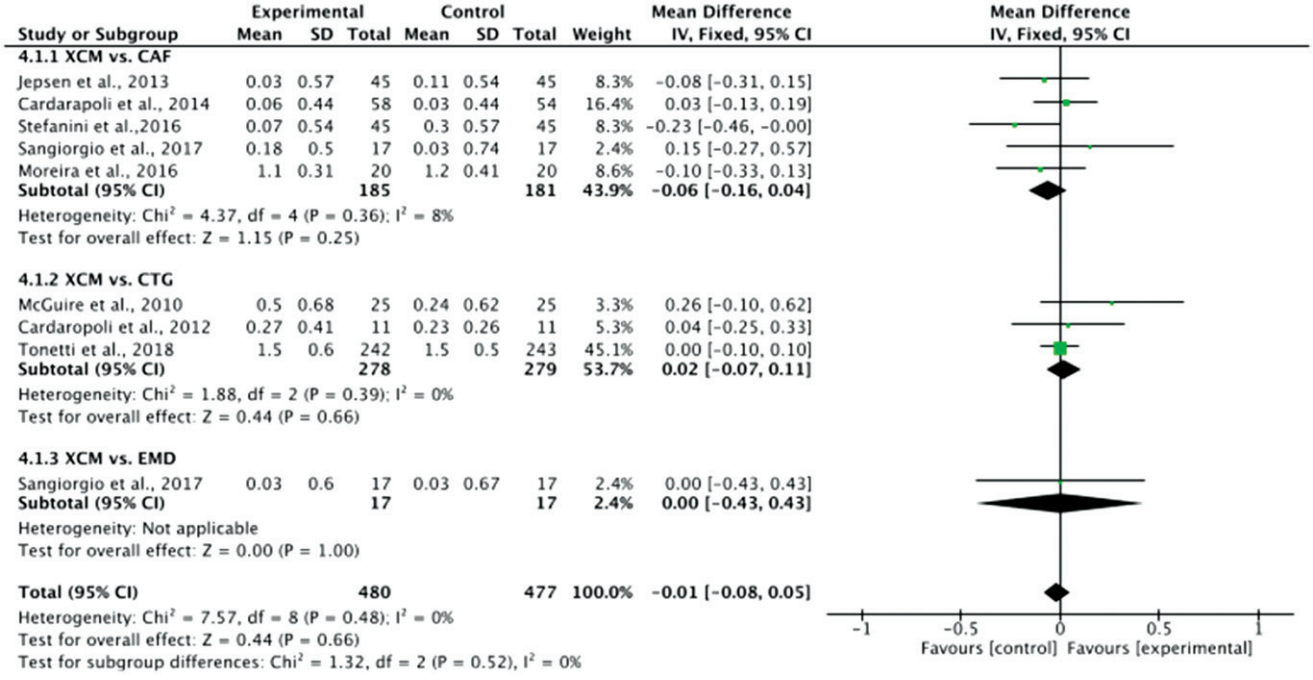

Figure 5. Forest plot for the *Probing Depth* parameter.

important because it helps to increase the quality and transparency of health studies [37].

In this SR, the effects of CAF + XCM were compared with the effects of three different techniques (CAF alone, CAF + CTG, and CAF + EMD) on the treatment of gingival recession. Only one study [27] used the CAT technique associated with the use of XCM for the treatment of gingival recessions. Due to this, it cannot be analysed through meta-analysis. The authors concluded that the use of XCM may represent an alternative to CTG by reducing surgical time and patient morbidity. Notably, however, XCM yielded lower RC than CTG in the treatment of Miller Class I and II gingival recessions. Evidence from some previous studies demonstrates that the CAT technique has some advantages over CAF, such as less surgical trauma [38,39], which leads to lower levels of postoperative discomfort [38,39]; improved complete RC [39]; and improved aesthetics [39]. However, a recent SR noted that the CAF technique appears to be associated with a higher percentage of RC than the CAT technique when using the same grafts [40].

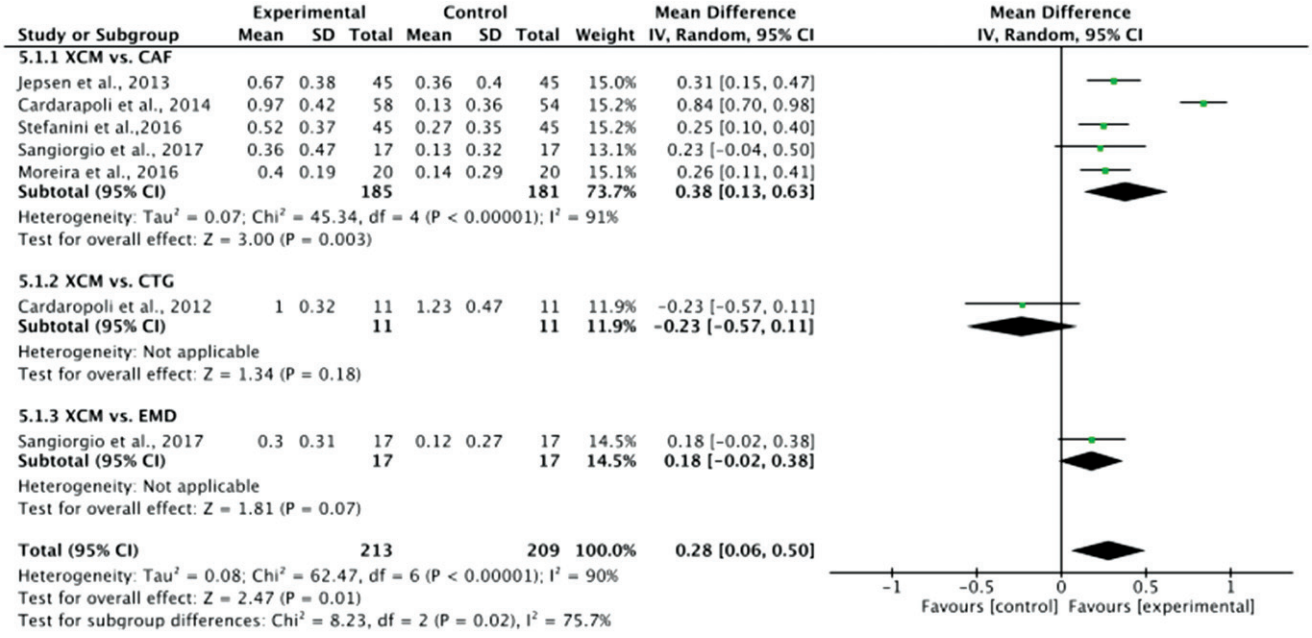

Figure 6. Forest plot for the gingival thickness parameter.

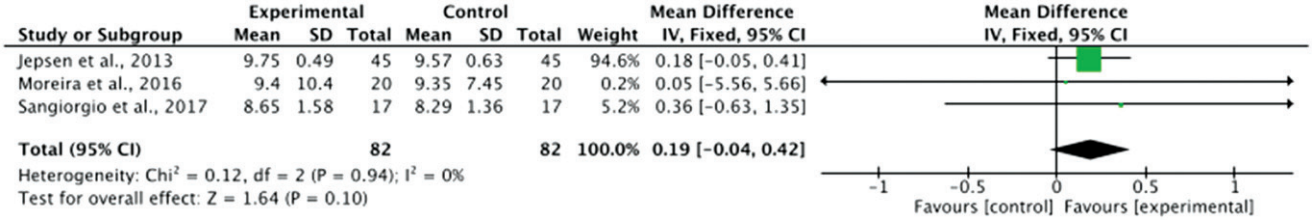

Figure 7. Forest plot for the *Participants' aesthetic satisfaction* parameter.

Table 3. Risk of bias of included studies.

Authors (year)	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Selective outcome reporting	Free of other sources of bias	Estimated potential risk of bias
Aroca et al., 2013 [27]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Cardaropoli. et al. 2012 [28]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Cardarapoli et al., 2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Jepsen et al., 2013 [30]	Yes	Yes	Yes	Yes	Yes	Yes	Low
McGuire et al., 2010 [4]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Moreira et al., 2016 [31]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Sangiorgio et al., 2017 [32]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Stefanini et al., 2016 [33]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Tonetti et al., 2018 [6]	Yes	Yes	Yes	Yes	Yes	Yes	Low

The results of this SR indicate that the addition of XCM to CAF provides benefits in terms of RC ($p = .003$), KMW ($p = .006$) and GT ($p = .003$) outcomes when compared to the use of CAF alone (mean of follow-up time of 9.3 months).

The evidence demonstrates that CTG presents the best results for the RC of single or multiple Miller class I or II gingival recessions [41]. In the present study, although the CTG showed superior outcomes for RC ($p = .09$), CAL ($p = .44$) and GT ($p = .18$) parameters, when compared to XCM, this difference was not statistically significant. The results of the present study may therefore encourage the use of XCM for the treatment of Miller class I or II gingival recessions when the use of CTG is not possible (e.g. treatment of multiple recessions, anatomical deficiencies, patient decision). In addition, alternative biomaterials may present potential advantages in relation to autologous tissue. These potential advantages include: (1) lack of need for a donor area; (2) no risk of transmission of human diseases; (3) shorter surgical

times; (4) shorter time to recovery; (5) no size limits on surgical sites; and (6) better patient perception compared to CTG [6].

One study [32] analysed the influence of EMD associated with CAF + XCM when compared to CAF + XCM. The EMD association improved the KMW outcome, but the difference was not statistically significant ($p = .95$). The rationale for using EMD in RC procedures, in addition to its clinical characteristics, is the possibility to regenerate the lost periodontal tissues, as demonstrated in several studies [42–44].

Patients' aesthetic perceptions were only analysed in four studies [27,30–32]. The study by Aroca et al. [27] was not included in the meta-analysis because it performed a surgical technique different from the other studies. Although the participants reported better aesthetic results with XCM than CTG, this difference was not significant. The meta-analysis indicates that although XCM also performed better than CAF alone, this difference was not statistically significant. Aesthetic perception is a subjective factor among patients, which makes the standardization of the analysis difficult [45]. Factors such as colour and gingival contour may often be judged more important than RC [46].

Strengths and limitations related to this SR

The present SR has several strengths, including the development and prior registration of a protocol, an unrestricted search process (including grey literature), and duplicate review procedures for the discovery and assessment of bias risk. In addition, the included studies presented low risk of bias in the analysis conducted, which increases the power of this SR. However, there are some limitations.

No included study provided information about the techniques and period of removal of sutures performed. The available data demonstrate that surgical outcomes might be influenced by the different conditions affecting a suturing protocol (i.e. the needle's characteristics, bite size, suture position and location of knots tied) [47]. Also, early suture removal (<10 days) can negatively influence RC outcomes in single-tooth defects treated by a CAF procedure [48]. Thus, it is strongly recommended that studies investigating RC techniques provide their suture protocols. One study [6] included smoking participants. Despite the controversy in the literature regarding the influence of smoking on periodontal surgery, some studies showed negative results related to the interaction of smoking and periodontal plastic surgery [49,50]. Tobacco smoking affects the oral environment and ecology, vascularization of the gingival tissues, immune and inflammatory responses and the healing potential of the periodontal connective tissues [51].

As there are relatively few relevant studies available, any comparison between XCM and CTG should be done cautiously. Although the meta-analysis did not show a statistically significant difference between the analysed parameters, CTG remains the most predictable graft for the treatment of RC [41,47,48].

Implications for clinical practice

Although CTG is currently considered the gold standard for the treatment of gingival recessions, new biomaterials have been researched as alternative treatments in complex cases. Data from this SR show that XCM can be used with alternative biomaterial in association with surgical techniques such as CAF and CAT for the treatment of Miller class I or II recessions when CTG cannot be used.

Recommendations for further research

A higher number of RCTs comparing the performance of XCM versus CTG for the treatment of isolated or multiple gingival recessions is critical in the future. Researchers are encouraged to control study bias (e.g. suturing protocol, flap design, inclusion of smokers, follow-up period, and number of participants) and standardize participants' outcomes (e.g. evaluation of pain and aesthetic satisfaction).

Conclusions

Based on both the individual studies' outcomes and the pooled estimates, it can be concluded that the use of XCM improves the RC, KTW and GT in the treatment of gingival recessions when compared to CAF alone. The use of XCM may be a viable alternative to CTG for the treatment of Miller class-I or -II gingival recessions. The use of XCM does not seem to increase the aesthetic satisfaction of patients when compared to CAF alone.

Disclosure statement

The authors declare that there was no conflict of interest during the elaboration of this study.

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