

The effect of hyaluronan (HA) as an adjunct to coronally advanced flap for the treatment of gingival recession defects – A systematic review

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Abstract

Background: Gingival health and appearance are essential components of a pleasant smile. Gingival recession results in an unpleasant smile. Gingival recession therapy still poses a challenge for clinicians. Despite sub-epithelial connective tissue graft (SCTG) being the gold standard for root coverage, research has been aimed at finding a suitable alternative to this procedure to reduce patient morbidity.

Aim: This systematic review of randomized controlled clinical trials aimed to analyze the effect of hyaluronan as an adjunct to coronally advanced flap for the treatment of gingival recession defects.

Materials and Methods: An electronic database search was performed at PubMed, EBSCOhost, Science Direct, EMBASE and Google Scholar from January 2020 to September 2020.

Results: A total of 248 articles were identified on electronic database search. Only three randomized controlled clinical trials qualified for the qualitative synthesis. The risk of bias assessment for the included studies was conducted.

Conclusion: Application of Hyaluronan (HA) as an adjunct to coronally advanced flap (CAF) for gingival recession defects showed promising results. However,

there remains a need for conducting studies evaluating the effect of HA in gingival recession defects.

Keywords: Gingival recession, Hyaluronan, Coronally advanced flap

Introduction

A perfect balance between: the pink (gum), the white (teeth) and the lips is required for an aesthetic smile. It enhances the personality and self-confidence of the individual. The gingiva is the most commonly affected intraoral tissue responsible for an unpleasant appearance and its morphology plays an important role in determining the final aesthetic outcome.^[1]

Apical displacement of the soft tissue margin, beyond the cemento-enamel junction, that affects either isolated / multiple root surfaces is defined as gingival recession.^[2]

The migration of the marginal gingival tissue to an apical position may lead to aesthetic concerns, dentin hypersensitivity, root caries and cervical wear.^[3] It is a common clinical finding seen in patients (90%) with high standards of oral hygiene and represents the most frequent reasons for these patients to seek treatment.^[4]

Although its etiology is complex, mechanical trauma and periodontal diseases are the primary factors involved in the pathogenesis of gingival recession. Additionally, predisposing factors such as areas with minimal or no keratinized tissue, orthodontic movement, direct trauma associated with Class II malocclusion, or acute infection with herpes simplex virus seem to exacerbate the problem.^[5] Untreated gingival recessions are likely to undergo further progression, even in the presence of good oral hygiene.^[6]

The ultimate goal of root coverage procedures is to attain complete coverage of the recession defect with an aesthetic appearance as compared to adjacent healthy soft tissues in combination with physiological probing pocket depths.^[7 & 8] Several surgical techniques have provided

good results and have shown to attain root coverage at individual recession sites with a variety of different methods.^[8-11]

Till date, connective tissue grafts (CTG) and enamel matrix derivatives (EMD) along with a coronally advanced flap (CAF) in Miller's class I and II isolated gingival recessions have shown to provide the highest probability of obtaining complete root coverage (CRC) as compared to CAF alone.^[6] Pilloni and co-workers (2006) suggested that, the application of EMD significantly enhanced the extent of root coverage, the keratinized tissue (KT) augmentation and the clinical attachment gain (CAL-gain).^[12]

A recent meta-analysis on the effect of EMD and CTG in root coverage procedures concluded that, EMD proved helpful for wound healing and resulted in a reduction of probing pocket depths, whereas CTG increases the width of keratinized tissue when combined with CAF.^[3] Despite sub-epithelial connective tissue graft (SCTG) being the gold standard for root coverage, research is aimed at searching a suitable alternative to this technique to reduce the patient morbidity.

Hyaluronic acid also known as Hyaluronan [HA], is a polysaccharide of the extracellular matrix (ECM). It plays an important role in the structural, physiological, rheological and biological functions in the body.^[14] It has a high daily turnover.^[15] The hyaluronic acid molecules rise during early wound healing and bind to the fibrin in the clot, which makes the clot swell and become more porous facilitating cell migration into the matrix.^[16] Due to the locally produced hyaluronidase, as the HA becomes less viscous, it not only facilitates motility and proliferation of macrophages and fibroblasts; but also collagen deposition.^[17] HA possesses a viscosity that delay the penetration of viruses and bacteria.^[18] High molecular weight HA stimulates osteoinduction during wound

healing.^[19] HA is a recent addition to the local chemotherapeutic agent with multiple clinical therapeutic properties.

HA binds with water and allows the transportation of key metabolites and therefore helps to maintain the structural and homeostatic integrity of tissues.^[20] It suppresses tissue breakdown activating metalloproteinase inhibitors.^[21] It represents one of the most hygroscopic molecules known in nature.^[22] One gram of HA can bind up to 6 Litres (L) of water. It acts as a physical background material in space filling, lubrication, shock absorption and protein exclusion.

In vitro and animal studies have demonstrated that HA significantly increases the tensile strength of granulation tissue^[23], stimulates clot formation^[24], induces angiogenesis^[25], increases osteogenesis^[26], and does not interfere in the calcification nodules during bone formation.^[27] Also, HA facilitates cell migration and differentiation during tissue formation and repair of both soft and hard tissues.^[28] It has been shown to improve ligament cell viability, and even early osteogenic differentiation in vitro recently.^[29]

Rationale

The use of HA as a dermal filler is common in dermatology. It has been used extensively in the field of dentistry for its various beneficial applications. Studies have been conducted to determine the effect of HA on non-surgical and surgical periodontal therapy. In Periodontics, HA has been used to treat gingivitis, periodontitis, interdental papillary tissue loss and more recently in the treatment of periodontal intra-bony defects. However, there are limited studies on the effect of HA as an adjunct to coronally advanced flap for the treatment of gingival recession defects. Therefore, this systematic review aimed to analyze the effect of hyaluronan as an

adjunct to coronally advanced flap for the treatment of gingival recession defects.

Focused question

The focused question adopted the population, intervention, comparison, and outcome criteria.

Does hyaluronan (HA) as an adjunct to coronally advanced flap (CAF) improve the treatment results, in terms of root coverage, compared to CAF alone in subjects with gingival recession defects?

Another research question

Does administration of hyaluronan as an adjunct to coronally advanced flap hasten root coverage in gingival recession defects?

Primary objective

To evaluate the effect of hyaluronan as an adjunct to coronally advanced flap for the treatment of gingival recession defects.

Secondary objective

To analyze the effect of hyaluronan administration as an adjunct to coronally advanced flap for root coverage.

Materials And Methods

Protocol and registration

The systematic review was conducted in accordance with the Preferred Reporting Items of Systematic Reviews (PRISMA) and Meta-analysis statement.

Registration number- CRD42021244102

Study design

This is a systematic review of randomized controlled clinical trials which aims to analyze the effect of hyaluronan as an adjunct to coronally advanced flap for the treatment of gingival recession defects.

Inclusion criteria

1. Randomized controlled clinical trials.
2. Full-text articles published in peer-reviewed Journals in English language.

- Parameters assessed were recession depth (RD), recession width (RW), clinical attachment level (CAL), probing pocket depth (PPD), keratinized tissue width (KTW), mean root coverage (MRC) and complete root coverage (CRC).

Exclusion criteria

- Case reports, case series, case-control studies, animal model studies & in vitro studies.
- Articles on use of HA for treatment of interdental papilla loss and gummy smile.
- Articles on use of HA for implants.
- Unpublished research.

Information sources and search strategy

An electronic database search for randomized controlled clinical trials published in peer-reviewed journals in English was conducted from the following databases: PubMed, EBSCOhost, ScienceDirect, EMBASE and Google Scholar from January 2020 to September 2020.

The search terms used were:

Hyaluronan OR Hyaluronic acid
AND coronally advanced flap OR CAF
AND Recession defects OR Gingival augmentation OR
Root coverage

Study selection

Study selection was carried out in two phases:

- Assessment of titles and abstracts
- Assessment of full text.

Data collection process

Data extraction sheet was prepared based on variables assessed, and the articles were analysed. Using data extraction sheet, the following data were collected: authors, year of publication, country, aim, parameters assessed, type of study, sample size, comparison group/control group, methodology and conclusion (Table 1).

Data items –Variables for which data was sought included coronally advanced flap, hyaluronan and gingival recession.

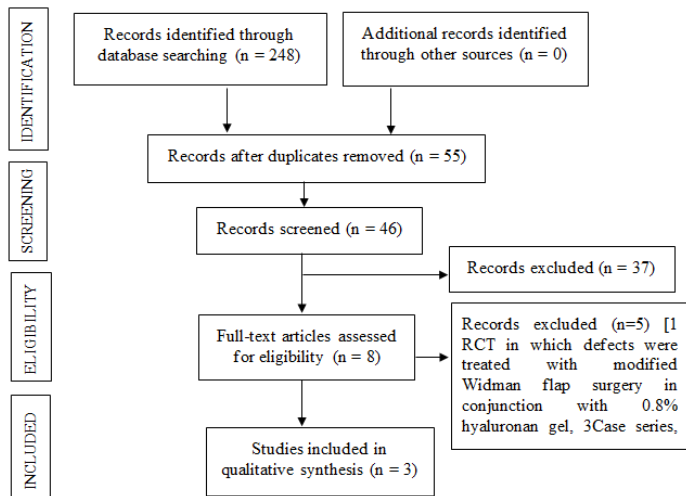
- Coronally Advanced Flap (CAF)** - The CAF is a surgical procedure in which there is a coronal shift of the soft tissues on the exposed root surface.
- Hyaluronan (HA)** – Hyaluronan is a glycosaminoglycan that is found in extracellular tissue space, the synovial fluid of joints, and the vitreous humor of the eyes and acts as a binding, lubricating, and protective agent.
- Gingival recession** - Gingival recession is defined as the displacement of the gingival margin apical to the cemento-enamel junction (Glossary of Periodontal terms).

Results

A total of 248 articles were found after electronic search. 193 articles, which were of other languages and duplicates, were excluded leaving 55 articles. 52 articles were excluded as they did not fulfill the eligibility criteria leaving 3 articles. Figure 1 shows the flow chart of literature search results and study selection.

Two reviewers independently assessed the risk of bias of each included study, by using the recommended approach for assessing risk of bias in studies included in Cochrane Reviews (Higgins 2011)^[30].

Figure 1: Flow chart of literature search, results and study selection



Studies included for the analysis

Only three randomized controlled clinical trials qualified for the qualitative synthesis. All the included studies suggested that HA increases the probability of achieving root coverage in Miller’s class I and II recession. An overview of the studies included for the analysis are presented in Table 1a and 1b.

Table 1a: Characteristics of the included studies for the analysis

Sn.	Authors & Year of Publication	Country	Type of study	Aim	Conclusion
1	Pilloni A, Schmidlin R, Sahrman P, Sculean A, Rojas MA. (2019) ³¹	Sapienza University of Rome	RCT	To evaluate the possible advantages of adjunctive hyaluronic acid (HA) application in the coronally advanced flap (CAF) procedure in single Miller class I/recession type 1 (RT1) gingival recession treatment.	The adjunctive use of HA was effective in obtaining CRC for single Miller class I/RT1 gingival recession sites.
2	Rajan P, Medanda Rao N, Nera M, Rahaman SM (2015) ³²	India	RCT	To evaluate the effectiveness of hyaluronan (HA) as an adjunct in root coverage procedures.	HA increased the probability of achieving root coverage in Miller’s class I and II recession.
3	Kumar R, Srinivas M, Pai J, Suragimath G, Prasad K, Polepalle T. (2014) ³³	India	RCT	To assess the efficacy of Hyaluronan (HA) in root coverage procedures as an adjunct to coronally advanced flap (CAF) procedure.	Use of HA may improve the clinical outcome of root coverage with CAF procedure.

Table 1b: Characteristics of the included studies for the analysis

Sn.	Authors & Year of Publication	Parameters assessed	Sample size, Comparison group & control group	Methodology
1	Pilloni A, Schmidlin R, Sahrman P, Sculean A, Rojas MA. (2019) ³¹	Recession reduction, CAL-gain, PPD, KTW, CRC, MRC, Post-operative patient morbidity	Thirty patients (14 females and 16 males). 15 were randomly assigned to comparison group (CAF + HA) and 15 to control group (CAF alone).	For the control group, only CAF was performed. For the test group, cross-linked HA (Hyaluronic acid, hyaDENT BG, Bioscience, Germany) was applied covering the root surface before flap suture.
2	Rajan P, Medanda Rao N, Nera M, Rahaman SM (2015) ³²	RD, RW, KTW, PD, CAL, GI and PI	20 patients (13 females and 7 males) Comparison group (HA+CAF) or control group (SCTG + HA) group.	Miller's class I and II gingival recession in a minimum of two sites were treated with HA gel combined with CAF on the test site and SCTG with CAF on the control sites.
3	Kumar R, Srinivas M, Pai J, Suragimath G, Prasad K, Polepalle T. (2014) ³³	RD, PPD, CAL	10 patients with 20sites (3 females and 7 males). Comparison group includes hyaluronan gel (gengigel 0.2% gel which is 0.2% hyaluronan gel marketed by Ricerfarma pharmaceuticals, Milan, Italy) with CAF and control group with CAF alone.	In the experimental group, hyaluronan gel (gengigel 0.2%) applied on the root surface using a sterile instrument prior to flap advancement and suturing whereas in the control group the flap was advanced coronally without application of HA gel.

Assessment of risk of bias in included studies

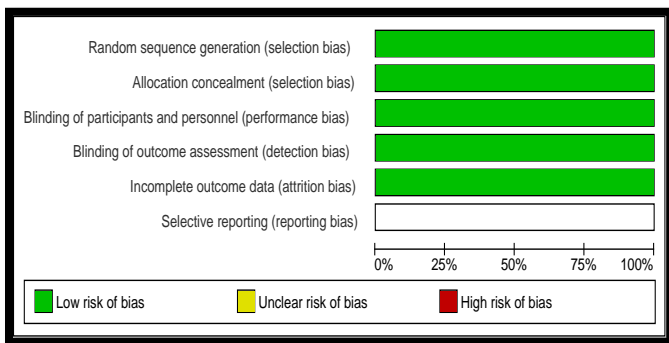
This assessment was conducted using the recommended approach for assessing the risk of bias in studies included in Cochrane Reviews (Higgins 2011) using the tool RevMan 5.0. We used the two-part tool to address the six specific domains (namely random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias). Each domain

includes one or more specific entries in a risk of bias table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry: either low risk, unclear risk or high risk. The risk of bias of the included studies is presented in Table 2 and Graphs 1, 2.

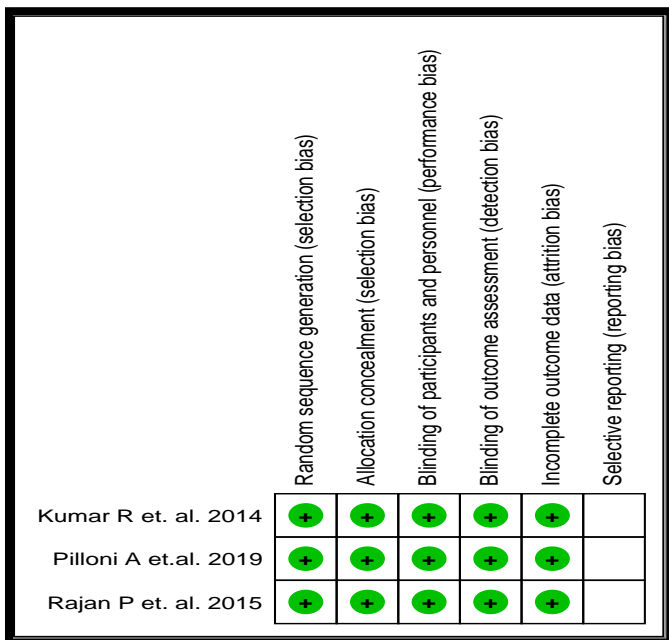
Table 2: Risk of Bias of the studies included in the Systematic Review

Sn.	Authors (Year)	Type of study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome	Incomplete outcome data	Selective Reporting
1	Pilloni A et al (2019) ¹	RCT	Low	Low	Low	Low	Low	Not clear
2	Rajan P et al (2015) ²	RCT	Low	Low	Low	Low	Low	Not clear
3	Kumar R et al (2014) ³	RCT	Low	Low	Low	Low	Low	Not clear

Graph 1



Graph 2



Studies excluded from the analysis

Five studies were excluded, in which 1 was a randomized controlled trial in which they have used Modified Widman Flap design for treating recession defects, 3 were case series, 1 was a review article. An overview of the excluded studies is presented in Table 3.

Table 3: Characteristics of Excluded Studies

Authors (Year)	Reason for Exclusion
Karim M, El-Sayed F, Moushira , Aboul-Ela S. & Mona S.(2011) ³⁴	RCT in which defects were treated with modified Widman flap (MWF) surgery in conjunction with 0.8% hyaluronan gel
Pini Prato GP, Roundo R, Magnani C, Soranzo C, Muzzi L, Cairo F. (2003) ³⁵	Case series
Lanzrein C, Guldener K, Imber JC, Katsaros C. (2020) ³⁶	Case series
Guldener K, Lanzrein C, Eliezer M, Katsaros C. (2020) ³⁷	Case series
Fallacara A, Manfredini S, Durini E, Vertuani S. (2017) ³⁸	Review

Discussion

Summary of evidence

Localized gingival recession defects can be treated with various methods. Till date, a robust body of evidence reports positive outcomes following the use of CAF, CAF + EMD and CAF + CTG in the treatment of localized gingival recession defects [9, 11, 13 & 14]. The consensus report of the AAP Regeneration Workshop^[43] concluded that, a subepithelial connective tissue graft (SCTG) represents the most effective treatment modality for Miller class I and class II single-tooth recession defects and

provides the best root coverage outcome. But it is important to highlight the fact that the incidence of adverse effects in gingival recession treatment, such as discomfort with or without pain, was directly related to the donor sites of SCTG.^[44] Therefore, research always aimed to find suitable alternatives to reduce patient morbidity and enhance the intervention predictability.

HA is a naturally occurring biopolymer, particularly concentrated in soft connective tissue extracellular matrix, skin dermis, vitreous humor of the eye, hyaline cartilage, synovial joint fluid, disc nucleus, and umbilical cord. It has unique and incomparable chemical-physical properties, and it is characterized by numerous biological functions.^[45] HA is extremely versatile, biocompatible, biodegradable, and mucoadhesive.^[46 & 47] These characteristics of the molecule, in addition to its unique viscoelastic nature, led to its use in different dental, medical, pharmaceutical, and cosmetic applications.^[46]

HA is being produced by means of biotechnology which is chemically identical to HA naturally produced by human body. Its major advantage is that, it can be used as a filler in almost all the patients. Therefore, normally, HA dermal fillers (DFs) do not provoke relevant side effects; only in very rare cases, HA can cause allergy manifested by transient erythema, oedema, itch, or mild swelling. However, these non-immune-mediated adverse events tend to spontaneously regress within a few hours or, at most, a few days.^[48] The main limitation of HA, when used as free chains (uncross-linked chains), is its poor durability, about ½ days, especially due to the rapid enzymatic degradation. There have been limited clinical studies in the field of root coverage procedures performed with application of HA. There is no consistent data with longer follow-ups on the usage of HA.

There has been no systematic review reported on the effectiveness of hyaluronan as an adjunct to coronally advanced flap for the treatment of gingival recession defects when compared to CAF alone; hence this systematic review was conducted. Only three randomized clinical trials with at least 6 months of follow up qualified for the qualitative analysis. The included studies^[31-33] showed that HA as an adjunct to CAF showed significant improvements in the clinical periodontal parameters among the study groups.

The results of the study conducted by Pilloni A et al (2019)^[31] showed that, 18 months after treatment, the test (CAF + HA) and the control (CAF alone) groups resulted in a consistent recession reduction, which was significantly higher for the test (CAF + HA) group. Also, the clinical stability of the root coverage achieved, MRC and CRC obtained after 24 weeks in the study by Kumar R et al^[33] were similar to the study conducted by Pilloni A et al (2019). Ballini et al^[49] stated that, the biological properties of hyaluronan promotes regeneration. It has been suggested from previous animal studies that there is an increase in hard tissue component of the periodontium following treatment with HA. It promotes wound healing by cell migration and proliferation, improving tissue hydration and facilitating white blood cell infiltration. This could contribute to better stability of the root coverage procedures with the use of HA. On the other hand, study conducted by Pilloni A et al (2019)^[31] reported lower swelling and discomfort values 7-day post-surgery with no significant difference for pain intensity. This may be due to the biological properties of HA in wound healing, HA might be an option to reduce overall patient morbidity and may lead to better clinical results when treating gingival recessions.

Rajan P et al (2015)^[32], compared CAF + HA versus CAF + SCTG in the treatment of recession defects. They found only significant differences in PPD between the groups, favouring the test group (HA). It is interesting to note that, PPD values in the control group (CAF alone) showed a broader range after 18 months. This was in accordance with Eric S et al, who analysed the effect of additional application of HA gel during scaling and root planing (SRP) and reported improved probing depth measurements. This fact, along with the enhanced recession coverage of the test group, emphasize the beneficial effect of the HA application. One possible reason may be due to the antibacterial effect of high molecular weight HA gel on periodontal pathogens. Also, Rajan P et al (2015)^[32] stated, significant differences in the other clinical parameters (Rec, KTW, CAL, MRC) was found after 3 months, but not at the end of the study.

The strengths of this systematic review are

- a) It included only RCTs which showed a low risk of bias,
- b) It included studies with atleast 6 months of follow-up,
- c) The inclusion was limited to single root coverage technique i.e., coronally advanced flap with or without HA, hence there was no selection bias.

Limitations

- a) Meta-analysis could not be performed with this systematic review, due to heterogeneity among data. In order to draw more robust conclusions about treatment of sites lacking attached gingiva: a) the number of Miller Class I and II should be balanced and equally distributed in the study groups (i.e., test and control); and b) the differences in response to treatment between these sites should be considered.
- b) The present systematic review included only published articles written in English.

- c) The effective sample size was small in all the three studies.
- d) Also, short duration follow-up (6 months) was seen in a study conducted by Kumar et al (2014)^[33]; which appears to be critical for the evaluation of the outcomes of root coverage. Whereas, studies by Pilloni A et al (2019)^[31] and Rajan P et al (2015)^[32] had a follow up of 18 months and 9 months respectively,

Within the limitations of the present systematic review, it can be concluded that, future randomized controlled clinical trials should be conducted with larger sample size and long-term follow-up to evaluate the effect of Hyaluronan in the treatment of gingival recession defects.

Conclusion

Hyaluronan has been used extensively in the field of dentistry for its various beneficial applications. In Periodontics, it has been used to treat gingivitis, periodontitis, treatment of interdental papillary loss and more recently in the treatment of periodontal intra-bony defects. Hyaluronan has shown promising results as an adjunct to coronally advanced flap for the treatment of gingival recession defects.

Implications for research

1. RCTs are required to be conducted to evaluate the effects of HA.
2. A split mouth design should be adopted to avoid the inter-patient variability.
3. Precise and objective aesthetic evaluations needs to be included in future studies.
4. The use of the VAS (or other standardized scale) will allow more precise evaluations of patient-based outcomes.

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