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Review

Systematic Review and Meta-Analysis of the Use of Hyaluronic Acid Injections to Restore Interproximal Papillae

Arturo Sanchez-Perez [1,*], Tania Rosa Vela-García [2], Bibiana Mateos-Moreno [2], Alfonso Jornet-García [4] and Carlos Navarro Cuellar [5]

1* Arturo Sanchez-Perez. arturosa@um.es; Medicine and Dentistry Faculty, Department of Periodontology, Murcia University, 30008 Murcia, Spain

2 Tania Rosa Vela-García. taniarosa.velag@um.es; Medicine and Dentistry Faculty, Department of Periodontology, Murcia University, 30008 Murcia, Spain

3 Bibiana Mateos-Moreno. bibimateos@um.es; Medicine and Dentistry Faculty, Department of Periodontology, Murcia University, 30008 Murcia, Spain

4 Alfonso Jornet-García. alfonsofelipe.jornet@um.es; Medicine and Dentistry Faculty, Department of Periodontology, Murcia University, 30008 Murcia, Spain

5 Carlos Navarro-Cuellar cnavarrocuellar@gmail.com; Department of Surgery, Complutense University, 28040 Madrid, Spain;

Abstract: :

The absence of interdental papillae leads to the appearance of black triangle. For most patients, the appearance of these triangles is an important reason for concern and affects their social relationships. Multiple reconstruction techniques have been developed with different degrees of success and predictability. The main aim of this study was to evaluate the efficiency of hyaluronic acid (HA) injected into interproximal papillae six months after injection and to perform a systematic review and meta-analysis. After a systematic review, five articles were selected: a clinical randomised controlled trial and four clinical trials. In total, eighty-five patients with a deficiency in upper papillae in the front of the maxilla and jaw were included in the study. The height variable was evaluated (mm) six months after HA injection. In total, one hundred and four interproximal papillae were studied. Three articles showed an important difference in favour of intervention. The total result regarding in the injection of AH was favourable with an approximate average filling of 0.7 mm in the height of the interdental papilla. The injection of HA for the reconstruction of deficient papillae in the region of the upper and lower maxilla was a possible option treatment strategy.

Keywords: aesthetics; gingiva; hyaluronic acid; injections; surgical procedures; minimally invasive

1. Introduction

The interdental papilla is a soft tissue found in the cervical area of the free gingiva, extending from the interproximal alveolar crest to the point of contact [1].

The loss of the interproximal papilla has both functional and aesthetic effects, which have been the subject of numerous studies [2–4].

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The cause of the loss of the papilla is multi-factorial; also, the loss of the papilla results in the appearance of so-called "black triangles".

In an attempt to reconstruct the interdental papilla, many surgical techniques have been developed, although the results of these techniques can be unpredictable [5]. Hence, most efforts have focused on conservation techniques with the main limiting factor being the delicate vascularity of the papilla [6–8].

Hyaluronic acid (HA) was discovered by Karl Meyer in 1934 and his assistant John Palmer, who isolated the chemical from the vitreous humour of cow eyes.

HA is a non-sulphated glycosaminoglycan consisting of disaccharide units (GAGs), D-glucuronic acid and N-acetyl glucosamine (NAcGlu) bound by heparin, heparan, chondroitin and dermatan sulphate.

The use of hyaluronic acid has been of particular interest as a volumetric filler to restore aesthetics. In this way, it has also been possible to use HA in dentistry. One of the applications of HA lies in the filling and reconstruction of interdental papilla [9].

The objective of our study was to review the literature of the last 10 years regarding the use of hyaluronic acid in the treatment of interproximal black triangles by rating the available evidence.

2. Material and Methods

2.1. Study Design

A bibliographic search was carried out with the intention of conducting a meta-analysis based on a systematic review of the literature of the articles published between 2009 and 2019.

2.2. Search Strategy

Through the PICO process, we identified and considered the studies for this systematic review (target population, intervention to be carried out, comparison, outcomes and studies) (Table 1 and Figure 1).

Table 1. Parameters used for PICO [P – Patient, problem or population. I – Intervention. C – Comparison, control or comparator. O – Outcome(s)].

PICO PROCESS	
Population	Patients with interproximal papilla deficiency
Intervention	Hyaluronic acid injection
Comparison	Treatment with saline serum/placebo/or control prior to the treatment
Outcome	Height of the papilla in mm

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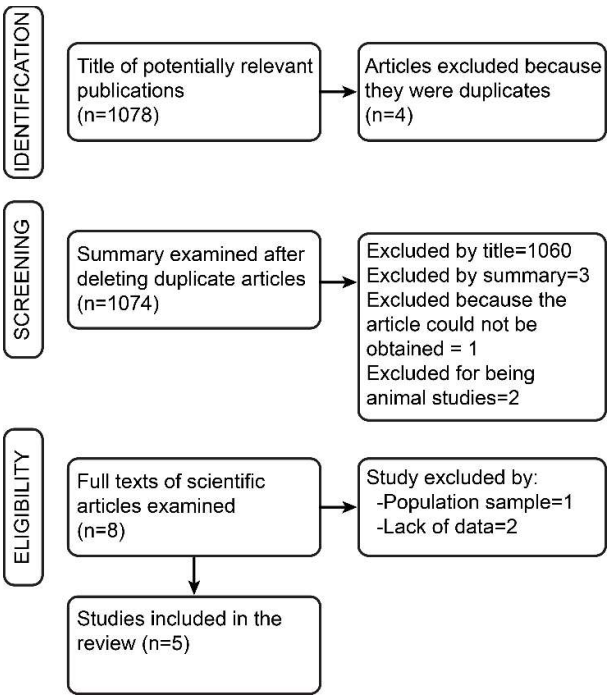

Figure 1. Flowchart of the process of searching for and selecting articles in databases.

Several electronic databases were used, including Scielo, Medline-PubMed, Google Academic, ScienceDirect, Dialnet, as well as journals from the Peruvian Association of Periodontics & Osteointegration, the Spanish Society of Periodontics & Osteointegration, and other research journals. The following keywords were used: "filler", "gingival increase", "hyaluronic acid", "hyaluronan", "papilla augmentation", "dental papilla" and "papillary remodelling".

2.3. Selection of Studies

The titles and summaries of the studies included in this systematic review were selected. Then, the validity of the studies was assessed according to the score obtained by Jadad, in which seven questions were used to evaluate the validity in a clinical trial. The score ranged from 0 to 5; the higher the score was, the better the methodological quality of the clinical trial being evaluated. In addition, the PRISMA guidelines for systematic review verification and meta-analysis were followed [10].

The search was limited to humans with loss of the interdental papilla with no active periodontal disease. The search was not restricted to any particular language. The time period of the studies was limited to the last 10 years.

2.4. Inclusion Criteria

The inclusion criteria taken into account for the meta-analysis were as follows: series of cases of at least 10 patients, at least 6 months of follow-up, papilla measurement in mm, adequate hygienic control and no active periodontal disease.

2.5. Exclusion Criteria

Exclusion criteria were as follows: no baseline data; loss of more than 15% of patients during follow-up; Jemt papilla index of 3-4; non-translatable language and inadequate

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data; such as no measurement in mm; no measurement in mm²; or lack of sample definition, as well as replication of articles.

3. Results

In this systematic review on the use of HA in interdental papilla reconstruction, a total of 85 patients were included, with a total of 133 papillae, all of which were in the anterior upper and lower jaw region.

Five articles, one randomised control trial and four clinical trials were included to evaluate the effect of HA injection. Singh's article provided three independent comparisons [11]. (Figure 2)

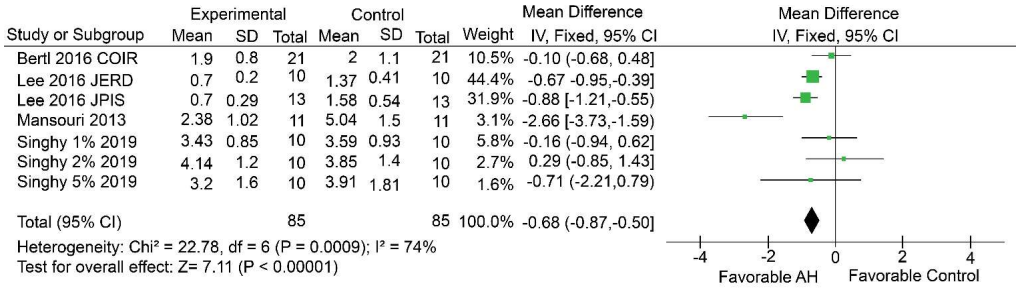

Figure 2. Forest plot reconstruction of interdental papilla deficiency with HA. Height values (mm) indicate a favourable result of HA injection.

The study by Bertl et al. [12] provided non-significant results, a very wide standard deviation and a small mean, reflecting a large population dispersion. The study of Lee et al. [13] was the only one that showed a significant difference after the intervention, as reflected in the greater weight of the study with 44.4%; the standard deviation, along with the mean, indicated more accurate variability.

The second study by Lee et al. [14] was also significant but has less weight than the previous study (31,9%), as its population dispersion was wider. The study by Mansouri et al. [15] had a very wide dispersion regarding measurements, which represented a wide dispersion of the results; the same was true for all the studies by Singh and Vandana [11].

The overall result was significant in favour of HA injection, with a maximum interdental papilla height of approximately 0.7 mm. Heterogeneity was high at I^2=74%. There was no statistical homogeneity.

All estimates appeared to be affected by publication bias according to the funnel plot, which shows an asymmetric funnel, i.e., clear publication bias, meaning that more studies about HA for interproximal papilla reconstruction are needed (Figure 3).

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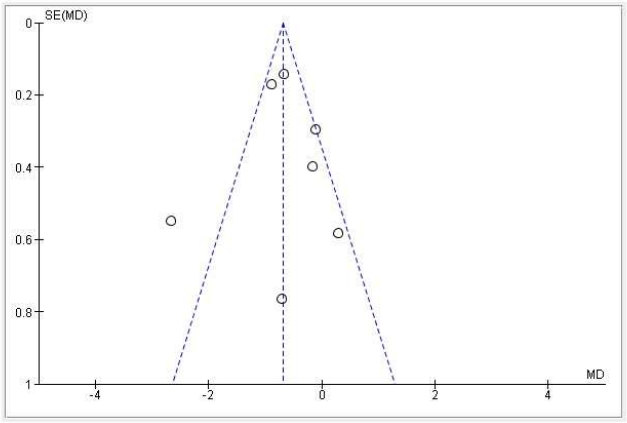

Figure 3. Funnel plot.

The ROBIN I non-randomised risk of bias assessment was used to assess the risk of bias [16]. All studies had a degree of bias risk (Table 2).

	Mansouri 2013 JIDAI	Bertl 2016 COIR	Lee 2016 JERD	Lee 2016 JPIS	Singh 1% 2019 JISP	Singh 2% 2019 JISP	Singh 5% 2019 JISP
Confusion Bias	-	+	+	+	-	-	-
Selection Bias	+	+	+	+	-	-	-
Classification Bias	-	+	-	¿?	¿?	¿?	¿?
Intercención? Intervention Bias	-	¿?	¿?	+	+	+	+
Lost Data Bias	+	¿?	-	¿?	-	-	-
Measurement Bias	¿?	+	-	+	-	-	-
Results Bias	+	-	¿?	+	¿?	¿?	¿?

Table 2: Assessing risk of bias in included studies. All studies have moderate to high risk of bias.

The only randomized clinical trial (RCT) present in this study was the articles by Bertl et al. [12], which presented an unclear risk of bias. This study ended before completion due to the absence of partial results.

4. Discussion

The prevalence of black triangles is considered to be between 15% and 41.9% in the general population depending on the dental procedure performed and the age of the patient [17,18].

This systematic review and meta-analysis was based on the application of HA to treat the presence of black triangles. A total of 133 papillae in 85 patients were included in the evaluated studies.

The study by Bertl et al. [12] included 13 papillae adjacent to implants in twenty-one patients (twelve women and nine men) who were injected with HA. The manufacturer's recommended technique was used in the study. (*Hyadent Barrier Gel,* E*laf Medical Supplies, Zagreb, Croatia*) Thus, 0.36 ml of HA was injected, of which 5.76 mg were crosslinked HA and 0.72 mg were non-crosslinked HA.

The average papilla defect at the beginning of the study was 2.0 +/- 1.1. At the end of the study (6 months later), the average was 1.9 +/- 0.8. This difference was not statistically significant.

In the first study by Lee et al. [13], ten patients (four men and six women) were studied and injected with HA (a total of 43 papillae adjacent to natural teeth). For the initial examination, papilla defects with cut-off values of 0.24 mm^2 for area, 1.0 mm in height and 0.5 mm for width were chosen.

In this study, a total of 0.01 cc was injected (*Teosyal Puresense Global Action, Teoxane, Geneva, Switzerland*), of which 0.25 mg consisted of crosslinked hyaluronic acid. A maximum of 5 sessions were performed or sessions were continued until black triangles were no longer visible. The initial mean area was 1.37 +/- 0.41 mm, which was reduced to 0.70 +/- 0.20 mm at 6 months. Their results represent a decrease in the percentage of area of the black triangle.

The results show 100% total reconstruction at 29 sites and a partial reconstruction of the remaining 14 sites, with percentages between 39% and 96%. Taking the data as a whole, an average reconstruction rate of 92.55% was achieved following an average number of 3.42 injections. Of note was the 100% interdental papilla reconstruction rate in most cases for initial values of up to 0.25 mm^2 area and a height of up to 1 mm. However, when the area exceeded 0.25 mm^2 and the height was 1 mm, the results showed a statistically significant negative correlation in relation to the rate of reconstruction.

An interesting finding was that the distance between the point of contact and the bone crest had to be less than 6 mm for optimal results to be achieved, a result consistent with those obtained by other authors [19–22].

In the second study by Lee et al. [14], thirteen patients (six men and seven women) with a total of 21 papillae from the anterior maxilla region were included. Only papillae that had adjacent teeth were included.

In each session, a single dose per 0.002 cc HA (*Teosyal Puresense Global Action, Teoxane, Geneva, Switzerland*) was used with a maximum of five applications. The time interval between applications was 3 weeks (or until black triangles were no longer visible). The total injected dose was 0.01 cc, of which 0.25 mg was crosslinked HA. The initial mean height in mm was 1.58 +/- 0.54, while at six months, the mean height of the papillae was 0.70 +/- 0.29, which was a statistically significant difference with appreciable clinical effects.

The positive effect of HA on interdental papilla reconstruction was also demonstrated in the study by Singh and Vandana [11] carried out in the anterior region of the maxilla and mandible in 10 patients (two men and eight women). In total the authors studied 35 papillae.

The selected patients were classified into three groups depending on the concentration of HA being injected (1% HA in group 1, 2% HA in group 2 and 5% HA in group 3). HA was prepared by the pharmacy faculty (*College of Dental Sciences, Davangere, Karnataka, India)*, and different HA concentrations were prepared by dissolving 10, 20 and 50 mg of powder into solution (Herb supply, LLC, Las Vegas, NV). The results demonstrated significant improvements in both the 1% and 5% groups, while paradoxically, the 2% group showed no significant improvement. The initial mean sizes of the triangles were 3.59 +/-

0.93 (group 1), 3.85 +/- 1.4 (group 2) and 3.91 +/- 1.81 in the 5% group. There were no statistically significant differences between the groups at the start of the study. Six months after injection, the average size in the 1% group was 3.43 +/- 0.85 (an increase of 0.16 mm) and 4.14 +/- 1.2 in the 2% group (a decrease of -0.29 mm). Finally, in the 5% group, the mean was 3.2 +/- 1.6, with a significant increase of 0.71 mm in the interdental papillae. It should be noted that the 5% group had a smaller relapse from the third and sixth months, unlike the 1% group, which showed signs of a relapse at six months.

Mansouri et al. [15] also found a positive effect of HA on papilla reconstruction in 11 patients (three men and eight women) with a total of 21 interdental papillae in the anterior maxillary region. The authors injected a total of 0.3 ml of HA gel in three injections.

The result of this study was an average change of 5.04 +/- 1.5 mm in the papilla defect. At the first follow-up, three weeks after the first injection, there was an improvement of 0.17 +/- 0.15. In the second follow-up, three months later, there was an improvement with an average of 1.48 +/- 0.94. In the third follow-up, six months after the injection, the size of the triangle was a further improved, with an average size of 2.38 +/- 1.02. The total filling of the interdental papillae at six months was 2.66 mm. In short, the application of HA was successful in reconstructing the interdental papilla at 6 months. In addition, this was the only article that pointed to a significant association between age and papilla reconstruction ($p<0.01$). An improvement between 58.72 +/- 20.84% was observed in patients under 40 years of age, while the percentage of change observed in subjects over 40 years of age was 34.80 +/- 9.55%; however, difference in the amount of change could possibly have been due to the small sample size and dispersion.

One thing that should be emphasized is the variability in the evaluation methods used in the different studies to evaluate papilla deficiency. For example, Bertl et al. [12] used an intraoral scanner (*Tríos TM, 3-Shape, Copenhagen, Denmark*) to assess fillings and increase in volume of the papillae [12]. For their research, Lee et al. [13,14] used a standardized photographic device at the outset and in each session in both their studies and analysed the photographs using the program *Adobe Photoshop CS5 (Adobe System Inc., San Jose, USA*). Singh and Vandana [11] used a modified occlusal stent (made of transparent acrylic resin) to measure interdental papilla deficiency. To evaluate photographs, the authors used ImageJ software (*National Institute of Health, United States*). Mansouri et al. [15] took a photograph at the start of each session and used the software program ImageJ (*National Institute of Health, United States*) to calculate the variations in height.

In terms of pain assessment and side effects after HA injection, most articles made little reference either [23]. Generally, pain was attributed to the hygroscopic nature of HA, which causes vascular compression and partial occlusion of neighbouring blood vessels. No side effects were reported in any patient within six months of the injection.

In the study by Bertl et al. [23], following the initial injection of HA, pain was classified as moderate (VAS: 50-60 points). In contrast, Singh and Vandana [11] used the Numerical Pain Rating Scale (NPRS) to assess patients' discomfort. Post-injection pain was lowest in the 1% group and highest in the 5% group. However, the perception of pain decreased in all groups between the first and third injections.

Adverse effects, probably due to the injection, were also reported in three patients. Two patients had severe pain and swelling of the lip after the second injection. In another patient, a painless granuloma of approximately 6 mm diameter was observed above the mucogingival junction after the first injection. The granuloma persisted for more than 4 weeks.

4.1. Study Limitations

We found little consistency in the presentation of results; most of the included studies were of low methodological quality and belonged to the category of case series. In general, there was a lack of blinded randomised studies that could have provided reliable guidance on indications.

Moreover, the small sample sizes of the studies (between 10 and 21 patients) signify that caution should be used when interpreting the results expressed in this meta-analysis. It should be noted that the 2 studies with the highest weight were conducted by the same author (Lee 2016 JERD [13] and Lee 2016 JPIS, [13]).

Finally, consideration should be given to the heterogeneity of the studies. We must accept a hypothesis of lack of homogeneity ($p<0.0009$) since the degree of heterogeneity was very high ($I^2 = 74\%$).

4.2. Future Research Suggestions

To decrease the heterogeneity of such studies, the inclusion criteria and clinical parameters to be evaluated should be clearly established. We consider that the easiest way to perform future research would be to examine standardised measurements of papilla height. The number of cases should be sufficient to reach an adequate degree of statistical power.

5. Conclusions

The HA injection technique is effective for the reconstruction of interproximal papilla defects within six months of injection. The main limitation of the technique is the maximum increase in papilla that can be achieved. This limitation is to be expected with the injection of HA. The average filler height is 0.7 mm, which needs to be maintained with subsequent injections. In addition, total papilla reconstruction is not predictable when the distance between the point of contact and the bone crest is greater than 6 mm or the area is greater than 0.25 mm^2. Regarding the number of injections, there was no consensus in the works studied, although the minimum number of injections was three.

Despite being a minimally invasive and safe technique, certain side effects may occur after the injection of HA, with the most common side effects being moderate pain and swelling of the lip. The appearance of a painless granuloma that disappears after four weeks is a very rare side effect.

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