



Application of Hyaluronic Acid for Treatment of Interdental Papillary Deficiency: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: The focused question of this systematic review was “does hyaluronic acid (HA) injection in areas of interdental papillary deficiency reduce black triangles?”

Materials and Methods: A systematic literature search was performed to find clinical studies on human patients with a minimum of 6-month follow-up, published in English from 2005 to May 2020. There were two outcome variables: black triangle area (BTA) change after treatment at different measurement time points compared with baseline, and patient reported outcome measures (PROMs), when available.

Results: Of eight eligible articles (2 randomized clinical trials (RCTs) and 6 non-randomized, non-placebo controlled clinical studies), seven reported that HA injections had a positive impact on reduction of BTA and subsequent papillary augmentation. Six studies were included in meta-analysis and showed that the intervention led to a pooled reduction percentage of 57.7% in BTA after 6 months. Although there were clinical diversities between the studies, all the studies applied the same concentration of HA (approximately 2%), 2-3 mm apical to the papilla tip in several intervals. Some degrees of relapse were reported in some studies.

Conclusion: Within the limits of this study, this systematic review and meta-analysis showed that HA injection can serve as an efficient minimally-invasive treatment for small interdental papillary deficiencies. It is essential to conduct further randomized clinical studies with prolonged follow-ups in order to support this conclusion.

Keywords: Hyaluronic Acid; Dental Papilla; Gingiva, Esthetics; Dental; Gingival Recession

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INTRODUCTION

Modern periodontology is expected to address patients' cosmetic concerns such as the health and appearance of the gingival tissue surrounding dentition and implants as the primary components of smile esthetics [1-3]. Interdental papillae are the most visible gingival tissue which fill the gap between

adjacent teeth and/or implants up to the contact point. Interdental papilla is located in the interdental triangular space (interproximal space) called the embrasure [4]. Deficiencies of interdental papillae and gingival recession that manifest as open embrasures are often referred to as black triangles [3,5]. These may trigger

pronunciation and phonetic problems and lead to food impaction [6-10]. Interdental papillae of the anterior maxillary teeth are esthetically the most important area for patients. In a study reported by Cunliffe and Pretty [3] patients rated black triangles as the third most displeasing esthetic factor after visible caries and crown margins. Interdental papilla loss may result from periodontal disease and its treatment, trauma, age, or iatrogenic causes [2, 11-13]. In many cases, interdental papilla loss is due to aggressive interdental tooth brushing or tooth picking [14]. Furthermore, the embrasure space around dental implants is not completely filled by the interdental papillae in over half of the cases. This is generally affected by the implant position and type, gingival biotype and peri-implant diseases [15].

Various sophisticated periodontal plastic surgical procedures, grafts, and flap designs have been suggested for papillary reconstruction [13,16-21]. However, limited blood supply and access render their predictability and outcomes uncertain [21, 22]. More recent less invasive techniques are generally based on injection of various fillers to enhance papillary regeneration. In the past decade, a number of studies and clinical trials reported the injection of hyaluronic acid (HA) gel as an effective minimally-invasive treatment for cases with interdental papilla loss, mitigating patients' postoperative discomfort [23-28]. HA is a polysaccharide member of the glycosaminoglycan family present in body tissues; it is a major component of the extracellular matrix of the skin and cartilage. Under physiological conditions, HA gel absorbs water, swells the tissues, and develops a smoother and fuller tissue contour. It is also frequently used as a filler and moisturizer in cosmetic dermatology and skin care [29,30]. This aim of this study was to systematically review the clinical studies on the efficacy of HA injections (as a minimally-invasive approach) for treatment of papillary deficiencies.

MATERIALS AND METHODS

This systematic review was carried out in

compliance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

PICO question: Do local injections of HA improve interdental papillary deficiencies and reduce black triangle area (BTA)?

Population: Sites with open gingival embrasures that received HA injections

Intervention: Injection of HA in areas of interdental papillary deficiency

Comparison: BTA following treatment compared with baseline

Outcome of interest: Any change or reduction in BTA

Inclusion and exclusion criteria:

This review was conducted on randomized clinical trials (RCTs), clinical studies, and case reports in English with at least 10 papillary deficiency sites treated with HA as well as a minimum follow-up of 6 months. Studies performed on animals or not fulfilling the aforementioned criteria were excluded.

Search strategy:

An electronic search was conducted in Medline, Scopus, EMBASE, and Google Scholar. In Medline, Scopus and EMBASE, the advanced search tool was used to build the following search combinations: Interdental papilla OR black triangle OR gingival embrasure OR papillae deficiencies OR papilla deficiency OR papillary deficiencies OR dental papilla OR papilla augmentation AND [Hyaluronic acid OR Hyaluronan]. In Google Scholar, the following search criteria were used (2005 up to May 1st, 2020): hyaluronic acid AND interdental papillae OR black triangle OR gingival embrasure OR papillae deficiencies OR papilla deficiency.

Subsequently, two independent researchers (J.M. & S.A.) combined the results, removed the duplicates, and assessed the articles to omit the irrelevant ones. The two researchers were to settle any disagreement by discussion. Any relevant article found through forward search or other sources (Google search, cross-referenced articles) were also added to the list. Then, the shortlist was critically screened for the final selection. Next, the relevant data and outcomes were extracted. The outcomes were:

BTA percentage change after treatment, the difference between the BTA before and after the treatment, and the outcome measures reported by patients. Additional data were also reported regarding the year of publication, number of patients/sites, type of papilla (between teeth or between tooth and implant), number of HA injections, volume of injected HA, and different measurement time points. If necessary, the authors of the original articles were contacted for further details.

Quality assessment:

Two authors (S.A. and H.A.R.) independently determined the risk of bias of the selected studies. First, the Cochrane Collaboration's tool for assessing the risk of bias in randomized clinical trials was used to determine the potential risk of bias of RCTs, including selection bias, performance bias, detection bias, attrition bias, and reporting bias [31]. There were three scenarios: 1) a low risk of bias with all the criteria met, 2) an unclear risk with a criterion either unmet or missing, 3) a high risk of bias with a minimum of two criteria either missing or unmet [32]. For the remaining case series, the same authors used a quality assessment tool based on a modified Delphi method to identify the risk of bias in terms of study objectives, study population, intervention and co-intervention, outcome measures, statistical analysis, results, and conclusions, and competing interests and sources of support. Again, any disagreement was to be resolved by discussion to achieve a consensus; however, it did not occur. The quality assessment was performed based on the frequency of three responses (Yes", "No" or "partial") to 18 parameters, where the threshold for the acceptable quality was to receive above 70% of 'YES' responses [33,34]. Besides, the publication bias was evaluated by the funnel plot and the Begg's and Egger's tests [35].

Statistical analysis:

Once the mean and standard deviation of the percentage change in the BTA (effect size of interest) were extracted from the articles, the forest plot analysis was used to combine the standard error effect sizes. The I^2 index and Chi-square test were utilized to assess the heterogeneity. Since both the I^2 index value (65.1%) and the Chi-square test ($P=0.014$)

indicated high heterogeneity among the studies, a random effect model was applied for pooling the size effects. Furthermore, to determine the possible source of heterogeneity in the pooled meta-analysis, we also performed a leave-one-out sensitivity analysis. The statistical analysis was performed using the STATA Software version 14.0.

RESULTS

Literature selection process:

The search through the electronic databases revealed 102 articles with three additional records from the forward search which were manually added; 34 articles were left after duplicate removal, and the rest underwent a primary screening based on title, abstract, and when needed full text screening, thus removing studies not performed on human patients, models, single case reports, etc. Nine full-text articles were eventually assessed for their eligibility; two of which (Lee et al., [27] and Lee et al, [36]) reported data on the same patient cohort; consequently, it was decided to add the more recent article [27]. Figure 1 illustrates the search and selection process (PRISMA flowchart). Finally, eight articles including two RCTs (Abdelraouf et al, [37] and Bertl et al, [38]), and six non-randomized, non-placebo controlled clinical studies (Becker et al, [23] Sadat Mansouri et al, [24] Awartani and Tatakis [26], Lee et al, [27] Singh et al, [39] and Ni et al. [40]) were selected to carry out the qualitative systematic review. Two articles (Bertl et al, [38] and Singh et al. [39]) were excluded from the meta-analysis. The reason was that Bertl et al. [38] had major differences in the injection procedure compared with other studies and their study was limited to papillary deficiency between implant-supported crowns; the study constituted a clear outlier. Although Singh et al. [39] tested 3 different HA concentrations, the study suffered a number of patient dropouts, leaving only seven sites in one group with comparable concentration of HA gel (2%) to the other included studies. The corresponding authors of both articles were contacted by e-mail to inquire about the raw data; but, no responses were obtained.

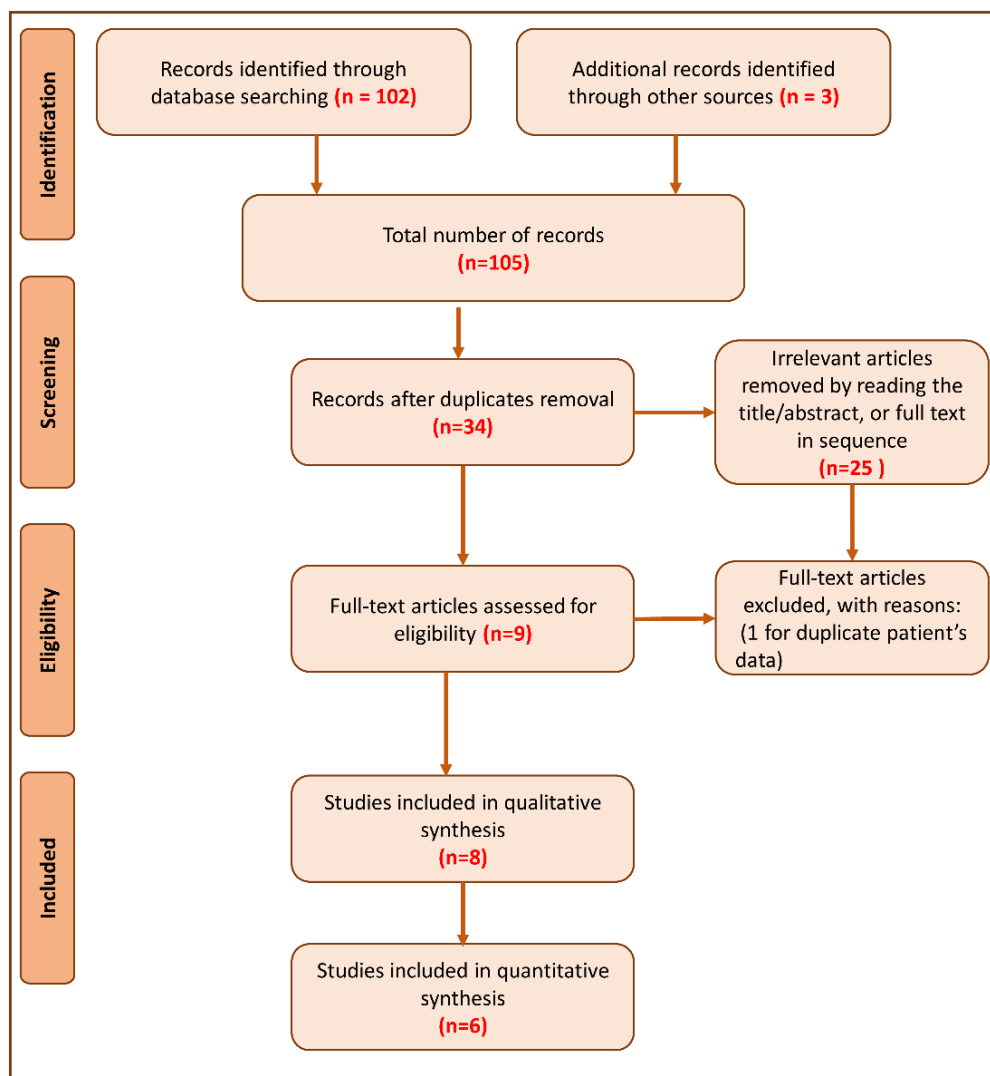


Fig. 1: Flowchart diagram of the search strategy, outlining the number of articles identified, screened, found eligible, and included in the systematic review

Characteristics of included studies:

Table 1 presents the general characteristics of 8 studies included in the systematic review.

Study design:

Two of the selected studies were RCTs [37,38]. They both had a parallel-arm design with a test group and a control group receiving HA and saline injections as placebo, respectively. The remaining studies were all case series with no control group. Only one of the clinical studies had three intervention groups, corresponding to the injection of different concentrations of HA (Singh et al. [39]). In the remaining studies, the intervention scheme was identical for all test samples.

Population, treatment site features, and setting:

All the studies were conducted in a university setting. Two recruited only females [26, 40], while the others evaluated both genders. Only two studies excluded smokers [26, 39], and one excluded both smokers and alcoholics [37]. Bertl et al, [38] only included patients with papillary deficiency between implant-supported crowns in the anterior maxilla, while Becker et al. [23] included patients with both implants and teeth with adjacent papillary deficiency. All other studies excluded patients with fixed prostheses and orthodontic appliances at affected sites.

Table 1: The general characteristics of the 8 included studies retained for the systematic review.

| Study (Year) | Study design | Patient number (sites) | Dropouts | Gender (F/M) | Mean age (y) | Inclusion of smokers | Location | Tooth or Implant | No(volume) of injections, intervals (d) | Follow-up (months) | Variables |
|---------------------------|--------------|---------------------------------|---|--------------|---|----------------------|-------------------------|----------------------|---|--------------------|--|
| Becker et al (2010) | Case series | 11(14) | NO | 7/4 | 55.8 (range: 50) | Unclear | Anterior Maxilla | 10 implants, 4 teeth | ≤3 (<0.2mL), 21 | 6-25 | % change in BTA |
| Mansouri et al (2013) | Case series | 11(21) | NO | 8/3 | 37.5±14.4 | NO | Anterior Maxilla | Teeth | ≤3 (0.2mL) 21 | 3 and 6 | Mean % change in BTA |
| Awartani & Tatakis (2015) | Case series | 9(17) | NO | 9/0 | 22–55y | NO | 13 maxilla, 4 mandible | Teeth | ≤3 (0.2mL), 21 | 4 and 6 | % change BTA BTA (mm ²) PROMs |
| Lee et al (2016) | Case series | 13(57) | NO | 7/6 | 32 (range: 27–35) | Unclear | Anterior maxilla | NR | ≤5 (0.01mL), 21 | 6 | ΔBTA (mm ²) ΔBTH (mm) ΔBTW (mm) % change in BTA |
| Bertl et al (2017) | RCT | 22(22: 11 tests, 11 Controls) | YES (1 patient/site) | 12/9 | 30±6.4 | Unclear | Anterior Maxilla | Implant | ≤2 (36mL), 28 | 3 and 6 | Mean ΔBTA (mm ²) Mean ΔBTH (mm) PROMs |
| Singh et al (2018) | Case Series | 10(1%HA: 16, 2%HA: 14, 5%HA 12) | YES (1 patient, 7 sites in 2%HA group) | 8/2 | ~30 | NO | 17 maxilla, 18 mandible | Teeth | ≤3 (<0.2mL), 7 | 1, 3 and 6 | Mean BTA (unit unclear) Mean BTH (mm) PROMs |
| Abdelraouf et al (2019) | RCT | 10(36: 18 tests, 16 Controls) | YES (2 patients, 6 sites in 2 tests/4 Controls) | 7/3 | Range: 21-47 | NO | Inter-bicuspid region | NR | ≤3 (0.1mL), 21 | 3 and 6 | Mean % change in BTA Mean ΔBTH PROMs |
| Ni et al (2019) | Case Series | 8(22) | NO | | 8F, 0M. Mean age 41.6 y, range 28–60 y | Unclear | 17 maxilla, 5 mandible | Teeth | ≤3 (0.05-0.1mL: 16mg/mL), 21 | 3, 6 and 12 | Mean ΔBTA (mm ²) Mean ΔBTH (mm) |

F: female; M: Male; year: y; d: days; BTA: black triangle area; BTH: black triangle height; BTW: black triangle width; PROMs: patient-reported outcome measures; * Δ black triangle area in unknown units

Three studies included outcomes from both mandibular and maxillary papillary deficiency sites [26, 39, 40] while others concentrated on those in the anterior maxilla. Three studies included only class I or II [41] gingival papillary loss [26,37,40]; while Singh et al. [39] included papillary deficiency sites with a Cardaropoli papilla presence index score of 2 and 3 [42]. Abdelraouf et al. [37] considered a distance between the contact point and the inter-proximal bone crest (below 7 mm) and a probing depth (≤ 4 mm) at the deficient sites as mandatory criteria for inclusion, while Bertl et al. [38] excluded sites with a probing depth > 5 mm, buccal gingival recession > 3 mm, or keratinized tissue < 2 mm in adjacent teeth. Other studies did not report on these parameters in their inclusion/exclusion criteria.

Follow-up time:

All included studies had a minimum follow-up of 6 months. Most studies reported their results between 3 and months. Becker et al. [23] reported the results with the maximum follow-up (6 to 25 months depending on patient) and Ni et al. [40] reported the results at three intervals of 3, 6, and 12 months.

Risk of bias, critical appraisal and quality assessment:

Case series were categorized at a low risk of bias as 5 of them met more than 70% of the quality assessment criteria (Table 2). Similarly, the two RCTs had a low risk of bias (Table 3). The Begg's and Egger's tests were both administered to assess the publication bias for the studies in the meta-analysis. The tests obtained P values of 0.452 and 0.041, respectively. Although the Begg's test was free of any significant publication bias, Egger's plot (Figure 2) revealed the presence of publication bias. All included studies reported no conflict of interest of their authors or their funding institutions.

Intervention modalities:

All interventions began with the application of local anesthesia followed by multiple injections of HA gel (apical to the tip of papillae), albeit with differences in the amount, concentration, frequency and number, as well as procedure of injections. Most studies used commercial forms of HA with a concentration near 2%. Three studies (Becker et al, [23] Sadat Mansouri et al, [24] and Awartani and Tatakis [26]) applied a 23-gauge needle to follow the same injection procedure (~0.2 mL of HA gel, 2-3 mm apical to the tip of the papilla).

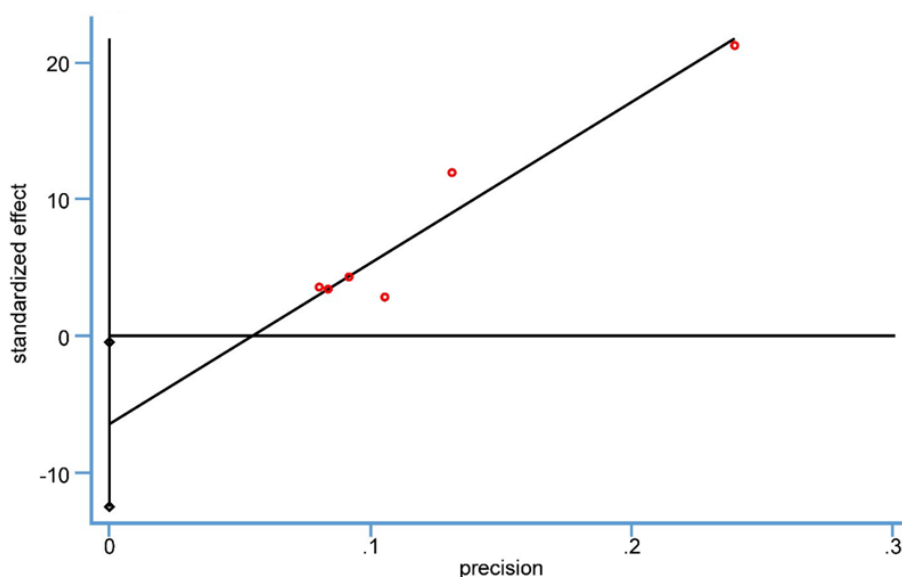


Fig. 2. Egger's publication bias plot

Table 2. Quality assessment of potential risk of bias of case studies based on modified Delphi method

| | Becker et al, 2010 | Sadat Mansouri et al, 2013 | Awartani & Tatakis, 2015 | Lee et al 2016 | Singh et al. 2018 | Ni et al, 2019 |
|---|-----------------------|-------------------------------|-----------------------------|-------------------|----------------------|-------------------|
| Study objectives | | | | | | |
| 1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section? | Yes | Yes | Yes | Yes | Yes | Yes |
| Study population | | | | | | |
| 2. Are the characteristics of the included participants described? | No | Yes | Yes | Yes | Yes | Yes |
| 3. Were the cases collected in more than one center? | unclear | No | No | No | Unclear | No |
| 4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate? | No | Yes | Partial | Yes | Yes | Yes |
| 5. Were participants recruited consecutively? | No | No | No | Yes | Yes | No |
| 6. Did participants enter the study at a similar point in the disease? | Yes | Yes | Yes | Yes | Yes | Yes |
| Intervention and Co-intervention | | | | | | |
| 7. Was the intervention clearly described in the study? | Yes | Yes | Yes | Yes | Yes | Partial |
| 8. Were additional interventions (co-interventions) clearly reported in the study? | Yes | Yes | Yes | Yes | Yes | Yes |
| Outcome measures | | | | | | |
| 9. Are the outcome measures clearly defined in the introduction or methods section? | No | No | Yes | Yes | Yes | Yes |
| 10. Were relevant outcomes appropriately measured with objective and/or subjective methods? | Yes | Yes | Yes | Yes | Yes | Yes |
| 11. Were outcomes measured before and after intervention? | Yes | Yes | Yes | Yes | Yes | Yes |
| Statistical analysis | | | | | | |
| 12. Were the statistical tests used to assess the relevant outcomes appropriate? | Yes | Yes | Yes | Yes | Yes | Yes |
| Results and Conclusions | | | | | | |
| 13. Was the length of follow-up reported? | Yes | Yes | Yes | Yes | Yes | Yes |
| 14. Was the loss to follow-up reported? | Unclear | Unclear | Yes | Yes | Yes | No |
| 15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes? | No | No | Yes | Yes | Yes | Yes |
| 16. Are adverse events reported? | Yes | Yes | Yes | No | Yes | Yes |
| Competing interests and sources of support | | | | | | |
| 18. Are both competing interests and sources of support for the study reported? | No | No | partial | partial | Yes | partial |
| Percentage of YES response to the questions | | | | | | |
| | 50% | 61% | 72% | 78% | 94% | 72% |

Table 3. Overview of black triangle area outcome results reported in the included studies (percentage change is between baseline and time point).

| Study | Groups | Mean % BTA change±SD | | Mean Δ* BTA (mm ²) | | |
|--------------------------|---------|----------------------|----------------|--------------------------------|-----------|------------|
| | | 3m | 6 m | BL-3m | BL-6m | BL-12m |
| Becker et al, 2010 | NA | NR | 91.1±12(6-25m) | NR | NR | NR |
| Mansouri et al 2013 | NA | 29.52±18.7 | 47.33±20.2 | NR | NR | NR |
| Awartani & Tatakis, 2015 | NA | 62.0±25.1(4m) | 41±36.3 | NR | NR | NR |
| Lee et al, 2016 | NA | NR | 88.8±19.4 | NR | 0.21±0.14 | NR |
| Bertl et al, 2016 | Test | NR | NR | -0.04±0.15 | 0.01±0.1 | NR |
| | Control | NR | NR | -0.02±0.07 | 0.03±0.1 | NR |
| Singh et al, 2018* | 1% HA | 18.8 | 14.2 | 89.0 | 67.2 | NR |
| | 2% HA | 6.1 | 1.7 | 19.6 | 5.3 | NR |
| | 5% HA | 42.9 | 39.8 | 142.8 | 132.5 | NR |
| Abdelraouf et al, 2019 | Test | 36.5±24.4 | 45.28±28.5 | NR | NR | NR |
| | Control | 0.9±10.6 | 2±11.4 | NR | NR | NR |
| Ni et al, 2019 | NA | NR | NR | 0.31±0.46 | 0.41±0.56 | 0.355±0.57 |

BL: baseline; NA: Not Applicable; NR: Not reported; m: months; BTA: black triangle area

* Δ black triangle area in unknown units

Becker et al, [23] and Sadat-Mansouri et al. [24] repeated the injection procedure between one to three times at three-week intervals until the black triangle totally disappeared, while in the study by Awartani and Tatakis [26], all cases equally received three injections at three-week intervals, regardless of whether the black triangle would disappear [26].

Lee et al. [27] used an injection assistance device set to 0.002mL of HA and a disposable 30-gauge needle. A single-point injection technique was employed with the needle inserted at a 45-degree angle to inject 0.002mL, 5 times (total of 0.1mL of HA), 2-3mm apical to the involved papilla. The procedure was repeated up to 5 times at three-week intervals until the black triangle was no longer clinically observable. Abdelraouf et al. [37] used a 30-gauge disposable insulin syringe to inject 0.1mL of HA (test group) or saline solution (control group) 2-3mm apical to the tip of an interdental papilla. The needle was inserted with a 45-degree angle directed coronally to the longitudinal axis of the tooth. Bertl et al. [38] applied a pressure syringe for standardized dose delivery (0.06mL/click) with a 30-gauge needle and a three-step technique.

They created a reservoir of a total amount of ~0.18mL in the mucosa immediately above the mucogingival junction.

They injected a total amount of ~0.12mL into the attached gingiva/mucosa right below the base of the deficient papilla and a total amount of ~0.06 mL 2-3mm apical to the tip of the deficient papilla. They repeated the whole injection procedure once after 4 weeks. Ni et al. [40] injected 0.05 to 0.1mL of a 16mg/mL HA solution at deficient papilla sites three times at three-week intervals without reporting the injection procedure. Singh et al. [39] was the only group using three different concentrations of HA: 1% HA (16 sites, 3 patients); 2% HA (14 sites, 3 patients), and 5% HA (12 sites, 4 patients). Insulin syringes were used to inject less than 0.2 mL of HA solutions at each site (according to its allocated group), 2-3mm apical to the coronal tip of the papilla. The procedure was repeated for two further weeks.

Outcomes reported

All studies relied on standardized clinical photographs with or without an intraoral calibration scale in order to measure BTA at baseline and at different follow-up time points. BTA was either reported in square

millimeters (mm²) or in pixel numbers, with some studies reporting the percentage change. Becker et al, [23] Awartani and Tatakis [26], and Sadat Mansouri et al. [24] reported only BTA as the clinical outcome. Other studies listed further outcomes such as the distance between the contact point of the papilla and the bone crest, the level of patient satisfaction, or the responses to surveys. Bertl et al. [38] added the change in gingival volume, a modified papilla index score, bleeding on probing, clinical attachment level, and probing depth. However, except for bleeding on probing, there were no significant differences for any of these outcomes between the baseline and measurement time points or between the test and control groups [38].

Measured clinical outcome: BTA change

Three studies reported BTA for each deficient interdental papillary site [23,26,27]. The remaining studies reported only the mean and standard deviation values. We requested the site by site data from the corresponding authors of other studies but only one provided them [24]. Table 4 provides an overview of BTA results of all the reviewed studies. Ni et al. [40] considered the difference between thick and thin gingiva (gingival biotype) and found that in patients with a thick gingival biotype, HA injections provided a more appreciable outcome for the papilla augmentation [40]. Except the study by Bertl et al, [38] all studies reported HA treatment with moderate to high levels of positive impact on BTA [23, 24, 26, 27, 37, 39, 40]. Becker et al. [23] obtained a 100 % fill in 3 out of 14 sites and 57%-97% papilla fill in the remaining 11 sites. They had variable follow-up periods (6 to 25 months) with only one patient followed for 25 months. They investigated 4 sites located between natural teeth and 10 between natural teeth and implants. They recommended the use of HA on small papillary defects [23]. Sadat Mansouri et al, [24] and Awartani and Tatakis [26] shared a similar methodology with a 6-month follow-up, yet they differed in time courses. They found rather moderate improvements

compared with Becker et al, [23] with 47% to 41 % BTA reduction. The results obtained by Sadat Mansouri et al. [24] indicated improvements over time (29% of mean BTA change in 3 months); Awartani and Tatakis [26] showed a relapse between 4 and 6 months with a mean BTA change of 62% at 4 months.

Lee et al. [27] performed the largest study with 57 sites in 13 patients. They obtained a mean percentage reduction of 88.8 ± 19.42 % at 6 months. They demonstrated both complete (36 sites with 100% reduction of black triangle) and partial (21 sites with 19% to 96% reduction with a mean percentage of $69.61\% \pm 21.06\%$) interdental papilla reconstruction. The authors did not report the intermediate follow-up time points. Abdelraouf et al. [37] reported moderate improvements in the test group (HA) with a mean BTA reduction of $36.5\% \pm 24.4\%$ at 3 months and $45.0 \pm 28.5\%$ at 6 months [37]. Their results are, therefore, comparable to those obtained by Sadat Mansouri et al [24].

Ni et al. [40] showed that HA injections had an appreciable effect on the augmentation of interdental papilla between natural teeth for patients with a thick gingival biotype at 6 months. Yet, the effect was not significant for the thin gingival biotype, and it demonstrated a relapse 12 months after the intervention [40]. All the studies used a constant concentration of HA (2% approximately). Singh et al. [39] was the only study comparing three concentrations of HA injections (1%, 2% and 5%), all causing a reduction of BTA at 1, 3, and 6-month follow-ups, but the highest percentage of improvement belonged to 5% HA group (39.8% BTA reduction). Nevertheless, intergroup comparison was not statistically significant. Their results indicated a relapse in all groups sometime between the third and sixth months.

Comparison of BTA results:

As mentioned earlier, meta-analysis was conducted on 6 out of 8 included studies. The forest plot analysis was first performed using the inverse-variance methodology to pool the

mean percentage of change. Since the I² index value of 91.8% (Chi-square test P<0.001) indicated high heterogeneity among the studies, a random effects model was applied to pool the effect sizes. Figure 3 shows the obtained forest plot from fitting this model. Accordingly, the overall (pooled) estimate of the effect size was 57.73% (95% CI: 34.0-81.47). That is, the intervention led to a reduction by 57.7% in the pooled percentage of BTA; i.e. there was a relative improvement by 58% in the mean BTA percentage change or papilla augmentation (Fig. 3). A leave-one-out sensitivity analysis was also performed to determine the possible source of heterogeneity. Figure 4 illustrates the obtained results. As shown, omitting each study from the analysis had no significant effect on the overall percentage of change of BTA. In other words, the pooled percentage of change of BTA was strong and did not depend on one single study.

Patient Reported Outcome Measures (PROMs):

Four studies relied on either a visual analog scale or “yes or no” questions to report PROMs [26, 37-39]. Awartani and Tatakis [26] found

that 6 out of 9 patients were “very satisfied” and one was “somewhat satisfied” after the treatment. Concerning the black triangle, all patients were “not satisfied” or “slightly satisfied” before the treatment. After the treatment, seven patients changed their response to “somewhat satisfied” (78%).

Bertl et al. [38] reported the level of pain during and one week after HA injections on a 0 to 100 scale. While there was no difference between the test and control groups during the injection, the control group who received saline injection reported significantly lower pain (by 20 units on the scale), one week after the injections. The authors found no significant difference between the values of patients’ esthetic assessment before and after the treatment.

In the study by Abdelraouf et al, [37] patients compared the photographs of their smiles before and after the treatment and gave them a satisfaction score on a 0 to 100 scale. The test group significantly outscored the control one (P=0.002).

| | | Abdelraouf et al. (2019) | Bertl et al. (2017) |
|----------------------------------|------------------------------------|--------------------------|---------------------|
| Selection Bias | Random Sequence Generation | + | + |
| | Allocation Concealment | + | + |
| Performance Bias | Blinding Of Participants/Personnel | + | + |
| Detection Bias | Blinding Outcome Assessment | + | + |
| Reporting Attribution Bias | Incomplete Outcome Data | + | + |
| | Selective Reporting | + | + |
| | Other Bias | - | + |
| Estimated potential risk of bias | | Low | Low |

Fig. 3: Quality assessment of potential risk of bias of included RCTs based on Cochrane risk assessment tool (green: low risk; yellow: unclear risk; red: high risk)

Pooled BTA Percentage change

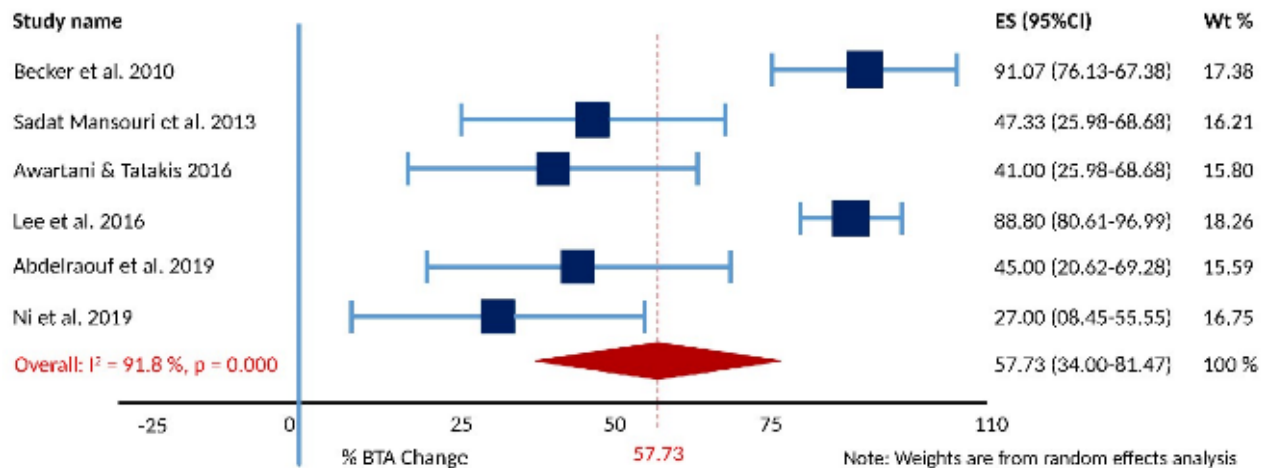


Fig. 4: Forrest plot of the pooled BTA percent change

Finally, Singh et al. [39] adopted the same approach as Awartani and Tatakis [26] to measure patient satisfaction before and after treatment. The PROMs were not categorized according to the three study groups (1%, 2% and 5% HA injections). Six out of eight patients described their smiles as “slightly impressive” and one selected “extremely impressive”.

DISCUSSION

The aim of this systematic review was to evaluate the effectiveness of a minimally invasive procedure. It reviewed how HA injections could be applied for treatment of papillary deficiencies or black triangles in the esthetic zone. Therefore, the major goal was to evaluate the level of reduction or change in BTA. To assess BTA, all studies used standardized clinical photography with slightly different standardization methods and image analysis software programs. Lee et al. [27] introduced a photographic standardization device to achieve more precision in analysis of any dimensional change in BTA. The studies also differed in the HA solutions, their concentrations, injection techniques, number of injections, follow-up duration, measurement time points, and position of black triangles (between teeth or implants).

Bertl et al. [38] were the sole group with no significant reduction in BTA. The study was a

RCT on the papilla between a natural tooth and an implant-supported crown. Accordingly, HA injections had no significant effects when comparing the groups or the time points. The study by Bertl et al. [38] had major differences with other studies. All other studies performed HA injections at one site 2 to 3 mm apical o the tip of the interdental papilla while Bert et al. [38] conducted their injections of HA at three different sites: in the nonattached mucosa, at the base, and 2 to 3mm apical to the tip of the interdental papilla. Furthermore, they only evaluated the effect of HA injections on deficient papillae between implants and natural teeth, while others dealt with deficient papillae between natural teeth. Papillae adjacent to implants possess different histological features than those adjacent to natural teeth; the peri-implant mucosa contains significantly smaller number of fibroblasts and blood supply compared with the gingiva which may negatively affect water sorption by the injected HA [38,43]. Added to the differences mentioned above, this might partially explain no significant effect reported by Bertl et al [38]. However, this is in contradiction with the results of Becker et al, [23] who showed positive effects of HA injections in deficient papillae adjacent to implants and even complete fill for three implant sites. Becker et al. [23] recommended using HA for small

papillary defects; however, they did not provide the BTA at baseline. Bertl et al. [38] had a mean BTA at baseline of $0.51 \pm 0.25 \text{ mm}^2$. Also, Lee et al. [27] showed complete fill for 36 sites with small BTAs ($0.13 \pm 0.09 \text{ mm}^2$) and partial fill ($69.61 \pm 21.06\%$) for 21 sites with larger BTAs ($0.58 \pm 0.38 \text{ mm}^2$); all these sites were adjacent to natural teeth. This shows that the BTA at baseline has a large effect on the level of papilla reconstruction but still does not explain the total absence of effect reported by Bertl et al [38].

The studies included in this meta-analysis displayed a high level of heterogeneity [I^2 index value of 91.8% (Chi-square test $P < 0.001$)], which were attributed to clinical and methodological diversity among the included studies. Concerning clinical diversity, the studies used different methods, dosages and frequency of injections (Table 1) when applying HA to papilla deficient sites. The dimension of the included defects (BTA at baseline) also differed among the studies. The studies used the BTA for the measurement of papillary deficiencies; however, black triangles are three-dimensional in nature, a feature difficult to clinically measure (the volume of the deficiency). Furthermore, Becker et al. [23] assessed defect sites adjacent to implants while others assessed defects adjacent to natural teeth, which is another potential source of heterogeneity. On the other hand, the critical appraisal of the included studies by risk of bias tools showed a certain degree of methodological diversity in the included studies. Consequently, these two types of diversities rendered a high level of heterogeneity identified in our statistical analysis.

The leave-one-out sensitivity analysis showed that the pooled percentage of BTA was not dependent on one single study. The pooled effect size or BTA change was 57.73% (95% CI: 34.00-81.47), showing that application of HA injections could bring about moderate to slightly high positive outcomes in treatment of interdental papillary deficiencies.

HA injections at smaller BTA (smaller areas to fill) tended to achieve a higher reduction in BTA. As a case in point, the mean baseline BTA obtained by Lee et al. [27] was three times lower

than that by Abdelraouf et al, [37] who introduced the size of the papillary defect before treatment as the most critical determinant for complete papilla reconstruction. Dissimilarities of the sites and gingival biotypes could account for these differences [40]. A limitation of all these studies was the relatively small number of patients and treated sites. Applying a two-dimensional photographic analysis was another limitation as it fails to consider the volume change of the papillae after the intervention.

What finally merits attention is that according to their outcome measurements, patients complained of postoperative discomfort and pain associated with HA injections. They generally reported moderate levels of satisfaction for the outcome of treatment (except those in the study by Bertl et al, [38]) and around two-thirds of them agreed to probably undergo the injection procedure again [26,37,39].

As there was a considerable source of heterogeneity in the literature and in order to obtain more precise results, randomized controlled clinical trials with larger sample sizes and long-term follow-ups are required. Studies should also evaluate the site of deficient papillae (implant or natural teeth), gingival biotypes, and papillary defect size before treatment. Standardization of the procedures and outcome measurement methods would be beneficial for such studies.

CONCLUSION

Despite the high rate of heterogeneity, the present systematic review and meta-analysis showed that HA injections can constitute an efficient minimally invasive treatment for small interdental papillary deficiencies. Overall, seven out of eight studies reported an appreciable positive effect of HA injections with moderate to complete papilla reconstruction at deficient sites.

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CONFLICT OF INTEREST STATEMENT

None declared.

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