

UNIVERSITÉ DE NANTES

UNITÉ DE FORMATION ET DE RECHERCHE D'ODONTOLOGIE

Année 2021

N° 3732

**Reconstruction papillaire à l'aide d'acide hyaluronique:
revue systématique de la littérature.**

THÈSE POUR LE DIPLÔME D'ÉTAT DE DOCTEUR

EN CHIRURGIE DENTAIRE

Présentée et soutenue publiquement par

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REMERCIEMENTS

À Monsieur le Professeur Assem SOUEIDAN

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Pour m'avoir fait l'honneur d'accepter la présidence de ce jury.

*Merci pour votre confiance, votre bienveillance et la richesse de vos
enseignements.*

*Veillez trouver ici l'expression de ma sincère reconnaissance et de mon
profond respect.*

À Monsieur le Docteur Xavier STRUILLLOU

Maître de Conférence des Universités

Praticien Hospitalier des Centres de Soins d'Enseignement et de Recherche Dentaires

Docteur de l'Université de Nantes

Département de Parodontologie

- Nantes -

Pour m'avoir fait l'honneur de diriger cette thèse.

*Merci pour votre aide, vos précieux conseils et votre réactivité tout au long de
la rédaction de ce travail.*

Pour vos grandes qualités pédagogiques, cliniques et théoriques.

Veuillez trouver ici l'expression de ma gratitude et de mon profond respect.

À Monsieur le Professeur Laurent LE GUEHENNEC

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Pour m'avoir fait l'honneur de siéger dans ce jury.

Merci pour votre investissement pendant mes années d'internat.

Pour vos compétences cliniques ainsi que votre grande disponibilité.

*Veillez trouver ici l'expression de ma sincère reconnaissance et de mon
profond respect.*

À Monsieur le Docteur Charles ALLIOT

Docteur en Chirurgie Dentaire

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Département de Parodontologie

- Nantes –

*Pour m'avoir fait l'honneur de siéger dans ce jury.
Merci pour ta collaboration et la co-écriture de cet article.
Pour ta grande réactivité, tes conseils, ton excellent travail et ton temps.
Trouve ici l'expression de mes remerciements les plus sincères.*

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Reconstruction papillaire à l'aide d'acide hyaluronique: revue systématique de la littérature.

Introduction

Depuis l'avènement de la dentisterie moderne, les espaces interdentaires dans le cadre de l'esthétique antérieure sont devenus l'un des sujets majeurs. La papille interdentaire est la partie gingivale qui occupe la zone interproximale sous le point de contact entre deux dents adjacentes. Les critères de réussite de la gestion des tissus mous dans le secteur antérieur reposent en grande partie sur l'existence d'une papille interdentaire saine et sur la formation d'un contour gingival adapté.^[1]

En plus d'avoir un effet positif sur l'esthétique du sourire, les papilles interdentaires sont importantes pour empêcher l'impaction des aliments entre les dents et contribuent à améliorer la phonétique. Donc, une déficience de la papille interdentaire aussi appelée triangle noir peut entraîner des problèmes de prononciation, d'impaction alimentaire, ainsi qu'esthétiques.^[2] Les "triangles noirs" ont été classés comme le troisième problème esthétique le plus détesté, après les caries et les mauvaises limites des couronnes.^[3]

Le problème du triangle noir entre les dents dû à une papille déficiente peut résulter de plusieurs facteurs dont entre autres^[4-6]: l'âge du sujet, la forme/taille des dents, la longueur du point de contact proximal, et l'épaisseur gingivale interproximale. Cependant, le facteur semblant le plus important restent l'augmentation de la distance point de contact-sommet de la crête alvéolaire.^[4,7] Au-delà de 5mm, il y aurait un risque de perte papillaire.

Différentes options de traitement sont souvent proposées pour fermer une embrasure gingivale ouverte, comme par exemple^[2,8-11]: l'orthodontie ou des soins restaurateurs (composite) et prothétiques (facettes, couronnes ...). Cependant, ce sont des procédures plutôt longues et/ou coûteuses, voire invasives pour les dents.

Certaines techniques ont été développées ces dernières années pour traiter la perte de papilles interdentaires, comme des techniques chirurgicales^[2,12,13]: jugées peu prédictibles, risquées, invasives et praticien-dépendant; ainsi que des méthodes d'ingénierie tissulaire, telles que l'utilisation d'une matrice dermique acellulaire régénératrice injectable^[14] et des injections de fibroblastes autologues.^[15]

En 2010, Becker et al^[16] ont été le premier à publier l'idée d'une méthode non chirurgicale consistant à injecter un gel d'acide hyaluronique dans la papille afin de reconstruire son volume.

L'acide hyaluronique est un membre de la famille des glycosaminoglycanes et un composant majeur de la matrice extracellulaire dans presque tous les tissus responsables de la résilience et du volume des tissus en raison de sa forte hygroscopicité^[17]. Il est, en effet, de plus en plus utilisé ces dernières années notamment en médecine cosmétique.

Par la suite, de nombreux auteurs se sont intéressés à cette technique comme entre autres Bertl et al^[18], Mansouri et al^[19], Awartani et al^[20], Lee et al^[21,22].

Dans ce contexte, une technique non chirurgicale, peu invasive, simple et relativement peu coûteuse de reconstruction des papilles interdentaires par injection d'acide hyaluronique apparaît comme une approche thérapeutique attrayante. Elle peut être associée probablement associée à une morbidité moindre ainsi qu'à peu de complications. De plus, elle serait, en général, plus rentable, par rapport aux techniques chirurgicales plus invasives.

Ainsi, cette étude vise à réaliser une revue systématique des études précliniques et cliniques sur l'utilisation de l'acide hyaluronique en injection dans la papille interdentaire afin de la reconstruire.

Article original

PAPILLARY RECONSTRUCTION USING HYALURONIC ACID: A SYSTEMATIC REVIEW.

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Key words : hyaluronic acid, periodontitis, gingival papilla, periodontal plastic surgery.

Declaration of interest: none

ABSTRACT:

Context: The loss of interdental papillae has become in modern dentistry, one of the most complicated aesthetic problem to resolve. A new non-surgical, minimally invasive and easy to perform technique has been proposed to reconstruct the volume of these deficient papillae: the intra-papillary hyaluronic acid injection.

Objective: The aim of this systematic review is to analyse the use of hyaluronic acid injection in the interdental space in order to reconstruct the papilla, among animal models and humans.

Methods: To January 2021, electronic databases were searched and additional hand search was performed. The search strategy was achieved according to the PRISMA guidelines. The inclusion criteria were: studies written in English, studies using hyaluronic acid, in vivo studies, studies with the specific number of specimens, case series > or = 6 patients, and studies published after 2010. The risk of bias was assessed for each study that could be assessed.

Results: A total of 20 articles was selected and investigated in this systematic review.

Conclusion: The results suggest that hyaluronic acid injections seem to be effective in reconstructing papillary volume. However, too few clinical trials with a high level of proof have been conducted on this technique at the moment. Future studies will have to work on: the size of the sample, the concentration of the product, the number and the injection method.

INTRODUCTION:

Since the advent of modern dentistry, interdental spaces in anterior aesthetic have become one of the most important topics. The interdental papilla is the gingival area that occupies the interproximal zone below the contact point between two adjacent teeth. The criteria for successful soft tissue management in the anterior region are largely based on the existence of a healthy interdental papilla and the formation of a suitable gingival contour.¹

In addition to having a positive effect on the aesthetics of smile, interdental papillae are important in preventing food impaction between teeth and contribute to improved phonetics. Therefore, a deficient interdental papilla, also known as black triangle, can lead to pronunciation problems, food impaction, as well as aesthetic problems.² "Black triangles" have been ranked as the third most hated aesthetic problem, after cavities and poor crown margins.³ The black triangle problem between teeth due to a deficient papilla can result from several factors including among others⁴⁻⁶: the age of the subject, the shape/size of teeth, the length of the proximal contact point, and the interproximal gingival thickness. However, the most important factor seems to be the increase in the distance from the contact point to the crest of bone.^{4,7}

Different treatment options are often proposed to close an open gingival embrasure, such as orthodontics or restorative and prosthetic care^{2,8-11} however, these are rather time-consuming and/or expensive procedures.

Some techniques have been developed in recent years to treat interdental papillae loss, such as surgical techniques^{2,12,13} which are considered to be unpredictable and risky, tissue engineering methods, such as the use of an injectable regenerative acellular dermal matrix¹⁴ and autologous fibroblast injections.¹⁵

In 2010, Becker¹⁶ was the first to publish the idea of a non-surgical method where the clinician injects a hyaluronic acid (HA) gel into the papilla to reconstruct its volume.

Hyaluronic acid is a member of the glycosaminoglycan family and a major component of the extracellular matrix in almost all tissues responsible for tissue resilience and volume due to its high hygroscopicity.¹⁷ It is, in fact, increasingly used in recent years, particularly in cosmetic medicine.

Subsequently, many authors have been interested in this technique, including Bertl et al¹⁸, Mansouri et al¹⁹, Awartani et al²⁰, Lee et al.^{21,22}

In this context, a non-surgical, minimally invasive, simple and relatively inexpensive technique of reconstruction of interdental papillae by HA injection appears to be an attractive therapeutic approach. It would probably be associated with less morbidity and few complications. In addition, it would generally be more cost-effective than more invasive surgical techniques. Thus, this study aims to perform a systematic review of pre-clinical and clinical studies on the use of hyaluronic acid injection in the interdental papilla in order to reconstruct it.

MATERIAL AND METHODS

The different studies concerning papilla regeneration using hyaluronic acid have been collected and analysed.

Question:

Based on the PRISMA directives²³ (Preferred Reporting Items For Systematic Reviews and Meta-Analyses), a specific question has been developed with the PICO (Participant, Interventions, Control, Outcomes) method²⁴:

« Could hyaluronic acid injection improve the reconstruction of interdental papillae in Human ? »

Information sources and search strategy:

The research strategy was achieved according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as much as possible. Original articles were searched using electronic and manual databases from January 2010 until January 2021. Furthermore, relevant articles were screened by hand to potentially add relevant new articles. This search was applied to Medline, Cochrane Library, Google Scholar and Science Direct. The following Medical Subject Heading (MeSH) terms and keywords were used:

« Hyaluronic Acid OR hyaluronan » AND « papilla OR interdental papilla OR black triangles OR open gingival embrasure »

Only English articles were included, and no publication dates or publication status restrictions were imposed.

Study selection and inclusion/exclusion criteria:

For the selection of studies, two investigators (TL, CA) screened the titles and the abstracts of the publications in an unblinded, standardized manner. Selection was based on the inclusion and exclusion criteria defined so as to include only the most valuable articles (**Table. 1**). Studies deemed to meet the inclusion criteria and those with insufficient information to make a clear decision were selected. The second phase consisted of assessing the whole articles by the same investigators to determine the eligibility of the study. The selection process was recorded in detail to a PRISMA flow diagram (**Figure. 1**). Any disagreements between the two investigators regarding inclusion of a study were resolved by discussion.

Inclusion criteria	Exclusion criteria
Studies written in English.	In vitro studies.
Studies using hyaluronic acid.	Retrospective studies.
In vivo studies, pre-clinical and clinical studies.	Studies without statistical analysis.
Studies with the precise number of specimen.	Reviews.
Case series > or = 6 patients	Case reports.
Studies published after 2010.	Case series < 6 patients

Table 1. Inclusion and exclusion criteria.

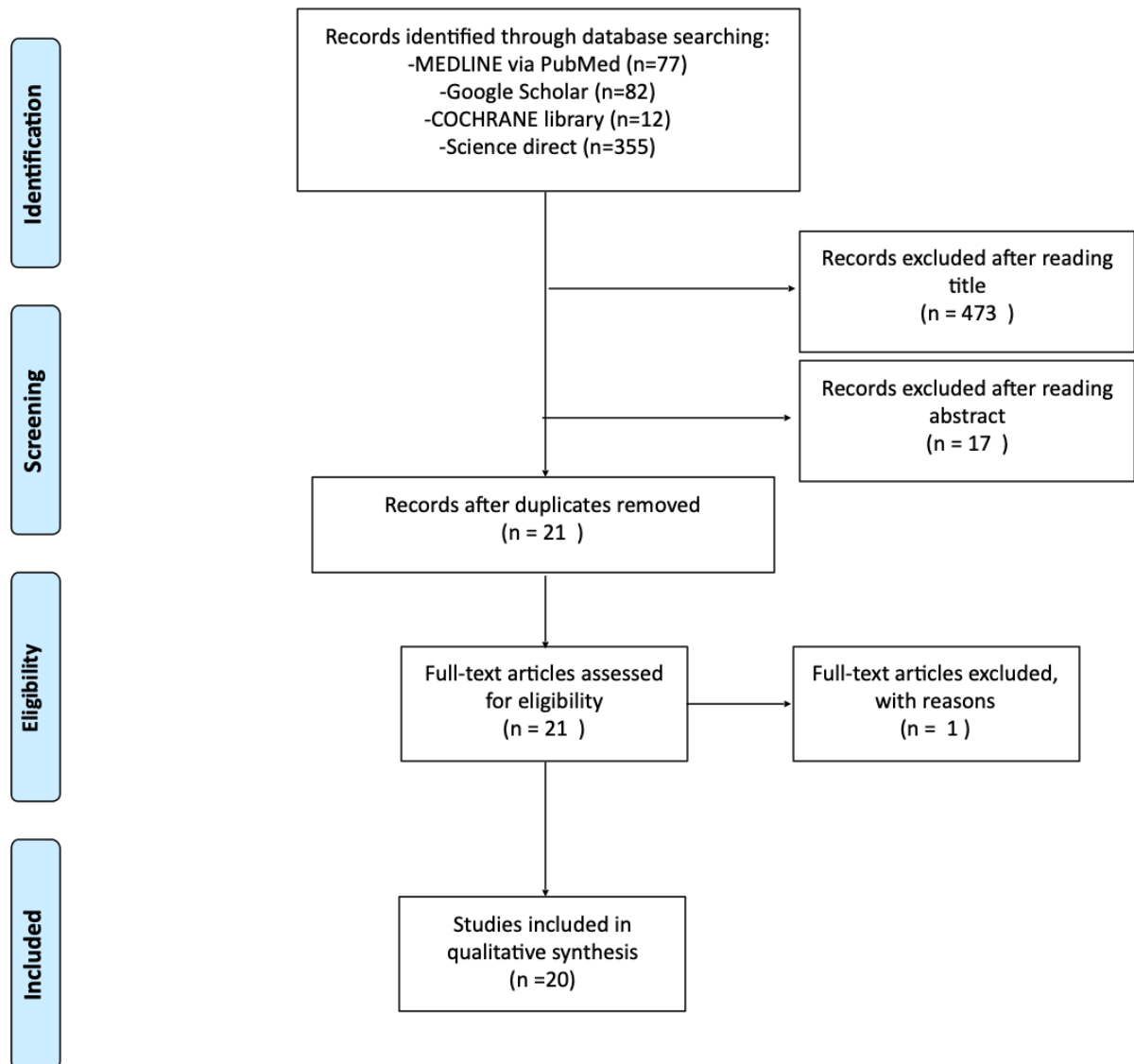


Figure 1. Flow chart PRISMA

Data collection process and data items:

The characteristics of the study were extracted independently by the same investigators and recorded. The data were compared for accuracy and any discrepancies were discussed and resolved by consensus.

Both reviewers extracted from the included studies the following data: (1) Type of study; (2) Cases; (3) Observation period; (4) Treated sites and classification used; (5) Drop out; (6) Biomaterials; (7) Injection method; (8) Measurement method; (9) Results; (10) Adverse

reaction (**Table 2 and 3**). If one of these data is not reported in the table, it means that the information is not mentioned by the authors.

For the systematic review²⁵, the two reviewers extracted the following data: (1) Type of study; (2) Number of included studies; (3) Inclusion period; (4) Inclusion criteria; (5) Exclusion criteria; (6) Results; (7) Conclusion. (**Table. 4**) If any of these data are not reported in the table, it means that the information is not mentioned by the authors.

Risk of bias in individual studies:

To ascertain the risk of bias in eligible articles, the same investigators in a blind manner evaluated their methodology either by SYRCLE's Risk of Bias tool²⁶ for animal intervention studies; or by the Cochrane Collaboration's tool²⁷ for human randomized trials. The case series were excluded from the risk of bias analysis because of the absence of adapted methodology.

Data synthesis:

A meta-analysis could not be performed because of the heterogeneity in protocols of the studies and the products used. Consequently, we conducted a descriptive and systematic analysis of the studies.

RESULTS

Study selection:

Taking into account the previously defined criteria, 526 studies were initially identified (**Figure. 1**). The electronic search of Medline, Cochrane Library, Google Scholar and Science Direct databases provided 526 articles. After adjusting for duplicates and reading the title and/or the abstract, 21 studies remained. Out of these, only 1 was discarded²⁸ because after reviewing the whole article, it appeared that these papers clearly did not meet the inclusion criteria (cases < 6). A total of 20 articles were included in the systematic review.

Study characteristics:

The 20 articles were then classified in comparative tables (**Table. 2, 3 and 4**).

The tables show an important variety in the types of hyaluronic acid used. Here are the main brands, each with a different formula: Restylane®, Hyadent BG®, Teosyal puresense Global action Teoxane®, Hyalgan®, Flex barrier®, Revident®.

The work began with an analysis of the type of population in each article. The study includes 2 pre-clinical animal studies^{29,30}, one on 20 female rats and the other on 20 male mice. It also includes 2 randomized clinical trials^{18,31} on humans containing respectively 10 patients/36 treated deficient interdental papillae (DIP) and 21 patients/21 treated deficient interdental papillae, as well as 15 case series on humans including between 6 and 40 patients and between 7 and 200 treated deficient interdental papillae.

Among these studies, we find heterogeneity in the classifications used to evaluate the papillary defect, the classification of Nordland and Tarnow³² is however the most used.

The same is true for the measurements and measurement methods used: clinical measurements, non-standardized photographs, standardized photographs, radiography, radiography with marker, digital impressions.

After local anaesthesia, two injection techniques were mostly used, the first consisting of injecting HA 2-3 mm apically to the top of the interdental papilla with variations depending on the orientation of the bevel. This technique was found in 15 of the 19 pre-clinical and clinical studies. The second, named "Three steps technique" consisting of: (1) creation of a reservoir in the mucosa immediately above the muco-gingival junction, (2) injection into the attached gingiva just below the base of the deficient papilla, and (3) injection 2-3 mm apically at the tip of the deficient papilla, was found in 4 of the 19 studies, all of which used Hyadent BG® (recommendations for use).

The frequency of injection of biomaterials varies greatly from one study to another. Some studies propose only one injection, while others propose up to 5 injections spaced 3 weeks apart. The observation period for these cases is generally 6 months, except for two studies which go to 24 and 25 months.^{16,33}

We completed our review by analysing the number of patients excluded by study and the analysis of possible side effects found after injection in the long or short term. Few side effects have been described in general. Bertl et al¹⁸ found two patients with varying degrees of swelling, hypersensitivity, burning sensation, and discoloration of the mucosa.

Risk of bias within studies:

The results of the risk of bias assessment are shown in **Figure 2**. A suitable methodology was applied for each subgroup of studies: pre-clinical animal studies (**Figure 2.a**), and randomized human trials (**Figure 2.b**). Case series were excluded from the risk of bias analysis because of the lack of adapted methodology.

Pre-clinical studies: Only 2 studies were included in this category. Our data show a high score of low risk of bias for selection bias (66%), attrition bias (100%) and other sources of bias (100%). However, it exists a high score of unclear risk of bias for reporting (100%) and detection (50%) bias; and a high risk of bias concerning the blinding of these studies which were never mentioned.

Randomized human trial: Only 2 studies were includes in this category. Our data shows a high score of low risk of bias for selection (100%), detection (100%), attrition (100%), and reporting bias (50%). 50% of reporting bias and 100% of others sources of bias were unclear after reading these studies. There is a high risk of bias concerning the performance bias because the clinician in these studies were not blinded whereas patients and the outcome assessor were blinded. In fact, it was impossible for the researcher to be blinded due to the difference in consistency and resistance to injection between hyaluronic acid gel and saline solution.

Synthesis of results:

For each selected study, the significant results are presented in **Table 2** for the pre-clinical animal models, **Table 3** for the human studies and **Table 4** for the systematic literature review.

DISCUSSION

Among all these studies, we note an important heterogeneity in the classifications of papillary loss used, in the biomaterials used, and in the more or less standardized methods of measurement making these studies difficult to analyse quantitatively. However, all agree on the aesthetic interest of this minimally invasive technique. Only anterior aesthetic regions (maxilla or mandible) have been treated.

In the two preclinical studies^{29,30} after having developed an animal model with deficient interdental papillae that is reliable and reproducible using a compression arch, the authors performed injections into these deficient papillae using Hyaluronic Acid. In these two studies of 20 animals each, significant decreases in the papilla-arch distance were found. Although these studies have biases and are difficult to translate to humans, the results are encouraging. Relatively few studies on humans have been yet carried out in the literature. Indeed, only 2 randomized clinical trials^{18,31} representing the highest level of evidence could be found in this study. These trials are different in many ways: in the biomaterial used, in the method and frequency of injection and in the methods of measurement.

The first trial, performed by Abdelraouf et al³¹, resulted in a significant decrease in the height and surface area of the black triangles in the hyaluronic acid group versus the saline group at 3 and 6 months compared to baseline.

This trial was performed only on natural teeth, unlike the Bertl¹⁸ et al trial where the injection was performed only on papillae in front of maxillary anterior implants. Indeed, Bertl et al found no difference between the groups (saline solution versus HA), either at 3 months nor at 6 months, a result that contradicts Abdelraouf et al. This result could be explained by the differences in histological characteristics between the peri-implant mucosa and the gingiva around natural teeth. Indeed, the peri-implant mucosa contains less fibroblasts than the gingiva and also presents a reduced blood perfusion due to the absence of periodontal ligament.³⁴ This reduced vascularity will limit the rheological effect of the hyaluronic acid injected at the site.

Since the 2010 pilot study by Becker et al¹⁶, which first described the innovative technique, several case series have been published. Of the 15 studies included in our systematic review, all found significant results. Although the case series are of the lowest level of evidence and include major biases, the overall results tend to converge towards a decrease in the height and surface area of post-injection black triangles.

In the study by Singh S et al³⁵, after comparison of different percentages of HA in injection, the results point towards the use of 5% HA, which would be more effective than 2% and 1% HA. In order to specify the ideal concentration to be injected, other studies with a larger number of patients and a greater follow-up must be conducted.

Shawky et al³⁶ compared the effects of an alternative to HA, Radiesse®, a product based on calcium hydroxyapatite, which is increasingly used in cosmetic medicine. A significant improvement was observed in both groups. However, the improvement was greater in the Radiesse group, which also had a longer-lasting effect but slightly more inflammation. Further studies on the use of Radiesse® in intra-papillary injection will have to be conducted to clarify the clinical superiority or not of Radiesse over hyaluronic acid gels.

Ficho AC. et al²⁵, carried out a systematic review of the literature on the same subject published in 2020, indicating that the percentage of papillary reconstruction after 6 months of application is, according to them, 77.41%, with an average number of applications of 3.17. However, with their chosen criteria they could only include 4 studies. We have chosen to include as many studies as possible in order to have the most global presentation possible of the current state of the literature on this technique. In all the publications studied, only that of Bertl et al¹⁸ presents undesirable effects, in addition to the mild postoperative pain already described.

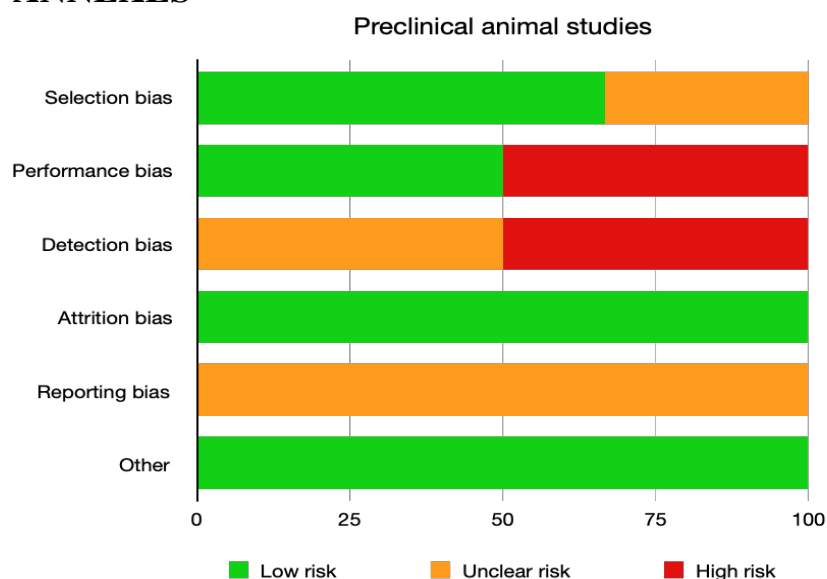
CONCLUSION

In conclusion, within the limitations of this study, the use of a commercially available hyaluronic acid gel for the treatment of interdental papillary deficiency seems to be effective and promising. In addition, a realistic prognosis must be presented to the patients regarding the expected results of the treatment and the possibility of reinjecting HA into the deficient papillae in the longer term must be explained. The indications must be very precisely defined and the patients well chosen.

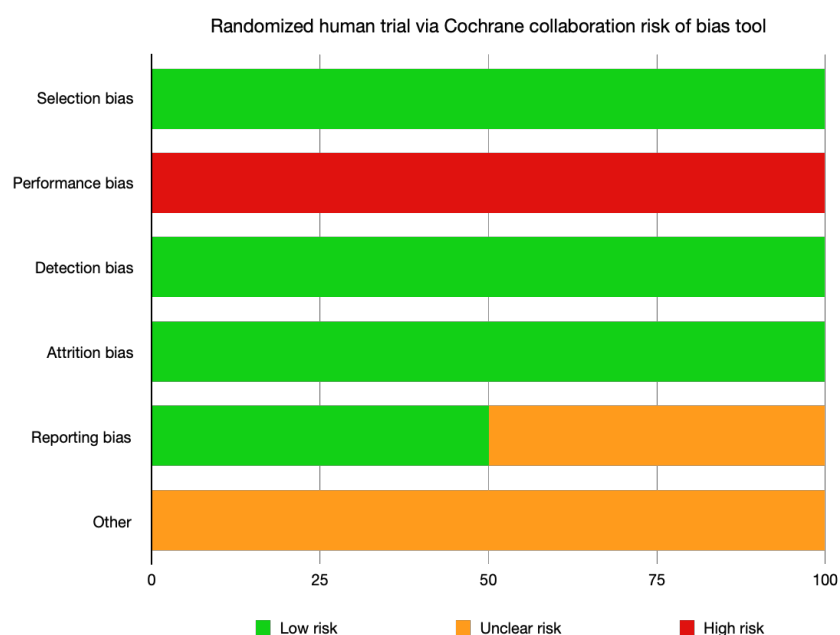
Randomized clinical trials will have to be carried out in the longer term in order to have studies with a better level of proof to validate or not this technique and the various indications.

Criteria that need to be worked on are: the size of the sample for more power and representativeness, the concentration of the product, the number and the injection technique in order to obtain a protocol more and more standardized and also to answer an aesthetic request of our patients.

ANNEXES



A. PRECLINICAL ANIMAL STUDIES



B. RANDOMIZED HUMAN TRIALS STUDIES

Figure 2. Risk of bias assessment of included studies.

- A. Risk of bias graph for animal studies, using the SYRCLE's tool, averaged per item.
- B. Risk of bias graph for randomized human trials, using the Cochrane Collaboration's tool, averaged per item.

The green, yellow and red colours depict the percentages of studies with low, unclear or high risk of bias of the total number of assessed studies.

Reference	Type of study	Cases	Observation period	Treated sites and classification used.	Drop out	Biomaterials	Injection method	Measurement method	Results	Adverse reaction
Pi S. <i>et al</i> 2017 ²⁹	Preclinical study	20 female rats (Orient bio, Seongnam, Korea) after 7 days of space opening with a spring.	At Day 0 and Day 2.	Open gingival embrasure is standardized between the lower incisors after 7 days.	No	Restylane® (a non-cohesive and cross-linked HA filler of non-animal origin)	-method: 20µl of either PBS (n=10) or HA fillers (n=10) was locally injected within the interdental papilla, approximately 5-6mm apical from the interdental papilla crest, using a 31G needle. -frequency: once	-standardized serial photographs: At day 0 before the injection and at day 2. interdental distance and SPD (spring papilla distance) was evaluated. -micro CT: was taken 2 days after the injection of PBS or HA filler. BPD (bone papilla distance) was evaluated. -histological Examination thickness of 4 µm	-standardized serial photographs: The interdental distance was comparable in both PBS and HA filler groups. SPD was significantly attenuated following the injection of HA filler compared to the injection of PBS ($p<0.05$). -micro CT: BPD was significantly increased after the injection of HA filler compared to PBS ($p<0.05$). -histological Examination: the interdental papilla became convex and inner granules containing hyaluronic acid were detected within the submucosal layer.	None.
Kim SB. <i>et al</i> 2020 ³⁰	Preclinical study	20 male mice (Orient bio, Seongnam, Korea) after 5 days of space opening with a spring.	At Day 0, 2 and 7 post-injection.	Open gingival embrasure is standardized between the lower incisors after 5 days.	No	Restylane®	-method: 10µl of either PBS (n=10) or HA fillers (n=10) was injected 1–2 mm below the IDP crest after upward the bevel of the syringe with a 30 G needle. -frequency: once	-standardized serial photographs: At day 0 before the injection, at Day 2, 4 and at Day 7. SPD (spring papilla distance) was evaluated. -histological analysis of IDP : was performed using H&E staining on days 2 and 7 post-PBS or -HA filler injection. -immunohistochemical analysis: was performed to determine the localization patterns of TNF- α , interleukin (IL)-1 β , IL-6, myeloperoxidase (MPO), and Ki67.	-morphological examination: The SPD of the HA filler injection group was significantly lower than that of the PBS injection group on days 2, 4, and 7 post-injection -histological analysis: HA filler was stable in the connective tissue underlying the epithelial tissue even on day 7 post-injection. -immunohistochemical analysis: TNF- α , IL-1 β , IL-6, MPO, and Ki67 were highly localized to the connective tissue surrounding the filler on day 2, which decreased on day 7 post-injection.	None.

Table 2. Comparative table of pre-clinical animal studies in the use of hyaluronic acid.

Reference	Type of study	Cases	Observation period	Treated sites and classification used.	Drop out	Biomaterials	Injection method	Measurement method	Results	Adverse reaction
Abdelraouf SA. <i>et al</i> 2019 ³¹	RCT	10 patients (3 males and 7 females) aged 21 to 47 years.	At baseline, 3 months and 6 months.	36 deficient interdental papillae (DIP) in the anterior region. 2 patients dropouts So, 30 DIP HY group (n=16 papillae) Saline group (n=14 papillae) Papillary deficiency types I or II (Nordland and Tarnow classification)	2 patients excluded.	Restylane Lidocaine® (concentration of 20 mg/ml.)	-method: 0.1 mm of HA gel or saline solution using a 30-gauge disposable insulin syringe was inserted 2-3 mm apical to the tip of the interdental papilla and directed coronally with an angulation of 45° to the long axis of the tooth, and the bevel directed apically. -frequency: at baseline, 3- and 6-weeks intervals.	-clinical measurement: height of the black triangle: distance between the deficient papilla tip and contact area (PT- CP distance) (probe+stent) -standardised digital clinical photographs: surface area of black triangles. (SABT) (0.5 X height X base)	After three and six months from baseline: the results revealed a statistically significant higher mean decrease in height and surface area of black triangles in favour of the HA group. From three to six months: there was no statistically significant difference between the two groups in both parameters. At 6 months: the HA group showed a statistically significant higher mean satisfaction score than the saline group.	Not detected.

Bertl K. <i>et al</i> 2017 ¹⁸	RCT	22 patients (9 males, 12 females) mean age 30 6.4 years. HA group (n=11) Saline group (n=10)	At baseline, 3 months and 6 months.	21 deficient interdental papillae (DIP) in the anterior maxilla. (after the one ejected) Modified papilla index score were used. (MPIS)	1 patient excluded because of a fracture of his crown.	Hyadent Barrier Gel ® (1 ml of the gel contains 16 mg cross-linked Na-hyaluronate and 2 mg Na-hyaluronate)	-method: Using pressure syringe for standardized dose delivery (0.06 ml per “click”) with a 30-gauge needle and a 3-step technique : -creation of a reservoir in the mucosa immediately above the mucogingival junction (total amount ca. 0.18 ml) -injection into the attached gingiva/mucosa just below the base of the deficient papilla (total amount ca. 0.12 ml) -injection 2–3 mm apically to the tip of the deficient papilla (total amount ca. 0.06 ml) -frequency: At baseline then repeat at 4 weeks.	-clinical measurement: Width of KT, Gingival phenotype, Tissue texture and colour, MPIS, Distance between the papilla tip (PT) and the contact point (CP), Pocket depth (PD), clinical attachment level (CAL), bleeding on probing (BoP), and plaque. -standardized digital clinical photographs: Area of the “black triangle”. -Intraoral scanner: Mucosal volume gain apically to the deficient papilla. -Radiographic examination: Bone level measurement. -Visual analogue scale (VAS): Pain level and aesthetic appearance.	No differences were observed between groups, neither at baseline nor at 3 and 6 months post-treatment. Mean PT-CP ranged between 1.8 mm and 2.3 mm without significant differences between groups or over time within groups; MPIS was 2 for all patients at all time points. Similarly, insignificant differences between groups or time points were observed for deficient area, gingival volume changes, bone level, and aesthetic appearance.	2 patients: discomfort, swelling, extreme tenderness with a burning sensation, skin discoloration. The symptoms lasted for up to 7 days, and in both cases, symptoms resolved without problems
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Becker W. <i>et al</i> 2010 ¹⁶	Case series	11 patients (7 females, 4 males) mean age of 55.8 years (ranging from 25 to 75 years).	From 6 to 25 months after the initial injections.	14 DIP in the anterior region.	No patients excluded.	Restylane®	-method: Less than 0,2mL of Gel was injected 2–3 mm apical to the tip of the papilla. -frequency: Three weeks after the initial treatment, (if the dark space remained) another injection was applied. This sequence was repeated up to three times.	-Digital clinical photographs (NOT standardized): the area of the black triangle was measured thanks to a computer program, (changes in pixels)	Three implant sites and one site adjacent to a tooth had 100% improvement between treatment examinations. Seven sites improved from 94 to 97%, three sites improved from 76 to 88%, and one site adjacent to an implant had 57% improvement. At final examination, none of the patients showed evidence of relapse, although this is possible over time.	Not described All patients judged the procedure painless.
Mansouri M. <i>et al</i> 2013 ¹⁹	Case series	11 patients (3 males and 8 females) mean age of 37.5±14.4 yrs (range 22-61 yrs.)	At baseline, 3 weeks, 3 months and 6 months.	21 DIP in the anterior maxillary region.	No patients excluded.	Hyaluronic acid gel (No reference).	-method: Less than 0.2 ml of the hyaluronic acid gel was injected at the respective sites 2-3 mm apical to the coronal tip of the papilla. -frequency: At baseline, 3 weeks if needed, 6 weeks if needed.	Clinical examination: -periodontal status (Maynard classification) -recessions (Miller classification) Radiographic examination: bone crest-contact point distance was calculated and recorded. Photograph examination: Photographs were assessed by Image J software based on image pixels.	Application of hyaluronic acid gel for reconstruction of interdental papilla was successful in a 6-month period. In the second follow up, 10% of subjects showed improvement in interdental papilla reconstruction by 50%. In the third follow up (at 6 months) 43% of samples showed 50% improvement or higher. The mentioned differences were statistically significant . (p<0.05).	No complication, hypersensitivity or allergy was noted.

Awartani FA. <i>et al</i> 2016 ²⁰	Case series	10 female patients mean age of 36.4 years (age range 22– 55 years)	At baseline, 3 months and 6 months.	17 anterior sites (13 maxillary, 4 mandibular) with DIP. 4 maxillary sites were classified as class II and 13 sites were classified as class I. (Nordland and Tarnow classification)	1 excluded because of smoking	Hyadent Barrier Gel®	-method: 0,2ml Injected directly into the middle of the papilla, 2– 3 mm apical to the tip of the papilla, using a 23-gauge needle. -frequency: at baseline, 21 days and then at 42 days.	-Digital clinical photographs standardized: surface area (in mm²) (0.5 X height X base) thanks to an image analysis software. % reduction area= (baseline area – postoperative area) × 100/baseline area. -Patient satisfaction: thanks to surveys.	The lost interdental papilla area at baseline and at the 3- and 6-month postoperative visits was 1.2 ± 1.8 mm² (mean ± SD), 0.6 ± 0.9 mm², and 0.7 ± 0.7 mm², respectively. Differences between baseline and postoperative visits were statistically significant ($p < 0.0001$) No statistically significant difference ($p > 0.12$) between the two postoperative time points.	Limited swelling and tenderness at the injection site, were reported and typically lasted for the first 2–3 postoperative days.
WP Lee. <i>et al</i> 2016 ²¹	Case series	13 patients (6 males 7 females) mean age of 32 years (age range 27-35 years)	At baseline and 6 months.	57 treated sites in the maxillary anterior region.	No patients excluded.	Teosyal puresense Global action Teoxane®	-method: The needle was inserted at a 45° angle, 2–3 mm apical to the involved papilla in a single-point injection technique, and the bevel of the injection needle was applied sloping upward. Each involved papilla was injected with a total of 0.01 cc by injecting 0.002 cc of hyaluronic acid gel each time. -frequency: injection was made 5 times every 3 weeks.	-Clinical photographs standardized and radiographic examination standardized: (thanks to a device) 3 measurements of the BT area(BTA), BT height (BTH), and BT width (BTW) were taken from clinical photographs. Radiographic measurements of the contact point-bone crest (CP-BC) and the interproximal distance between roots (IDR) were undertaken. The interdental papilla reconstruction rate (IPRR) was calculated to find the percentage change of BTA.	All sites showed improvement between treatment examinations. Thirty-six sites had complete interdental papilla reconstruction and 21 sites showed improvement ranging from 19% to 96%. The CP-BC correlated with the IPRR. More specifically, when the CP-BC reached 6 mm, virtually complete interdental papilla reconstruction via injectable hyaluronic acid gel was achieved.	None

WP Lee et al 2016 ²²	Case series	10 patients (4 male and 6 female) mean age of 32 years (from 27 to 35 years)	At baseline and 6 months.	43 treated sites in the maxillary anterior region.	No patients excluded.	Teosyal pureSense Global action Teoxane®	-method: The needle was inserted at a 45° angle, 2–3 mm apical to the involved papilla in a single-point injection technique, and the bevel of the injection needle was applied sloping upward. Each involved papilla was injected with a total of 0.01 cc by injecting 0.002 cc of hyaluronic acid gel each time. -frequency: injection was made 5 times every 3 weeks.	-Digital clinical photographs standardized: Three measurements of the BT area(BTA), BT height (BTH), and BT width (BTW) were taken for each of the acquired clinical photographs. The image analysis program was used for the measurements.	29 sites had complete papilla reconstruction and 14 sites improved from 39 to 96% of interdental papilla reconstruction rate. Complete interdental papilla reconstruction was performed when black triangle at initial examination had area of < or =0.25 mm ² , height of < or =1mm, or width of < or = 0.5mm.	None
Shawky et al 2017 ³⁶	Case series	30 female patients (from 25 to 35 years)	At baseline, 3 weeks, 3 months, six months.	40 DIP in the anterior maxilla were divided into 2 groups, one received HA filler and the other one received Radiesse, a Calcium hydroxylapatite (CaHA) fillers. Papilla Presence Index (PPI) were used.	No patients excluded.	Group A: HA, HYALGAN® (Sodium Hyaluronate) Group B: RADIESSE® (calcium hydroxylapatite)	Group A : a 23-gauge needle was used to inject less than 0.2 mL of HYALGAN, 2-3 mm apical to the coronal tip of the involved papillae. Group B: 0.2 mL of a RADIESSE®**/LIDOCAINE*** blend was injected 2-3 mm apical to the coronal tip of the papillae.	-Clinical measurement: Papilla Presence Index (PPI) ,Papillary Marginal Gingival Index (PMGI), Probing Depth (PD) and Clinical Attachment Loss (CAL). -Standardized digital clinical photographs: measure the height of the papilla thanks to Image J software.	Significant improvement occurred in both groups but this improvement was more prevalent in Radiesse group compared with HA group. There was a decline in the papillary height in the HA group after three and six months while in Radiesse group more long-lasting effect was denoted.	Radiesse filler showed mild inflammation after 3 weeks in 3 patients while in the HA group, inflammation was initially denoted in only 2 patients (after 6 months).

Singh S. <i>et al</i> 2019 ³⁵	Case series	10 patients 25-40 years old.	At baseline, 1 month, 3 months, and 6 months.	42 DIP into 3 groups: HA 1%: 16 sites HA 2%: 14 sites HA 5%: 12 sites Total 35 sites were followed up out of 42.	2 patients excluded.	HA was prepared without adding any cross linked agents. (known to cause allergic reaction) The preparation of injectable from HA from raw powder was performed in college of Pharmacy.	-method: Injection 2-3mm apical to the coronal tip of the papilla -frequency: Injection was repeated on 2nd and 3rd weeks.	-Clinical measurement: from contact point to tip of the papilla using the fixed reference point of stent. -Photographic analysis: distance between the reference point and the tip of papilla using Image J software. Changes in the area of interest was calculated. -Pain with a numeric scale	-Clinical measurement: -5% of HA showed highly significant enhancement ($P=0,001$) of 19.2%, 20.6% 18.2% at 1, 3, and 6 months respectively. -2% of HA showed no significant enhancement ($P = 0.125$) -1% of HA showed significant enhancement ($P = 0.004$) -Photographic analysis: 5% of HA showed highly significant enhancement of 41%, 42.9%, and 39.8% at 1, 3, and 6 months, respectively. However, intergroup comparison showed non significant improvement	No significant perception of pain in 1% and 2% at each injection, in 5%, there was pain perception at all 3 injections. No adverse reaction
Ni J. et al 2019 ³⁷	Case series	8 female participants. Mean age 41.6 years (from 28 to 60 years).	At baseline, 3 months, 12 months.	22 DIP in the anterior (maxillary or mandibular) region with class I or II of Tarnow and Nordland classification.	No patients excluded.	QI sheng biological agent 16mg/ml HA.	-method: Every site received 0.05 to 0.1 mL of 16 mg/mL hyaluronic acid gel at the base of the deficient papilla. -frequency: at baseline, 3 weeks and 6 weeks.	-Photograph examination: Photographs were assessed by a software based on image pixels to measure the height of the papilla and the area of the papilla.	The height of the gingival papilla increased 0.311, 0.45, and 0.4 mm from baseline at 3, 6, and 12 months, respectively, after treatment ($P < .05$), whereas the area of the black triangle was reduced by 0.31, 0.41, and 0.36 mm ² at the same time points ($P < .05$).	None

Turgut Z. <i>et al</i> 2020 ³³	Case series	20 patients (10 male and 10 female) mean age of 34 years (range 24 to 44 years).	At baseline 3 months, 12 months, 24 months.	200 DIP into consecutive papillae regions in both arches. modified papilla index score (MPIS) with a score 2 were included.	No patients excluded.	Hyadent Barrier Gel®	-method: Three equidistant injections (27G needle) were made to the region corresponding to the triangle base; one injection was made to the top of the triangle, and two injections were made to the area between these two points. (amount of injection was decided by checking the pressure and tissue colour). -frequency: After the first session, injections were applied to the same points at 3-week intervals. (2nd or 3rd injection)	-digital impression method: area of interdental space percentage change in the area value over time	A significant improvement was determined in the area values of both arches at 3, 12, and 24 months compared to the baseline values. The filling percentage was found to be 55% at 3 months, 72% at 12 months, and 79% at 24 months. (more quickly and at a higher level in the maxilla)	None
Alhabash R. et al 2020 ³⁸	Case series	21 (7 male 14 female) mean age of 36.9 years. (±9.16 years)	At baseline, 3 weeks, 3 months, and 6 months.	86 treated DIP (58 sites in the maxillary jaw and 28 sites in the mandibular jaw) Classification Nordland et Tarnow.	No patients excluded.	Hyadent Barrier Gel®	-method: Three step technique A 0.2 ml of Hyaluronic acid was injected with the three step technique on each papilla. -frequency: injections were repeated after 21 days.	-Photograph examination: Black triangle height and the amount of papilla fill were measured thanks to a software.	The mean reduction of black triangle (BT) height was 0.17 mm (8% reduction) (P-value <0.001), at the 3 month interval there was a mean reduction of BT height of 0.83 mm (39% reduction) (P-value <0.001). At 6 months however, the reduction in BT height was 0.62 mm (29% reduction) (P-value <0.001).	None

Firkova et al 2020 ³⁹	Case series	19 patient (range 23 - 72 years)	At baseline, 1 month, 3 months, and 6 months.	57 treated DIP class I and class II of Nordland Tarnow classification were included.	No patients excluded.	Hyadent Barrier Gel®	-method: HA was injected 2-3 mm apical to the papilla tip, with a 23 gauge needle, directed coronally. The volume of the injected gel was tailored individually, till whitening of the adjacent tissue was noticed. Then few droplets of HA were topically applied and massages onto the treated area. -frequency: The injection was repeated after 20 days	-Photograph examination: Photographs were assessed by a software based on image pixels to measure the height of the papilla and the area of the papilla.	There was a statistically significant change in the papilla level and fill of the interproximal space, ranging from 59% papilla gain on the first month, 72% to the third month and 77% on 6 months. In total, a significant reduction in papilla height of 1.92 mm was observed between baseline and the sixth month following treatment.	None
Mandel et al 2020 ⁴⁰	Case series	40 patients (30 females and 10 males) mean age 44.0 (±13.03) Flex Barrier: n=20 Revident : n=20	At baseline, one week , one month.	160 DIP (98 treated site and 62 control site) Nordland and Tarnow Classification NB: at least one upper and one lower papillary defect was left untreated and served as a negative control.	9 patients were excluded (8 not attend the control appointment and 1 got herpetic lesion)	Reference material: Flex barrier gel: (2/3 cross-linked and 1/3 non-cross-linked HA) VS Revident : (Moscow , Russia) 1% HA	-method: “Three Step Technique” : (1) injection of the gel with a 30G needle along the mucogingival junction at the base of the papilla at 4-5 sites, creating depots of 0.1ml per site, (2) injection of the gel into the attached gingiva at the base of the papilla at 2-3 sites, creating depots of 0.1ml per site, (3) injection of the gel into the papilla 2-3 mm from its tip at one site, creating a depot of 0.1 ml. -frequency: once	-Photograph examination: Photographs were assessed by a software based on image pixels to measure the size of the black triangle.	As a general rule, we can state that the smaller the initial lesion, the greater the improvement in the reduction of the “black triangle” lesion. However, the long-term results are largely dependent on the patient’s individual interdental oral hygiene rather than on the type of hyaluronic acid gel	None

Kapoor et al 2020 ⁴¹	Case series	6 patient (4 females and 2 males) mean age 37.5 (range 20 - 61 years).	At baseline 3 weeks 3 month and 6 month.	7 treated sites in the maxillary anterior teeth. Nordland and Tarnow classification. (class I and II)	All participant were followed-up.	A commercially available hyaluronic-based gel,(<0,2 ml) 0,2%.	-method: Local anaesthesia and injection of 0,2ml of 0,2% HA 2-3 mm to the tip of the papilla. -frequency : 2nd and 3rd doses at 3 weeks and 3 month.	-Clinical measurement: Measurements of the black triangle were done clinically from the tip of the papilla to the contact point of the associated teeth using the periodontal probe and stent as a reference.	There was a statistically significant difference observed at 3 month in all seven cases.	No complication hypersensitivity or allergy was noted.
Patil et al 2020 ⁴²	Case series	8 patients (3 males and 5 females) mean age 32 (range 27 - 35 years)	At baseline and 3 weeks 3 months	14 treated DIP in the upper anterior region.	None	A commercially available hyaluronic-based dermal filler (<0.2 mL)	-method : injected 2–3 mm apical to the tip of the papilla -frequency: Patients were seen 3 weeks after the initial treatment, and if the dark space remained another injection was applied. This sequence was repeated up to three times.	-Photograph examination: Clinical photographic measurements of the black triangle area (BTA), black triangle height (BTH), and black triangle width (BTW) were undertaken. For the analysis of the effects of the injectable HA gel, the interdental papilla reconstruction rate (IPRR) was defined as the percentage of change in the initial BTA to the final BTA after 3 months.	After performing interdental papilla reconstruction using injectable HA gel, a mean IPRR of 89.25% was found with 2.57 injections, whereas BTA, BTH, and BTW showed a mean decreased of 0.25, 0.85, and 0.34 mm ² , respectively.	None

Pitale U. et al 2021 ⁴³	Case series	7 patients (2 males 5 females) 25 sites mean age 30,96 .	At baseline, 3 months and 6 months.	25 treated DIP . Nordland and Tarnow classification.	No patients dropped out	A commercially available cross-linked mild type, 20 mg/ml concentrated, 400 µm was obtained from GENOS S®	-method: injection was made 2–3 mm apical to the coronal tip of papillae with a 23G × 25 mm intraoral injection needle at a 45° angle. -frequency: once	-Photograph examination: Photographic analysis was performed by using the Image analysis software- GNU Image Manipulation Program (GIMP)	At 3 month 52 % (13 of 25) had complete papillary coverage clinically but 12 of 25 with image analysis. At 6 month clinical measurement and image analysis method showed the same results 12 of 25 sites had complete papillary coverage and 13 of 25 had partial papillary coverage.	Not described
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Table 3. Comparative table of human studies in the use of hyaluronic acid.

Reference	Type of study	Number of included studies	Inclusion period	Inclusion criteria	Exclusion criteria	Results	Conclusion
Ficho AC. <i>et al</i> 2020 ²⁵	Systematic-review	4 studies were included (Becker, Mansouri, Lee, Lee)	The bibliographic search ended in June 2019.	-Population: patients with black triangles in aesthetic regions; -Intervention: application of HA; -Comparison: evaluation before and after HA; -Outcome: picture analysis of the size of black triangles; -Study design: clinical before-after studies (prospective or retrospective) without restrictions of year, language, or publication status (in press publications were included).	-Studies not related to the topic; -Studies in animals; -Review studies, letters to the editor or editorials, congress abstracts, personal opinions, and books and/or book chapters. -Studies with pregnant women.	The studies showed the percentage of papillary reconstruction after 6months of application, the weighted average by sample size was 77.41% (SD = 20.68), with an average number of applications of 3.17 (SD = 0.31).	The application of HA may be used to repair aesthetic defects in the papilla.

Table 4. Table of systematic review in the use of hyaluronic acid.

BIBLIOGRAPHY:

1. Choquet V, Hermans M, Adriaenssens P, Daelemans P, Tarnow DP, Malevez C. Clinical and radiographic evaluation of the papilla level adjacent to single-tooth dental implants. A retrospective study in the maxillary anterior region. *J Periodontol*. 2001 Oct;72(10):1364–71.
2. Prato GPP, Rotundo R, Cortellini P, Tinti C, Azzi R. Interdental papilla management: a review and classification of the therapeutic approaches. *Int J Periodont Restor Dent*. 2004 Jun;24(3):246–55.
3. Cunliffe J, Pretty I. Patients' ranking of interdental 'black triangles' against other common aesthetic problems. *Eur J Prosthodont Restor Dent*. 2009 Dec;17(4):177–81.
4. Chen M-C, Liao Y-F, Chan C-P, Ku Y-C, Pan W-L, Tu Y-K. Factors influencing the presence of interproximal dental papillae between maxillary anterior teeth. *J Periodontol*. 2010 Feb;81(2):318–24.
5. Chow YC, Eber RM, Tsao Y-P, Shotwell JL, Wang H-L. Factors associated with the appearance of gingival papillae. *J Clin Periodontol*. 2010 Aug ;37(8):719–27.
6. Souza CA, Pinho RCM, de Siqueira RAC, de Andrade ALFS, Vajgel B de CF, da Silva Neto JC, et al. Factors influencing the presence of papilla between adjacent implants and between a tooth and an implant. *Acta Stomatol Croat*. 2019 Dec;53(4):337–46.
7. Tarnow DP, Magner AW, Fletcher P. The effect of the distance from the contact point to the crest of bone on the presence or absence of the interproximal dental papilla. *J Periodontol*. 1992 Dec;63(12):995–6.
8. Kokich VG. Esthetics: the orthodontic-periodontic restorative connection. *Semin Orthod*. 1996 Mar;2(1):21–30.
9. Heymann HO. Conservative concepts for achieving anterior esthetics. *J Calif Dent Assoc*. 1997 Jun;25(6):437–43.
10. Kandasamy S, Goonewardene M, Tennant M. Changes in interdental papillae heights following alignment of anterior teeth. *Aust Orthod J*. 2007 May;23(1):16–23.
11. Sharma AA, Park JH. Esthetic considerations in interdental papilla: remediation and regeneration. *J Esthet Restor Dent*. 2010 Feb;22(1):18–28.
12. Nemcovsky CE. Interproximal papilla augmentation procedure: a novel surgical approach and clinical evaluation of 10 consecutive procedures. *Int J Periodont Restor Dent*. 2001 Dec;21(6):553–9.
13. Lee E-K, Herr Y, Kwon Y-H, Shin S-I, Lee D-Y, Chung J-H. I-shaped incisions for papilla reconstruction in second stage implant surgery. *J Periodont Implant Sci*. 2010 Jun;40(3):139–43.
14. Geurs NC, Romanos AH, Vassilopoulos PJ, Reddy MS. Efficacy of micronized acellular dermal graft for use in interproximal papillae regeneration. *Int J Periodont Restor Dent*. 2012 Feb;32(1):49–58.
15. McGuire MK, Scheyer ET. A randomized, double-blind, placebo-controlled study to determine the safety and efficacy of cultured and expanded autologous fibroblast injections for the treatment of interdental papillary insufficiency associated with the papilla priming procedure. *J Periodontol*. 2007 Jan;78(1):4–17.

16. Becker W, Gabitov I, Stepanov M, Kois J, Smidt A, Becker BE. Minimally invasive treatment for papillae deficiencies in the esthetic zone: a pilot study. *Clin Implant Dent Relat Res*. 2010 Mar;12(1):1–8.
17. Sutherland IW. Novel and established applications of microbial polysaccharides. *Trends Biotechnol*. 1998 Jan;16(1):41–6.
18. Bertl K, Gotfredsen K, Jensen SS, Bruckmann C, Stavropoulos A. Can hyaluronan injections augment deficient papillae at implant-supported crowns in the anterior maxilla? A randomized controlled clinical trial with 6 months follow-up. *Clin Oral Implants Res*. 2017 Sep;28(9):1054–61.
19. Sadat Mansouri S, Ghasemi M, Salmani Z, Shams N. Clinical application of hyaluronic acid gel for reconstruction of interdental papilla at the esthetic zone. *J Islam Dent Assoc Of Iran*. 2013;25(3):208–13.
20. Awartani FA, Tatakis DN. Interdental papilla loss: treatment by hyaluronic acid gel injection: a case series. *Clin Oral investig*. 2016;20(7):1775–80.
21. Lee W-P, Seo Y-S, Kim H-J, Yu S-J, Kim B-O. The association between radiographic embrasure morphology and interdental papilla reconstruction using injectable hyaluronic acid gel. *J Periodont Implant Sci*. 2016;46(4):277.
22. Lee W-P, Kim H-J, Yu S-J, Kim B-O. Six month clinical evaluation of interdental papilla reconstruction with injectable hyaluronic acid gel using an image analysis system. *J Esthet Restor Dent*. 2016 Jul;28(4):221–30.
23. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *The BMJ [Internet]*. [cited 2021 Apr 29]. Available from: <https://www.bmj.com/content/339/bmj.b2700>
24. da Costa Santos CM, de Mattos Pimenta CA, Nobre MRC. The PICO strategy for the research question construction and evidence search. *Rev Lat Am Enfermagem*. 2007 Jun;15(3):508–11.
25. Ficho AC, de Souza Faloni AP, Pennisi PRC, Borges LGF, de Macedo Bernadino Í, Paranhos LR, et al. Is interdental papilla filling using hyaluronic acid a stable approach to treat black triangles? A systematic review. *J Esthet Restor Dent*. 2021 Apr;33(3):458-465.
26. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol*. 2014 Mar;14:43.
27. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br Med J*. 2011 Oct 18;343:d5928.
28. Tanwar J, Hungund S. Hyaluronic acid: hope of light to black triangles. *J Intl Soc Prev Community Dent*. 2016;6(5):497.
29. Pi S, Choi YJ, Hwang S, Lee D-W, Yook JI, Kim K-H, et al. Local injection of hyaluronic acid filler improves open gingival embrasure: validation through a rat model. *J Periodontol*. 2017;88(11):1221–30.
30. Kim S-B, Cho J, Jue S-S, Park JH, Kim J-Y. Effect of hyaluronic acid filler injection on the interdental Papilla in a mouse model of open gingival embrasure. *Int J Environ Res Public Health*. 2020;17(14):4956.
31. Abdelraouf SA, Dahab OA, Elbarbary A, El-Din AM, Mostafa B. Assessment of hyaluronic acid gel injection in the reconstruction of interdental papilla: a randomized clinical trial. *Open Access Maced J Med Sci*. 2019 Jun 15;7(11):1834–40.

32. Nordland WP, Tarnow DP. A classification system for loss of papillary height. *J Periodontol*. 1998 Oct;69(10):1124–6.
33. Çankaya ZT, Tamam E. An examination of the 2-year results obtained from hyaluronic acid filler injection for interdental papilla losses. *Quintessence Int*. 2020;51(4):274–84.
34. Chow YC, Wang H-L. Factors and techniques influencing peri-implant papillae. *Implant Dent*. 2010 Jun;19(3):208–19.
35. Singh S, Vandana KL. Use of different concentrations of hyaluronic acid in interdental papillary deficiency treatment: A clinical study. *Journal of Indian Society of Periodontology*. 2019;23(1):35.
36. Shawky HA, Darwish MM. Clinical application of radiesse and hyaluronic acid gel for treatment of papillae deficiencies in the esthetic zone. *Egypt Dent J*. 2017;63(1):533–45.
37. Ni J, Shu R, Li C. Efficacy evaluation of hyaluronic acid gel for the restoration of gingival interdental papilla defects. *J Oral Maxillofac Surg*. 2019;77(12):2467–74.
38. Alhabashneh R, Alomari S, Khaleel B, Qinawi H, Alzaubi M. Interdental papilla reconstruction using injectable hyaluronic acid: A 6 month prospective longitudinal clinical study. *J Esthet Restor Dent*. 2021 Apr;33(3):531–537.
39. Firkova E. Minimally invasive reconstruction of deficient papillae with hyaluronic acid-treatment protocol and 6-months results. *J IMAB Ann Proceed Sci Papers*. 2020;26(4):3408–15.
40. Mandel I, Farkasdi S, Varga G, Nagy ÁK. Comparative evaluation of two hyaluronic acid gel products for the treatment of interdental papillary defects. *Acta Stomatol Croat*. 2020;54(3):227.
41. Kapoor S, Dudeja A. Derma fillers: Ray of light in black triangles—A pilot study. *Contemp Clin Dent*. 2020;11(1):55.
42. Patil SC, Dhalkari CD, Indurkar MS. Hyaluronic acid: ray of hope for esthetically challenging black triangles: a case series. *Contemporary Clinical Dentistry*. 2020;11(3):280.
43. Pitale U, Pal PC, Thakare G, Verma M, Dhakad S, Pandey R. Minimally invasive therapy for reconstruction of lost interdental papilla by using injectable hyaluronic acid filler. *J Indian Soc Periodontol*. 2021;25(1):22.

Discussion et conclusion

Parmi toutes ces études, nous remarquons une grande hétérogénéité dans les classifications de perte papillaire utilisées, dans les biomatériaux utilisés, et dans les méthodes de mesures plus ou moins standardisées rendant ces études difficilement analysables quantitativement. Cependant, toutes s'accordent sur l'intérêt esthétique de cette technique peu invasive, seulement des régions esthétiques antérieures (maxillaire ou mandibulaire) ont été traitées.

Dans les deux études précliniques^[23,24], après avoir développé un modèle animal avec des papilles interdentaires déficientes qui est fiable et reproductible à l'aide d'un arc de compression, les auteurs ont réalisé des injections dans ces papilles déficientes à l'aide d'acide hyaluronique. Dans ces deux études de 20 animaux chacune, des diminutions significatives de la distance papille-arc ont été retrouvées. Bien que ces études aient des biais et soient difficiles à transposer à l'Homme, les résultats sont encourageants.

Relativement peu d'étude sur l'Homme ont été encore réalisées actuellement dans la littérature. En effet, seulement 2 essais cliniques randomisés^[18,25] (meilleur niveau de preuve) ont pu être inclus dans cette étude. Ces essais sont différents en nombreux points: dans le biomatériau utilisé, dans la méthode et la fréquence d'injection et dans les méthodes de mesures.

Le premier essai, réalisé par Abdelraouf et al^[25], a eu pour résultat une diminution significative de la hauteur et de la surface des triangles noirs dans le groupe acide hyaluronique versus le groupe solution saline à 3 mois et à 6 mois comparé au point de départ. Cet essai, étant réalisé seulement sur des dents naturelles est à l'inverse de l'essai de Bertl et al^[18] où l'injection n'a été réalisée que sur des papilles en regard d'implant antérieur maxillaire. En effet, Bertl et al n'ont retrouvé aucune différence entre les groupes (solution saline versus HA), que ce soit au départ à 3 mois ou à 6 mois, résultat contradictoire avec Abdelraouf et al. Ce résultat pourrait s'expliquer par les différences de caractéristiques histologiques existantes entre la muqueuse péri-implantaire et la gencive autour de dents naturelles. En effet, la muqueuse péri-implantaire contient beaucoup moins de fibroblastes que la gencive et présente également une perfusion sanguine réduite en raison de l'absence de ligament parodontal^[26]. Une perfusion sanguine réduite peut, à son tour, influencer négativement l'attraction de l'eau par l'acide hyaluronique injecté.

Depuis, l'étude pilote de Becker et al^[16] de 2010, qui a décrit en premier la technique prometteuse, plusieurs séries de cas ont été publiées. Sur les 15 études incluses dans notre revue systématique, toutes retrouvent des résultats significatifs ou d'amélioration de la situation. Bien que les séries de cas soient du plus bas niveau de preuve et comprennent des biais majeurs, la globalité des résultats tendent à converger vers une diminution de la hauteur et de la surface des triangles noirs post injection.

Dans l'étude de Singh S. et al^[27], après comparaison de différents pourcentages d'HA en injection, les résultats nous orientent vers une utilisation d'un HA à 5% qui serait plus efficace que ceux à 2% et 1%.

Shawky et al^[28] ont comparé à l'acide hyaluronique, les effets d'une alternative à l'acide hyaluronique, le Radiesse®, produit à base d'hydroxyapatite de Calcium, à priori de plus en plus utilisé en médecine cosmétique. Une amélioration significative a été constatée dans les deux groupes. Néanmoins, cette amélioration était plus importante dans le groupe Radiesse ayant également un effet plus durable mais entraînant une inflammation légèrement plus marquée. D'autres études sur l'utilisation de Radiesse® en injection intra-papillaire devront être menées pour clarifier la supériorité clinique ou non de Radiesse® par rapport aux gels d'acide hyaluronique.

Ficho AC. et al^[29], ont réalisé une revue systématique de la littérature sur le même sujet, nous indiquant que le pourcentage de reconstruction papillaire après 6 mois d'application est, selon eux, de 77,41%, avec un nombre moyen d'applications de 3,17. Cependant, cette revue n'inclut que 4 séries de cas que nous avons aussi incluses, donc moins significatif et moins représentatif de la littérature présente à l'heure actuelle.

Seulement l'étude de Bertl. et al^[18] a trouvé des effets indésirables, en plus de la légère douleur post-opératoire déjà décrite.

En conclusion, dans les limites de cette étude, l'utilisation d'un gel d'acide hyaluronique disponible dans le commerce pour le traitement de la déficience papillaire interdentaire s'est avérée efficace et prometteuse. De plus, un pronostic réaliste doit être présenté aux patients concernant les résultats attendus du traitement et la possibilité de réinjecter de l'acide hyaluronique à plus ou moins long terme dans les papilles déficientes. Les indications doivent être très précisément définies et les patients bien choisis.

Des essais cliniques randomisés devront être réalisés à plus long terme afin d'avoir des études avec un meilleur niveau de preuve pour valider ou non cette technique et ces différentes indications.

Les critères sur lesquels il faudra travailler sont : la taille de l'échantillon pour plus de puissance et de représentativité, la concentration du produit, le nombre et la technique d'injection dans le but d'obtenir un protocole de plus en plus standardisé et de répondre à une demande esthétique de nos patients.

Bibliographie:

1. Choquet V, Hermans M, Adriaenssens P, Daelemans P, Tarnow DP, Malevez C. Clinical and radiographic evaluation of the papilla level adjacent to single-tooth dental implants. A retrospective study in the maxillary anterior region. *J Periodontol* 2001;72(10):1364–71.
2. Prato GPP, Rotundo R, Cortellini P, Tinti C, Azzi R. Interdental papilla management: a review and classification of the therapeutic approaches. *Int J Periodont Restor Dent* 2004;24(3):246–55.
3. Cunliffe J, Pretty I. Patients' ranking of interdental 'black triangles' against other common aesthetic problems. *Eur J Prosthodont Restor Dent* 2009;17(4):177–81.
4. Chen M-C, Liao Y-F, Chan C-P, Ku Y-C, Pan W-L, Tu Y-K. Factors influencing the presence of interproximal dental papillae between maxillary anterior teeth. *J Periodontol* 2010;81(2):318–24.
5. Chow YC, Eber RM, Tsao Y-P, Shotwell JL, Wang H-L. Factors associated with the appearance of gingival papillae. *J Clin Periodontol* 2010;37(8):719–27.
6. Souza CA, Pinho RCM, de Siqueira RAC, de Andrade ALFS, Vajgel B de CF, da Silva Neto JC, et al. Factors influencing the presence of papilla between adjacent implants and between a tooth and an implant. *Acta Stomatol Croat* 2019;53(4):337–46.
7. Tarnow DP, Magner AW, Fletcher P. The effect of the distance from the contact point to the crest of bone on the presence or absence of the interproximal dental papilla. *J Periodontol* 1992;63(12):995–6.
8. Kokich VG. Esthetics: the orthodontic-periodontic restorative connection. *Semin Orthod* 1996;2(1):21–30.
9. Heymann HO. Conservative concepts for achieving anterior esthetics. *J Calif Dent Assoc* 1997;25(6):437–43.
10. Kandasamy S, Goonewardene M, Tennant M. Changes in interdental papillae heights following alignment of anterior teeth. *Aust Orthod J* 2007;23(1):16–23.
11. Sharma AA, Park JH. Esthetic considerations in interdental papilla: remediation and regeneration. *J Esthet Restor Dent* 2010;22(1):18–28.
12. Nemcovsky CE. Interproximal papilla augmentation procedure: a novel surgical approach and clinical evaluation of 10 consecutive procedures. *Int J Periodont Restor Dent* 2001;21(6):553–9.
13. Lee E-K, Herr Y, Kwon Y-H, Shin S-I, Lee D-Y, Chung J-H. I-shaped incisions for papilla reconstruction in second stage implant surgery. *J Periodont Implant Sci* 2010;40(3):139–43.

14. Geurs NC, Romanos AH, Vassilopoulos PJ, Reddy MS. Efficacy of micronized acellular dermal graft for use in interproximal papillae regeneration. *Int J Periodont Restor Dent* 2012;32(1):49–58.
15. McGuire MK, Scheyer ET. A randomized, double-blind, placebo-controlled study to determine the safety and efficacy of cultured and expanded autologous fibroblast injections for the treatment of interdental papillary insufficiency associated with the papilla priming procedure. *J Periodontol* 2007;78(1):4–17.
16. Becker W, Gabitov I, Stepanov M, Kois J, Smidt A, Becker BE. Minimally invasive treatment for papillae deficiencies in the esthetic zone: a pilot study. *Clin Implant Dent Relat Res* 2010;12(1):1–8.
17. Sutherland IW. Novel and established applications of microbial polysaccharides. *Trends Biotechnol* 1998;16(1):41–6.
18. Bertl K, Gotfredsen K, Jensen SS, Bruckmann C, Stavropoulos A. Can hyaluronan injections augment deficient papillae at implant-supported crowns in the anterior maxilla? A randomized controlled clinical trial with 6 months follow-up. *Clin Oral Implants Res* 2017;28(9):1054–61.
19. Sadat Mansouri S, Ghasemi M, Salmani Z, Shams N. Clinical application of hyaluronic acid gel for reconstruction of interdental papilla at the esthetic zone. *J Islam Dent Assoc Iran* 2013;25(3):208–13.
20. Awartani FA, Tatakis DN. Interdental papilla loss: treatment by hyaluronic acid gel injection: a case series. *Clin Oral Investig* 2016;20(7):1775–80.
21. Lee W-P, Seo Y-S, Kim H-J, Yu S-J, Kim B-O. The association between radiographic embrasure morphology and interdental papilla reconstruction using injectable hyaluronic acid gel. *J Periodont Implant Sci* 2016;46(4):277.
22. Lee W-P, Kim H-J, Yu S-J, Kim B-O. Six month clinical evaluation of interdental papilla reconstruction with injectable hyaluronic acid gel using an image analysis system. *J Esthet Restor Dent* 2016;28(4):221–30.
23. Pi S, Choi YJ, Hwang S, Lee D-W, Yook JI, Kim K-H, et al. Local injection of hyaluronic acid filler improves open gingival embrasure: validation through a rat model. *J Periodontol* 2017;88(11):1221–30.
24. Kim S-B, Cho J, Jue S-S, Park JH, Kim J-Y. Effect of hyaluronic acid filler injection on the interdental papilla in a mouse model of open gingival embrasure. *Int J Environ Res Public Health* 2020;17(14):4956.
25. Abdelraouf SA, Dahab OA, Elbarbary A, El-Din AM, Mostafa B. Assessment of hyaluronic acid gel injection in the reconstruction of interdental papilla: a randomized clinical trial. *Open Access Maced J Med Sci* 2019;7(11):1834–40.
26. Chow YC, Wang H-L. Factors and techniques influencing peri-implant papillae. *Implant Dent* 2010;19(3):208–19.

27. Singh S, Vandana KL. Use of different concentrations of hyaluronic acid in interdental papillary deficiency treatment: a clinical study. *J Indian Soc Periodontol* 2019;23(1):35.
28. Shawky HA, Darwish MM. clinical application of radiesse and hyaluronic acid gel for treatment of papillae deficiencies in the esthetic zone. *Egypt Dent Journal* 2017;63(1): 533–45.
29. Ficho AC, de Souza Faloni AP, Pennisi PRC, Borges LGF, de Macedo Bernadino Í, Paranhos LR, et al. Is interdental papilla filling using hyaluronic acid a stable approach to treat black triangles? A systematic review. *J Esthet Restor Dent*. 2021 Apr;33(3):458-465.

LIEPPE (Thibault). – Reconstruction papillaire à l'aide d'acide hyaluronique: revue systématique de la littérature. – XX f. ; ill. ; tabl. ; 43 et 29 ref. ; 30 cm (Thèse : Chir. Dent. ; Nantes ; 2021)

RÉSUMÉ :

Introduction : La perte des papilles interdentaires est devenue, dans la dentisterie moderne, l'un des problèmes esthétiques les plus compliqués à résoudre. Une nouvelle technique non chirurgicale, peu invasive et facile à réaliser a été proposée pour reconstruire le volume de ces papilles déficientes: l'injection intra-papillaire d'acide hyaluronique. Cette étude vise à réaliser une revue systématique des études précliniques et cliniques sur l'utilisation de l'acide hyaluronique en injection dans la papille interdentaire afin de la reconstruire.

Méthodes : Les bases de données électroniques ont été consultées jusqu'en janvier 2021 et une recherche manuelle supplémentaire a été effectuée. La stratégie de recherche a été réalisée conformément aux directives PRISMA. Les critères d'inclusion étaient les suivants : études rédigées en anglais, études utilisant l'acide hyaluronique, études in vivo, études avec le nombre spécifique de spécimens, séries de cas > ou = 6 patients, et études publiées après 2010. Le risque de biais a été évalué pour chaque étude qui pouvait l'être.

Résultats : Au total, 20 articles ont été sélectionnés et étudiés dans le cadre de cette revue systématique.

Conclusion : Les résultats suggèrent que les injections d'acide hyaluronique semblent être efficaces pour reconstruire le volume papillaire. Cependant, trop peu d'essais cliniques à haut niveau de preuve ont été réalisés avec cette technique pour le moment. Les études futures devront travailler sur : la taille de l'échantillon, la concentration du produit, le nombre et la technique d'injection.

RUBRIQUE DE CLASSEMENT : Odontologie - Parodontologie

MOTS CLÉS MESH :

Acide Hyaluronique – Hyaluronic acid

Parodontite – Periodontitis

Papille dentaire – Dental papilla

Chirurgie plastique – Surgery, plastic

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