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Research Article

Applications of Hyaluronic Acid in Treatment of Periimplant Diseases. A Systematic Review

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Abstract

Objective: Hyaluronic acid is a viscous glycosaminoglycan detected in all periodontal tissues in varying quantities. It may act as a mediator of periodontal tissue regeneration, because of its presence in periodontal tissues and its anti-inflammatory capacity. The objective of this systematic review was to evaluate the potential effect of hyaluronic acid in the treatment of perimucositis and peri-implantitis.

Methods: The international literature in 9 electronic databases was thoroughly studied, using a specific search strategy. The screening process included 6 publications, 5 of them regarding to peri-implantitis and 1 of them relating to perimucositis.

Results: Four RCTs and 2 split mouth studies were examined that showed that although there is a significant difference in BOP, PD and CAL indices were not improved, after the use of hyaluronic acid.

Conclusion: This is the first systematic review regarding HA and treatment of periimplant diseases. The use of hyaluronic acid as an adjunct may have a positive effect in peri-implantitis and no noticeable effect in perimucositis treatment.

Keywords: *Hyaluronic Acid; Hyaluron; Peri-Implantitis; Perimucositis; Treatment*

Introduction

Hyaluronic acid (HA) belongs to the category of glucosamines [1] and participates in many important biological processes [2]. It has a high molecular weight, and its structure consists of glucuronic acid and N-acetyl glucosamine polyanionic disaccharide units, linked by bl-3 and bl-41 alternating bonds. It acts as a mediator of cellular signaling, regulation of adhesion, proliferation and cell differentiation [2]. The effect of HA on cell proliferation and differentiation depends on its molecular weight (MW) and concentration. In addition, the properties of high viscosity, elasticity, biocompatibility, biodegradability and non-immunogenicity make HA a promising material for the treatment of diseases [2].

HA has been detected in all periodontal tissues. It is particularly evident in non-mineralized tissues such as the gums and periodontal ligament, and only in small amounts in inorganic tissues such as cementum and alveolar bone. The high molecular weight HA present in periodontal tissues is synthesized by hyaluronan synthetase (HAS) enzymes (HAS1, HAS2 and HAS3) in various cells of the periodontal tissues, including fibroblasts and keratinocytes in the gingival and periodontal ligament, cementoblasts in the cementum and osteoblasts in the alveolar bone [3].

Compared to low MW HA, high MW HA has higher viscosity, longer residence time and higher biocompatibility [4]. High MW HA also has anti-inflammatory activity. High MW HA inhibits angiogenesis and interleukin (IL) 21b, IL-6, tumor necrosis factor-α, and prostaglandin production [5-7]. In contrast, low MW HA has been reported to stimulate angiogenesis [8] and cause inflammatory effects [9]. However, the mechanism of effect of MW and HA concentration on cell proliferation and differentiation is not fully understood.

Treatment of periodontal diseases includes non-surgical and surgical procedures [10]. Non-surgical therapy aims to remove the microbial cause and to modify the periodontal habitat through scaling and root planing of the affected teeth. Surgical procedures can either focus on pocket elimination or periodontal regeneration to correct tissue damage and to eradicate the unfavorable for the host ecological conditions created by the disease [11]. A number of adjunct products have been proposed to improve the clinical post-treatment course, when combined with the main treatment modalities [12]. The list of these adjuncts includes a variety of anti-inflammatory agents, antibiotics and antiseptics, e.g. chlorhexidine and essential oils, as well as substances that may help healing and tissue regeneration, such as enamel matrix proteins and hyaluronic acid (HA).

Only few systematic reviews have been published in this field and examined the potential effect and safety of topical use of hyaluronic acid in periodontal tissues [1,13] while only one of them tested the possible change in the level of quality of life [14]. In the field of treatment of periimplant diseases, merely few trials exist regarding hyaluronan, and no systematic reviews has been conducted yet.

The present systematic review focused on investigating whether topical application of hyaluronic acid as an adjunct agent to treatment of periimplant tissues may lead in improved clinical outcomes.

Materials and Methods

The current systematic review was conducted in accordance with PRISMA guidelines [15]. The focus question was stated as follows: In subjects with periimplant diseases (perimucositis and periimplantitis) does hyaluronic acid as adjunct to non-surgical and/or surgical periimplant therapy result in better clinical periimplant parameters (inflammation, periimplant pocket depth, clinical attachment level) comparing to no treatment, or non-surgical and/or surgical periimplant therapy".

Eligibility criteria

Inclusion and exclusion criteria were reported following PICOS criteria (Table 1).

	Inclusion Criteria	Exclusion Criteria
Participant characteristics	Studies on humans with periimplant disease	Animal or experimental studies, patients without periimplant disease
Intervention	Hyaluronic acid as an adjunct to surgical or non-surgical periimplant therapy	Studies without hyaluronic acid as intervention
Comparison	Periimplant patients that have not received hyaluronic acid	Studies without a control group that received no mouthwash or received a placebo mouthwash
Outcome	Studies providing clinical dental measurements	Studies not providing clinical outcomes
Study design	Randomized controlled clinical trials	Editor's choices, replies to the author/editor Interviews, commentaries Books'/conferences' abstracts Summaries Cross-sectional surveys Case series without control Case reports or reports of cases Case-control observational studies Cohort studies Prospective controlled clinical trials Retrospective clinical trials Narrative reviews, systematic reviews, meta-analyses

Table 1: *PICO inclusion and exclusion criteria of the study.*

Search strategy

Two authors (P.K. and S.D.) searched independently and systematically in 9 electronic databases (PubMed, Scopus, Science Direct, Google Scholar, Cochrane CENTRAL register of controlled trials/reviews/protocols/trials, Web of Science, Ovid) from outset to 31st March 2021. The principal search strategy consisted of the Mesh terms "(hyaluronic OR hyaluronate OR hyaluronan) AND (perimucositis OR periimplant OR periimplantitis)". No limitations were set regarding demographic characteristic of studies population, language, or publication date. The complete search strategy is presented in table 2.

Electronic databases	Search strategy used	Limits	Hits	Date
Pubmed	("Hyaluronic acid" [MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "hyaluronan"[All Fields] OR "hyaluronans"[All Fields]) AND ("peri implantitis"[MeSH Terms] OR "peri implantitis"[All Fields] OR "periimplantitis"[All Fields])	No	5	31/03/21
Scopus	(ALL (hyaluronic OR hyaluronate OR hyaluronan) AND TITLE-ABS-KEY (periimplantitis OR peri AND implantitis OR peri-implantitis))		40	31/03/21
Science direct	(ALL (hyaluronic OR hyaluronate OR hyaluronan) AND TITLE-ABS-KEY (periimplantitis OR peri AND implantitis OR peri implantitis))		3	31/03/21
Google scholar	Allintitle: hyaluronate OR hyaluronic OR hyaluronan periimplantitis OR "peri implantitis" OR "peri implantitis"	All in title	3	31/03/21
Cochrane central reviews	(Hyaluronic OR hyaluronate OR hyaluronan) AND (periimplantitis OR peri AND implantitis OR peri-implantitis) in Title Abstract Keyword	No	1	31/03/21
Cochrane central protocols	(Hyaluronic OR hyaluronate OR hyaluronan) AND (periimplantitis OR peri AND implantitis OR peri-implantitis) in Title Abstract Keyword	No	0	31/03/21
Cochrane central trials	(Hyaluronic OR hyaluronate OR hyaluronan) AND (periimplantitis OR peri AND implantitis OR peri-implantitis) in Title Abstract Keyword	No	7	31/03/21
Web of science	ALL FIELDS: ((hyaluronic OR hyaluronate OR hyaluronan) AND (periimplantitis OR peri AND implantitis OR peri-implantitis))	All fields	3	31/03/21
Ovid	((Hyaluronic or hyaluronate or hyaluronan) and (periimplantitis or (peri and implantitis) or peri-implantitis)).mp. [mp=tx, bt, ti, ab, ct]	Included related terms	41	31/03/21
Sum			103	

Table 2: *Search strategy used per each electronic database. The limits put for each search, the number of studies found (hits) in each database, and the date of search are given.*

Data extraction

Clinical variables referring to inflammation of periimplant tissues, periimplant probing depth and clinical attachment level were set as primary outcomes due to their direct connection to the course of periimplant diseases. In case of different indices used for the same clinical variable among trials, they were grouped per outcome criterion. We designated three main outcome criteria: periimplant inflammation, periimplant pocket depth and clinical attachment level.

The risk of bias in included studies was evaluated by two reviewers (P.K. and N.G.) with the use of the revised Cochrane risk of bias assessment tool for randomized trials [16]. This tool permits the evaluation of seven separate domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was reported having either low risk, high risk or unclear risk of bias.

Additionally, all information regarding side effects related to application of hyaluronic acid, if any, were selected and evaluated.

Results

This systematic search of 9 electronic databases resulted initially in 103 papers (Figure 1). After removing duplicates, 88 articles were screened by title. In the next step of screening process, 20 trials were evaluated at abstract level while only 7 publications met the criteria to be assessed by full-text. One study was excluded by full-text screening for not meeting eligibility criteria. Finally, 6 studies were included [17-22]. The main characteristics of the included studies are described in the table 3.

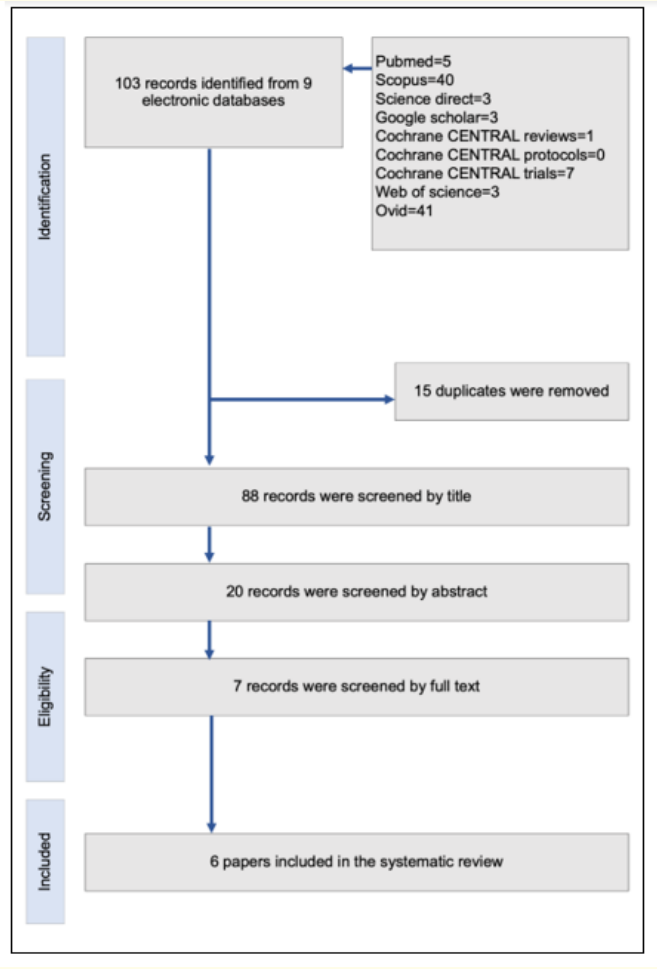

Figure 1: *Flowchart of the results of the screening process.*

Author (year)	Study design	Sample and Intervention	Outcome criteria	Follow-up	Results
Nombre., *et al*. 2009	RCT	18 patients Group 1:0,2% CHX gel Group 2: 0,8 HA gel	PD, Mob, Sup, AL DIM	12 months	Success rate: 55% for HA and 89% for CHX. Sig. improvement in clinical indices. No sig. differences found between the two groups in treatment success.
Bertl., *et al*. 2016	RCT	22 patients (with deficient papilla) Group1: twice HA Group 2: twice saline solution	PD, BL, CAL PT-CP, MPIS. Pain level after injection was recorded on VAS	3 months, 6 months	No significant differences in the area of black triangle, in distance between PT-CP and in MPIS. Similarly, insignificant differences between groups in gingival volume changes, bone level, and esthetic appearance.
Lopez., *et al*. 2017	Pilot study (split-mouth)	5 patients, HA was injected in one arch	PI, TI, PD, BOP	15 days	No sig. difference in PD. Improvement of BI on HA side and 60% deterioration in the control side. TI and PI: 100% improvement in both sides
Lopez., *et al*. 2017	Pilot study (split-mouth)	5 patients, HA was injected in one arch	PI, TI, PD, BOP	15 days	No sig. difference in PD in 15 days. Improvement of TI and PI tartar without a clear correlation with the injection of HA
Soriano-Lerma., *et al*. 2019	RCT	54 patients 108 samples were analyzed, 3 strata microbiomes were studied which had received HA Group 1: non specific bacterias, Group 2: *Streptococcus, Veillonella, Rothia, Granulicatella*, Group 3: *Prevotella* and *Campylobacter*	Non specific bacterias, *Streptococcus, Veillonella, Rothia, Granulicatella, Prevotella, Campylobacter*	45 days	In the 1st group no difference was observed while in the 2nd and 3rd ↓ of the bacteria
Sánchez-Fernández., *et al*. 2021	RCT	61 patients (100 implants): test group, control group 1, control group 2	PD, CAL, BL, IL-1β, TNF-a	45 days, 3 months	↓ PD in the test group in 45 and 90 days, ↓ BOP in 90 days in test group than in the control group 2, implants with PD ≥5mm had ↑ IL-1β in the control group 2 than in the test group
RandomizedClinical Trial: RCT, Probing Depth: PD, Bone Loss: BL, Bleeding on Porbing: BOP, Mobility: Mob, Suppuration: Sup, Attachment Level: AL, Distance between implant shoulder and mucosal margin: DIM, Papilla Tip and Contact Point: PT-CP, Modified Papilla Index Score: MPIS, Visual Analogue Scale: VAS, Plaque Index: PI, Tartar Index: TI					

Table 3: *Main characteristics of the included studies.*

To minimize the bias, only randomized clinical studies (RCTs) and split mouth studies were examined. In the present systematic review, six clinical trials in humans, 4 RCTs and 2 split mouth trials, were finally included to investigate the adjunct effect of hyaluronic acid on peri-implantitis and peri-mucositis. One study concerned the peri-mucositis treatment and 5 the peri-implantitis treatment.

Each study included 5 - 61 patients over 18 years old. All the patients were from Europe and the research was conducted either in a private clinic or in university institutions.

Five studies analyzed the classic periodontal parameters with some differentiations including the MPIS, DIM, PT-CP, crevicular fluid IL-1β levels and one study focused on the examination of microbiomes. In 3 trials, high molecular cross linked HA gel was used and in two studies spray HA. Two studies were double blinded, one study was single blinded and in three of them, the blindness was unclear.

The follow up period ranged from 15 days to 1 year. Only 1 study had a follow up period which approaches the year and the rest of them had recalls which reach the ultimate 3 months. Four of the 6 studies show a positive effect of HA for reducing inflammation and controlling bleeding. However, there is no clear indication whether this is due to improvement of oral hygiene of the patients or the injection of hyaluronic acid. Moreover, besides follow-up period, significant differences were observed between studies regarding the chemical characteristics of HA applied (Table 4). More specifically hyaluronic acid had a positive effect on pockets up to 5 mm, decreased the implant-related microorganisms, especially in early colonizing bacteria and might have reduced inflammation and crevicular fluid IL-1β levels. Two studies showed that there were no significant differences in PD and one study concluded that there were no significant differences in the area of black triangle, in distance between PT-CP and in MPIS. The overall effect in 4 studies is high risk and in 1 study low risk. Although, there is a significant difference in BOP in 5 studies, the PD and the CAL improved only in one case.

Brand name	Substance	*M*olecular weight	Company
Gengigel	Hyaluronic acid	High	Ricerfarma
	Cross-linked HA	6-7 x 10^6 Pa	
Hyadent Barrier Gel	Cross-linked Na-hyaluronate	Low	BioScience
	Na-hyaluronate		
Spray sol	Sodium hyalunorate	High	IBSA

Table 4: *Brand name and chemical characteristics of the commercial products applied in the included studies.*

Table 5 presents the significant effect, if any, per outcome of all included studies as well as the overall effect of hyaluronic acid application, as stated by authors.

Author (year)	Inflammation of periimplant tissues	Periimplant probing depth	Clinical attachment level	Overall effect
Nombre., *et al*. 2009	-	-	-	-
Bertl., *et al*. 2016	-	-	-	-
Lopez., *et al*. 2017	+	-	?	-
Lopez., *et al*. 2017	+	-	?	-
Soriano- Lerma., *et al*. 2019	+	-	-	+
Sánchez-Fernández., *et al*. 2021	+	+	+	+

Table 5: *Effect per each main outcome of included studies, as stated by authors.*
[(-): No significant effect, (+): Significant effect, (?): Unclear data].

Discussion

HA is a non-sulfated glycosaminoglycan found in the extracellular matrix of all vertebrate tissues and participates in healing of the tissues. Most recently, the hyaluronic acid (HA) application has been recognized as an adjuvant in several invasive or non-invasive procedures in dental and oral health treatment.

The present systematic review aimed to evaluate the potential effect of local application of HA to peri-implant and peri-mucositis treatment. This systematic review meets rigorous inclusion/exclusion criteria. The main limitation was the small number of included studies, the small number of patients in each study and the difficulty of generalizing the results outside the studied population. Moreover, the short duration of the follow up raises concerns about the therapy outcomes.

Three main clinical parameters PD, CAL and inflammation of periodontal tissues, were used to evaluate the effect of HA as an adjuvant in each treatment. According to the results of a bias risk assessment, allocation concealment and the blinding of participants and personnel appeared to be the most critical domains. Three out of 6 studies had a low risk of bias (Table 6).

Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall bias
Nombre., *et al*. 2009	+	+	?	?	+	+	+	-
Bertl., *et al*. 2016	+	+	-	-	+	+	+	-
Lopez., *et al*. 2017	?	?	?	?	+	+	+	-
Lopez., *et al*. 2017b	?	?	?	?	+	+	+	-
Soriano- Lerma., *et al*. 2019	+	+	+	-	+	+	+	-
Sánchez-Fernández., *et al*. 2021	+	+	+	+	+	+	+	+

Table 6: *Quality assessment of all studies included. [(+): Low risk of bias, (-): High risk of bias, (?): Unclear data].*

The results of the present systematic review showed that the adjunct use of HA to the treatment of peri-implantitis and peri-mucositis did not have an appreciable effect. Barely noticeable and clinically irrelevant differences were observed for most of the evaluated clinical parameters (Table 5).

Different commercial products with different regimens were applied in the studies included (Table 4). Araújo Nobre., et al. compared the health status of the peri-implant complex during the healing period of immediate function implants, using HA or CHX gels. Significant lower inflammation in the HA group was reported versus the control group treated with CHX. It might be an adjunct benefit of combined treatment to HA 0.2% gel in the first 2 months and 0.2% CHX from months 2 to 6 [23].

Conclusion

This is the first systematic review regarding HA and treatment of periimplant diseases. Within the limitations of this systematic review, the present data suggests that the adjunctive use of HA may lead to additional clinical benefits in peri-implantitis treatment and no noticeable effect in peri-mucositis treatment. Furthermore, future laboratory-based research and randomized controlled clinical trials on a larger sample should be based on adequate methodological procedures to improve the overall quality of the reporting and to reduce the risk of bias as well as to confirm these promising results.

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Volume 20 Issue 11 November 2021