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VIŠESTRUKA ULOGA HIJALURONSKE KISELINE U STOMATOLOGIJI

THE MULTIFACETED ROLE OF HYALURONIC ACID IN DENTISTRY

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Sažetak

Uvod: *Poznato je da lokalni tretmani efikasno omogućavaju da visoke doze lekova direktno dospeju u meka tkiva gingive i parodontalni ligament, kao i u tvrde strukture kao što su alveolarna kost i cement. Pored svoje dobro utvrđene uloge u promovisanju zarastanja nakon stomatoloških procedura, hijaluronska kiselina (HA) je sada prepoznata kao održiva potporna terapija za hronična upalna stanja.*
Materijal i Metode: *Naša studija je sprovedena da bi sistematski pregledala dostupna literatura iz dveju oblasti: efikasnost HA kao dodatnog lečenja hronične upale i prednosti HA u lečenju zuba. Pretražen je PubMed, Google Scholar i Ovid koristeći kombinaciju ključnih reči i MeSH termina;*
Rezultati: *od 28 studija odabranih na osnovu naših kriterijuma za uključivanje, koje su pokrivale tri rada u vezi sa gingivitisom, trinaest za hroničnim parodontitisom, 7 sa implantološkim procedurama za oralne ulcerima.*
Zaključci: *Utvrđeno je da lokalna primena HA ne samo da značajno pomaže postoperativnom dentalnom oporavku, već je dobra i za pacijente sa hroničnom inflamacijom gingive/parodonta i onima koji pate od oralnih ulkusa.*

Ključne reči: *hijaluronska kiselina, oralno zdravlje, biokompatibilni materijal*

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Abstract

Background: *Topical treatments are known to effectively deliver high doses of drugs directly to both the soft tissues of the gums and periodontal ligament, as well as to the hard structures like the alveolar bone and cementum. In addition to its well-established role in promoting healing post dental procedures, hyaluronic acid (HA) is now being recognized as a viable supportive therapy for chronic inflammatory conditions.*
Materijal and Methods: *Our study was conducted to systematically review the available literature on two fronts: the efficacy of HA as an adjunctive treatment for chronic inflammation and the benefits of HA in dental healing. We searched PubMed, Google Scholar, and Ovid using a combination of keywords and MeSH terms;*
Results: *from the 28 studies selected based on our inclusion criteria, which covered three papers related to gingivitis, thirteen to chronic periodontitis, seven to dental surgeries (including implants and sinus lifts), and three to oral ulcers.*
Conclusions: *we found that topical HA application not only significantly aids postoperative dental recovery but also bodes well among patients with chronic gingival/periodontal inflammation and those suffering from oral ulcers.*

Key words: *hyaluronic acid, oral health, biocompatible material*

Introduction

Hyaluronic acid (HA) is not a sulphated glycosaminoglycan but a natural one. What makes it stand out is its high molecular weight which ranges from 4,000 to a whopping 20,000,000 Daltons[1]. This polymer's unique structure comprises polyanionic disaccharide segments made up of glucuronic acid and N-acetyl glucosamine linked in a complex pattern by alternating β-1,3 and β-1,4 glycosidic bonds. HA can be found all over the body— from connective tissues' extracellular matrix to joints' synovial fluid (embryonic mesenchyme, vitreous humor) — due to its presence it significantly affects other organs like skin as well as various other tissues among them dentine [1]. In dentistry it plays key roles not only in maintaining healthy soft periodontal issues (gingiva plus ligament) but also in extending into hard tissue such as alveolar bone & cementum: thus, covering different structural functions across these tissues. HA plays an indispensable role in the maintenance and health of soft periodontal tissues, the gingiva and periodontal ligament, and extends its utility to hard tissues, including alveolar bone and cementum[2,3]. The most important function of HA is its regulatory capacity in the inflammatory response. In the specific context of periodontal tissues, the gingiva, periodontal ligament and alveolar bone, HA is synthesized in high molecular weight forms by the action of hyaluronan synthase enzymes4. However, under conditions of chronic inflammation, such as gingival tissue inflammation or during post-operative recovery after implant or sinus lift surgery, high molecular weight HA is largely degraded into lower weight molecules[4]. This degradation process is accelerated by reactive oxygen species (ROS), including superoxide and hydroxyl radicals, which are predominantly produced by polymorphonuclear leucocytes and other inflammatory cells during phagocytosis of bacteria in periodontal diseases[5]. The resulting low molecular weight HA fragments play a critical function in signaling tissue damage and orchestrating the mobilization of immune cells to the site of injury or infection. In contrast, intact high molecular weight HA plays a critical role in modulating the immune response to prevent an excessive inflammatory reaction[6]. Low molecular weight HA is predominantly found in the gingival tissues of patients in the early stages of periodontitis, probably due to the action of bacterial hyaluronidases7. In addition to its role in inflammation and immune modulation, HA contributes to the structural and homeostatic balance of tissues by influencing osmotic pressure and facilitating tissue lubrication due to its exceptional hygroscopic nature[6,7] . This property of HA allows it to form hydrogen bonds with adjacent carboxyl and N-acetyl groups when incorporated into an aqueous solution, thus maintaining its conformational rigidity and retaining water. In addition, HA boasts remarkable viscoelastic properties that hinder the penetration of viruses and bacteria into tissues, emphasizing its protective function [7,8]. Furthermore, HA is an integral part of the sequential steps of the wound healing process, which includes inflammation, granulation tissue formation, epithelialization, and tissue remodeling in both mineralized and non-mineralized tissues [8]. The broad spectrum of functions attributed to HA has stimulated advances in the development and application of HA-based biomaterials for the treatment of various inflammatory conditions10. Given the multifunctional role of HA in wound healing and the similarity of biological principles governing gingival and bone healing, it is plausible that HA exerts comparable beneficial effects in the healing processes of mineralized and non-mineralized periodontal tissues [9].The use of HA spans several branches of medicine and its safety profile is further exemplified by the absence of contraindications or drug interactions. Recent years have seen the development of HA formulations for topical administration aimed at the adjuvant treatment of acute and chronic dental and gingival conditions, such as tissue healing after oral surgery, supported by abundant evidence from animal model studies on the role of HA in dentistry[10,11]. While existing literature reviews have explored the dental applications of HA, particularly in the context of treating periodontal disease, a comprehensive evaluation covering the full spectrum of HA's therapeutic effects on acute and chronic inflammatory diseases within the oral cavity remains elusive [12,13]. Our study aims to systematically review the published literature on the therapeutic impact of HA, to clarify and classify its main applications in dentistry, to demystify the pathophysiological basis and protocol for the application of HA in the post-operative setting, and to evaluate the most effective parameters for the use of HA in dentistry.[14]

Materials and Methods

The review was registered in the PROSPERO database (the International Prospective Register of Systematic Reviews hosted by the National Institute of Health Research, University of York, Centre for Reviews and Dissemination) on 25 March

2024, according to the guidelines with the identification number CRD-42024535008. To gather the necessary research for our study, we conducted a systematic search across several databases, including PubMed, Google Scholar, and Ovid. Our research, which began in June 2015, systematically examined the potential benefits of topical HA application in the management of both acute and chronic inflammatory diseases. After an initial screening of 278 articles, only 78 were reviewed, of which only 28 were selected for the above review. The PICO question was: ''Is the use of HA in randomized controlled clinical trials effective for oral health for the management of gingivitis, ulcers, wounds, and gingival recession compared with the control group?'' (Table 1). We used a combination of keywords and, for PubMed, specific medical subject headings to refine our search. These terms included combinations such as "hyaluronic acid and periodontitis," "hyaluronic acid and gingivitis," and similar phrases targeting various dental conditions and treatments involving hyaluronic acid without imposing any restrictions on the publication year. Our approach to selecting literature adhered strictly to the PRISMA guidelines. We set specific inclusion criteria for our review: articles had to be in English, involve human - controlled trials, and present either histological or clinical evaluations of hyaluronic acid effect size in dental disease contexts. We excluded a variety of document types that did not meet our criteria for primary research, such as literature reviews, technical notes, letters to editors, and instructional courses. The evaluation and selection of articles were carried out independently by two of our authors, AR and AMP, who reviewed the full texts for relevance to our topic. They excluded any paper that lacked the specific content we required for our analysis. Additionally, we examined the reference lists of all articles that passed our initial criteria to uncover any pertinent studies that our electronic search might have missed. Initially, we removed duplicates and identified articles strictly related to our topic of interest in each journal. At this point, we excluded studies conducted on animal models and in vitro studies, focusing solely on human trials. We further narrowed our selection by removing studies investigating the use of hyaluronic acid in treating oral mucositis caused by chemotherapy, radiation therapy, allogeneic hematopoietic stem cell transplantation, or in palliative care settings. After completing our meticulous selection process, we concluded with a final tally of 28 relevant publications for our review, as depicted in Figure 1 of our study documentation.

Quality Assessment and Risk of Bias

Two reviewers (A.P. and L.A.) assessed the risk of bias using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). Any disagreement was discussed until a consensus was reached with the help of a third reviewer (A.M.P.) (Figure 2). Using RoB 2, the risk of bias among the studies analyzed was estimated and is reported in Figures 2 and 3. Regarding the randomization process, 75% of studies had a high risk of bias. Regarding allocation concealment, 100% of studies had a low risk of bias. Only 25% of studies excluded performance bias, and 25% reported all outcome data; however, 85% of the included studies presented a low risk of reporting bias.

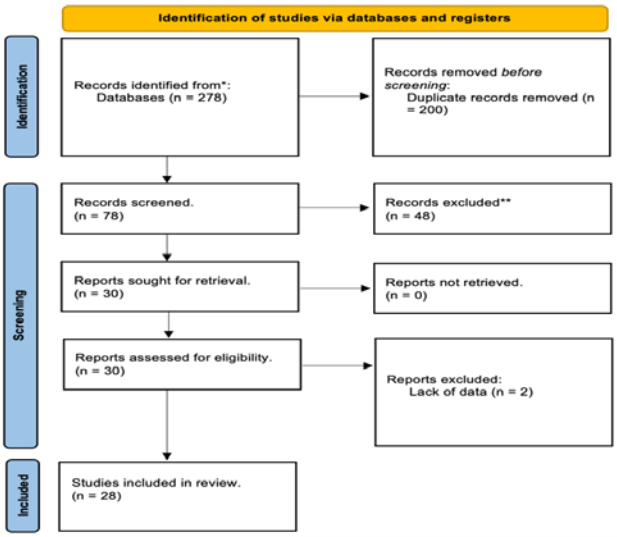

Figure 1: Search strategy flow chart from database (*Scopus, Embase, Google Scholar, Pubmed, Web of Science). **Reports excluded for lack of data

Table 1: Explication of PICO

PICO'S QUESTION	
Participants	Healthy participants with no restrictions on age and sex who were in good general health with gingival recession, periodontitis, oral ulcers, surgery wounds
Intervention	Application of HA in conjunction with surgical procedures.
Comparison	The same surgical procedures without HA or substitute
Outcomes	Pathology reduction

Table 2: Main studies included in this review

AUTHORS	MEAN AGE	HA GROUP	CONTROL GROUP	TYPE OF TREATMENT	PARAMETERS EVALUATED	CLINICAL EVIDENCE
Jentsch [15]	50 male (17 +- 39 y)	25 with use of HA	25 with placebo	Gel on gingivitis	The study evaluated oral health through clinical indices (Approximal Plaque Index, Turesky Plaque Index, Papilla Bleeding Index) and crevicular fluid markers (peroxidase, lysozyme) initially and after 4, 7, 14, and 21 days.	The test group exhibited notable enhancements in plaque indices from day 4 and in PBI from day 7, outperforming the placebo group.
Pistorius[1]	60 mixed (32 +- 41 y)	40 with use of HA	20 with reduced use of HA	Spray on gingivitis	Clinical measurements including DMF-T index, API, sulcus bleeding index, PBI, and gingival crevicular fluid were recorded at the start, then after 3 and 7 days.	Clinical parameters were assessed initially, and then at 3 and 7 days. The HA group saw decreases in sulcus bleeding index at both time points, with significant drops in PBI values and gingival crevicular fluid.
Bagde[18]	21 mixed (22 +- 34 y)	11 with use of HA	10 with placebo	Gel in periodontal pocket	A gingival biopsy for histopathological and immunohistochemical analysis, focusing on Ki-67 expression and inflammatory infiltrate evaluation, was conducted 30 days post-treatment.	Treatment with HA gel notably decreased the proliferation index of gingival epithelium and fibroblast cells.
Sahayata[13]	105 mixed	50 with use of HA	50 with reduced use of HA and short follow up	Gel in periodontal pocket	Clinical parameters (API, GI, PBI) were assessed at 1, 2, and 4 weeks from baseline; microbiological parameters were checked at 4 weeks.	Significant improvements in GI and PBI were observed in the test group compared to others. At 4 weeks, all treatment groups saw a significant decrease in anaerobic gram-negative bacilli and an increase in gram-positive coccoid cells from baseline.
Xu[22]	20 mixed (48	10 with use of	20 with placebo	Gel in periodontal	SFFR and sulcus bleeding index were	This study showed an

	+- 64 y)	HA		pocket	measured initially and weekly up to 12 weeks; probing depth and clinical attachment level were checked at the start, and at 6 and 12 weeks. Dentists collected subgingival plaque samples to identify specific bacteria at baseline, and at 6 and 12 weeks.	improvement of all clinical variables in both groups. There are not clinical and microbiological differences between test and control sites.
Johannsen[23]	11 mixed (23 +- 56 y)	10 with use of HA	11 with use of placebo	Spray in periodontal pocket	SFFR and sulcus bleeding index were measured initially and weekly up to 12 weeks; probing depth and clinical attachment level were checked at the start, and at 6 and 12 weeks. Dentists collected subgingival plaque samples to identify specific bacteria at baseline, and at 6 and 12 weeks.	There are not clinical and microbiological differences between test and control sites.
Polepalle[16]	36 mixed (30 +- 65 y)	26 with use of HA	10 with use of reduced HA and short follow up	Gel in periodontal pocket	Bleeding on probing (BOP), API, probing pocket depth (PPD), and clinical attachment level (CAL) were assessed at baseline, 1, 4, and 12 weeks. Colony-forming units (CFU) per mL were assessed at baseline, after treatment, and after 2 weeks.	There was a significant reduction in BOP, API, PPD, and CAL in the test sites than control group. In the test sites there was also a significant reduction of CFUs.
Gontiya[24]	26 mixed (25 +- 55 y)	20 with use of HA	6 with use of placebo	Gel on gingivitis	Clinical parameters GI, PBI, PPD, and Relative Attachment Level (RAL) evaluated at baseline (day 0), and weeks 4, 6, and 12.	The test sites showed statistically significant improvement in GI and PBI at 6 and 2 weeks than control sites.

Rajan[10]	Not specified	33 with use of HA	Not specified	Gel on gingivitis	The clinical parameters evaluated: GI, API, BOP, PPD, CAL at three appointments: before SRP, 4 weeks and 12 weeks after SRP.	The test sites showed statistically significant improvement in GI and PBI at 6 and 2 weeks than control sites.
Cairo[25]	19 mixed (15 +- 41 y)	15 with use of HA	4 with use of placebo	Gel and spray in mild chronic periodontitis	These clinical parameters were evaluated before treatment and repeated at 14 and 21 days: API, BOP, GI, PAL (probing attachment level).	HA gel treatment was more effective, reducing BOP by 92.7% and GI by 96.5%, compared to 75.8% and 79.0% in controls. Periodontitis reduction was significantly greater in the HA-treated area.
Eick[6]	42 mixed (41 +- 72 y)	17 with use of HA	17 with use of placebo	Gel and spray in mild chronic periodontitis	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	The test sites showed statistically significant improvement in GI and PBI at 6 and 2 weeks than control sites.

Chauhan	60 mixed (30 +- 65 y)	30 with use of HA	30 with use of reduced HA	Gel and spray in mild chronic periodontitis	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	At 3 months, change in PPD and CAL was more in Group test than Group control, but the difference was non-significant.
Engstrum[26]	15 mixed (23 +- 54 y)	8 with use of HA	7 with use of placebo	Not specified	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	After 12 months, the test and control groups in surgery showed a bone height difference under 1 mm, visible only in radiographs. Both groups experienced bone height reduction post-scaling. Probing depth decreased as anticipated following surgery and SRP.
Briguglio[8]	15 mixed (23 +- 54 y)	8 with use of HA	7 with use of placebo	Not specified	PD and CAL measurements were taken at the start, 3 months, and 6 months, with subgingival plaque and sulcus fluid samples collected for analysis.	The use of hyaluronic acid in treating infrabony defects provided additional advantages, including improved clinical attachment levels, reduced probing depths, and enhanced predictability, compared to traditional open flap debridement methods.

Bevilacqua[27]	24 mixed (+-51 y)	11 with use of HA	13 with use of placebo	Gel in moderate-severe chronic periodontitis	Clinical variables assessed included API, BOP, CAL, PPD, calprotectin, MPO, and GCF volume on days 45 and 90. Calprotectin, MPO, and GCF quantities were measured at test and control sites on days 7 and 45.	At baseline and 45 days, the HA group showed a significant decrease in probing depth and BOP compared to the control group. Both groups experienced a notable reduction in calprotectin and myeloperoxidase per sample after 1 week, followed by an increase at 45 days.
Fawzy El-Sayed [28]	14 mixed (23 +- 34 y)	7 with use of HA	7 with reduced use of HA	Gel in Chronic periodontitis	BOP, API, PPD, and CAL were assessed at baseline, 1, 4, and 12 weeks. CFUs per mL were assessed at baseline, after SRP and after 2 weeks.	The test sites showed significant improvements in BOP, API, PPD, and CAL compared to the control group, alongside a notable decrease in CFUs.
Araujo Nobre[29]	30 mixed (58.4 +- y)	15 with use of HA	15 with use of CHX	Management of the implant platform and healing screw at implant uncovering with gel	The clinical parameters evaluated: modified plaque index (mPlI), modified bleeding index (mBI), PPD in mL, suppuration (Sup), clinical implant mobility (mob). Both groups were followed up for 6 months, and the clinical observations were performed on day 10, and at 2, 4, and 6 months post surgery	HA and CHX effectively supported peri-implant health. The HA group had significantly better modified bleeding index at the second check. At 6 months, CHX showed potentially superior outcomes in modified plaque and bleeding indices.

Galli[12]	8 mixed (36 +- 67 y)	4 with use of HA	Not specified	Post implant wound management with gel	The PPDs, gingival recession, and CAL were evaluated before treatment and after 1 year.	After 1 year there were this following result: PPD reduction, gingival recession increase, and CAL gain.
Ballini[7]	19 mixed (43.8 +- y)	19 with use of EHA	Not specified	Post implant wound management with gel	The PPDs, gingival recession, and CAL were evaluated before treatment and after 1 year.	Clinical results showed a mean gain of CAL (gCAL) of 2.6 mm of the treated sites, confirmed by radiographic evaluation.
Koray[11]	34 mixed (23 +- y)	34 with use of HA	34 with use of BnzHCl	Management of Bilateral extraction of the lower octaves with gel HA or BnzHCL spray	Swelling was measured with a tape, and trismus by the maximum inter-incisal opening. Evaluations occurred on the surgery day, and 2- and 7-days post-surgery.	The patients with HA spray experienced statistically significant results for the swelling and trismus values than those with the BnzHCl spray.

Romeo[30]	49 mixed (45.5 +- y)	31 with use of HA	18 with use of placebo	Management of excisional biopsy with HA gel	The lesion area was measured after surgery (T0) and after 7 days (T1). A percentage healing index (PHI) was calculated indicating healing extension in 7 days.	Not specified
Srinivas[31]	Not specified	1 with use of HA	Not specified	Gel on gingival recession	RD, PPD and CAL, was tracked at baseline, and then at 1, 3-, 6-, 12-, and 24-weeks post-surgery.	Despite the lack of statistical significance, the experimental group's root coverage was observed to be more clinically stable than the control group at 24 weeks.
Lee[19]	50 mixed (40 y)	33 with use of HA	17 with placebo	Gel on oral ulcers in Behcet's Disease	Subjective assessment: number of ulcers, healing period and VAS; Objective assessment: number and maximal size of ulcer.	Ulcer inspection revealed a 57.6% reduction in numbers and a 78.8% decrease in area among patients. Post-treatment, significant improvements were seen in swelling and local heat.

Nolan[3]	106 mixed (37 y)	60 with use of HA	56 with use of placebo or reduced level of HA	Gel on oral ulcers	Average ulcer count, ulcer history over 7 days, patients experiencing ulcers in this period, and treatment assessment scores ranging from very good to not recorded.	Both groups noted quick discomfort relief from ulcers, lasting around 30 minutes before reverting towards initial levels. Ulcer counts slightly dropped over 7 days, regardless of treatment. By day 5, the HA group reported significantly fewer ulcers compared to the placebo group. Despite new ulcers appearing in both groups during the study, the HA group saw a notably lower incidence of new ulcers by day 4.
Lopez[21]	1 man (32 y)	1 with use of HA	Not present	Application of HA gel in intracrestal sinus lift	The filling volume obtained was measured with a comparative software programme and using an ellissoid formula. This technique allows the surgery to be performed in a way that is both minimally traumatic and invasive, fully careful of the membrane and represents a viable alternative to those surgical techniques for crestal sinus lift currently in use.	Not specified
Schwartz[14]	26 mixed (45 +- y)	26 with use of HA	Not present	Application of HA gel and bone graft in lateral sinus lift	All 32 sinus lifts succeeded, with Cone Beam scans showing bone height increasing from 2.84 mm pre-treatment to 15.2 mm post-treatment.	This study confirmed the hypothesis that new bone formation is graft dependent alone or in combination with other materials.

Weindl[9]	45 mixed (23 +- 45 y)	25 with use of HA	20 with use of placebo	Treatment of gingival recession with use of HA gel	Recession depths in the first, third, and sixth month were 1.82 ± 0.442, 1.31 ± 0.47 mm, and 0.91 ± 0.29, respectively, which showed a significant reduction.	Within the limitations of the present study, the data obtained by periodic assessment of the clinical parameters indicate the use of amnion membrane and hyaluronic acid, and proper technique may thus be the panacea for root coverage procedure.
Gorski[32]	24 mixed (34 +- y)	24 with use of HA	Not applicable	Use of HA gel in the treatment of multiple gingival recession using the modified coronally advanced tunnel technique (MCAT) combined with subepithelial connective tissue graft (SCTG), with or without cross-linked hyaluronic acid (HA).	No significant improvement in root coverage was observed because of adding HA. After 6 months, mean root coverage (MRC) was 85% for SCTG + HA group and 83% for SCTG group (p = 0.9819). Complete root coverage (CRC) was observed in 91% (test) and 93% (control) of the cases (p = 0.9001).	Both treatments were similarly effective in treating multiple GRs and led to comparable improvements in clinical parameters. However, application of HA improved the appearance of soft tissue texture.

(y:years; PBI: papilla bleeding index; HA; hyaluronic acid; API: Approximal plaque index; DMF-T:Decayed – Missing – Filled – Teeth; GI:gingival index; SFFR: Sulcus-Fluid-Flow-Rate; BOP: bleeding on probing; PAL: Probing Attachment Level; CAL clinical attachment level; PD: probing depth; SRP: Scaling root planning; MPO: myeloperoxidase; GFC: crevicular fluid volume; Chlorhexidine; EHA: esterified low molecular HA; BnzHCL: BenzydamineHCL; RD: recession deep)

Figure 2. Quality assessment

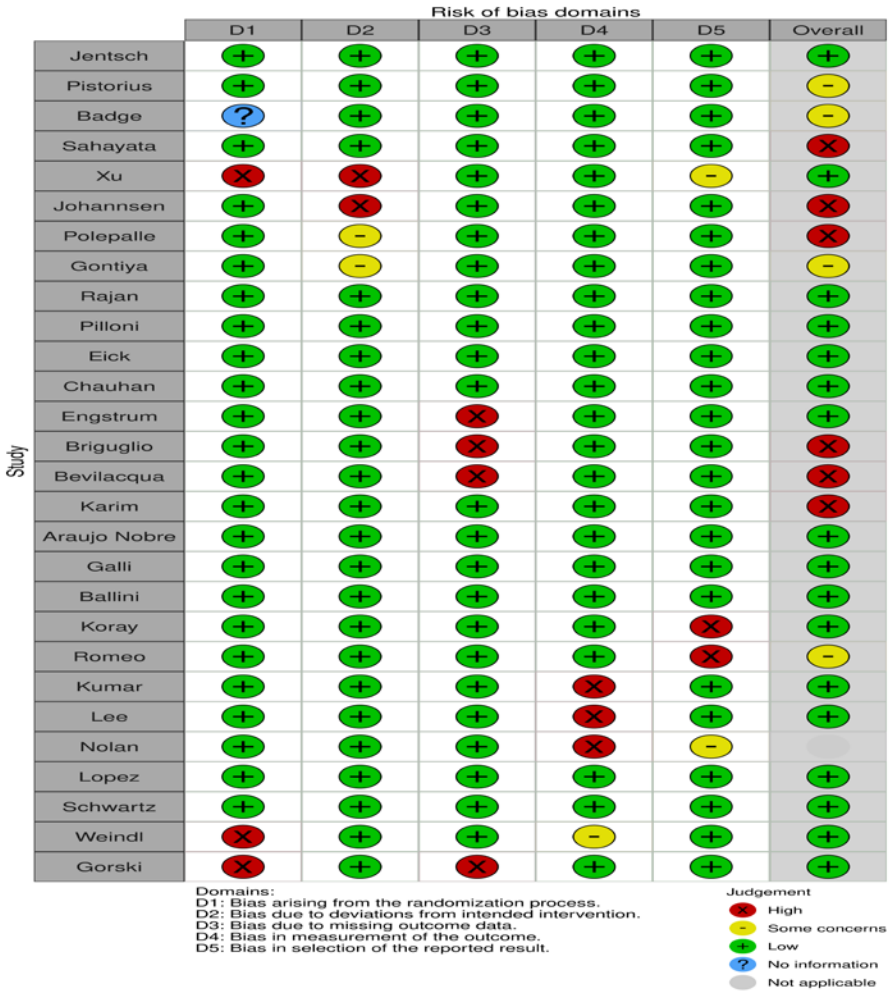

Figure 3. Risk of bias.

Resluts

Navigating through the world of dentistry, the role of Hyaluronic Acid (HA) emerges not just as a treatment modality but as a beacon of innovation, bridging traditional practices with the promise of enhanced healing and patient comfort. The journey into its application spans various facets of dental care, each illuminated by studies that not only underscore its efficacy but also hint at the broader potential of HA in revolutionizing dental treatments (Table 2).

In the Battle Against Gingivitis

The story of HA begins in the realm of gingivitis, where its capabilities are put to the test. The study by Jentsch et al.[15] revealed how a seemingly simple regimen of topical application of 0.2% HA twice daily can lead to significant improvements in oral health markers such as plaque indices and papillary bleeding index (PBI), heralding almost a new dawn in the non-invasive management of gingivitis. The test group showed a significant improvement in the study area for plaque indices from day 4 (P = 0.011) and PBI from day 7 (P = 0.001) compared to the placebo group. Crevicular fluid variables improved significantly in the centre of the area of inflammation studied in the test group. This narrative is further enhanced by Pistorius et al. [1], who, through their exploration of an HA-based spray, reveal its powerful effect in containing fissure bleeding. This is a testament to the versatility of HA, demonstrating that whether in gel or spray form, its therapeutic potential remains undiminished. The work of Sahayata [13] et al. adds depth to this story, highlighting how HA, when used in conjunction with conventional oral cleansing and hygiene practices, can significantly outperform placebo treatments. It is as if HA whispers to

the inflamed gum, restoring it to health more effectively than conventional methods alone. Clinically, a significant difference ($p<0.05$) was found for GI and PBI in the test group compared to the other groups, but the reduction in PI was not significant. In the negative control and placebo groups, the difference between the clinical parameters was not significant.

Chronic Periodontitis: A New Frontier

The narrative then shifts to the difficult terrain of chronic periodontitis, where the role of HA expands from supporting actor to protagonist. The local application of HA gel emerges not only as a treatment, but as a beacon of hope, reducing the indications of proliferation and sedating the inflammatory assault, thus charting a new course in periodontal healing. Jentsch [15] demonstrated that subgingival application of a 0.2% hyaluronic acid gel (GENGIGEL®) with SRP in patients with chronic periodontitis improved GI and bleeding index (BI) compared to control sites, as confirmed by a gingival biopsy, which showed a significant reduction of the inflammatory infiltrate.

The saga deepens with the collaborative efforts of Johannsen et al. and Polepalle et al. [16], who, through their meticulous research, unveil the symbiotic potential of HA and Scaling and Root Planing (SRP). Their findings praise HA's ability to significantly reduce bleeding, improve clinical attachment levels and even alter the microbial landscape, painting a picture of a future where HA could be a cornerstone of periodontal therapy [16]. Subgingival administration of 1 mL 0.2 mL 0.8% HA gel once a week for 6 weeks improved sulcus fluid flow rate (SFFR).

Surgical Frontiers and Implant Surgery

The versatility of HA transcends the non-surgical realm, boldly entering the surgical arenas. Here, the work of Araújo Nobre [17] et al. highlights the role of HA in improving the healing milieu of the peri-implant complex, offering a glimpse into its potential to improve implant success rates. Statistically significant differences were found in favour of the HA group in the modified bleeding index at the second observation ($P = 0.003$). The difference was more pronounced in axial implants placed in the fifth sextant ($P = 0.05$). The correlation coefficient between plaque and bleeding index revealed a potentially better outcome for CHX at 6 months.

Bagde [18] et al.'s exploration of HA in the treatment of deep periodontal defects not only highlights its efficacy in reducing pocket depth, but also subtly hints at its role in regenerative dentistry. Meanwhile, research by Ballini [7]et al. suggests the promise of HA in bone regeneration, providing a beacon of hope for those facing the daunting prospect of bone loss. Recession depths in the first, third, and sixth month were 1.82 ± 0.442, 1.31 ± 0.47 mm, and 0.91 ± 0.29, respectively, which showed a significant reduction from the baseline. Recession widths in the first, second, and third weeks were 3.04 ± 0.442 mm, 1.31 ± 0.47 mm, and 1.49 ± 0.59 mm, respectively. There was a statistically significant reduction ($P > 0.005$).[18]

The Healing Touch on Oral Ulcers

In the field of oral ulcers, HA emerges as a gentle healer. Research by Nolan [3]and Lee [19] et al. on its efficacy in the treatment of recurrent aphthous ulcers and Bechet's disease not only emphasizes its therapeutic potential, but also offers comfort to sufferers, promising a future in which pain and discomfort will be only a distant memory26,27. A subjective reduction in the number of ulcers was observed in 72.7% of patients. A reduction in the ulcer healing period was observed in 72.7% of patients; 75.8% reported an improvement in the SEA of pain.

Through this detailed narrative, hyaluronic acid emerges not only as a molecule, but as the harbinger of a new era in dentistry[1,2]. Each study, each discovery adds a layer to our understanding, painting a picture of a future in which HA stands as a pillar of dental care, bridging the gap between traditional methods and the promise of regenerative and minimally invasive treatments [16,20,21]. It is a story of transformation, hope and the relentless pursuit of improvement in dental care, heralding a future where patient comfort and healing are paramount[6,7].

Discussion

Hyaluronan, a versatile glycosaminoglycan embedded in the very tissue of the extracellular matrix of vertebrate tissues, is notable not only for its critical role in wound healing, without leaving scars, but also for its profound implications for oral

health and dentistry [33,34]. Delving deeper into the literature reveals intriguing insights that place hyaluronan at the heart of periodontal tissue healing, suggesting its promising utility in the management of periodontal disease [15,30,34]. HA has proven to be a valuable clinical tool in various fields of medicine, such as ophthalmology, osteology and dermatology, due to its unique biochemical and biophysical properties. Its application in dentistry has recently received increased attention, with HA-based products demonstrating efficacy in the management of gingivitis through both anti-inflammatory and anti-edematous effects. Studies have shown that HA gels, particularly when used in conjunction with mechanical treatments such as scaling, significantly reduce gingival inflammation [26,28]. However, the overall effectiveness of HA in periodontal therapy varies, attributed to different product formulations, application methods and study biases, making it difficult to recommend a specific approach [8,29,35]. Research on the use of HA in the treatment of chronic periodontitis has shown improvements in gingival health when combined with scaling and root planning, although the impact on deeper periodontal parameters is less pronounced[36]. Other studies have explored the role of HA in surgical periodontal therapy and bone regeneration, with positive results in bone growth when used with autologous bone or as a bone cyst filler. The application of HA in the management of temporomandibular joint (TMJ) disorders and oral ulcers, including those of Behçet's disease, has also been reported, highlighting its potential to reduce pain and improve healing[19]. Despite these advances, the exact mechanisms by which HA influences cell behavior and tissue regeneration remain unclear, highlighting the need for further research. After gingivectomy surgery, wounds heal through a process known as secondary intention, which can lead to discomfort and slower recovery than wounds that heal by primary intention. To accelerate the healing process and alleviate discomfort, photo biomodulation (PBM) has emerged as a promising adjunctive treatment, attracting the interest of numerous researchers. Studies have consistently shown that PBM therapy is an effective supportive method that can improve recovery after gingivectomy. In addition, the literature cites several other topical agents that have been shown to contribute to improved wound healing after gingivectomy, including HA gel, herbal gels, non-thermal atmospheric pressure plasma applications, and vitrocure® gel[12]. Furthermore, in agreement with our results, Turgut Çankaya[36] et al. evaluated the effect of HA application after laser-assisted frenectomy. The authors concluded that HA is a viable option to reduce the wound surface within 14 days and act as a wound dressing after frenulectomy. The soft tissue healing potential of HA in our study can be explained based on a histological study conducted by Araujo Nobre [29]et al., who concluded that HA gel (0.2%) has anti-inflammatory properties and induces a increased formation of epithelial tissue and increased vascular supply of connective tissue, histologically. This includes understanding the effects of HA molecular weight and concentration on cells, evaluating the potential toxicity resulting from HA modification techniques, and conducting comprehensive clinical studies to consolidate their effectiveness in dentistry and other medical applications [32]. The future of HA in the clinical setting appears promising, with expected advances in line with the goals of translational and evidence-based medicine, paving the way for personalized therapeutic approaches. The essence of the benefit of hyaluronic acid extends well beyond the superficial layers of the marginal gingiva, reaching the depths of the periodontal tissues [37,38]. It takes advantage of its well-documented wound healing mechanisms to promote remission of symptoms, acting as a relief for those suffering from periodontal disease. This ability to alleviate discomfort and accelerate healing is particularly beneficial in the context of gingivitis and chronic periodontitis, offering a glimpse into a future where treatments align perfectly with the body's natural healing process[18,31,39,40]. Furthermore, the potential of hyaluronan shines through following surgical procedures, such as implants and sinus lifts, where its topical application can significantly accelerate the healing process[41,42]. This not only results in faster recovery times, but also significantly alleviates the discomfort patients experience after surgery, making the healing process smoother and more bearable. In the fight against oral ulcers, Hyaluronan emerges as a formidable ally. Its therapeutic ability underlines its value in a comprehensive dental care strategy, offering hope and healing to those struggling with these painful lesions[36]. The discussion of hyaluronan also brings to light the superior efficacy of topical treatments in delivering pharmacological agents directly to the teeth

and oral mucosa. This localized approach ensures the delivery of high concentrations of therapeutic agents where they are most needed, in stark contrast to systemic routes that may dilute their efficacy[41]. The forward path invites more granular research, especially laboratory investigations and large-scale randomized clinical trials. These future studies are key to unlocking the full potential of hyaluronan as a carrier for periodontal tissue cells, potentially revolutionizing tissue regeneration techniques for both mineralized and non-mineralized periodontal tissues. Still, the questions linger regarding the optimal modes of administration, whether through spray, gel, or nebulization-and more effective post-operative treatment programs tailored to each dental condition. These investigations pave the way for a deeper exploration of the role of hyaluronan in dentistry, suggesting a future in which its application is as nuanced as it is transformative[25,32,42,43]. As we peer into the horizon, hyaluronan's promise to improve dental care and patients' healing pathways is undeniable. His journey from the extracellular matrix component to the cornerstone of dental therapy is a testament to the power of harnessing nature's healing mechanisms, offering a brighter and painless future for patients around the world[15,44,45].

Conclusion

Hyaluronic Acid (HA) is currently widely used in various medical fields, demonstrating considerable potential in dentistry — particularly for the management of inflammatory conditions. A detailed analysis of 28 clinical studies has shed light on the positive effects of HA in tissue repair and wound healing. The findings imply that the application of HA topic-ally could play a significant role not only during the recovery phase post dental surgeries but also in dealing with gingivitis and periodontitis: conditions affecting some patients. It could lead to substantial improvement with quality life among those affected by these dental ailments, given that HA possesses therapeutic properties. While based on these promising findings, it is considered prudent to embark on more investigations through laboratory research, as well as larger randomized controlled trials at a wider scale. This is important to help establish the full effectiveness of HA and further widen its use in dental practices.

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