

Effect of Hyaluronic Acid Gel as an Adjunct Therapy After Scaling Root Planing in Chronic Periodontitis: A Rapid Review

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Abstract

The most important treatments of periodontal disease is scaling root planing (SRP) but that is not always efficient to eradicating all periodontal pathogens, local subgingival application of chemotheurapeutic agents may used as an adjunct for optimal result. Hyaluronic acid has demonstrated its ability as an inflammatory treatment.

The potential effect of local subgingival application of HA adjunctive to scaling and root planing were evaluated in this study. This research was conducted using a rapid review method through the PICO framework based on Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). A total of 10 articles with an RCT research design were obtained based on the inclusion criteria and then analyzed qualitatively. An experimental study on 10 articles over a period of 3 to 6 months showed that additional hyaluronic acid treatment was able to produce better clinical or microbiological parameters in chronic periodontitis patients.

Hyaluronic acid has results in improving PPD, CAL, BOP, and also reduce the bacterial periodontopathogens such as *Fusobacterium nucleatum*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans* and *Campylobacter rectus* so that HA has the potential to be an alternative as an additional treatment after SRP for chronic periodontitis patients.

Review (J Int Dent Med Res 2022; 15(2): 858-866)

Keywords: Hyaluronic acid, adjunct therapy, chronic periodontitis.

Received date: 29 January 2022

Accept date: 06 March 2022

Introduction

Periodontal disease occurs as a result of complex interactions between bacteria in biofilm, especially in the subgingival and the inflammatory activity of immune cells that develop in the periodontal tissues in response to the activity of periodontal pathogens.¹ Periodontal disease is classified into gingivitis and periodontitis, the most common periodontal disease is periodontitis.¹ Based on data from Riskesdas 2018, the prevalence of periodontitis is relatively high, with the prevalence in all age groups in Indonesia reaching 74.1%.² Chronic periodontitis is the most common form of periodontitis, and generally indicates an inflammatory condition in the periodontium that

develops slowly which induces an immune response and results in the damage of tooth supporting tissue of the teeth involving the gingiva, periodontal ligament, alveolar bone, and cementum.¹

Porphyromonas gingivalis, *Tannerella forsythia*, and *Treponema denticola*, are often associated with the cause of attachment loss and bone loss in chronic periodontitis.³ One of the most important treatments of periodontal disease is non-surgical mechanical therapy, known as scaling root planing (SRP).^{4,5} Although SRP is an effective method for the treatment of periodontal disease, mechanical debridement alone is not sufficient to remove pathogens in the subgingival connective tissue.^{6,7} Combination of mechanical and chemical treatments is needed to obtain optimal results. Chemical treatment can be achieved by application of a chemical agent to the subgingival area as an adjunct therapy post SRP.^{9,11}

In recent years, Hyaluronic Acid (HA) has received attention because of its promising results.^{12,13} Hyaluronic acid which is an extracellular constituent of connective tissue is

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known as a local chemotherapeutic agent and has shown many optimal clinical therapeutic properties.¹⁴⁻¹⁸ Hyaluronic acid plays a role in the adhesion and migration of polymorphonuclear leukocytes and macrophages to the site of inflammation to carry out phagocytosis and kill microbes.¹⁵ At the granulation stage, hyaluronate will play a role in migrating matrix cells in the granulation tissue, initiating angiogenesis, stabilizing granulation tissue, and restoring epithelial tissue.^{15,22} Hyaluronic acid also plays an important role in accelerating bone regeneration through chemotaxis, proliferation and differentiation of mesenchymal cells.²⁴⁻²⁷

Considering the possible positive effect on chronic periodontitis patients, the subgingival application of hyaluronic acid gel as an adjunct treatment post-SRP has the potential to affect the healing rate of chronic periodontitis patients. The aim of this study was to identify the effect of subgingival application of hyaluronic acid gel as an adjunct treatment post-SRP in chronic periodontitis patients using the rapid review method.

Materials and methods

This research was conducted using the rapid review method which refers to a systematic review of the literature.²⁸⁻³⁰ Specific research questions were then designed based on the concept of the PICO framework. The literature search for this article was conducted on databases and search engines using PubMed, Cochrane, EBSCOhost, SAGE, and Google Scholar within the past 10 years of publication. The search and selection of articles to be analyzed qualitatively was carried out based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.²⁸⁻³⁰ Search scientific articles in databases and search engines using the keywords “((Hyaluronic acid) OR (adjunct therapy scaling root planing) AND (periodontal therapy) OR (scaling root planing) OR (non surgical periodontal therapy)).”

Inclusion criteria as a reference for article selection in this study are articles published within the last 10 years, articles that have been indexed by Scopus, articles consisting of full text, articles with Randomized Control Trials (RCTs) research designs with the following conditions: aims to assess the effect of hyaluronic acid gel

as an adjunct treatment in chronic periodontitis patients, human subjects with chronic periodontitis disease, the experimental group is the group that received post-SRP hyaluronic acid gel treatment intervention, the outcome variables are changes in the value of clinical or microbial parameters.

In the initial search, 126 articles were collected from 5 electronic databases, four articles were collected from the hand manual searching. At the end of the search process, ten articles were obtained for qualitative analysis. PRISMA's flow chart as an article selection process can be seen in Figure 1.

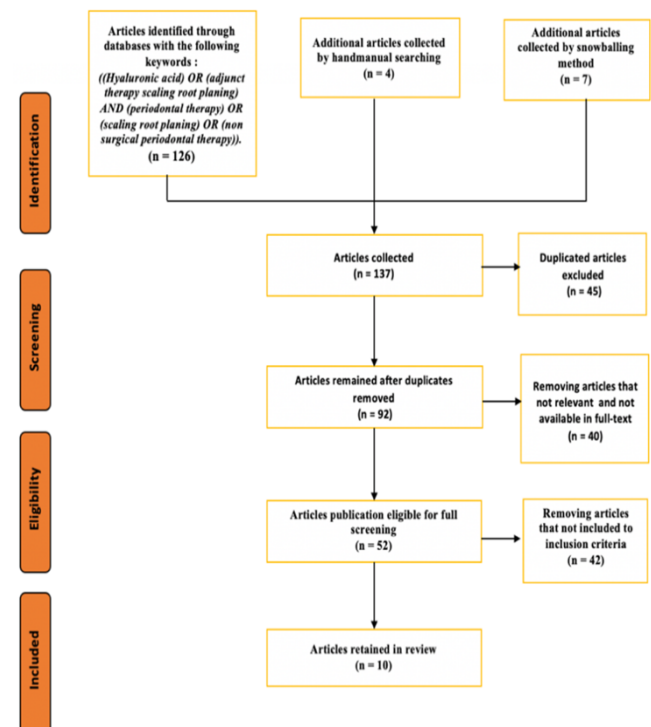


Figure 1. PRISMA diagram flow for search and selection.

Results

After searching and selecting articles, 10 articles were obtained that were included in the inclusion criteria. All of study consisted of 269 participants. Ten articles intervened of additional treatment with hyaluronic acid gel which was applied using a syringe to the subgingival area after SRP. All articles assess PPD and CAL which are the primary parameter in chronic periodontitis. In the primary parameter, 6 articles showed a significant decrease in PPD, 5 articles of them showed a more significant decrease in

CAL, and 3 of these articles showed a significant reduction of bleeding rates in the test group when compared to the control group. The results of data extraction from ten articles are summarized in Table 1.

Discussion

Chronic periodontitis is an infection caused by the accumulation of plaque and maturation of pathogenic biofilms on the tooth surface and oral mucosal surfaces. Non-surgical therapy can be the prior therapy for periodontal treatment, but the clinician's ability to gain access to deep pockets during SRP often results in substantial variation in its effectiveness.³⁶ Adjunct treatment post-SRP in the form of herbal therapies such as mangosteen peel or synthetic materials such as carbonate apatite membrane can reduce MMP-8 levels as one of the important biomarkers in chronic periodontitis.^{37,38} Hyaluronic acid with SRP resulted in statistically significantly greater reductions in clinical or microbiological parameter scores than SRP alone.³⁶ The main clinical parameters in assessing the healing rate of chronic periodontitis patients were PPD, CAL, and BOP.

In the study of Nguyen et al (2021)³¹, subgingival application of hyaluronic acid gel produced a positive effect on dental plaque formation. The experimental group showed a significant reduction for the mean plaque score compared to the control group at each time interval. This is in accordance with research conducted by Salavathi et al (2016)³², Alshammari et al (2018)⁸, Eick et al (2012)³³, Shah et al (2016)³⁶ and Polepalle et al (2015)³⁹ which showed a decrease in PI scores were greater in patients with hyaluronic acid gel application post-SRP. The reduction in plaque formation is due to the routine actions of maintaining better oral hygiene of the patient. Alshammari et al. (2018)⁸ revealed a significant decrease in the gingival index in the experimental group indicating that hyaluronic acid gel acts well as an anti-inflammatory to reduce the level of gingival inflammation. HA in promoting the migration of various cells including fibroblasts at the site of injury, thereby reducing vascularization due to inflammation by causing fibrosis in the connective tissue. This will provide a conducive environment for the gingiva to carry out the healing process.^{34 35}

Periodontal pockets are a pathognomic sign of periodontal disease.³⁵ In combination with SRP, Rajan et al. (2014)⁶ Salavathi et al. (2016)³² Eick et al.(2012)³³ Mallikarjun et al. (2016)³⁴ Shah et al. (2016)³⁶ and Polepalle et al. (2015)³⁹ revealed a statistically significantly greater reduction in probing depth for the experimental group than for the control group. The reduction in probing depth is also associated with the nature of hyaluronic acid which promotes new attachment due to stimulation of fibroblasts to synthesize collagen. Hyaluronic acid also has a role in maintaining the integrity of the periodontal tissue through its complex interactions with the extracellular matrix (ECM) and its components.

The role of hyaluronic acid is associated with an improvement in clinical attachment levels in chronic periodontitis patients. The improvement in the outcome of this clinical parameter was associated with the regenerative effect that hyaluronic acid has by promoting adhesion, migration, proliferation, and cellular activation. Hyaluronic acid is able to store and spread growth factors in the periodontal tissues. Therefore, hyaluronic acid will contribute to the formation of the extracellular matrix, tissue regulation, and fixation of the gingival epithelium to the basal lamina so that it will increase the clinical attachment level of chronic periodontitis patients. There was improvement in PPD and CAL/RAL at a higher time interval at the experimental site compared to the control site, indicating the ability of hyaluronan to prevent lesion progression and stop pocket formation.³⁵ The difference in the value of decreasing PPD and CAL in each study can be influenced by the frequency of use of hyaluronic acid gel, the level of patient compliance following the study protocol, and the operator's ability to apply the HA gel as well as the calibration process when measuring the index carried out by the assessment team.

The anti-inflammatory and bacteriostatic properties of HA play a role in the reduction of periodontal inflammation and bleeding. Decreased bleeding rate (BOP) was revealed by Alshammari et al. (2018)⁸ Gontiya et al. (2012)³⁵ and Lobato et al. (2020)¹³. The anti-inflammatory properties of HA were also strengthened by Gontiya et al. (2012)³⁵ who revealed that the levels of mild inflammatory infiltrates were more in the experimental group. This positive effect is driven by the properties of HA which is able to

reduce cell proliferation in epithelial cells, fibroblasts, and lymphocytes, reduce the inflammatory process, and repair periodontal lesions in patients with chronic periodontitis.³⁵ The role of hyaluronic acid is not only limited to improving clinical parameters, Nguyen et al (2021)³¹, Eick et al.(2012)³³, and Polepalle et al. (2015)³⁸ similarly revealed a decrease in the number of bacterial colonies in the experimental group. This positive influence on microbiological parameters further strengthens the bacteriostatic effect of hyaluronic acid to prevent the growth and spread of periodontopathogenic bacteria. The mechanism of action of HA will produce a physical barrier against bacteria and their products in the extracellular matrix and stimulate the migration process of polymorfonuclear leukocytes and macrophages to carry out microbial phagocytosis so that HA is able to stabilize low microbial counts for a long time and prevent regrowth of this bacterial species significantly in the gingival sulcus and periodontal tissue.³⁵

In addition to measuring clinical and microbiological parameters, there are studies that assess inflammatory biomarkers including NE and hBD-2. Mallikarjun et al. (2016)³⁴ revealed a decrease in NE levels in the experimental and control groups but there was no significant difference between the two group. NE is one of the biomarkers in periodontal disease that has a role in soft tissue damage and causes gingival inflammation.⁴⁰ HA plays an important role in inhibiting the release of NE into tissues.³³ The ability of HA to inhibit the release of NE will prevent further damage to the periodontal tissue thereby accelerating the healing process in periodontal therapy.³³ However, in this study, no significant effect was found on neutrophil enzymes.³³

Research conducted by Alshammari et al. (2018)⁸ proved that administration of HA in the experimental group will help wound healing and tissue repair processes at the periodontal site by increasing levels of the enzyme hBD-2.⁴¹⁻⁴⁴ The hBD-2 enzyme has the ability to bind to microbial membranes and form gaps in the microbial membrane, resulting in a change in membrane permeability which results in lysis of microbial cells. Therefore, the anti-microbial action of hBD-2 has a major role in host defense against microbial colonization in the mucosa and gingival environment.^{42,45}

Conclusions

The findings from all RCTs included in this study show that Hyaluronic acid has results in improving PPD, CAL, BOP, and also reduce the bacterial periodontopathogens such as *Fusobacterium nucleatum*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans* and *Campylobacter rectus* so that HA has the potential to be an alternative as an additional treatment after SRP for chronic periodontitis patients.

Acknowledgements

The authors would like to express our gratitude for Warta Dewi, drg., M.Kes., Dr. Nanan Nur'aeny, drg., Sp.PM (K)., Agus Nurwiadh, drg., Sp.BM (K)., (Universitas Padjadjaran) for the advice that have been given to this manuscript.

Declaration of interest

The author report no conflict of interest.

| No | Author | Participant | Research time | Intervention | Parameter | Research result | Conclusion |
|----|---|---|---|--|---------------------------------------|---|--|
| 1. | Rajan <i>et al.</i> (2014) ⁶ | 33 patients with moderate to severe chronic periodontitis with 66 selected sites were divided into a control group and an experimental group using the split-mouth design method. | 3 months with the following follow-up time: 1. Baseline 2. Week 4 3. Week 12 | Experimental group: SRP + 0,2% HA gel (reapplication after 1 week) + OHI Control group: SRP + OHI | BOP PPD CAL | <ul style="list-style-type: none"> • There was significant decrease of PPD and CAL in test group • There was no significant difference in BOP but the decrease is higher in test group. | Application of HA produces a positive effect in patients with chronic periodontitis. |
| 2. | Nguyen <i>et al.</i> (2021) ³¹ | 28 patients with moderate to severe chronic periodontitis using the Randomized split-mouth study method were divided into a control group and a test group. | 3 months with the following follow-up time: 1. Baseline 2. Week 6 | Experimental group: Subgingival plaque sample collection + SRP + Pocket cleaned 0,9% NaCL + 0,2% HA gel (reapplication at week 1,2,3) + OHI Control group: Subgingival plaque sample collection + SRP + OHI | PI GI BOP PPD CAL CFUs | <ul style="list-style-type: none"> • The use of HA reduced the clinical periodontal parameters, but without significant differences in PI, GI, PPD, BOP, and CAL. • HA provided a significant reduction in the level of CFUs specifically for <i>Fusobacterium nucleatum</i> and <i>Tannerella forsythia</i>. | Hyaluronic acid showed a positive effect in increasing CAL and reduce inflammation. |
| 3. | Salava dhi <i>et al.</i> (2016) ³² | 12 Participants with chronic periodontitis were divided into control group and experimental group by split-mouth design method. | 3 months with the following follow-up time: 1. Baseline 2. Week 6 3. Week 12 | Experimental group: SRP + 0,8% HA gel Control group: SRP | PI BOP PPD CAL | HA significantly reduced BOP, PPD, and CAL at sites that received HA, compared to control. Although the PI also showed reductions, these were not significant. | The use of hyaluronic acid (HA) gel has a beneficial effect in the treatment of chronic periodontitis. |

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| 4. | Alshamari <i>et al.</i> (2018) ⁸ | A total of 48 locations were selected from 24 patients with moderate to severe chronic periodontitis using the split mouth study method and were divided into a control group and an experimental group. | 3 months with the following follow-up time: 1. Baseline 2. Week 6 3. Week 12 | Experimental group: SRP + 0.8% HA gel + GCF sample collection + OHI Control group: SRP + GCF sample collection + OHI | PI GI BOP PPD CAL hBD-2 | <ul style="list-style-type: none"> • HA significantly reduced GI and BOP at test sites compared to control. The other periodontal parameter such as PI, PPD, and CAL showed an improvement compared to the control side but the difference was not statistically significant. • The level of hBD-2 was more higher in sites that received subgingival application of HA. | Local application of 0.8% HA gel with SRP has a positive effect on the periodontal health of patients with moderate to severe chronic periodontitis. |
| 5. | Eick <i>et al.</i> (2012) ³³ | 42 periodontitis patients were divided into 21 participants for the control group and another 21 for experimental group with the parallel method. | 6 months with the following follow-up time: - Baseline - month 3 - month 6 | Experimental group: SRP + chlorhexidine gluconate + 0.8% HA gel (reapplication 0,2% HA gel twice for a day) + Collection of plaque samples + OHI. Control group: SRP + chlorhexidine gluconate + Plaque sample collection + OHI. | PI BOP PPD CAL CFUs | <ul style="list-style-type: none"> • HA provided a significant reduction in PPD, compared to the control group. • No significant differences were found between the groups for PI, BOP, and CAL evaluated. • HA significantly reduced the pathogen of <i>Aggregatibacter actinomycetemcomitans</i> and <i>Campylobacter rectus</i> in the test group compared to the control. | There is an antibacterial effect from using hyaluronic acid gel in addition to SRP and is able to reduce the depth of PPD. |
| 6. | Mallikarjun <i>et al.</i> (2016) ³⁴ | The study was conducted at 80 sites in the maxillary quadrant of the posterior teeth of 20 chronic periodontitis patients with a randomized split-mouth study divided into a control group and an experimental group. | 6 months with the following follow-up time: 1. Baseline 2. Week 6 | Experimental group: SRP + 0.2% HA gel + GCF sample collection + OHI Control group: SRP + GCF sample collection + OHI | PI GI PPD CAL NE | <ul style="list-style-type: none"> • The HA provided a significant reduction in PPD and CAL, but no significant improvement were observed on the other parameters. • There was no improvement in the levels of NE in both of test sites and control sites. | There was a positive effect in repairing tissue damage with the application of hyaluronic acid after SRP. |

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| 7. | Gontiya <i>et al.</i> (2012) ³⁵ | 26 patients with chronic periodontitis with a total of 120 sites selected by the split-mouth design method were divided into a control group and An experimental group. | 3 months with the following follow-up time: - Baseline - week 4 - Week 6 - Week 12 | Experimental group: SRP + 0.2% HA gel (reapplication at week 1,2,3) + OHI Control group: SRP + OHI. | GI BOP PPD RAL | HA significantly reduced BOP and RAL at test sites. There were also no significant differences regarding the inflammatory infiltrate but mild infiltrate was higher can be found at test sites compared to control. | Hyaluronan improves SRP results by improving gingival parameters. |
| 8. | Lobato <i>et al.</i> (2019) ¹³ | 16 patients with chronic periodontitis, test and control groups were determined by the split-mouth design method. | 3 months with the following follow-up time: - Baseline - Week 6 - Week 12 | Experimental group: Anesthesia + SRP 0.8% HA gel + OHI Control group: Anesthesia + SRP + OHI | GI BOP PPD CAL | <ul style="list-style-type: none"> •HA provided a significant reduction in GI and PPD at test sites compared to the control. •The other periodontal parameter showed an improvement but the difference was not statistically significant. | There's an improvement of BoP which might be attributed to the anti-inflammatory properties of HA. |
| 9. | Shah <i>et al.</i> (2016) ³⁶ | In 50 chronic periodontitis patients, the test and control sites were determined by the split-mouth design method. | 3 months with the following follow-up time: - Baseline - week 4 - Week 12 | Experimental group: SRP + 0.8% HA gel (reapplication after 1 week) + OHI. Control Group: SRP + OHI. | PI GI PPD RAL | <ul style="list-style-type: none"> •HA significantly reduced PPD and RAL at test sites compared to the control. •The other periodontal parameter showed an improvement but the difference was not statistically significant. | Hyaluronic acid has a good effect in decreasing probing depth and clinical attachment level. |
| 10. | Polepalle <i>et al.</i> (2015) ¹⁰ | 18 Chronic periodontitis patients with a split-mouth design method in a total of 72 locations were divided into an experimental group and a control group. | 3 months with the following follow-up time: - Baseline - week 1 - week 4 - Week 12 | Experimental group: SRP + 0.8% HA gel (reapplication after 1 week) + Plaque sampling + OHI Control group: SRP + Plaque sampling + OHI. | PI BOP PPD CAL CFUs | <ul style="list-style-type: none"> •HA significantly reduced the periodontal clinical parameters with the exception of BOP. •There was a possible antimicrobial activity of HA through significantly reduced of CFUs in the test sites compared to the control. | Subgingival application of 0.8% HA gel with SRP provided a positive improvement in periodontal parameters in influencing inflammation and wound healing |

Table 1. Data Extraction from 10 articles about the effect of Effect of Subgingival Application of Hyaluronic Acid Gel as an Adjunct Therapy After Scaling Root Planing in Chronic Periodontitis Patient. HA : hyaluronic acid, SRP : scaling root planing, pi : plaque index, gi : gingival index, PPD : periodontal probing depth, BOP : bleeding on probing, CAL : clinical attachment level, RAL : relative attachment level, NE : neutrophil elastase, hBD-2 : human beta defensins-2, CFUs : colony forming units, GCF : gingival crevicular fluid, OHI : oral hygiene index, PCR : polymerase chain reaction.

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