Journal of Biosciences and Medicines, 2025, 13(5), 285-295
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Enhanced Regeneration of Periodontal Tissues Using Low Molecular-Weight Hyaluronic Acid Combined with Radon-Rich Mineral Water from Tskaltubo

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How to cite this paper: Ani, G., Zurab, S. and Sofo, C. (2025) Enhanced Regeneration of Periodontal Tissues Using Low Molecular-Weight Hyaluronic Acid Combined with Radon-Rich Mineral Water from Tskaltubo. *Journal of Biosciences and Medicines*, **13**, 285-295.
https://doi.org/10.4236/jbm.2025.135022

Received: March 31, 2025
Accepted: May 23, 2025
Published: May 26, 2025

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Abstract

Periodontal diseases, characterized by chronic inflammation and progressive tissue destruction, remain a major global public health concern. Hyaluronic acid (HA), a naturally occurring glycosaminoglycan, has emerged as a promising agent in periodontal therapy due to its hydrating, anti-inflammatory, and regenerative properties. This study investigates the therapeutic efficacy of combining low-molecular-weight hyaluronic acid (HA) with radon-rich mineral water from Tskaltubo in the non-surgical treatment of mild Stage 1 chronic periodontitis. Thirty patients were enrolled and divided into two groups: one receiving conventional HA therapy and the other receiving HA in conjunction with radon water rinses. Clinical assessments, including oral hygiene index (OHI-s), bleeding on probing (BOP), and microvascular perfusion via Doppler ultrasonography, were performed at baseline, one week, and one month post-treatment. Both groups demonstrated clinical improvement, but the combination group showed more rapid and sustained reductions in inflammation, bleeding, and improved gingival microcirculation. The results suggest that radon water may potentiate the regenerative and anti-inflammatory properties of HA, supporting its potential as an effective adjunct in periodontal therapy.

Keywords

Periodontal Diseases, Chronic Inflammation, Tissue Destruction, Hyaluronic Acid (HA), Glycosaminoglycan, Periodontal Therapy, Hydrating Properties, Anti-Inflammatory Properties, Regenerative Properties, High-Molecular-Weight HA

1. Introduction

Hyaluronic acid (HA) is a hydrophilic polymer known for its strong capacity to adsorb water molecules, contributing to its elastic yet flexible (soft) gel-like nature. As a low molecular weight glycosaminoglycan, HA is a key component of the extracellular matrix and is found within various connective tissues, including embryonic mesenchymal tissues, the vitreous humor of the eye, skin, and several body fluids such as synovial fluid, serum, saliva, and gingival crevicular fluid [1]. Structurally, HA consists of repeating disaccharide units linked alternately by β-1,4- and β-1,3-glycosidic bonds [2]. Chemically, HA is always identical, with differences arising solely from its molecular weight: low molecular weight (LMW), typically ranging from 10^5 to 10^7 and composed of 3 - 5 repeating disaccharide units; intermediate molecular weight; and low molecular weight (LMW), which can include up to 25,000 or more disaccharide repeats [3]. HA plays diverse physiological and structural roles, mediating both cellular and extracellular interactions. These interactions not only broaden its range of biological functions but also contribute to the regulation of osmotic pressure.

All of these functions contribute to the preservation of tissue structure and the maintenance of homeostatic integrity. The trophic, barrier, and structural (plastic) roles of connective tissue are largely attributed to the physical and chemical properties of hyaluronic acid (HA), including its high viscosity, unique ability to bind water and proteins, and its role in forming proteoglycan aggregates [4]. These characteristics are particularly important for the regeneration of periodontal tissues and oral mucous membranes.

Short-chain HAs—those with a molecular mass (MM) of 400 to 10,000 Da—promote angiogenesis, while medium-sized HAs (MM 50,000 - 100,000 Da) support cell migration and proliferation. In contrast, high-molecular-weight HAs (MM > 500,000 Da) exhibit inhibitory effects on these processes, suppressing angiogenesis as well as cell migration and proliferation [5]. Consequently, the use of HA in therapeutic applications requires careful selection of its molecular weight, which is strictly regulated for specific purposes.

In the early stages of inflammation, HA plays a crucial role by blocking the arachidonic acid cascade without disrupting the synthesis of essential compounds. This mechanism is associated with the protective effects of prostaglandins [6] and includes the activation of metalloproteinase inhibitors, thereby limiting tissue destruction. Additionally, HA reduces the production of pro-inflammatory cytokines, such as TNFα, further contributing to tissue preservation during inflammatory responses.

According to Becker *et al.*, HA also exhibits bacteriostatic properties, particularly against microorganisms found in periodontal tissues, such as *Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia*. This antimicrobial effect provides biological protection following professional dental hygiene and supports surgical treatment of periodontal diseases. HA stimulates fibroblast activation and collagen fiber production, while also enhancing cytokine synthesis in fibroblasts, keratinocytes, cementoblasts, and osteoblasts. This cascade leads to the endogenous synthesis of HA through endothelial pathways [7]. Moreover, HA is involved in regulating cell migration, proliferation, and differentiation, with favorable clinical outcomes observed in the treatment of soft tissue injuries [8].

While endogenous hyaluronic acid levels naturally decline with age, factors such as dehydration, environmental exposure, and systemic stress may further compromise HA synthesis and tissue hydration. These changes can affect the structure and immune function of oral mucosa, underscoring the clinical relevance of HA supplementation in periodontal care.

Modern hyaluronic acid (HA) production is conducted under strict bacteriological control, ensuring a high level of product purity and quality. Today, HA is increasingly derived from plant-based substrates, such as wheat, as well as from bacterial cultures, most commonly *Streptococcus zooepidemicus* or *Streptococcus equi*. HA is extensively used in pharmaceuticals to enhance chemical, enzymatic, and mechanical stability. To this end, cross-linking of its macromolecules is achieved via hydrogels. These hydrogels—chemically modified versions of natural HA—are hydrophilic, cross-linked polymers capable of absorbing significant amounts of water, thereby forming stable, insoluble structures.

In dental practice, HA preparations are most frequently applied via injections, topical gels, and ointments. These formulations are used in anti-inflammatory therapy, comprehensive periodontal treatment, and soft tissue correction, including the mitigation of gum inflammation and the management of peri-implant tissues. HA plays a vital role in regulating inflammatory responses within gingival tissues [9].

In our study, we used a 0.2% hyaluronic acid gel produced by Intermed—HA + AL Gel (Certificate of Analysis: Product Inspection Lot: 000266168, Intermed, Greece)—marketed under the trade name Hyalgel. This formulation was selected for its clinical efficacy and stability.

To accelerate healing processes associated with inflammation in the oral cavity, we combined the use of HA with radon inhalation therapy, utilizing naturally radon-rich waters from Tskaltubo. This approach was implemented for patients residing in Kutaisi and nearby regions. We compared treatment outcomes between two groups: one receiving only low-molecular-weight HA, and another receiving both Low-molecular-weight HA and radon therapy.

Our primary research focus was on the efficacy of HA and its interaction with radon as an adjunct therapy, particularly in implantology. The data suggest that this combined treatment supports the natural regeneration of periodontal barriers—structures crucial for the trophic and plastic integrity of periodontal tissues—and that radon therapy notably accelerated these processes compared to HA alone.

The delivery system used in this study, based on the Hyadent model, is depicted in **Figure 1**, which illustrates the structure and clinical application method of dental HA gel preparations. Accordingly, the objective of this study was to evaluate the clinical effectiveness of combining Low-molecular-weight hyaluronic acid (HA) with radon-rich mineral water from Tskaltubo in the comprehensive, non-surgical treatment of mild Stage 1 chronic periodontitis.

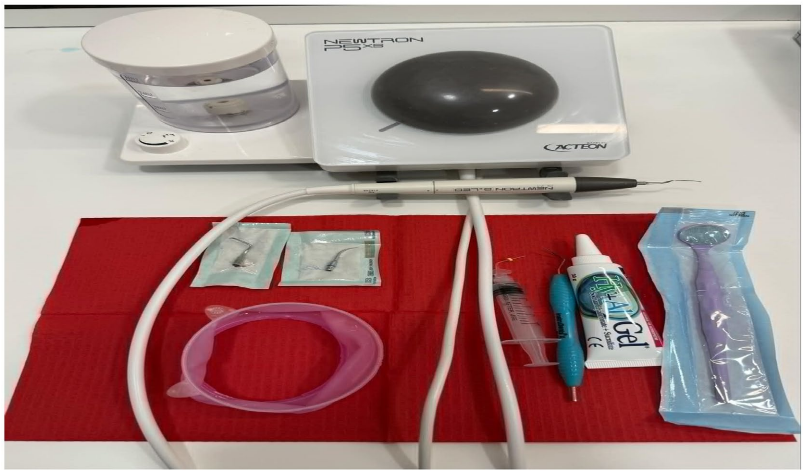

Figure 1. Structure and clinical application of a dental Hyadent delivery system used for HA administration.

2. Materials and Methods

This randomized, controlled clinical study included 30 patients diagnosed with mild (Grade 1, A-type) chronic periodontitis, all of whom also had stable somatic conditions. Patients were randomly allocated into two equal groups of 15. Group 1 (control) received conventional non-surgical periodontal therapy supplemented with a 0.2% high-molecular-weight hyaluronic acid gel (Hyalgel®, Intermed, Greece). Group 2 (experimental) received the same HA therapy in addition to topical and rinsing applications using radon-rich mineral water sourced from the Tskaltubo spa region. Written informed consent was obtained from all participants in accordance with the Helsinki Declaration.

Before treatment, each patient underwent comprehensive clinical evaluation, including intraoral examination, periodontal charting, radiographic imaging (panoramic and cone-beam computed tomography), and assessment of oral hygiene (OHI-S), bleeding on probing (BOP), and periodontal status using the PMA index. Doppler ultrasonography was employed to evaluate microvascular perfusion in the gingival tissues, based on methods described in previous literature [8] [10].

All patients received initial professional cleaning, which included supragingival and subgingival scaling using ultrasonic instrumentation (Acteon Piezo). The HA gel was administered weekly by subgingival injection and topical application to affected areas. In Group 2, radon water was applied as a rinse and as a mucosal salve concurrently with HA treatment. The combination protocol was applied for four weeks. No systemic antibiotics or additional therapies were used during the trial period.

Before initiating treatment, a comprehensive dental assessment was conducted for each patient. This included a patient survey, external and intraoral examinations, evaluation of oral mucosal and periodontal changes, assessment of periodontal indices (PMA and BOP), and hygiene indices (OHI-S, Silness, and Loe). Radiographic examinations—both panoramic imaging and computed axial tomography (CAT)—were performed to evaluate the extent of bone tissue involvement, as well as to determine the stage and severity of the periodontal pathology. A photographic protocol was also established for documentation.

Both groups underwent initial professional oral hygiene, including supragingival and subgingival instrumentation, as well as individual oral hygiene instruction and correction when necessary. Depending on the clinical condition, additional anti-inflammatory therapies, including radon baths, were administered.

Patients in the main group received additional therapy with dental applications and subgingival injections of Hyalgel (Registration Certificate No. RZN 2016/3617, dated 06.06.2018), a preparation containing 0.2% natural low-molecular-weight HA (up to 3.3 MDa). Figure 2 shows the topical application of Hyalgel combined with radon-rich water, demonstrating the technique used on the mucous membrane.

Figure 2. Topical application of Hyalgel combined with radon-rich water on oral mucosa.

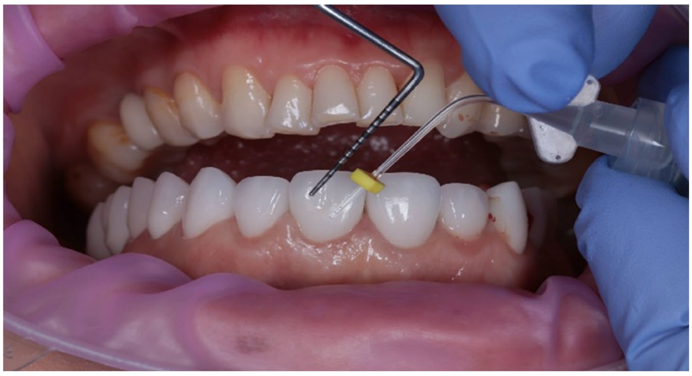

Figure 3. Insertion of a hyadent into a periodontal pocket.

This treatment was administered at weekly intervals. Figure 3 illustrates the direct insertion of a Hyadent into a periodontal pocket, which allows for targeted HA delivery.

The treatment protocol included:

1. Radiographic assessment

2. Diagnosis and creation of a periodontal chart
3. Supragingival and subgingival debridement
4. Introduction of *Hyalgel* into periodontal pockets
5. Individualized oral hygiene planning and the recommendation of appropriate oral care products

Additionally, to evaluate the effect of treatment on local microcirculation, Doppler ultrasonography was employed. Figure 4 shows the method of external HA application to the mucosal surfaces along with radon water salve usage. Periodontal instrumentation was performed using an Acteon Piezo ultrasonic scaler, both supragingivally and subgingivally.

Figure 4. External application of hyalgel to the mucous membrane and use as a radon salve.

3. Results and Discussion

Clinical examination of patients in the main group revealed a marked reduction in gingival swelling and hyperemia. Figure 5 presents the baseline clinical appearance of a 20–25-year-old patient with exacerbated mild generalized periodontitis prior to treatment.

Figure 5. The patient is 20 - 25 years old. Chronic mild generalized periodontitis severity, exacerbation, before treatment.

Improvements were also observed in periodontal health indices, including PMA and BOP. Furthermore, Doppler ultrasonography indicated enhanced microvascular blood flow in the periodontal tissues. As shown in Figure 6, the same patient exhibited significant visual improvement one month following the combined therapy protocol.

Figure 6. Patient K, 25 years old. Chronic mild generalized periodontitis, remission, 1 month after treatment.

Doppler ultrasound has proven to be an effective, non-invasive method for evaluating the vitality of dental pulp and surrounding tissues. In this study, it was successfully applied to monitor periodontal tissue perfusion. The technique is widely recognized in dentistry for assessing pulpal vitality in both adults and children, differentiating between apical radiolucencies based on pulp condition, evaluating responses to pharmacological and thermal stimuli, and monitoring tissue reactions to orthodontic treatment and traumatic injuries.

Our findings suggest that the combined use of low-molecular-weight HA and radon therapy not only supports tissue regeneration but also enhances local blood circulation—contributing to faster and more effective recovery in periodontal disease management compared to HA therapy alone.

Further analysis revealed that patients in the first group—who used radon-enriched water as an oral rinse—demonstrated more pronounced improvements across the studied clinical parameters compared to the second group, which did not utilize radon rinses. Patient-reported outcomes indicated that those using radon water experienced more rapid relief from gingival inflammation, including reduced pain, diminished bleeding, and an overall faster improvement in gum condition.

Intragroup analysis showed statistically significant improvements in both the Oral Hygiene Index (OHI-s) and the Bleeding on Probing (BOP) index across both groups. Baseline oral hygiene scores (OHI-s) prior to treatment were 2.4 in the first group and 2.5 in the second group, indicating a generally unsatisfactory level of hygiene. One month following treatment, the OHI-s scores improved markedly: 0.5 in the first group—corresponding to a good level of hygiene—and 0.9 in the second group, which, while improved, remained within the range of a satisfactory hygiene level (Figure 7).

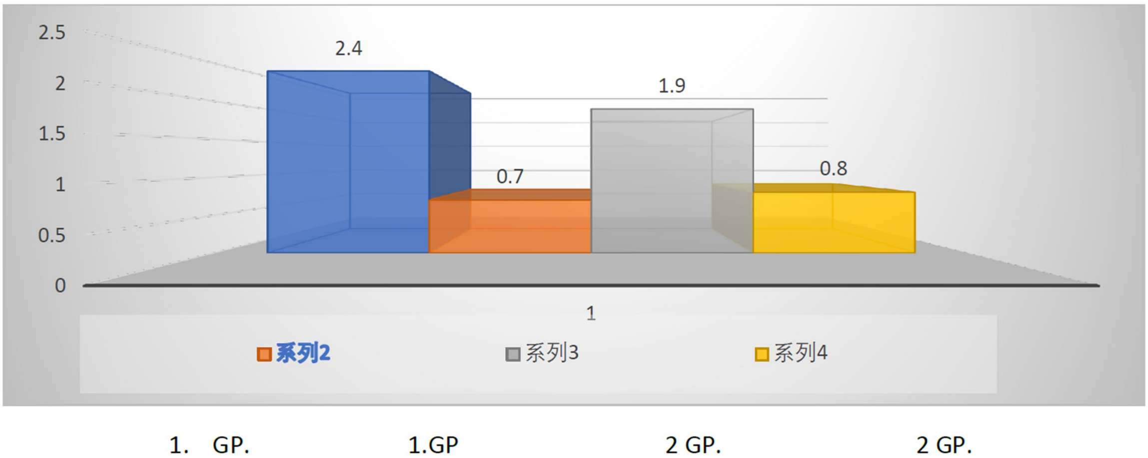

Figure 7. Illustrates the change in Oral Hygiene Index-Simplified (OHI-s) scores between groups. At baseline, the first group's OHI-s was 2.4 and the second group's was 2.5—both reflecting unsatisfactory oral hygiene. After one month of treatment, the OHI-s dropped to 0.5 in the first group (indicating good hygiene) and to 0.9 in the second group (indicating satisfactory hygiene).

As shown in Figure 7, both groups demonstrated a statistically significant improvement in oral hygiene over the course of treatment. The mean OHI-S score in the experimental group decreased from 2.4 ± 0.3 at baseline to 0.5 ± 0.2 at one month ($p < 0.01$), reflecting a transition from poor to good hygiene. In the control group, OHI-S scores decreased from 2.5 ± 0.4 to 0.9 ± 0.3 ($p < 0.01$), indicating an improvement to a satisfactory hygiene level. Although both groups improved, the change in the experimental group was significantly greater ($p = 0.04$).

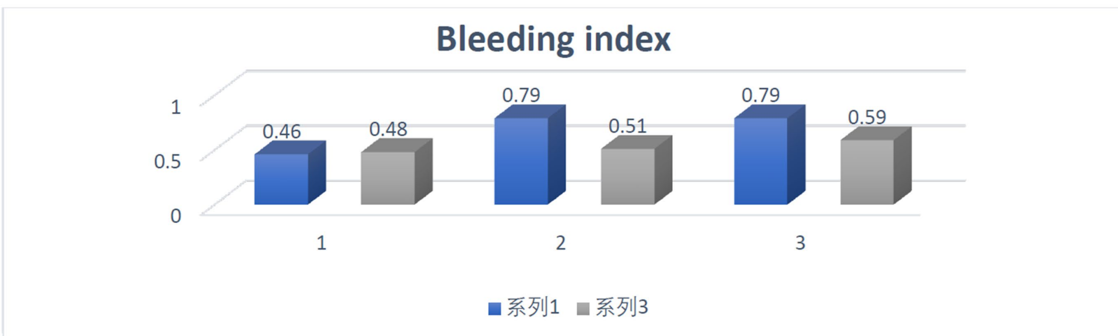

Figure 8. Bleeding index after 1 month.

Figure 8 presents changes in the Bleeding on Probing (BOP) index. The experimental group showed a rapid decline from 58% ± 6.2 at baseline to 24% ± 4.1 after one week, and further to 20% ± 3.8 at one month. The control group exhibited a reduction from 55% ± 6.5 to 35% ± 5.3 after one week, and to 24% ± 4.6 at one month. The between-group difference in BOP reduction was statistically significant after the first week ($p < 0.05$), though by one month, both groups had comparable BOP values.

All data are expressed as mean ± standard deviation, and comparisons were made using paired and unpaired t-tests. Error bars representing standard deviation have been included in all graphs to visualize variability. Axis labels and data series were also corrected for clarity.

4. Assessment of Changes

The data obtained in this study indicate that the inclusion of hyaluronic acid (HA) and radon water therapy in the treatment protocol creates favorable conditions for improving oral hygiene and enhancing periodontal health. HA demonstrated a pronounced anti-inflammatory effect, contributing significantly to therapeutic outcomes.

Blood flow velocity was assessed using Doppler ultrasound, incorporating both qualitative and quantitative parameters. The qualitative analysis of the Doppler curve revealed that waveforms varied depending on gingival phenotype [11] [12]. In cases of mixed blood flow, the Doppler spectrum exhibited a wave-like color pattern without pronounced peaks. Among quantitative markers, the most diagnostically relevant indicator of periodontal microcirculation was the mean linear blood flow velocity (Vam), which reflects the degree and severity of circulatory disturbance in the periodontal tissues.

At baseline, both groups showed comparable Vam values: 0.54 cm/s in Group 1 and 0.53 cm/s in Group 2. After one week of treatment, Vam increased to 0.77 cm/s in Group 1 (HA + radon water) and 0.60 cm/s in Group 2 (HA alone). After one month, Group 1 maintained a consistently high Vam of 0.76 cm/s, while Group 2's Vam declined slightly to 0.58 cm/s, approaching its initial level (**Figure 8**).

These findings demonstrate a notable increase in blood flow velocity in both groups, though the improvement was significantly more pronounced in the group receiving the combined HA and radon water therapy. Throughout the study, patients were regularly monitored for possible allergic or irritant reactions to either the HA+AL Gel or the Tskaltubo radon water. Oral examinations of the mucosa, gingiva, tongue, and lips showed no signs of hypersensitivity or local irritation in any participant [11].

5. Conclusions

This study demonstrates that the combined application of low-molecular-weight hyaluronic acid (HA) and radon-rich mineral water from Tskaltubo offers a significant therapeutic advantage in the management of mild Stage 1 chronic periodontitis. While HA alone has well-documented anti-inflammatory and regenerative properties, our findings show that its integration with radon therapy not only enhances the speed of recovery but also leads to more stable improvements in gingival health and microcirculation.

Clinical indices such as oral hygiene (OHI-s) and bleeding on probing (BOP) showed more pronounced and sustained improvements in the group receiving the combined therapy, as confirmed by both subjective patient reports and objective measurements, including Doppler ultrasonography. Notably, no adverse reactions were observed, underscoring the safety of this combined approach.

These results underscore the potential for incorporating naturally derived adjuncts like Tskaltubo radon water into non-surgical periodontal protocols, especially in early-stage disease. The synergistic effect between HA and radon therapy could mark a new direction in regenerative periodontal treatment—bridging biologically driven healing with minimally invasive clinical methods.

Further studies with larger cohorts and longer follow-up periods are warranted to validate these findings and explore applications in more advanced periodontal conditions or implantology. Nonetheless, this research contributes meaningful insight into the evolving role of biocompatible, multi-modal therapies in periodontal care.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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