ARTICLES SCIENTIFIQUES

Benefits of hyaluronic acid in the management of oral mucosa ulcers

Apport de l'acide hyaluronique dans la prise en charge des ulcérations de la muqueuse buccale

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Abstract

Hyaluronic acid is a non-sulfated glycosaminoglycan. It is a major component of the extracellular matrix of various body tissues such as vitreous humor, synovial fluid, skin, and connective tissue. Many tissue healing functions are attributed to hyaluronic acid. It plays an important role in activating and mitigating the inflammatory response, promoting cell proliferation and migration. It also promotes angiogenesis and re-epithelialization. In addition, its strong penetrating properties enable control of tissue hydration during inflammatory responses and response to tissue injury that causes oral mucosa ulceration. Based on these findings, the development of hyaluronic acid-based biomaterials to treat various diseases is underway. Currently, hyaluronic acid is used in many medical fields such as ophthalmology, orthopedics, dermatology, and cancer treatment. It also has interesting uses in dentistry for the treatment of acute and chronic inflammatory diseases. In fact, the use of topical hyaluronic acid in the treatment of stomatitis, particularly aphthous ulcers and oral lichen planus, has been reported. It has advantages over topical steroids because it is safe for all patients, including infants and pregnant women. The current literature review presents the mechanism of action, indications and efficacy of topical hyaluronic acid by summarizing the results of all studies evaluating hyaluronic acid therapy as an innovative alternative in the management of different oral ulcers.

Key words
Hyaluronic Acid; Oral Ulcer; Stomatitis, Aphthous; Lichen Planus, Oral; Mouth Mucosa

Résumé

L'acide hyaluronique est un glycosaminoglycane non sulfaté. C'est un composant majeur de la matrice extracellulaire de divers tissus tels que l'humeur vitrée, le liquide synovial, la peau et le tissu conjonctif. L'acide hyaluronique favorise la cicatrisation tissulaire par différentes fonctions. Il joue un rôle important dans l'activation et l'atténuation de la réponse inflammatoire, en favorisant la prolifération et la migration cellulaire. Il favorise également l'angiogenèse et la réépithélialisation. En outre, ses fortes propriétés de pénétration permettent de contrôler l'hydratation des tissus pendant les réponses inflammatoires et la réponse aux lésions tissulaires qui provoquent l'ulcération de la muqueuse buccale. Sur la base de ces résultats, le développement de biomatériaux à base d'acide hyaluronique pour traiter diverses maladies est en cours. Actuellement, l'acide hyaluronique est utilisé dans de nombreux domaines médicaux tels que l'ophtalmologie, l'orthopédie, la dermatologie et le traitement des cancers. Il a également des applications intéressantes en médecine dentaire pour le traitement des maladies inflammatoires aiguës et chroniques. En fait, l'utilisation de l'acide hyaluronique topique dans le traitement de la stomatite, en particulier les aphtes et le lichen plan buccal, a été rapportée. Il présente des avantages par rapport aux cortico-stéroïdes topiques car il est anodin pour tous les patients, y compris les nourrissons et les femmes enceintes. La présente revue de la littérature présente le mécanisme d'action, les indications et l'efficacité de l'acide hyaluronique topique en résumant les résultats de toutes les études évaluant la thérapie à l'acide hyaluronique en tant qu'alternative innovante dans la gestion de différentes ulcérations buccales.

Mots clés
Acide hyaluronique ; Ulcère buccal ; Stomatite aphteuse ; Lichen plan buccal ; muqueuse buccale.

INTRODUCTION

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan. It is a major component of the extracellular matrix of various body tissues, primarily in vitreous humor, synovial fluid, skin and connective tissue 1. It is also an important component of periodontal tissues such as gingiva, periodontal ligament, alveolar bone, and cementum. In 1934, Karl Meyer and John Palmer were the first to isolate it from bovine vitreous humor. The first biomedical application was in ophthalmology in 1950. Since then, applications of HA have been widespread in several other medical fields (orthopaedics, dermatology, cancer therapy, dentistry: gingivitis, implant surgery, temporomandibular disorders, oral surgery, stomatitis) 1.

MECHANISM OF ACTION

For the treatment of stomatitis, topical HA formulations such as gels, mouthwashes and sprays are preferred over injectables because they provide a barrier effect in addition to all other properties. Its hygroscopicity and high ability to retain moisture help regulate osmotic pressure and improve tissue lubrication. It also plays an important role in wound healing processes (inflammation, granulation tissue formation, epithelialization and tissue remodeling). In fact, chronic tissue inflammation causes extensive degradation of the high-molecular-weight HA to lower-molecular-weight molecules. While these low-molecular-weight fragments play a role in tissue damage signaling and immune cell recruitment, high-molecular-weight HA suppresses the immune response and prevents excessive exacerbation of inflammation 2. As for the barrier effect, it manifests double interest. First, topical HA formulations form a protective layer around the oral mucosa, protecting exposed nerve endings in ulcerated areas from overstimulation. Second, thanks to its important viscoelastic properties, HA reduces tissue penetration of viruses and bacteria3.

INDICATIONS AND CONTRAINDICATIONS

Topical hyaluronic acid (HA) finds applications in the treatment of various oral mucosal conditions, including: oral mucositis, recurrent aphthous ulcers (RAS), Behçet's disease, oral lichen planus, xerostomia, Sjogren's syndrome, ulcers due to drug reactions, ulcers due to radiotherapy/chemotherapy, after CO2 laser treatments, traumatic ulcers (orthodontic brackets and wires, ill-fitting dentures).

However, it is crucial to note that the use of topical HA is contraindicated in individuals with a known history of hypersensitivity or allergy to any of the product's ingredients. In such cases, alternative treatments should be considered to avoid potential adverse reactions or complications.

HA IN THE TREATMENT OF APHTHOUS ULCERS

Several studies have focused on the use of HA in the treatment of stomatitis.

In 2006, a randomized, placebo-controlled, double-blind trial evaluated the efficacy of a topical HA formulation (0.2%) in treating recurrent aphthous ulcers in 120 patients. Patients treated with topical HA had fewer new ulcers by day four and fewer ulcers by day five than patients treated with placebo. It concluded that twice-daily topical application for two weeks appears to be an effective and safe treatment for recurrent aphthous ulcers 4.

Lee et al. in 2007, tested the efficacy of topical 0.2% HA gel on recurrent oral ulcers in 33 patients with recurrent aphthous ulcers or Behcet's disease. Patients were asked to use topical 0.2% HA gel twice daily for two weeks. After treatment, approximately 75% of patients reported a subjective reduction in ulcer counts, faster ulcer healing time, and an improvement in VAS for pain. Objective examination of the number and area of ulcers and signs of inflammation showed a significant improvement. It was concluded that topical application of 0.2% HA gel appeared to be an effective and safe treatment in patients with recurrent oral ulcer and Behçet's disease 5.

Dalessandri et al. in 2015, performed a single-center, retrospective study in systemically healthy patients with mild recurrent aphthous stomatitis and treated with HA-containing mouthwashes or topical gels. Results showed significant normalization of lesion color, pain relief, and smaller lesion size in all patients. After three days of treatment, there was a significant difference between the two groups. 72% of lesions in the gel group showed an improvement in lesion size compared to 40% in the rinse group. It can be concluded that both HA containing mouth rinses and topical gel formulations are effective in treating mild, recurrent aphthous stomatitis, with topical gel formulations tending to accelerate healing initiation

Zheng et al. in 2020, compared in a retrospective observational study compared the safety and efficacy of topical 0.2% HA gel and topical dexamethasone ointment in treating recurrent aphthous stomatitis in children. 104 patients were included. Efficacy parameters assessed were ulcer size and pain scores at baseline and after seven days. Results showed no significant difference between the two groups. Neither treatment showed significant differences in body temperature, respiratory rate, pulse, or systolic/diastolic blood pressure. This study concluded that HA and dexamethasone had similar efficacy in reducing ulcer size and pain scores and were similarly well tolerated in children 7.

HA IN THE TREATMENT OF ORAL LICHEN PLANUS

Nolan in 2009 conducted a randomized, placebo-controlled, double blind trial to evaluate the efficacy of a topical HA gel preparation (0.2%) in the management of oral lichen planus (OLP). A total of 124 patients with erosive OLP were treated for 28 days. The results showed that application of topical HA significantly reduced pain scores up to four hours after application compared to placebo. Ulcer area size decreased significantly from baseline in all patients, but it was not significantly different between treatment groups. It was concluded that very frequent use should be considered to achieve more significant clinical benefit. Topical HA gel may be a useful addition to OLP treatment options 8.

Hashem in 2019 compared the therapeutic efficacy of a triamcinolone formulation (topical glucocorticoid) (0.1%) and HA formulation (0.2%) in treating OLP. The randomly divided 40 symptomatic OLP patients into two groups were instructed to use this treatment three times a day for four weeks. Both triamcinolone and HA were found to reduce Visual Analogue Scale scores, erythema severity, and lesion size after treatment. The use of HA was recommended and concluded to be an effective alternative to triamcinolone in the treatment of OLP9.

HA AND ORAL MUCOSITIS INDUCED BY CHEMOTHERAPY OR IRRADIATION

High-dose radiation and chemotherapy are among the greatest risk factors of oral mucositis with very painful lesions.

Bardellini conducted a double-blind, placebo-controlled trial in 2016 to evaluate the efficacy of a solution containing sodium hyaluronate in treating chemotherapy-induced oral mucositis in children with acute lymphoblastic leukemia. 56 patients were included (28 patients per group). There was a statistically significant reduction in oral mucositis after eight days in the treatment group. There was a statistically significant difference in pain relief between the two groups on both day three and day eight. The use of Mucosyte® mouthwash for children with oral mucositis resulting from chemotherapy can be recommended as a supportive care 10.

Ruggiero in 2018 conducted a case-control study to evaluate the clinical effects of Mucosamin® (a spray preparation containing sodium hyaluronate combined with a pool of amino acids) on wound healing and pain management of oral mucositis after hematopoietic stem cell transplantation. 137 patients were included. Results showed that the combination of careful debridement, good oral hygiene during hospitalization, and the use of Mucosamin® exponentially reduced the severity and duration of mucositis and the extent of chemotherapy lesions. It can be concluded that HA and amino acid-based sprays can be a valuable therapeutic adjunct in the treatment of mucositis 11.

ADVANTAGES

Topical hyaluronic acid (HA) offers several advantages in the treatment of oral ulcers:

-Versatility: HA can be used effectively for oral ulcers of varying degrees of severity, making it a versatile option for managing a wide range of oral mucosal conditions.

-Safety in Long-Term Use: Unlike topical steroids, which can have adverse effects with prolonged use, HA is considered safe for long-term application. Prolonged use of steroids may lead to complications like the development of candidiasis, whereas HA does not pose such risks.

These advantages highlight the suitability of topical HA as a safe and versatile option for the management of oral ulcers, making it a valuable choice for patients with different types and degrees of oral mucosal conditions.

POSOLOGY

HA formulations can be applied topically, at a concentration of 0.2%. It is recommended to not eat or drink anything for at least one hour after applying the topical agent. This allows the HA to effectively interact with the affected area and provide its therapeutic benefits.

CONCLUSION

Today HA is used in many fields of medicine and has interesting applications in dentistry for the treatment of acute and chronic inflammatory diseases. HA forms a protective coat on the oral mucosa to improve hydration and promote healing. Data from this review demonstrate that topical HA can be an efficient and safe adjunctive therapy in the management of stomatitis. Further clinical studies are recommended to confirm these promising results.

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