# Assessment of the efficacy of a hyaluronic acid- and amino acid-based oral spray formulation in “burning mouth syndrome”, with specific regard to gender

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## Summary

Burning mouth syndrome entails major discomfort to patients. Following this, research has progressively validated medical devices that facilitate the healing of the oral mucosa and, therefore, reduce the undesirable effects induced by the inflammation and ulceration of the mucous membranes. Hyaluronic acid- and amino acid-based preparations stand out in terms of the latest generation devices. Various studies are reported in scientific literature on the reparative efficacy of this association in the mucous membranes of the oral cavity. In this paper, a prospective study was conducted to assess the efficacy of a new hyaluronic acid- and amino acid-based oral spray formulation (Mucosamin®) in the clinical course of patients with secondary burning mouth syndrome following local or systemic pathological symptoms, with specific regard to the female population, which has a significantly higher prevalence for the condition. Based on the data obtained, the study product can be recommended for local treatment to reduce the degree of mucosal de-epithelialisation. Mucosamin® spray also seems to have a positive effect on the degree of satisfaction regarding the reduction of the subjective sensation of pain.

**Key words**: burning mouth syndrome, hyaluronic acid, aminoacids, stomatopyrosis, mucositis.

## Introduction

Burning mouth syndrome entails major discomfort to patients. Following this, research has progressively validated medical devices that facilitate the healing of the oral mucosa and, therefore, reduce the undesirable effects induced by the inflammation and ulceration of the mucous membranes. Hyaluronic acid- and amino acid-based preparations stand out in terms of the latest generation devices. Various studies are reported in scientific literature on the reparative efficacy of this association in the mucous membranes of the oral cavity. In this paper, a prospective study was conducted to assess the efficacy of a new hyaluronic acid- and amino acid-based oral spray formulation (Mucosamin®) in the clinical course of patients with secondary burning mouth syndrome following local or systemic pathological symptoms, with specific regard to the female population, which has a significantly higher prevalence for the condition.

Burning mouth syndrome can be considered a symptom of atypical orofacial pain due to its expression and presentation, characterised by clinical-symptomatologic context that produces a spontaneous burning sensation that affects the tongue, palate, lips and/or other mucous membranes of the oral cavity. . It affects a rather significant proportion of the population, with a general prevalence ranging from 0.7% to 3.7% and an average age of approximately 60 years, with a maximum peak incidence in women over 50 years of age between 18% and 33% of the population.

The pathognomonic symptom is “burning”, most often of a moderate intensity that persists for long periods of time, which makes it hard to tolerate.

The symptoms have a chronic course - which can be continuous or intermittent - and persist for a very variable period of time that can range from a few months to many years.

The burning sensation can be widespread, may affect any site of the oral mucosa and often has a multifocal location, which is sometimes bilateral and symmetrical.

The symptoms are sometimes described as a sensation of burning heat or swelling of the oral mucosa, often accompanied by a sensation of dry mouth and dysgeusia, difficulty swallowing and olfactory disorders.

Patients often have irritability, insomnia, anxiety, depression, a dislike of socialising and disordered eating habits.

Two classification schemes have been proposed for the disease:

1) The first subdivides cases of burning mouth syndrome into three types, based on the daytime variations of the symptoms.
2) The second is based on the aetiology of the disease. It can be divided into primary or idiopathic stomatopyrosis, in which there are no organic causes, or secondary stomatopyrosis resulting from local or systemic pathological manifestations.

The possible local causes taken into consideration in recent years include lesions or irritations of the oral cavity mucosa or lesions due to inflammatory or infectious mechanisms, allergic contact processes, immune processes, degenerative processes, tobacco consumption in all its forms, smoking marijuana and its derivatives, regular alcohol consumption, large consumption of beverages containing caffeine (coffee and cola) and other stimulants, use of mouthwashes or rinses containing alcohol or powerful detergents, regular ingestion of very hot, very spicy or acidic foods (lemon, citron, grapefruit), xerostomia, oral candidiasis, oral lichen planus and, micro-traumatic components (prosthetic trauma, occlusal disorders) and vascular components.

The general causes include gastroesophageal reflux, autoimmune diseases, Sjogren's Syndrome, the outcomes of radiation or cytostatic therapy, the use of certain drugs (ACE inhibitors, levodopa, etc.), multiple vitamin deficiencies (B6, B12, folic acid), diabetes mellitus, menopause, iron deficiency anaemia, hypothyroidism and HIV infections.

In the case of secondary stomatopyrosis due to local or systemic manifestations, the pharmaceutical industry has progressively developed medical devices to facilitate the healing of the oral mucosa with lesions such as ulcerations, aphthae, whitish mycosis, blisters, submucosal bruising, arborescences, erythema, atrophy, leucoplakia, post-traumatic erosion and oedema.
Hyaluronic acid and amino acid-based preparations stand out in terms of the most recent therapeutic innovations. Hyaluronic acid (HA) is a glycosaminoglycan (GAG) formed by the repetition of disaccharide units consisting of glucuronic acid and N-acetylglucosamine; it occurs naturally in the connective tissues and gives them their hydration, turgidity, plasticity and viscosity. Most cells are able to synthesise HA at some point in the cell cycle. The main function of HA appears to be in the healing of tissues. In this process, HA is involved in a range of activities, including the activation and modulation of inflammatory responses, supporting cell proliferation, migration and angiogenesis, increased re-epithelialisation through the proliferation of basal keratinocytes, collagen deposition and scar formation. Fibroblasts are the only source of collagen, the main component of connective tissue and an adequate synthesis of collagen is essential in the healing process. As with other proteins, its synthesis depends entirely on the local availability of the amino acids present in the final molecule. Glycine, L-Proline and L-Lysine have been found in extremely regular patterns in the collagen molecule. Lysine is inserted in a well-defined position in relation to Glycine and Proline. In fact, following the assembly of the triple helix of the collagen precursor, tropocollagen, a specific hydroxylase is activated to promote a hydroxylation of Proline and Lysine in hydroxy-proline and

hydroxy-lysine in specific sites to ensure intermolecular and intramolecular bonds that confer cohesion, flexibility and tensile strength, which are features of the collagen molecule.
HA is found in high concentration in granulation tissue, where it supports s cell migration and proliferation, as well as the organisation of the granulation tissue. The interaction between HA and amino acids has been shown to act on the ulcerative phase of mucositis by both reducing pain and burning, as well as during the regenerative phase of said mucositis.

# Materials and methods

The study was conducted on 60 patients (30 males and 30 females) aged between 42 and 93 years old (average age: 65.21; median: 66.1, who underwent an ENT examination + biopsy of the most significant lesion of the oral cavity at Voghera Hospital (Local Health Authority of the Province of Pavia) during the period between October 2015 and 30 September 2016.

All patients had stomatopyrosis secondary to local or general causes and had single or multiple lesions of the oral cavity, which were present from a minimum of one month to a maximum of 6 months from the date of onset.

Inclusion criteria: burning pain in the oral cavity for at least one month, age >18 years, absence of systemic diseases or medical therapies in progress that are capable of interfering with the healing processes.

Exclusion criteria: primary stomatopyrosis, neurological diseases or psychiatric diseases.

The 60 patients were distributed into two groups, A and B, of 30 patients each (15 males and 15 females, respectively, for each group analysed), depending on the therapeutic strategy used for the oral cavity. Group A (study group) included 30 patients who were prescribed a local application of Mucosamin spray 3 times a day after main meals for 1 month; group B (control group) included 30 patients who were prescribed oral rinses containing sodium bicarbonate diluted in water (1 glass of water + 2 tablespoons of sodium bicarbonate).

| **Group A:** | | |
|---|---|---|
| | **M** | **F** |
| keratosis due to friction caused by prosthetic trauma (1 with initial pseudoepitheliomatous hyperplasia) | 3 | |
| lymphoid hyperplasia | 1 | |
| lymphoplasmacytic and granulocytic inflammatory infiltrates | 3 | |
| pseudoepitheliomatous hyperplasia and lymphogranulocytic inflammation | 2 | |
| acanthotic hyperplasia and hyperkeratosis of the epithelial lining with chronic inflammation of the chorion and fibrosis | 1 | |
| reactive fibrosis | 1 | |
| cytopathic lesions with suspected viral aetiology | 2 | |
| histiocytic cell infiltrate | 1 | |
| lymphohistiocytic inflammatory infiltrates | 1 | |
| granulocytic inflammatory infiltrates | | 1 |
| hyperkeratosis | | 2 |
| hyperkeratosis and acanthosis | | 2 |
| pseudoepitheliomatous hyperplasia | | 1 |
| pseudoepitheliomatous hyperplasia in inflammatory lesion | | 1 |
| cytopathic lesions with suspected viral aetiology | | 3 |
| mild, focal parakeratosis | | 1 |

| | | |
|---|---|---|
| lichen planus | | 1 |
| keratosis, fibrosis and inflammatory cellularity | | 1 |
| keratosis with mild atypia | | 1 |
| cytopathic lesions with suspected viral aetiology | | 1 |
| | | |
| **GROUP B:** | | |
| | | |
| keratosis due to friction caused by prosthetic trauma with variable pseudoepitheliomatous hyperplasia | 1 | |
| keratosis and epithelial acanthosis | 1 | |
| lymphoplasmacytic inflammatory infiltrates | 1 | |
| reactive/reparative pseudoepitheliomatous hyperplasia | 1 | |
| cytopathic lesions with suspected viral aetiology | 1 | |
| lymphoplasmacytic and granulocytic inflammatory infiltrate with marked cytological atypia | 1 | |
| inflammatory infiltrate with atypical cellular elements | 1 | |
| chronic inflammation and moderate cytological atypia of the stratified epithelium | 1 | |
| keratosis and epithelial acanthosis | 1 | |
| lymphoplasmacytic inflammatory infiltrates | 1 | |
| reactive-inflammatory fibrosis | 2 | |
| cytopathic lesions with suspected viral aetiology | 1 | |
| lymphohistiocytic inflammatory infiltrates | 1 | |
| lymphoplasmacytic and granulocytic inflammatory infiltrate | 1 | |
| lymphoplasmacytic and histocytic inflammatory infiltrates | | 1 |
| hyperkeratosis and acanthosis of the stratified epithelium and chronic inflammation of the chorion | | 1 |
| hyperkeratosis with overlapping lymphogranulocytic inflammatory infiltrates | | 1 |
| frictional keratosis | | 3 |
| acanthotic hyperplasia and epithelial spongiosis | | 1 |
| cytopathic lesions with suspected viral aetiology | | 1 |
| cytopathic lesions of the epithelium consistent with HPV infection | | 1 |
| granulocytic inflammatory infiltrates | | 1 |
| hyperkeratosis and acanthosis of the stratified epithelium and chronic inflammation of the chorion | | 1 |
| hyperkeratosis with overlapping lymphogranulocytic inflammatory infiltrates | | 1 |
| lymphoplasmacytic and histocytic inflammatory infiltrates | | 1 |
| hyperkeratosis | | 1 |
| hyperkeratosis and acanthosis | | 1 |

The objective parameters assessed were as follows:

1-healing time

2-degree of injury of the oral mucosa

The subjective parameters assessed through questionnaires were as follows:

3-pain: VAS scale

4-degree of patient satisfaction

The oral mucosa healing time was assessed by means of an otorhinolaryngological examination at 7 days, 15 days and at one month after the performance of the biopsy and concomitant initiation of treatment of the oral cavity. the initiation of treatment coincided with the day on which the patient was examined and subjected to a biopsy of the oral cavity.

In order to "measure" the extent of the phenomenon in the various treatment contexts, scientific literature has proposed a wide range of scales over the last thirty years. The most commonly used are "numerical" scales, which assign a degree based on the severity of specific signs or symptoms, are easy to use and are considered to be objective and reproducible.
Thus, the assessment of the degree of oral mucositis can be achieved through the use of scales, which enable to detect the complication severity and therefore help in choosing the best treatment for the single patient

The most commonly used scales international scores are the WHO (World Health Organization) scale and the OMAS (Oral Mucositis Assessment Scale) scale., the scales mentioned are based on a numerical scale in increasing order of severity as shown in Table I.

**Table I: Degrees of mucositis and assessment parameters of the most commonly used scales**

| **Degrees of mucositis and assessment parameters** | **WHO** | **OMAS** |
|---|---|---|
| **0** | No symptom | No change in colour of the mucosa and no lesions |
| **1** | Pain (slight discomfort) without Ulcers +/_- Erythema | Increased intensity of the colour of the mucosa and lesions < $1cm^2$ |
| **2** | Pain in the mucosa with ulcers, erythema; normal eating | Bright blood-coloured mucosa and lesions > $1cm^2$ and < $3cm^2$ |
| **3** | Erythema, ulcers. The patient only manages to consume a liquid diet | Surface areas of the lesions > $3cm^2$ |
| **4** | Extensive mucositis. The patient can neither eat nor drink | / |

The OMAS (Oral Mucositis Assessment Scale) scale was designed and validated by clinical trials and is, therefore, the most specific and sensitive reference for assessing oral mucositis. This tool refers to specific objectivity and morphological aspects. The severity of oral mucositis is divided into 5 different degrees

| | | | | |
|---|---|---|---|---|
| **Erythema** | **0** | **1** | **2** | |
| | No change in the colour of the mucosa | Increased intensity of the colour of the mucosa | Bright blood-coloured mucosa | |
| | | + | | |
| **Ulcerations/ pseudomembranes** | **0** | **1** | **2** | **3** |
| | No lesions | Surface areas of lesions less than 1 $cm^2$ | Surface areas of lesions greater than 1 $cm^2$ and equal to or less than $3cm^2$ | Surface areas of lesion greater than 3 $cm^2$ |
| | | = | | |

The overall assessment of mucositis according to the OMAS scheme is expressed by adding up the scores (from 0 to 5)related to the degree of erythema, ulcers and pseudomembranes in certain regions of the oral cavity, which then assess the epithelialisation/de-epithelialisation.

The patients were assessed at 7 days, 15 days and at one month with the OMAS (Oral Mucositis Assessment Scale) assessment scale

To assess the degree of oral mucositis, it was decided to use the OMAS scale, given that it takes many features into consideration and, therefore, is accurate and objective, as well as being an internationally approved scale.
The assessment of the mucous membranes condition was performed each time by inspecting the oral cavity in the same room, under the same light.

4) The degree of satisfaction was quantified on a scale of 1 to 4: negative, moderate, good and excellent, respectively. The statistical analysis was performed using T-student.

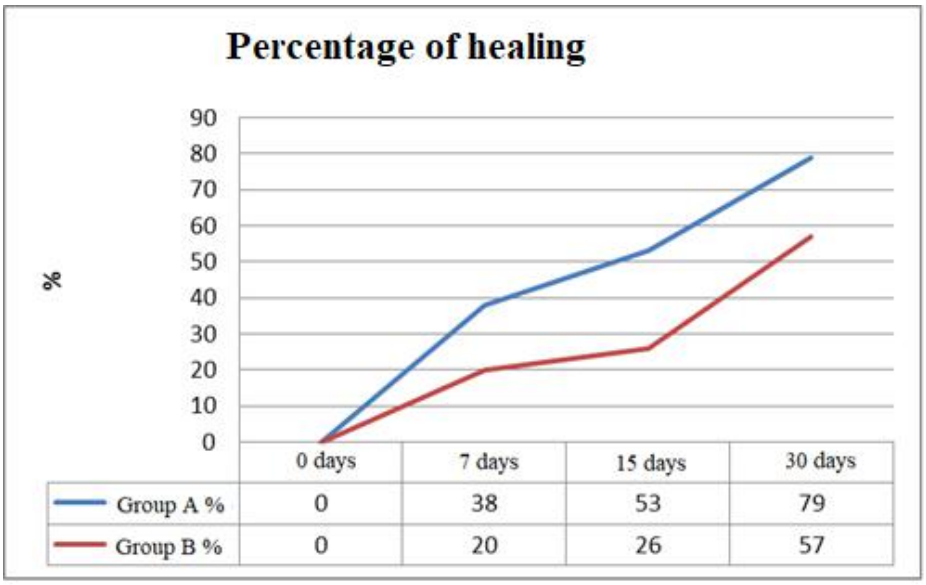
# RESULTS

The patients, all underwent biopsy of the oral cavity and showed the following results:

The healing time assessed by means of otorhinolaryngological examination of the oral mucosa at 7 days, 15 days and after 1 month from the start of therapy produced the following results:

Group A: healing in 7 days in 38% of patients, in 14 days in 53% and in 30 days in 79% of patients.

Group B: healing in 7 days in 20% of patients, in 14 days in 20% and in 30 days in 57% of patients (Chart 1).




**The table shows that, overall, group A achieved healing in shorter times than group B.**

, The difference in percentage of healing between the two groups was assessed, considering the study to be statistically significant for estimated values of $p < 0.05$.

The objective assessments - using the OMAS scale - of the oral cavity of the mucous membranes revealed a reduction in the degree of de-epithelialisation. The comparison between the two group shows that the reduction in de-epithelialisation is greater in the study group, with highly significant results at 7 days, 15 days and one month.

| Percentage of healing | Study % | Study % female population |
|---|---|---|
| 0 days | 0 | 0 |
| 7 days | 38 | 47 |
| 15 days | 53 | 65 |
| 30 days | 79 | 85 |

The table above shows a significant percentage of overall objective improvement of the female population during each time interval.

Pain - assessed using the VAS scale - in each group showed a reduction at all controls, but this reduction is not significant at 1 week after the start of local therapy. However, the statistical comparison between the averages of group A and group B for each control did not show statistically significant differences.

The degree of patient satisfaction increased on average from the start of therapy to the controls in both groups, up to 1 month after the start thereof. The comparison of the mean values between the 2 groups for each control revealed significant differences at 7 days, 15 days and one month.


## Discussion

Hyaluronic acid is applied in various medical fields, including the orthopaedic, ophthalmological, oncological and dental fields. Various studies have been conducted in dentistry on the efficacy of hyaluronic acid- and amino acid-based local medicinal products which, when applied to wounds in the oral cavity, lead to their rapid healing and reduced local symptoms of pain compared with common emollient gels (14-19). The mechanism of action involves the stimulation of neoangiogenesis, promoting the formation of granulation tissue and collagen by stimulating the activity of fibroblasts (20,21). The function of assisting the tissue regeneration processes depends on its high biocompatibility, by means of a protective mechanical action, also enabling ideal humidity conditions for the re-epithelialisation of the injured area to be maintained (16). These features make it ideal in the treatment of mucosal lesions and it is in this context that this study is placed, aimed at assessing the efficacy of the new compound compared with the use of a common mouthwash for the oral cavity. The product used for this study is a medical device, formulated as an oral spray. It is composed of glycine, L-Proline; L-Leucine, L-Lysine, Sodium hyaluronate, purified water and excipients.
No patient shows any adverse drug reactions to the study product in this clinical trial. The study group (group A) had statistically significant healing times in the treated group of patients in the study. The degree of mucosal de-epithelialisation and pain was reduced in both groups. The significantly better improvement in the female gender was interpreted as greater adherence and compliance with the proposed therapy. The degree of patient satisfaction increased in both groups, but was statistically significant in the group of patients treated with the study product.

## Conclusions

There are already many studies on the oral mucosa which show that the combination between hyaluronic acid and amino acids plays an adjuvant role in the healing processes of the oral mucosa and this significantly promotes the patient's healing and compliance.
In conclusion, based on the data obtained, the study product can be recommended for local treatment to reduce the degree of mucosal de-epithelialisation. The product also seems to have a positive effect on the degree of satisfaction regarding the reduction of the subjective sensation of pain.