EFFICACY OF A SPRAY COMPOUND CONTAINING A POOL OF COLLAGEN PRECURSOR SYNTHETIC AMINOACIDS (L-PROLINE, L-LEUCINE, L-LYSINE AND GLYCINE) COMBINED WITH SODIUM HYALURONATE TO MANAGE CHEMO/ RADIOTHERAPY-INDUCED ORAL MUCOSITIS: PRELIMINARY DATA OF AN OPEN CLINICAL TRIAL

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Oral mucositis (OM) is a very frequent and potentially severe complication experienced by patients receiving chemotherapy and/or radiotherapy, which often leads to significant morbidity and mortality, and decreased quality of life, and is very costly. Despite its severity and prevalence, there is no standard recognised management today. The aim of this open clinical trial is to evaluate the efficacy and compliance of a new spray compound containing sodium hyaluronate (SH) and a pool of collagen precursor amino acids (AAs) combined with sodium hyaluronate (SH) to manage radio/chemotherapy-induced OM. Twenty-seven consecutive patients with OM were treated according to the manufacturer's instructions. At time T0 (baseline – before intervention), we evaluated the following parameters: (i) pain score (by linear visual analogue scale; 0–100) and (ii) severity of OM scored according to WHO Mucositis scale. The treatment efficacy was evaluated on i) pain score, ii) clinical resolution index (CRI) and iii) patient compliance at times T01 (after 2 hours), T1 (after 24 hours), T2 (after 72 hours), T3 (after 7 days) and T4 (after 14 days). Results showed that painful symptoms were significantly reduced after only 2 hours of spray administration compared with baseline measurements ($p<0.0001$; $z=-4.541$). A progressive reduction of pain through the 2 weeks was also noted ($p<0.0001$). Patient lesions treated with SH-AAs-based spray also significantly improved after 72 hours of treatment ($p=0.0051$; $z=-2.803$). During the two-week observation, all patients significantly improved from the baseline ($p<0.0001$) and progressively ameliorated their ability to swallow foods and liquids. The compliance of all patients to the product was very good, and at the end of the study there were no adverse effects. The results suggest that the SH-AAs-based spray accelerates lesion healing and above all helps to manage mucositis pain, especially in terms of immediate pain relief (after 2 hours from application). Although further randomized controlled studies are recommended, our findings suggest that frequent applications of this spray may offer rapid and effective pain management, aiding faster mucosal wound healing.

Key words: hyaluronic acid, amino acids, oral mucositis, oral ulcer, spray compound, pain, wound healing

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Oral mucositis (OM) is one of the most frequent and potentially severe acute side effect of non-surgical cancer therapy (1-2). It is clinically characterised by erythema, ulcer formation with or without pseudo-membranes, bleeding, exudate formation, and/or localized super-infection (3), and may develop into a debilitating form compromising the patient's quality of life.

The real problem of OM from the patient's point of view ranges from a complex interaction between the perception of mouth pain up to several altered oral functions (4). Indeed, it may be associated with pain symptoms such as dysgeusia, dysphagia, difficulty in talking, chewing and, swallowing which could compromise a patient's nutritional status, leading to weight loss, and making naso-gastric tube feeding necessary in many cases.

All these signs may not only have a negative impact on a patient's quality of life, but also be so severe as to require an interruption or a curtailment of therapy or lead to dose reduction or delayed cancer therapy reducing the likelihood of long-term survival (5). It is also clear that OM may significantly increase health care costs. Indeed, in OM patients, economic resources are directed at managing pain and nutritional problems, with frequent hospitalization for pain control, fluid support and parenteral feeding, assistance for home parenteral nutrition and intravenous hydration and drug prescription (e.g. analgesic and antibiotics) (6-7).

Despite the severity and prevalence of OM and the considerable research carried out to date, today a standard and universally accepted management strategy to prevent and treat this potentially severe complication does not exist. Several preventive and therapeutic approach studies have been found to avoid or reduce the severity of OM. However evidence-based reviews of the literature and a recent Cochrane review have shown that most clinical OM prevention or treatment studies are not randomised-controlled clinical trials with a sufficient numbers of participants and do not meet adequate standards to allow for clinical practice guidelines (8-11).

To date, OM management and related pain include: basic topical anesthetics, systemic analgesics, anti-inflammatory agents, mucosal coating agents, bland oral rinses, general oral care, antimicrobial agents (5, 12-15). Furthermore, several other agents have been tested, such as growth factors and cytokines, mucosal biological protectants, criotherapy and low level laser therapy (13, 16). Hyaluronic acid (HA) plays an important role in tissue healing by means of several mechanisms (17-19). Clinical studies have also confirmed that it enhances the healing process. The compound has been evaluated in healing leg ulcers (20), and nasal mucosa after surgery (21). HA has also been shown to reduce high-grade-epithelitis in patients who have undergone radiotherapy for the head and neck, breast or pelvic carcinomas (22).

Recently, it has been shown that topical 0.2% HA gel not only gives relief from pain/burning associated with recurrent aphthous stomatitis and atrophic/erosive oral lichen planus, but also aids a clinical resolution of atrophic/erosive/ulcerative areas (23-24).

Finally, the application of a concentrated oral gel composed of poly-vinylpyrrolidone and sodium hyaluronate (SH) seems to provide good results in managing various forms of OM. In particular, both polyvinylpyrrolidone and SH may accelerate wound healing, besides its action as a muco-adherent and a barrier-forming agent reduce OM associated pain (25-27).

Here, we clinically tested the efficacy and compliance of a new spray compound (SH-AAs, Errekappa Euroterapici, Milan, Italy) containing SH and combined to a pool of collagen precursor amino-acids (AAs) (L-Proline, L-Leucine, L-Lysine and Glycine) and combined to SH, to manage radio/chemotherapy-induced OM.

MATERIALS AND METHODS

Study design

We designed an open clinical trial. A total of 27 adult patients (12 F and 15 M; mean age: 61±18.6 years; range: 18-96 years) affected by OM were consecutively recruited in two centers, the Department of Head and Neck Pathology of the Second University of Naples and the Department of Stomatological Sciences, Oral Medicine Unit of the University Hospital of Palermo. Criteria for inclusion were as follows i) patient of either sex; ii) age $\geq$ 18 years; iii) recent experience (two weeks) of head and neck radiotherapy for oral, oropharyngeal, nasopharyngeal and/or hypopharyngeal cancers, daily doses of radiotherapy over a 4 to 6 week period,

chemotherapy for haematological malignant neoplasms and/or solid malignant tumours in other areas; iv) signs of at least grade 1 OM according to the World Health Organization (WHO) scale (28) (see Table I); v), pain not alleviated by paracetamol/codamol/acetylsalicylic acid; vi) OM affecting any of the anatomical structures that could be reached by a spray (posterior faucal arches, labial and buccal mucosa, floor of mouth, hard and soft palate, tonsillar fossa); vii) informed consent and ability to complete the trial.

Exclusion criteria included age under 18 years, known allergy to any of the constituents of the compound, inability to check results, no oral symptoms, intake of any type of antibiotic, anti-inflammatory or analgesic medication by the patient in the week before the trial, patients with systemic diseases, such as diabetes, which could impair wound healing, not being able/willing to give informed consent.

Each patient was instructed by a single doctor for each centre to apply SH-AAs-based spray on the lesions 3-4 times/day for 14 days, after a meal, keeping it *in situ* for at least 2 minutes, avoiding drinking, eating and rinsing the mouth for at least 1 hour.

During the first visit all patients with OM underwent oral swab for microbiological investigations, and in case of mycotic infections they were instructed to use adequate antimycotic drugs at least 1 hour before the AAs-SH based spray.

During the whole period of the trial, all patients were invited to maintain good oral hygiene, including oral rinses with non-alcoholic 0.12% chlorhexidine gluconate-based mouthwashes used as a disinfectant 3 times/day, at least 1 hour before the application of the spray and tooth brushing with non-irritating toothpaste and a soft toothbrush where possible. No alcohol, smoking, acid, hot spicy or very irritating foods were also advised as these could further exacerbate inflammation within the oral cavity.

Each patient was evaluated using a record chart compilation, oral examination, registration of signs and symptoms, and photo recording at baseline (first examination – before intervention - T0), control at 2 h (T01), after 24 h (T1), after 72 h (T2), 7 days (T3), 14 days (T4) after the first application of the spray.

For each centre, a single observer, expert in oral medicine and trained for the clinical trial, conducted the survey and took the measurements. In all patients tested, severity of OM was scored at baseline (T0), according to WHO Mucositis scale (28) ranging from 0 = no symptoms to 4 = oral alimentation not possible.

Efficacy of treatment with SH-AAs based spray was evaluated based on the following parameters:

1. pain score using the visual analogue scale (VAS), linear type and range 0-100 (29);
2. clinical resolution index (CRI) according to Carrozzo and Gandolfo (30), was assessed at T1, T2, T3 and T4 using the following nominal variables: a) complete; b) partial; c) absent, considering as complete disappearance of atrophic/ erosive/ulcerative areas and symptoms;
3. compliance for SH-AAs-based spray was evaluated as a) good (1); b) sufficient (2); c) scarce (3).

Before each new session, any adverse effect of previous treatment was recorded.

Data were analyzed using STATVIEW for Windows (SAS Inc v. 5.0.1, Cary, NC, USA). The Wilcoxon's test was used to demonstrate intra-group differences for VAS and CRI at the five measurement stages (T01, T1, T2, T3 and T4), whilst the equivalent intra-group analysis was performed for the same variables in repeated measurement designs using the Friedman's test. *P*-values ≤ 0.05 were considered to be statistically significant.

RESULTS

Demographic details of patients and other baseline information of those who participated to this open clinical trial are shown in Table II-III. None of the patients with OM who underwent treatment with SH-AAs-based spray suspended the radio-chemotherapeutic treatment.

Pain score evaluated with VAS progressively decreased at the different measurement steps with a mean value of 74.1 ± 17.6 at baseline, 49.3 ± 18.2 after 2 h, 39.4 ± 22 after 24 h, 24.8 ± 19 after 72 h, 11.8 ± 15.5 after 7 days and 6.2 ± 10.8 after 14 days. Subsequently, a significant reduction of pain through the 2 weeks period of treatment was noted ($p<0.0001$; Friedman's test) (see Table IV).

In particular, the symptomatic effect on pain significantly reduced after only 2 hours following

Table I. *WHO mucositis scale.*

Grade	Clinical Features
0	none
1	Soreness/erythema
2	Erythema, ulcers but able to eat solids
3	Ulcers but requires liquid diet
4	Oral alimentation not possible

Table II. *Demographic details and other baseline information of patients.*

	n (%)
Total number of patients	27
Gender: number (percent)	
Males	15 (55.6)
Females	12 (44.4)
Age: mean ± SD* (range in years)	61±18.6 (18-96)
Diseases: number (percent)	
Acute lymphoblastic leukemia	1 (3.7)
Chronic lymphoid leukemia	2 (7.4)
Multiple myeloma	4 (14.8)
Waldenström's disease	1 (3.7)
Hepatocarcinoma	1 (3.7)
Oral squamous cell carcinoma	10 (37)
Breast carcinoma	5 (18.5)
Colon carcinoma	1 (3.7)
Gastric carcinoma	2 (7.4)
Treatment: number (percent)	
Radiotherapy	6 (22.2)
Chemotherapy	19 (70.4)
Radio-chemotherapy	2 (7.4)
WHO mucositis score at T0	
Grade 1	2 (7.4)
Grade 2	17 (63)
Grade 3	8 (29.6)
Mean baseline (T0) pain scores (mm) ± SD as recorded on 100-mm VAS	74.1 ± 17.6

**SD: Standard Deviation*

spray administration compared with baseline measurements (p<0.0001; z=-4.541; Wilcoxon's test). Furthermore, the Wilcoxon's test showed statistically significant differences (p<0.0001 ; z=-4.541) for VAS after 24 h, 72 h, 7 and 14 days compared with the baseline, confirming the very considerable benefits of the SH-AAs-based spray both for short- and long-term pain relief.

Table V shows the effects of SH-AAs based spray on CRI during the treatment period. Patients treated with the spray showed a significant clinical improvement of the lesions after only 72 h (p=0.0051; z=-2.803; Wilcoxon's test) of treatment compared to the baseline. In particular, the Friedman's test highlighted a significant clinical improvement (p<0.0001) from baseline through the various measurement steps. Patients treated with SH-AAs-based spray progressively improved in their their ability to swallow foods and liquids. All patients complied well to the product and at the end of the study no adverse effects to the spray were noted.

DISCUSSION

OM is the most common and severe complication of non-surgical therapy of cancer. The prevalence and severity of OM varies depending both on the type and dose of cancer treatment and on patient-related risk factors (1, 6, 8, 31-32).

Although OM is considered one of the main clinical problem in oncology, whose high prevalence during radio-chemotherapy treatment has a significant clinical and economic impact, no standard and universally accepted management yet exists (8-11). For this reason, we need clinical trials to evaluate the efficacy of new formulations to treat OM. The identification of innovative methods of treating OM cannot be divorced from the pathogenetic mechanisms that contribute to the onset of OM.

Although clinical manifestations of OM are most prominent in the epithelium, mechanically, changes in the sub-mucosal endothelium and connective tissue may precede epithelial damage, thus playing an important role in OM pathogenesis. Indeed, OM is the result of a complex process of interactive biologic phenomena involving both epithelium with atrophy and ulcerations, and *lamina propria* resulting in destruction of collagenous matrix and endothelial damage (33). The early phases of OM onset are characterised by the production of a range of destructive proteins and molecules which destroy the collagenous sub-epithelial matrix and

Table III. *Chemotherapeutic agents used to treat the cancer in our study population.*

Diseases	Type of treatment (number of patients)	Chemotherapeutic agents
Acute lymphoblastic leukemia	Chemotherapy (1)	Vincristine, Doxorubicin, L-asparaginase and Prednisone
Chronic lymphoid leukemia	Chemotherapy (2)	Chemotherapy Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
Multiple myeloma	Chemotherapy (4)	Melphalan and Methylprednisolone
Waldenström's disease	Chemotherapy (1)	Bortezomib Dexamethasone and rituximab
Hepatocarcinoma	Chemotherapy (1)	Sorafenib followed by Sunitinib
Oral squamous cell carcinoma	Chemotherapy (2), radiotherapy (6), radio-chemotherapy (2)	Cis-platin in patients underwent also to radiotherapy; 5-fluoruracil and Cis-platin in patients underwent only to chemotherapy
Breast carcinoma	Chemotherapy (5)	Epirubicin, Cyclophosphamide and Docetaxel
Colon carcinoma	Chemotherapy (1)	Oxaliplatin plus 5-FU and leucovorin (Folfox) followed by Irinotecan plus 5-FU and leucovorin (FOLFIRI) and Cetuximab
Gastric carcinoma	Chemotherapy (2)	Epirubicin and oxaliplatin

break down the epithelial basement membrane and induce apoptosis of the basal epithelial cells (1, 33-35). This leads to ulceration of the oral mucosa and consequently to OM clinical symptoms.

Hence, given the key role played by connective damage in OM pathogenesis, the use of a compound which promotes neo-collagen-genesis and regenerates the extracellular matrix could be a valid therapeutic strategy. Hyaluronic acid (HA), composed of repeating units of D-glucuronate and N-acetylglucosamine, is the most important glycosaminoglycan produced by fibroblasts during wound and ulcer healing and seems to be able to promote cell proliferation, differentiation and motility and is involved in wound repair (36).

Collagen deposition by fibroblasts is one of the key factors in reconstituting the supporting matrix at sites of scar formation and it is the nature of this deposition which largely determines scar quality. HA is naturally biocompatible, biodegradable and a non-immunogen and it has been shown, both *in vitro* and *in vivo* studies (37-39), to act principally during tissue healing. In this process, HA is implicated in a range of activities including activation

Table IV. *Pain Scores assessed with VAS at the different steps of evaluation.*

Pain Score	Mean (mm) ± DS	Intra-group analysis (Wilcoxon's Test)	Intra-group analysis in repeated measurement designs (Friedman's Test)
Pain T0 (baseline)	74.1 (± 17.6)	**Significant differences at T01 ($p<0.0001$) and after 24 h, 72 h, 7 and 14 days ($p<0.0001$) compared with baseline**	**$p<0.0001$**
Pain T01 (after 2 h)	49.3 (± 18.2)		
Pain T1 (after 24 h)	39.4 (± 22)		
Pain T2 (after 72 h)	24.8 (± 19)		
Pain T3 (after 7 days)	11.8 (± 15.5)		
Pain T4 (after 14 days)	6.2 (± 10.8)		

Table V. *Effects of SH-AAs-based spray on CRI* during the treatment period.*

Steps of measurement	Clinical Resolution Index	Number of patients (%)
T1 (after 24 hours)	Complete	1 (3.7)
	Partial	14 (51.9)
	Absent	12 (44.4)
T2 (after 71 hours)	Complete	3 (11.1)
	Partial	20 (74.1)
	Absent	4 (14.8)
T3 (after 7 days)	Complete	5 (18.5)
	Partial	22 (81.5)
	Absent	0 (0)
T4 (after 14 days)	Complete	21 (77.8)
	Partial	6 (22.2)
	Absent	0 (0)

**CRI: clinical resolution index.*

and moderation of the inflammatory responses, promoting cell/fibroblast proliferation, migration and angiogenesis, promoting re-epithelization via proliferation of basal keratinocytes and reducing collagen disposition and scarring (24). There is also evidence that extracellular matrix remodelling following HA application is enhanced and collagen deposition more orderly (40-42). These properties make it one of the most important molecules to regenerate the extracellular matrix (18-19).

Tissue regeneration and wound healing start with the proliferation of fibroblasts and their ordered production of collagen and glycosaminoglycans, with a speed depending not only on the patient's general conditions (age, infection, drug assumption, systemic diseases), but above all on local conditions such as vascularization, *in situ* availability of matrix glycosaminoglycan precursors (i..e. HA), amino-acid precursors of collagen (glycine, proline, leucine and lysine) and (43) small leucin rich proteoglycan.

Therefore, the addition of amino-acid precursors of collagen to a compound composed of HA, as recently showed by Favia et al. (44) and by Mariggiò MA et al. (43) could promote and accelerate wound healing. The Authors (43-44) showed that a gel compound (Aminogam®) containing four collagen precursor amino acids (glycine, L-proline, L-leucine and L-lysine), SH and polyvinylpyrrolidone increased the fibroblast proliferative activity, collagen I and III and fibronectin synthesis, the expression of transforming growth factor beta, connective tissue growth factor, interleukin-6 and -8 and VEGF expression in cultures of human fibroblasts. Thus Aminogam® gel being involved in several stages of wound healing, such as fibroblast proliferation, granulation tissue formation, extracellular matrix component deposition, and production of cytokines, may be useful to accelerate wound closure.

For OM management, the application of a concentrated oral gel composed of polyvinylpyrrolidone and SH (Gelclair®) seems to have provided good results in managing various forms of OM. In particular, both polyvinylpyrrolidone and SH, as well as accelerating wound healing (25-27) also act as muco-aderent polymers aiding muco-adhesion, so allowing a more prolonged contact on the mucosal surface and potential penetration of the "drug" in the deep epithelial layers and connective tissues. Furthermore, HA acting as a barrier-forming agent (21) together with its inherent "analgesic" activity (45) could reduce OM-associated pain.

Here, we used Aminogam® in the form of a spray to assess its effect on OM. The spray formulation used had the same composition as Aminogam® gel used by Favia et al. (44) and thus exploited the properties of the four collagen precursor amino acids, SH and polyvinylpyrrolidone in tissue regeneration and pain management. Furthermore, the spray allowed better distribution of the product on oral surfaces.

The most remarkable effect of the SH-AAs-based spray was the immediate effect on pain relief. Indeed, painful symptoms were significantly reduced after only 2 hours from spray administration compared with baseline measurements. Furthermore, patients treated with the SH-AAs-based spray also had significantly improved lesions after 72 hours of treatment and progressive improvement on swallowing foods and liquids during the two weeks of observation. Interestingly, all patients tolerated the product well and at the end of the study no adverse effects of the spray were noted.

In conclusion, in spite of study design limitations, such as the lack of a control group and the need to perform further randomized-controlled, our preliminary findings suggest that spray formulation, easy to apply all over the oral mucosa, may offer a rapid and effective management of OM. Furthermore, the spray compound, containing a pool of collagen precursor amino acids combined with SH (SH-AAs-based spray), appears to benefit and accelerate lesion healing and, above all, to manage pain, consequently improving the ability to eat and drink which usually are compromises in patients suffering from OM.

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The authors declare that they have no competing interests.

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