JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 32, no. 3, 737-743 (2018)

LETTER TO THE EDITOR

TREATMENT OF SYMPTOMATIC ORAL MUCOSITIS WITH SODIUM HYALURONATE AND SYNTHETIC AMINO ACID PRECURSORS OF COLLAGEN IN PATIENTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION

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Received September 26, 2017 – Accepted March 1, 2018

The purpose of the study is to evaluate the clinical effects of Mucosamin® (a spray preparation containing sodium hyaluronate combined with a pool of amino acids of precursor collagen, including L-Proline, L-Leucine, L-Lysine and glycine) on wound healing and pain management of oral mucositis after hematopoietic stem cell transplantation. The importance of professional dental hygiene by dental hygienist in reducing the severity of oral mucositis as unique therapy or in addition to therapy with Mucosamin® was also evaluated. One hundred thirty-seven patients undergoing hematopoietic stem cell transplantation were recruited in a case-control study and divided into 4 groups: Group A: professional oral hygiene + Mucosamin®; Group B: professional oral hygiene + standard treatment with chlorhexidine 0.20%; Group C: only Mucosamin®; Group D: only standard treatment with chlorhexidine 0.20%. The following evaluations were made: WHO mucositis scale, OMAS mucositis scale, VAS, periodontal recording, days of mucositis. Comparing the groups at the onset of OM on WHO scale, it was observed that Group A grade 1 occurrence was more statistically significant than Group B (p= 0.03*); comparison between Group A and D showed a statistically significant difference in favour of Group A (p= 0.0002*). Also OMAS scale showed a statistically significant difference between groups who assumed Mucosamin, who developed lower OM grade (p = 0.001*). There was a statistically significant difference between group A compared with group B over the overall duration of OM (p = 0.02*), as well as between group A and group D (p=0.03*). According to the present study the combination of a careful debridement, correct oral hygiene during hospitalization and the use of Mucosamin® exponentially reduces the severity and duration of mucositis and consequently the discomfort of the patient. Moreover, it can be stated that the use of Mucosamin® also results in a reduction in the extent of chemotherapy lesions. Hyaluronic acid and amino acid-based sprays can be a valuable therapeutic aid in the treatment of mucositis.

To the Editor,

Oral mucositis (OM) can affect up to 80% of patients undergoing hematopoietic stem cell transplantation (HSCT) and it has a direct and significant impact on quality of life and health care costs, other than effects on patient survival, such as for the risk of infections on oral lesions (1-2); analgesic management is necessary when pain

Key words: oral mucositis, mucosamin, bone marrow, HSCT, sodium hyaluronate, dental care

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0393-974X (2018)

prevents the patient's intake of food and fluids, requiring parenteral nutrition, and increasing days of hospitalization (3).

There is no standardized therapy for OM, the first-line treatment consists in the elimination of oral infectious foci associated with a scrupulous oral hygiene, before HSC with the aim to reduce intraoral bacterial colonization and prevent infection of ulcers, with mouthwashes and antibiotics (4-5). However, both treatments have been found ineffective in the prevention of OM. Antibiotics and mouthwashes are not able to penetrate the bacterial plaque if it is not previously disintegrated mechanically, as reported in a recent Cochrane review (6).

A new treatment used on patients suffering from oral mucositis is Mucosamin®: a spray compound with sodium hyaluronate (SH) and a pool of collagen precursor amino acids (AAs), which acts on wound healing and pain management. SH acts as a muco-adherent polymer and as an agent barrier, relieving pain thanks to the prolonged contact of the product on the mucosa; the amino acids are collagen precursors and stimulate fibroblast to product collagen and glycosaminoglycans, for tissue reconstitution during the healing process (7). Thanks to the properties of its components, this spray acts on the stage of ulcerative mucositis, creating a protective layer that reduces pain and accelerates clinical recovery. Our group has recently published a study where 68 patients scheduled for HSCT were treated with Mucosamin®: patients who assumed Mucosamin® on initial lesions developed a less severe OM, and the maximum OM pain, measured with the VAS (Visual Analoug Scale) for pain, was higher in patients who did not assume Mucosamin® (9).

We decided to extend our study to evaluate the clinical efficacy of Mucosamin® in wound healing and pain management in OM after HSCT. We also evaluated the importance of professional oral hygiene by a dental hygienist to reduce the severity of OM in combination with the Mucosamin®.

MATERIALS AND METHODS

A randomized clinical trial study with four groups was drawn up: a total of 137 adult patients (average age 51, range 21-70) prepared for HSCT for allogenic and autologous transplant were recruited at the Stem Cell Transplant Unit, and in the Oral Surgery Department, Dental School, University of Turin from 2012 to 2016.

Inclusion criteria were: i) age> 18 years; ii) candidate to HSCT; iii) informed consent and ability to complete the trial. Exclusion criteria were: i) known allergy to any of the constituents of the compound; ii) inability to check results; iii) patients with systemic disease, other than haematological malignancies, which impair wound healing (i.e. diabetes); iv) muco-cutaneous diseases; v) presence of graft versus host disease; vi) severe deterioration of general health conditions; vii) unable/ unwilling to give informed consent.

The study was approved by the Internal Review Board of our Centre and was conducted in accordance with the Helsinki Declaration, and all patients provided informed consent to the proposed study. Each patient was randomly assigned to one of the four groups and the allocation was concealed.

Group A patients (37) underwent a full session of professional oral scaling and root planing by dedicated staff; at the end of the session they were informed about the correlation between oral health and mucositis, instructed on correct oral home hygiene and motivated to continue these insructions even during the hospitalization period. Patients with periodontal issues were subjected to a second session of professional oral scaling and root planing of pathological sites. Patients who received further dental treatment, such as conservative, endodontic or extractive treatment, were reminded to maintain high oral hygiene standards before and after HSCT. In addition, these patients were instructed by the same doctor to recognize the symptoms of oral mucositis and apply Mucosamin spray on these lesions 3-4 times a day after meals and oral hygiene, keeping it *in situ* for about 2 min, and to avoid drinking, eating, and rinsing the mouth for at least an hour. The same doctor controlled the patients during hospitalization to recognize initial and advanced signs of OM and to remind patients how to apply the compound.

Group B patients (32) underwent a full session of professional oral scaling and root planing by dedicated staff; at the end of the session they were informed about the correlation between oral health and mucositis, instructed on the correct oral home hygiene manoeuvres and motivated to continue these manoeuvres even during

the hospitalization period. Patients with periodontal issues were subjected to a second session of professional oral scaling and root planing of pathological sites. However, these patients did not receive Mucosamin but the usual treatment with Chlorhexidine 0.20%.

Group C patients (34) did not undergo a full session of professional oral scaling and root planing by dedicated staff; these patients were instructed by the same doctor to recognize the symptoms of oral mucositis and apply Mucosamin spray on these lesions 3-4 times a day after meals and oral hygiene, keeping it in situ for about 2 min, and to avoid drinking, eating and rinsing the mouth for at least an hour. The same doctor controlled the patients during hospitalization to recognize initial and advanced signs of OM and to remind patients how to apply the compound.

Group D patients (34) did not undergo a full session of professional oral scaling and root planing by dedicated staff and did not receive Mucosamin but the usual treatment with Chlorhexidine 0.20%. In addition, patients were asked whether they had undergone professional hygiene sessions in the previous 6 months.

At the first visit each patient was asked to complete an oral hygiene questionnaire and a mucositis information questionnaire. The staff filed the Periodontal Folder where Plaque Control Record, Full Mouth Bleeding Score and Periodontal Screening and Recording (PSR) were recorded (10).

Starting the day after HSCT, the same observer, blinded to the treatment, an expert trained for the clinical trial, evaluated patients of all groups every day during hospitalization.

The evaluation of patients of the four groups included three scores for OM:

i) The classification of OM according to the World Health Organization of 1979 provides a general assessment of the degree of severity of mucositis by combining some objective characteristics of oral mucosa (erythema and ulcerations) with the ability to drink or eat. The WHO mucositis scale ranges from 0= no symptoms; 1=soreness, erythema; 2=erythema, ulcers but able to eat solids, 3=ulcers but required liquid diet; 4= oral feeding not possible (11);

ii) Visual analogue scale (VAS) ranging from 0=no pain to 10=worst pain in the world (12);

iii) OMAS Scale: Introduced in 1996 by a team of oral medicine specialists from oncologists and nurses in the United States, Europe and Canada, evaluates the anatomical extension and the severity of OM. The Oral Mucositis Assessment Scale (OMAS) evaluates the presence and size of ulcerations or pseudo membranes for each site of the oral cavity (upper lip, lower lip, right cheek, left cheek, vertical tongue and right side, vertical tongue and left side, oral floor, soft palate and hard palate). The overall evaluation of the mucosal according to the OMAS scale is expressed by adding the scores for the degree of erythema, ulcers and pseudo membranes in certain regions of the oral cavity. OMAS scale: Oral cavity for Ulceration 0=No lesion; 1= Lesion <1 cm^2; 2=Lesion 1 to 3 cm^2; 3 =Lesion >3 cm^2; Oral cavity for Erythema: 0= None; 1=Not severe; 2=Severe (13).

According to WHO and OMAS scales, we divided the lesions into two groups: light mucositis (WHO grade 1 and 2, OMAS grade 1) and severe mucositis (WHO grade 3 and 4, OMAS grade 2 and 3). Primary indicators of mucositis were the degrees of ulceration and redness measured in specific sites in the mouth. Secondary indicators included oral pain, difficulty swallowing and the ability to eat as assessed by the patient. A single score is not produced from this scale, rather a score for ulceration and redness based on different locations in the mouth are used.

Statistical analysis

The results included continuous and categorical variables. The former are reported as mean and standard deviation. Nonparametric tests were used: the Wilcoxon signed-rank test for comparisons of two correlated samples involving matched pairs and the Mann-Whitney test for comparisons of two independent distributions. Categorical variables, reported as count and percentage, were arranged in cross-correlation tables and compared using the χ^2 test with the Yates correction when all expected values were higher than 5 or the Fisher test. Statistical significance corresponded to a probability less than 0.05.

RESULTS

Table I shows demographic detail of patients and other baseline information. All patients were candidate to HSTC for haematological malignancies. The four groups

were homogeneous for age, sex, type of pathology, HSCT type (autologous or allogeneic), conditioning regimen (total body conditioning myeloblative or reduced), Plaque Index, Bleeding Index and PSR. All these variables did not show statistically significant differences among the various groups.

As for the onset of mucositis, 87% of the whole sample developed a mucositis and the distribution among groups was homogeneous: 30 patients of group A (76.6%), 29 patients of group B (90.6 %), 29 patients of group C (85.3%) and 31 of group D (91.2%). The position of lesions is described in Table II and it is according to those reported in literature (5-10). Patients who did not develop OM, were excluded from further analysis.

Treatment administration

There was no indication of any intolerance to the product. Based on the interview, all patients, except two, liked the consistency of the product in the mouth and they were able to use it during the day based on the instructions of the dentist.

Table III shows WHO scale occurrence in the 4

Table I. *Patients' baseline characteristics.*

		Group A	Group B	Group C	Group D	P value
	No.	37	32	34	34	
Sex	Male	24	19	13	18	0.13
	Female	13	13	21	16	
Age	< 30 y.	3	2	3	1	0.74
	31-40 y.	6	1	5	3	
	41-50 y.	10	9	5	10	
	51-60 y.	12	10	12	13	
	> 60 y.	6	10	9	7	
Transplant	Autologous	5	7	6	10	0.39
	Allogenic	32	25	28	24	
TBI	Yes	7	4	5	6	0.88
	No	30	28	29	28	
Pathology	Acute Myeloid Leukaemia	11	9	7	11	0.052
	Chronic Myeloid leukaemia	4	1	2	0	
	Hodgkin's Lymphoma	4	2	0	1	
	Non Hodgkin's Lymphoma	4	3	5	8	
	Myelofibrosis	0	1	2	0	
	Lymphoblastic leukemia	7	5	2	1	
	Multiple Myeloma	2	6	3	8	
	Myelodysplastic Syndrome	1	1	5	3	
	Others	4	4	8	2	
FMPS	0-100%	61.0	28.5	58.5	43.5	0.98
FMBS	0-100%	54.5	22.5	32.0	33.5	0.42
PSR	0-4	3	2	3	3	0.09

no.: number of patients; TBI: total body conditioning regimen; FMPS: full mouth plaque score; FMBS: full mouth bleeding score; PSR: periodontal score recording.

groups. All comparisons between Group A and group D were statistically significant (P<0.05), and also Group C *vs* group D showed a statistically significant presence of lower gravity of mucositis in patients treated with Mucosamin®.

With regard to the OMAS scale, results are shown in Table IV: patients in group A and C developed lighter lesions. In group B there was higher prevalence of the worst lesions, while Group D had a higher number of lesions of all grades.

A statistically significant difference was observed for the OMAS scale mucositis grade 1 between groups A and B for the former group (p= 0.009*) and for grade 3 (p = 0.04*) in favour of the latter group, while between group

Table II. *Position of lesions of oral mucositis.*

	Group A (% lesions)	*Group B (% lesions)*	*Group C (% lesions)*	*Group D (% lesions)*
Upper/ Lower Lip	5.4 (2)	3.1 (1)	26.5 (9)	5.9 (2)
Tongue	40.5 (15)	21.9 (7)	26.5 (9)	38.2 (13)
Soft Palate	29.7 (11)	6.25 (2)	17.6 (6)	29.4 (10)
Hard Palate	18.9 (7)	9.4 (3)	29.4 (10)	38.2 (13)
Cheek	35.1 (13)	15.6 (5)	26.5 (9)	32.3 (11)
Gums	8.1 (3)	9.4 (3)	35.3 (12)	26.5 (9)
Oral Floor	13.5 (5)	3.1 (1)	20.6 (7)	26.5 (9)

Table III. *Evaluation of gravity of oral mucositis.*

	WHO 1	WHO 2	**WHO 3**	**WHO 4**
	% (n. pts)	% (n. pts)	% (n. pts)	% (n. pts)
Group A	60 (18)	23.3 (7)	6.7 (2)	10 (3)
Group B	17.2 (5)	24.1 (7)	38 (11)	20.7 (6)
Group C	31 (9)	48.3 (14)	13.8 (4)	6.9 (2)
Group D	9.7 (3)	3.2 (1)	51.6 (16)	35.5 (11)
P- value	**WHO 1**	WHO 2	**WHO 3**	**WHO 4**
Group A *vs* B	**0.03***	0.76	**0.02***	0.19
Group A vs D	**0.0002***	0.03*	**0.00005***	**0.01***
Group C *vs* D	**0.007***	0.0002*	**0.0007***	**0.01***

WHO scale P<0.05 (*).

Table IV. *Evaluation of gravity of oral mucositis.*

	OMAS 1	**OMAS 2**	**OMAS 3**
	% (n. lesions)	% (n. lesions)	% (n. lesions)
Group A	73.3 (22)	30 (9)	20 (6)
Group B	31 (9)	44.8 (13)	41.4 (11)
Group C	41.4 (12)	37.9 (11)	24.1 (7)
Group D	48.4 (15)	48.4 (15)	51.6 (16)
P- value	**OMAS 1**	**OMAS 2**	**OMAS 3**
Group A *vs* B	**0.009***	0.20	**0.04***
Group C *vs* D	0.08	0.07	**0.04***

OMAS scale P<0.05 (*).

C and D for Grade 3 (p= 0.04*) it was higher in the latter.

For statistical analysis it was decided to divide lesions into two groups: light mucositis (WHO grade 1 and 2, OMAS grade 1) and severe mucositis (WHO grade 3 and 4, OMAS grade 2 and 3). Comparing subjects who contracted a light mucositis in group A *vs* group B, there is a statistically significant difference (p = 0.001*), as well as when comparing the same groups with severe mucositis (p = 1.8 x 10-6*)

Finally, the duration of the lesions was analysed: it was observed that more than 70% of Group A injuries disappeared within 7 days (70.3%) and only 37.6% for Group B, 50% for Group C and only 32.4% for Group D. In addition, lesions lasted up to 3 weeks in 25% of Group B and only in 10.8% of Group A, 17.6% in Group C and 14.7% in Group D. Comparing group A with group B, for the overall duration of OM, a statistically significant difference between the two groups (p = 0.02*) was found, as well as between group A and group D (p=0.03*).

DISCUSSION

Data show that subjects in Group A have predominantly developed lighter mucositis in respect to group B. Since both groups were subjected to a professional oral hygiene session and had the same initial conditions, we can assumed that use of Mucosamin® in Group A played a decisive role on the appearance lower OM degree. Comparing groups C and D, similar results were obtained: even the two groups who did not receive a professional oral health care (POHC) by a dedicated operator, showed a statistically significant difference for higher grades of mucositis in patients who had not received Mucosamin®. The OMAS Scale confirms that Mucosamin® has played a protective role against the severity of mucositis. The study also shows a duration reduction in patients using Mucosamin® and undergoing POHC: data confirm our previous study on OM treatment (9), emphasize the importance association of POHC and Mucosamin® and reinforce the need to create a team haematologist-dentist-hygienist to manage oral cavity complications in patients undergoing HSCT, (14-15). Moreover, the risk of developing high levels of OM decreases drastically if Mucosamin is associated with POHC by a dedicated operator.

The use of Mucosamin® may influence OM type and severity, allowing patients to improve their quality of life. Mucosamin's® effectiveness in reducing pain and accelerating wound healing is due to its ability to repair tissues, activate and modulate inflammatory response, promote proliferation and cell migration, angiogenesis, increase re-epithelisation, deposition of new basal keratinocytes and collagen layers, allowing to form a protective layer on the ulcerative layers (8); it seems more effective than other drugs tested (16).

According to the present study the combination of a careful debridement, correct oral hygiene during hospitalization and the use of Mucosamin® exponentially reduce the severity and duration of mucositis and consequently the discomfort of the patient. Finally, it can be stated that the use of Mucosamin® also results in a reduction in the extent of chemotherapy lesions. Hyaluronic acid and amino acid-based sprays can be a valuable therapeutic aid in the treatment of OM.

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