

Treatment of mucositis in patients undergoing bone marrow transplantation: a systematic review*

Tratamento da mucosite em pacientes submetidos a transplante de medula óssea: uma revisão sistemática

Tratamiento de la mucositis en pacientes sometidos a transplante de médula ósea: una revisión sistemática

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ABSTRACT

Objective: To identify therapeutic measures to reduce the severity of oral mucositis in adult patients undergoing bone marrow transplantation (BMT). **Methods:** A systematic review using the following databases: LILACS, MEDLINE, CINAHL, EMBASE, CENTRAL (Cochrane Central) and DARE (Database of abstracts of reviews of effects), for the period between 1972 to July 2010, using the key words mucositis, stomatitis and bone marrow transplantation. **Results:** We identified 3,839 abstracts, 22 of which were included in the systematic review; these articles identified 14 topical and systemic interventions, among which eight showed statistical significance for the reduction of this complication. The topical therapies were: cryotherapy, chlorhexidine, glutamine, laser and Traumeel®. The systemic therapies were: amifostine, Granulokine®, and palifermin. **Conclusion:** The heterogeneity of the results of these interventions and the lack of better elucidation for healthcare practice indicate the need for more accurate research to identify the effectiveness of topical therapies for repair of mucosal cells.

Keywords: Mucositis/therapy; Stomatitis; Bone marrow grafted; Nursing care

RESUMO

Objetivo: Identificar as medidas terapêuticas para redução da gravidade da mucosite oral em pacientes adultos submetidos ao Transplante de Medula Óssea (TMO). **Métodos:** Revisão sistemática nas bases de dados: LILACS, MEDLINE, CINAHL, EMBASE; CENTRAL (Cochrane Central) e DARE (*Database of abstracts of reviews of effects*), no período de 1972 a julho de 2010, utilizando os descritores *mucositis*, *stomatitis* e *bone-marrow-transplantation*. **Resultados:** Identificaram-se 3.839 resumos, dos quais 22 foram incluídos na revisão sistemática que descreveram 14 intervenções tópicas e sistêmicas, dentre as quais oito com significância estatística para a redução dessa complicação. As terapias tópicas foram a crioterapia, clorexidina, glutamina, laser e Traumeel® e as sistêmicas, amifostina, Granulokine® e palifermin. **Conclusão:** A heterogeneidade dos resultados dessas intervenções e a falta de melhor elucidação para a prática assistencial indicam a necessidade de pesquisas mais precisas para identificar a efetividade de terapias tópicas para a reparação celular das mucosas.

Descritores: Mucosite/terapia; Estomatite; Transplante de medula óssea; Cuidados de enfermagem

RESUMEN

Objetivo: Identificar las medidas terapéuticas para la reducción de la gravedad de la mucositis oral en pacientes adultos sometidos a Transplante de Médula Ósea (TMO). **Métodos:** Se trata de una revisión sistemática en las bases de datos: LILACS, MEDLINE, CINAHL, EMBASE; CENTRAL (Cochrane Central) y DARE (*Database of abstracts of reviews of effects*), en el período de 1972 a julio del 2010, utilizando los descriptores *mucositis*, *stomatitis* y *bone-marrow-transplantation*. **Resultados:** Se identificaron 3.839 resúmenes, y de éstos 22 fueron incluídos en la revisión sistemática que describieron 14 intervenciones tópicas y sistémicas, de las cuales ocho con significancia estadística para la reducción de esa complicación. Las terapias tópicas fueron la crioterapia, clorexidina, glutamina, laser y Traumeel® y las sistémicas, amifostina, Granulokine® y palifermin. **Conclusión:** La heterogeneidad de los resultados de esas intervenciones y la falta de mayor claridad para la práctica asistencial indican la necesidad de investigaciones más precisas para identificar la efectividad de terapias tópicas tendientes a la reparación celular de las mucosas.

Descritores: Mucositis/terapia ; Estomatitis; Trasplante de médula óssea; Cuidado de enfermería

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INTRODUCTION

The Bone Marrow Transplant (BMT) is a therapeutic option for oncohematological diseases, which is considered effective increasing patients' survival rates.

According to the Associação Brasileira de Transplantes de Órgãos (Brazilian Association for Organ Transplants), 1.129 transplants occurred in Brazil between January and September 2010, 648 of which were autologous and 481, allogeneic⁽¹⁾.

However, it is important considering the side effects caused by BMT, among which are: bone marrow aplasia, nausea, vomiting, diarrhea, Graft-Versus-Host Disease, and mucositis. Mucositis affects approximately 75% of the patients who undergo ablative chemotherapy sessions, or total body irradiation, as preparation means to the transplant, which directly impact on patients' general state and are significantly associated with an increase in general mortality⁽²⁾.

Oral mucositis is an inflammation of the mucosa that is characterized by colour alteration, atrophy, ulceration, edema, and alteration of the local perfusion. Early signals that indicate the mucosa is compromised are visible during the chemotherapy / radiation therapy sessions. In the first two weeks after the transplant, these signals will worsen⁽³⁾.

Despite the morbidity and the impacts brought by oral mucositis to patients' quality of life during the treatment and control of oncohematological diseases, there is no effective evidence of prophylactic agents, or agents for its treatment⁽⁴⁾. The lack of evidence limits the ability to measure benefits, risks, and costs associated to the prevention, diagnosis and treatment of mucositis and its complications. Therefore, to identify intervention actions that can be taken to minimize the seriousness of mucositis is the objective of the present investigation.

Considering the above said, this study aimed to answer the questions described below:

- What are the recommended actions to prevent and treat oral mucositis in adult patients who have undergone BMT?
- How effective are the interventions identified in reducing the seriousness of oral mucositis in adult patients who underwent a BMT?

METHODS

The present study is a systematic literature review (SLR), performed through a retrospective analysis of primary studies that focused on the oral mucositis treatment. The methodological procedures were based on *Cochrane Collaboration*⁽⁵⁾ recommendations, characterized by a thorough analysis of the selected studies, according to their evidences and relevance in

the area; data synthesis and interpretation. The search strategy used to identify the articles was based on an initial selection of articles from Literatura Latino-Americana and of Caribe em Ciências da Saúde (LILACS), Medical Literature Analysis and Retrieval System on-line (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE; CENTRAL (*Cochrane Central register of controlled trials*), and DARE (*Database of abstracts of reviews of effects*), all available at Cochrane Library. At this stage, besides primary studies, narrative reviews and clinical guidelines were also selected in order to synthesize the literature related to such theme. Inverse search was also utilized: this method consists of selecting primary documents recovered from the previous search. After the first study identification phase was concluded, studies were selected for a quality assessment.

The descriptors used were: *Mucositis*, *Mucositis AND Bone Marrow Transplantation*, *Stomatitis AND Bone Marrow Transplantation*. The search began in 2004 and had updates until July 2010, covering the period from 1972 to 2010, with no language restrictions.

The inclusion criteria for the selected articles were: randomized controlled clinical trials (RCT), double-blind and mono-blind studies, studies with no blinding method that tested treatments so as to verify their efficacy and safety preventing and controlling serious oral mucositis. The study population was comprised of adult patients who had undergone BMT, aged 18 or more.

The exclusion criteria were: studies that, further than approaching mucositis and stomatitis assessment, prevention, and treatment, included the candidiasis treatment in patients who had gone through chemotherapy and/or radiation therapy sessions that were not related to BMT, and studies whose population was comprised exclusively of children and adolescents. In order to enable the analysis in the present SLR, only RCTs were included.

Analysis Method

The studies analysis was performed by three experts in the area that independently verified the agreement regarding the pre-selection of articles, and in case of disagreement, read the article integrally for the final selection. The pre-selected primary articles were submitted to analysis, based on Hadorn et al.⁽⁶⁾ criteria, with regard to the quality of the controlled studies. Those which presented methodological problems were excluded. In order to extract data from the articles included in the SLR, an instrument with the following items was used: publication date, authors, title of the study, country of publication, type of publication (journal, book, dissertation, thesis, etc), type of study, objective, context (experimental, hospital-related,

ambulatory-related), population/sample (experimental and controlled), randomization method description, blinding, population characteristics (age bracket, gender, race, education, diseases, and type of conditioning), caregiver's professional category, patients' inclusion criteria, intervention performed – both for the controlled and experimental groups – results assessment and measurement, statistical tests used, scales utilized to assess the intervention, research findings, and evidence level.

RESULTS

Three thousand eight hundred and thirty nine summaries were identified with the uniterm *mucositis*. Two thousand eight hundred and twenty seven of which were excluded due to the fact they did not analyse the mucositis treatment in patients who had undergone a BMT. From the 1,012 summaries with *Mucositis AND Bone Marrow Transplantation, Stomatitis AND Bone Marrow Transplantation*, 188 were selected, for they were Randomized Controlled Trials (RCT). After the articles were read, 166 were excluded because they included children in their population, or because their main aim was not to reduce serious mucositis. Therefore, 22 RCTs were selected for being related to the theme “mucositis treatment in adult patients who underwent a BMT”.

The synthesis of the 22 studies identified with regard to their authors, country of origin, study population, treatment type and time, results obtained, and scale utilization to assess the results can be observed through Table 1 data.

Amifostine is a selective antioxidant cytoprotective agent with a wide action range. When compared to the group who had not received any previous treatment, this drug demonstrated a protective effect, reducing the oral mucositis average degree (Degree 1 *versus* 2 $p=0,01$) and the frequency of serious mucositis (WHO degrees 3 or 4; respectively, 12% vs 33% $p=0,02$)⁽⁷⁾.

Caphosol® (calcium phosphate) is an artificial saliva solution, indicated to lubricate the mucosa. When compared to the control group, it did not present a significant statistical difference diminishing the seriousness of mucositis⁽⁸⁾.

By using ice, cryotherapy, has been widely used for the oral mucositis treatment in oncology patients. The present review identified a study with 80 patients that analysed the topical use of cryotherapy compared to the use of a physiological solution in room temperature. Results showed its protective and therapeutic effect, diminishing the seriousness of mucositis (Degree 3-4) from 14% to 74%, $p=0,0005$ ⁽⁹⁾.

Chlorhexidine digluconate is an important antiseptic that can be used on the skin and mucosae due to its low

toxicity. It is also used for mouth rinsing due to its antimicrobial action. This type of therapy presented a protective effect when compared to the placebo⁽¹⁰⁻¹¹⁾.

Glutamine (l-glutamine or L- alanyl-L- glutamine) is used in high doses by rapid division cells, including leukocytes, to provide energy and favour the biosynthetic process of nucleotides 11. No relevant statistical difference was observed reducing oral mucositis⁽¹²⁻¹⁴⁾.

Granulokine® (Filgrastim G-CSF), a human granulocyte colony stimulating factor whose action over the bone marrow increases the production and mobilization of neutrophils, did not present a significant statistical difference reducing the mucositis seriousness⁽¹⁵⁻¹⁸⁾.

A study which compared the intensive oral hygiene regime (IOH) with limited oral hygiene (LOH) did not present significant statistical difference⁽¹⁹⁾. It is relevant highlighting that the IOH included a complete exam of the mouth, in order to detect and treat cavities, periodontal lesions, periapical disease, mispositioned teeth, and assess dental prostheses adequacy, while the LOH excluded the preventive treatment, as well as teeth and gums brushing. Both groups rinsed their mouths with chlorhexidine.

Histamine presents a topical application, as a gel that reduces tissue damage, diminishing the generation of reactive oxygen species through the connection with H2 receptors, and the production of proinflammatory cytokines stimulating the phagocytes. The analysis performed did not show any significant difference reducing the mucositis severity⁽²⁰⁾.

Misoprostol (Prostaglandin E1 - Cytotec®) is a drug that reduces the ulceration risk, induced by nonsteroidal anti-inflammatory drugs⁽²¹⁾. With regard to the use of Misoprostol, a synthetic analog of prostaglandin E1, one of the studies compared it to a placebo; both were presented in a tablet format to patients who had gone through Cyclophosphamide and Total Body Irradiation (TBI) conditioning⁽²¹⁾. Another study used Misoprostol in tablets, comparing it to a placebo group, concomitantly with etoposide, carboplatin, iphosphamide and conditioning regimens⁽²²⁾. The present review verified after analysing both studies that no significant statistical difference was found⁽²¹⁻²²⁾.

The Helium –Neon Laser (He- Ne) 60mW is a current topical therapy that was assessed by a study that compared its action in parts of the mucosa in relation to the contralateral area, where a reduction on the mucositis seriousness was observed, on the 6th and 9th days after the transplant⁽²³⁾. Another study also verified this therapy beneficial effects, however, the methodology did not adopt a control group comparison⁽²⁴⁾.

Palifermin is a human recombinant keratinocyte growth factor, a trial⁽²⁵⁾ revealed it reduces the incidence of degrees III and IV, while also reducing the febrile

Table 1 – Synthesis of the selected studies on mucositis treatment in patients who have undergone Bone Marrow Transplant.

Therapy	Author	Method	Patients (n)	Interventions	Variables	Results	Assessment Scale
Amifostine	Spencer A, Horvath N, Gibson J, Prince HM, Hemmann R, Bashford J, et al. ⁽⁷⁾	RCT, Multi-centric, Hospital-based. Follow up: 18 months	90 SG = 43 CG = 47	Amifostine 910mg/m ² before the BMT conditioning (SG) vs no Amifostine before the BMT conditioning (CG)	Mucositis occurrence and seriousness, analgesic and NPT use	Reduction of the oral mucositis degree SG 1 vs CG 2 (p=0.01) and degrees 3 and 4 SG 12% vs CG 33% (p= 0.02)	WHO e EORTC
Caphosol	Papas AS, Clark RE, Martuscelli G, O'Loughlin KT, Johansen E, Miller KB. ⁽⁸⁾	Double-blind RCT	95 SG = 50 CG=45	Mouth rinse with Caphosol (Calcium Phosphate - SG) vs fluorine solution (CG)	Mucositis seriousness	Mucositis days (p=0,001) Duration of pain (p=0,0001) Morphine days(p=0,0001)	NIDCR
Cryotherapy	Lilleby K, Garcia P, Gooley T, McDonnell P, Taber R, Holmberg L, et al. ⁽⁹⁾	Double-blind RCT	40 SG = 20 CG=20	Cryotherapy (SG) before and after the melphalan perfusion, compared to a mouth rinsing with saline solution (CG) in room temperature	Mucositis seriousness, narcotic use, NPT days, hospital admission and weight loss	Reduction of the mucositis seriousness when compared to the saline solution in room temperature (p=0,0005)	NCI grading system
Chlorhexidine	Ferretti GA, Ash RC, Brown AT, Parr MD, Romond EH, Lillich TT. ⁽¹⁰⁾	Double-blind RCT	51 SG = 24 CG = 27	Mouth wash with chlorhexidine (SG) VS no chlorhexidine (CG), both for 60 days	Mucositis seriousness and colonization by streptococci and candida	Reduction of mucositis seriousness by the 7 th day: p<0,05 Mucositis resolution by the 25 th day after the BMT: p<0,05 Reduction of the colonization by streptococci p<0,001	Lindquist and Tanner modified index
	Weisdorf DJ, Bostrom B, Raether D, Mattingly M, Walker P, Pihstrom B, et al. ⁽¹¹⁾	Double-blind RCT	100 SG = 50 CG = 50	Mouthwash for 30s, three times a day, from D-8 to D+35	Reduction of dental plaque	Reduction of dental plaque (p=0,06)	Lindquist and Tanner modified index
Glutamine	Anderson PM, Ramsay NK, Shu XO, Rydholm N, Rogosheske J, Nicklow R, et al. ⁽¹²⁾	Double-blind RCT	193 SG = 98 SG = 95	Glutamine (SG) vs placebo (CG).	Oropharyngeal mucositis seriousness, oral pain, opioids use, NPT use, and hospital admission days.	Reduction of oral mucositis in autologous BMT (p=0,05)	Not mentioned
	Blijlevens NM, Donnelly JP, Naber AH, Schattenberg AV, DePauw BE. ⁽¹³⁾	Double-blind RCT	32 patients with haematological cancer (SG). The number of patients in the CG was not mentioned	Glutamine supplement in the NPT (SG) vs only NPT (CG)	Transplant days, oral mucosa integrity, RCP concentration	Improvement in the Mucosa Integrity, reduction in the concentration of Reactive C Protein (RCP) D+21 after the BMT for patients in the SG (p=0,003)	WHO and DMS
	Coghlin Dickson TM, Wong RM, Offrin RS, Shizuru JA, Johnston LJ, Hu WW, et al. ⁽¹⁴⁾	Double-blind RCT	58 SG = 29 CG = 29	Oral administration of Glutamine (SG) vs placebo administration (CG)	NPT use, mucositis seriousness, and diarrhea	There was no significant difference reducing the seriousness of mucositis in either group	Stanford University Hospital BMT toxicity scale.

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Therapy	Author	Method	Patients (n)	Interventions	Variables	Results	Assessment Scale
GM-CSF	Nemunaitis J, Rosenfeld CS, Ash R, Freedman MH, Deeg HJ, Appelbaum F, et al. ⁽¹⁵⁾	Double-blind RCT	109 SG = 53 CG = 53	SG (G-CSF) IV administration for 4 hours vs placebo Perfusion from D 0 up to D+20	Neutrophil count, oral infection, hospital admission duration	The absolute neutropenia time was shorter for the SG (p=0,0001) Reduction of Degrees III and IV mucositis incidence (p=0,005) and infection (p=0,001)	Not mentioned
	Van der Leij H, Thomas BL, Van Oers RH, Ek-Post M, Sjamsoedin SA, Van Dijk-Overtoom ML, et al. ⁽¹⁶⁾	Double-blind RCT	36 SG = 18 CG = 18	SG: 300 mg GM-CSF in 2% methylcellulose gel CG: methylcellulose gel Both applied daily in the mouth mucosa	Mucositis seriousness and pain. Secondary outcomes: need for NPT, and morphine, fever and infection incidence, neutropenia and hospital admission duration.	There was no significant reduction of the mucositis seriousness comparing both groups.	WHO
	Valcárcel D, Sanz MA Jr, Sureda A, Sala M, Muñoz L, Subirá M, et al. ⁽¹⁷⁾	Double-blind RCT	41 SG = 18 CG = 23	Mouthwash with GM-CSF (SG) vs saline solution (CG)	Mucositis seriousness	There was no significant difference between the groups	Not mentioned
	Dazzi C, Cariello A, Giovanis P, Monti M, Vertogen B, Leoni M, et al. ⁽¹⁸⁾	Double-blind RCT	36 SG = 18 CG = 18	GM-CSF vs placebo, mouthwash once a day	Mucositis seriousness	There was no significant reduction of the mucositis seriousness comparing both groups	NCI-CTC
Oral Hygiene	Borowski B, Benhamou E, Pico JL, Laplanche A, Margainaud JP, Hayat M. ⁽¹⁹⁾	RCT	150 SG = 75 CG = 75	Limited oral hygiene compared to intensive oral hygiene	Mucositis risk and duration	There was no significant reduction of the seriousness comparing both groups	NCI-CTC
Histamin	Elad S, Ackerstein A, Bitan M, Shapira MY, Resnick I, Gesundheit B, ET al. ⁽²⁰⁾	Double-blind RCT	44 SG = 21 CG = 23	Histamine	Mucositis duration, number of admission days	No significant reduction of mucositis duration p=0.06.	NCI and OMAS score
Misoprostol	Dueñas-Gonzales A, Sobrevilla-Calvo P, Frías-Mendivil M, Gallardo-Rincon D, Lara-Medina F, Aguilar-Ponce L, et al. ⁽²¹⁾	Double-blind RCT	16 SG = 9 CG = 7	Misoprostol vs placebo	Mucositis seriousness and duration, diarrhea and number of admission days	Mucositis seriousness and duration were significantly high in patients who were treated with misoprostol	WHO
	Labar B, Mrsic M, Pavletic Z, Bogdanic V, Nemet D, Aurer I, et al. ⁽²²⁾	Double-blind RCT	60 SG = 31 CG = 29	Misoprostol vs placebo	Mucositis seriousness and incidence	There was no statistically significant difference	WHO

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Therapy	Author	Method	Patients (n)	Interventions	Variables	Results	Assessment Scale
Laser therapy	Barasch A, Peterson DE, Tanzer JM, D'Ambrosio JA, Nuki K, Schubert MM, et al. ⁽²³⁾	Double-blind RCT	22 autologous BMT patients were in the SG; treatment on one of the sides of the mouth mucosa CG: contralateral side of the mucosa, which did not receive treatment	Laser therapy with helium-neon, daily, during 5 consecutive days, beginning on D-2 or D-1, with assessments on days +3, +6, +9, +12, +15, +18 and +21.	Mucositis incidence and seriousness, and pain intensity	20 out of 22 patients completed the study. Reduction of the mucositis seriousness, but no incidence reduction.	Oral Mucositis Index Scale (OMI-A and OMI-B), ECOG, and Visual Analogue scale (VAS) to analyse the pain intensity
	Cowen D, Tardieu C, Schubert M, Peterson D, Resbeut M, Faucher C, Franquin JC. ⁽²⁴⁾	Double-blind RCT	30 SG= Laser therapy with helium-neon (He-Ne) CG = light application, no mention of the number of patients	SG: Laser therapy with helium-neon (He-Ne) daily applications as of D-5 up until D-1, in five different anatomic sites. CG: light application.	Mucositis seriousness and incidence, oral pain, morphine use, xerostomy and need for NPT	Laser application reduced the mucositis seriousness (p=0.03)	Mucositis Index (DMI) and cumulative oral mucositis score (COMS)
Palifermin	Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, et al. ⁽²⁵⁾	Double-blind, phase III RCT, with a 19 month duration	212 SG = 106 CG = 106	SG: palifermin (60mg/kg of body weight/ day) vs IV placebo (CG)	Mucositis incidence and seriousness, xerostomy, opioid and NPT use	The incidence of Degrees 3-4 in the SG as of 63%, and 98% in the CG (p=0,001)	WHO, RTOG, WCCNR
Povidine	Vokurka S, Bystrická E, Koza V, Scudlová J, Pavlicová V, Valentová D, et al. ⁽²⁶⁾	Double-blind RCT	132 SG = 67 CG = 65	Mouthwash with povidine (SG) – iodine 1:100 vs physiological solution (CG), prepared in the morning	Mucositis seriousness	There was no significant difference between the two groups	WHO
Sucralphate	Castagna L, Benhamou E, Pedraza E, Luboin ski M, Formi M, Brandes I, et al. ⁽²⁷⁾	Double-blind RCT, divided into 4 groups, according to the conditioning regimen, based on the probability of developing radiation-induced mucositis (RT)	105 SG = 53 CG = 52	Mouthwash with one dose of sulcraphate (2g) vs placebo. Guidance: ingest one dose (2g) of sulcraphate every three hours, up to a maximum of seven mouthwashes in 24 hours	Mucositis incidence and seriousness, diarrhea	Mucositis incidence was similar for both groups, but the proportion of patients with degree 3-4 mucositis was higher for the placebo group	OMAS
Traumeel S®	Oberbaum M, Yaniv I, Ben-Gal Y, Stein J, Ben-Zvi N, Freedman LS, Branski D. ⁽²⁸⁾	Double-blind RCT	30 SG = 15 CG = 15	Placebo (CG) vs TRAUMEEL S® (SG), 5 times a day, for at least 14 days	Mucositis seriousness	Significant reduction of mucositis seriousness and /or duration when compared with the placebo group (p<0.01)	Not mentioned

neutropenia, and infection incidence, as well as parenteral nutrition use. It suggests a significant reduction for Degree IV mucositis; nevertheless, insufficient data were presented regarding the confidence interval and the relative risk, necessary for the significance analysis.

Povidine is an antiseptic. A study compared Povidine with a saline solution, and it did not present a significant statistical difference, but revealed risks with regard to its significant use⁽²⁶⁾.

Sucralphate (sucrose octasulfate, polyaluminium hydroxide) is often utilized in the treatment of gastric

and duodenal ulcer diseases. It did not present a significant statistical difference reducing oral mucositis, however, it reduced diarrhea p=0,005⁽²⁷⁾.

Traumeel® is a plant extract and mineral salts compound: *Arnica Montana*, *Calendula officinalis*, *Achillea millefolium*, *Matricaria chamomilla*, *Symphytum officinale*, *Atropa belladonna*, *Aconitum napellus*, *Bellis perennis*, *Hypericum perforatum*, *chinacea angustifolia*, *Echinacea purpurea*, *Hamamelis virginica*, *Mercurius solubis* and *Herba sulfuris*. When compared with a placebo, given to a group of 15 patients, investigators observed a slight protective effect⁽²⁸⁾.

DISCUSSION

In the theme review regarding the importance of a thorough assessment of the mouth as an essential tool to identify early alterations to the mucosa integrity, the most mentioned outcomes were the assessment of oral hygiene activities, nutrition, and oral self-care⁽²⁹⁻³¹⁾. The need for assessments and control of the pain presented by serious mucositis patients was also mentioned, mainly considering patients' quality of life⁽³⁰⁾. Although the above mentioned studies highlight the importance of oral hygiene and patients' education to reduce mucositis incidence and seriousness, they did not describe the protocol for such interventions.

With regard to oral care, no studies thoroughly described specific interventions for patients who underwent a BMT. Such gap impacts the clinical practice, considering that such patients' immunosuppression conditions, associated to an inappropriate oral hygiene, and periodontal diseases, makes them vulnerable to systemic infections, caused by exogenous microorganisms, or the resident flora, such as the *Staphylococcus*⁽³²⁾.

The primary data found by this investigation point to an important topical therapy to reduce serious mucositis: the cryotherapy, which is a low cost and risk free therapy, with high efficacy and easy clinical application. Probably due to its vasoconstrictor effect, it reduces the concentration of cytotoxic drugs in the salivary glands, and causes less cellular damage in the gastrointestinal mucosa. The same result was found in patients with colon cancer, who underwent chemotherapy sessions with Fluorouracil⁽³³⁾.

The findings of this investigation evidence a gap in systematizing care provided to BMT patients with an oral mucositis diagnosis. The protocols and algorithms identified present generic conducts that allow assessment accuracy to be developed, but with a low technical

specificity. However, it is relevant to say that international algorithms to handle mucositis in patients under anti-neoplastic treatment were proposed by researchers from the *Cochrane Collaboration*⁽³⁴⁾, *National Comprehensive Cancer Network- NCCN*⁽³⁵⁾, *European Oncology Nursing Society-EONS*⁽³⁶⁾, and *Oncology Nursing Society – ONS*⁽³⁷⁾, based on the opinion of experts and studies with evidence analysis, and recommendations.

When comparing the treatments proposed by such recommendations and the results of the present investigation, it is possible to verify that treatments with effective results, such as the Traumeel S[®], were not mentioned in the NCCN, EONS and ONS guidelines. These algorithms highlight the need for multi-professional care to reduce serious oral mucositis induced by chemotherapy and/or radiation therapy, as well as educating patients, families and the healthcare team to handle such disease.

CONCLUSION

This review identified 22 studies that described 14 topical and systemic interventions for the oral mucositis treatment, eight of which presented statistical significance to reduce the seriousness of this complication. Among them, the topical therapies were cryotherapy, chlorhexidine, glutamine, laser and Traumell S[®]; and the systemic were amifostine, granulokine, and palifermin.

Some results favour the topic therapies, which do not demand high technology and affect the ulceration co-factors, are easy to apply, and can contribute to a better quality of life.

However, considering the result heterogeneity of the analysed interventions, as well as a lack of details for the healthcare practice, researches with a strict methodology should be performed to identify the effectiveness of topical therapies to repair the mucosae cells, with the nurse professional competence as the main scope.

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