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Comparison of the use of *Solidago chilensis* (Arnica) and low-level laser therapy for the prevention of oral mucositis in patients submitted of head and neck radiotherapy and/or high toxicity chemotherapy

Comparação do uso de *Solidago chilensis* (Arnica) e laserterapia de baixa intensidade para prevenção de mucosite oral em pacientes submetidos radioterapia de cabeça e pescoço e/ou à quimioterapia de alta toxicidade

Comparación del uso de *Solidago chilensis* (Árnica) y la terapia con láser de baja intensidad para la prevención de la mucositis oral en pacientes sometidos a radioterapia de cabeza y cuello y / o quimioterapia de alta toxicidade

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Ana Cristina Lopes
ORCID: https://orcid.org/0000-0003-0804-5011
Federal University of Triângulo Mineiro, Brazil
E-mail anaaccari@hotmail.com
Giovana Ferreira Gonçalves
ORCID: https://orcid.org/0000-0002-4441-012X
Federal University of Triângulo Mineiro, Brazil
E-mail: gih.f.goncalves@gmail.com
Anna Cecília Dias Maciel Carneiro
ORCID: https://orcid.org/0000-0003-4865-1286
Federal University of Triângulo Mineiro, Brazil
E-mail: annaceciliamaciel@gmail.com
André Luiz Pantoja dos Santos
ORCID: https://orcid.org/0000-0002-2084-4257
Federal University of Triângulo Mineiro, Brazil
E-mail: andre.santos@uftm.edu.br
Frederico Nobrega Tomas
ORCID: https://orcid.org/0000-0003-0967-088X
Federal University of Triângulo Mineiro, Brazil
E-mail: frederico.tomas@ebserh.gov.br
Leonardo Rodrigues de Oliveira
ORCID: https://orcid.org/0000-0003-1882-1694
Federal University of Triângulo Mineiro, Brazil
E-mail: leonardorodoli@hotmail.com
Karina Ferrazzoli Devienne
ORCID: https://orcid.org/0000-0002-9390-9517
Federal University of Triângulo Mineiro, Brazil
E-mail: karina.vicentine@uftm.edu.br
Virgínia Oliveira Crema
ORCID: https://orcid.org/0000-0001-5219-532X
Federal University of Triângulo Mineiro, Brazil
E-mail: virginia.crema@uftm.edu.br

Abstract

The oral mucositis is an adverse event of radiotherapy and/or high toxicity chemotherapy. The *Solidago chilensis* (Arnica) has been used for its antiseptic, analgesic, healing and anti-inflammatory properties. *Objective:* The purpose of this study was to evaluate the uses of Arnica for oral mucositis prevention in patients submitted to radiotherapy for head and neck tumors treatment and/or high toxicity chemotherapy. *Methodology:* The determination of the cytotoxicity index of the aqueous extract was determined *in vitro*. The oral mucosa was evaluated in days 0, 10 and 14 of patients in the groups: treated with lasertherapy (L, n=18), treated with Arnica (A, n=24) and, treated with lasertherapy associated with Arnica (LA, n=4). It was considered significant $p<0.05$. *Results:* It was determined IC_{50}=90,74 μg/mL of Arnica's aqueous extract in SCC-4 cells. The development of oral mucositis was associated with the type of treatment for oral mucositis prevention: L, A, and LA (χ^2 = 24,72, $p<0.0001$). The level of oral mucositis had significant interaction with the type of prevention treatment [F(2) = 9.545, $p<0.0001$] and, within 14 days [F(2) =

11.995, p<0.0001]. *Conclusions:* The results obtained suggest which the use of *Solidago chilensis* (Arnica) can be an important therapeutic option for treatment with low-level laser therapy for oral mucositis prevention in patients submitted of head and neck radiotherapy and/or high toxicity chemotherapy.
Keywords: Arnica; Laser therapy; Oral mucositis; *Solidago chilensis*; *Solidago microglossus*.

Resumo

A mucosite oral é um efeito adverso, decorrente da radioterapia de cabeça e pescoço e/ou à quimioterapia de alta toxicidade. A *Solidago chilensis* (Arnica) tem sido utilizada por possuir propriedades antissépticas, analgésicas, cicatrizantes e anti-inflamatórias. *Objetivo:* Este estudo visou avaliar o uso de Arnica para a prevenção de mucosite oral em pacientes submetidos à radioterapia para tratamento de tumores de cabeça e pescoço e/ou quimioterapia de alta toxicidade. *Metodologia:* A determinação do índice de citotoxicidade do extrato aquoso foi determinada in vitro. A mucosa oral foi avaliada nos dias 0, 10 e 14 de pacientes dos grupos: tratados com laserterapia (L, n=18), tratados com Arnica (A, n=24) e tratados com laserterapia associada à Arnica (LA, n=4). Foi considerado significante p<0,05. *Resultados:* Foi determinado IC_{50}=90,74 μg/mL do extrato aquoso de Arnica em células SCC-4. O desenvolvimento de mucosite oral foi associado ao tipo de tratamento para prevenção de mucosite oral: L, A e LA (χ^2 = 24,72, p<0,0001). O grau de mucosite oral teve interação significante com o tipo de tratamento preventivo [F(2) = 9,545, p<0,0001] e com o decorrer do tempo de 14 dias [F(2) = 11,995, p<0, 0001]. *Conclusões:* Os resultados obtidos sugerem que o uso da *Solidago chilensis* (Arnica) pode ser uma opção terapêutica importante para o tratamento com a laserterapia de baixa intensidade para a prevenção da mucosite oral em pacientes submetidos radioterapia de cabeça e pescoço e/ou à quimioterapia de alta toxicidade.
Palavras-chave: Arnica; Laserterapia; Mucosite oral; *Solidago chilensis*; *Solidago microglossus*.

Resumen

La mucositis oral es un efecto adverso resultante de la radioterapia de cabeza y cuello y / o quimioterapia de alta toxicidad. *Solidago chilensis* (Árnica) se ha utilizado por sus propiedades antisépticas, analgésicas, cicatrizantes y antiinflamatorias. *Metas:* Este estudio tuvo como objetivo evaluar el uso de Árnica para la prevención de la mucositis oral en pacientes sometidos a radioterapia para el tratamiento de tumores de cabeza y cuello y / o quimioterapia de alta toxicidad. *Metodología:* La determinación del índice de citotoxicidad del extracto acuoso se determinó in vitro. Se evaluó la mucosa oral en los días 0, 10 y 14 de los pacientes de los grupos: tratados con láser (L, n = 18), tratados con Árnica (A, n = 24) y tratados con láser asociado a Árnica (LA , n = 4). Se consideró significativo p <0,05. Resultados: Se determinó IC_{50} = 90,74 μg / mL del extracto acuoso de Árnica en células SCC-4. El desarrollo de mucositis oral se asoció con el tipo de tratamiento para prevenir la mucositis oral: L, A y LA (χ^2 = 24,72, p <0,0001). El grado de mucositis oral tuvo una interacción significativa con el tipo de tratamiento preventivo [F (2) = 9.545, p <0.0001] y en el transcurso de 14 días [F (2) = 11.995, p <0.0001]. *Conclusión:* Los resultados obtenidos sugieren que el uso de *Solidago chilensis* (Árnica) puede ser una opción terapéutica importante para el tratamiento con láser de baja intensidad para la prevención de la mucositis oral en pacientes sometidos a radioterapia de cabeza y cuello y / o quimioterapia de alta toxicidad.
Palabras clave: Arnica; Terapia con láser; Mucositis oral; *Solidago chilensis*; *Solidago microglossus*.

1. Introduction

The mucositis is considered the most serious and stressful complication of non-surgical cancer treatment and, in severe levels it can take to hospitalization for nutritional questions and, to increase secondary infections risks (Barkokebas et al., 2015). The radiotherapy in head and neck and the toxicity of chemotherapy can cause mucositis (Rose-Ped et al., 2002). About 20% to 40% of patients who receive solid tumors chemotherapy, more than 80% of patients submitted to radiotherapy in head and neck region and, about 80% of patients exposed to high doses of chemotherapy before hematopoietic stem cell transplantation developing oral mucositis (Bowen & Wardill, 2017). The appearance of oral mucositis occurs approximately from the third to the fifth day after the use of chemotherapeutic agents, and it usually stops around 15 days after stopping the treatment. On the other hand, patients exposed to cumulative radiation present the first lesions when they reach 30 Gy accumulated in the tissue and spontaneous healing can occur after three to four weeks after the end of the exposure (Sonis, 2009). Currently, the use of low-level laser therapy for the prevention of oral mucositis is recommended, as it is a non-invasive treatment known to significantly reduce pain, severity and duration of symptoms (Mallick et al., 2016).

In radiotherapy period and after chemotherapy, complex biological and cellular events occur in the mucosa and submucosa (Treister & Sonis, 2007). These events affect the epithelial cells and mucosal connective tissue, causing a

disbalance in them, resulting in loss of proliferation and apoptosis (Sonis, 2007). Thus, mucositis results from direct effects on the cellular DNA and indirect effects due to myelosuppression and immunological deficiency of the patient (Wilkes, 1998). The pathophysiology of oral mucositis has been defined by the Sonis model in five phases: (1) initiation, there is direct DNA damage due to the release of reactive oxygen species (ROS); (2) response to primary damage, ROS degrade fibronectin, leading to the activation of matrix metalloproteinases (MMPs), nuclear factor-κB (NF-κB), which stimulates the expression and release of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6); (3) amplification and signaling, there is a new stimulation of tissue damage and apoptosis by the mechanisms already described; (4) ulceration, involvement of the basement membrane and increase in secondary infection caused by yeasts and Gram-negative bacteria; and (5) healing, with onset of basal epithelial cell activity (Redding, 2005; Sonis, 2007).

The use of medicinal plants in dentistry has increased significantly in recent years, because herbal medicines applied in the oral cavity have several important mechanisms of action (Baharvand et al., 2017). *S. chilensis* has been studied in its chemical and pharmacological properties, as well as used in folk medicine mainly in the treatment of inflammatory reactions such as rheumatism, pain and local edema, in addition to gastrointestinal stimulant, healing, antiseptic and burn treatment (Valverde-Soares et al., 2012; Valverde et al., 2021). This genus is known for its landscape and ornamental importance, in addition to presenting species with medicinal, aromatic potential, production of essential oils used in modern and popular medicine, manufacture of cosmetics, medicines, beverages and also antibacterial and anti-inflammatory properties (Sung et al., 1999).

Due to its pharmacological properties of *S. chilensis*, its application as a therapeutic option for the prevention of oral mucositis is promising. Thus, this study aims to compare the use of *S. chilensis* with the use of low-level laser therapy for the prevention of oral mucositis in patients undergoing head and neck radiotherapy and/or high toxicity chemotherapy.

2. Methodology

This is a prospective, experimental, quantitative and analytical study (Pereira et al, 2018).

Preparation of the aqueous extract of Solidago chilensis (Arnica)

Dry leaves of *Solidago chilensis* (Arnica) were commercially obtained from Santosflora Comércio de Ervas LTDA (Mairiporã, SP, Brazil), Lot AUTO 2587. The aqueous extract was prepared with dry leaves of Solidago chilensis, submitted to infusion in water (20 g/L) and decoction for 10 minutes. The tea was filtered, frozen and lyophilized.

Solidago chilensis cytotoxicity assay on SCC-4 cells

The cells of Oral Squamous Cell Carcinoma SCC-4 (American Type Culture Collection - ATCC®) were cultured in Dulbecco's modified Eagle's medium-F12, with 10% fetal bovine serum (FBS), 100 U/mL of penicillin, 100 µg/mL of streptomycin and 400 µg/mL of hydrocortisone, in a humid incubator with an atmosphere of 5% CO_2 at 37°C.

SCC-4 control cells, vehicle control (Cvv greater volume) and treated with Arnica extracts at concentrations: 40, 80, 160, 320 and 640 µg/mL were cultured for 24 hours. The cytotoxicity index (IC_{50}) was determined by the incorporation test of the vital dye 3-amino-7-dimethylamino-2-methylphenazine (neutral red) by conventional methods (Borenfreund & Puerner, 1985).

Evaluation of the use of Solidago chilensis for the prevention and treatment of oral mucositis

This study was approved by the Research Ethics Committee of the Federal University of Triângulo Mineiro (CAAE 26257119.2.0000.5154). This study included 46 patients who underwent head and neck radiotherapy and/or high toxicity

chemotherapy at the UFTM Clinical Hospital. A survey was carried out in the medical records of patients of gender, age, cancer treatment protocol: head and neck radiotherapy and/or high toxicity chemotherapy.

Chemotherapy treatments were classified according to toxicity for the development of oral mucositis. The patients studied were analyzed according to low toxicity chemotherapy: Cytarabine (Lacayo et al., 2002), Etoposide, or of high toxicity: 5-FU (Saini et al., 2003), Cisplatin (Wang et al., 2014), CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) (Shin et al., 2008), FOLFOX (5-FU, Oxaliplatin and Leucovorin) (Bano et al., 2014), Doxorubicin (Anderson et al., 1993) and Daunorubicin (Bishop et al., 1990).

To evaluate the effect of Solidago chilensis as a therapeutic for the prevention of oral mucositis, patients were randomly assigned to the groups: treated with laser therapy (L, n=18), treated with Arnica (A, n=24) and treated with laser therapy associated with Arnica (LA, n=4).

Oral mucositis was clinically classified according to the NIH (National Cancer Institute, 2009) and Eduardo et al (2019): (0) absence of lesions; (1) erythema and discomfort, with or without painful symptoms, asymptomatic or with mild symptoms; (2) moderate pain, not interfering with oral intake; (3) presence of ulcers, with possible ingestion of only liquid foods, presence of pseudomembranes and ulcers, with possible ingestion of solid foods, intense pain, interfering with food intake; (4) presence of ulcers, not being possible ingestion of liquid foods, requiring artificial nutrition, life-threatening consequences; (5) death. Data obtained in the oral examination were analyzed at three times: 0, 10 and 14 days after the inclusion of patients.

The Solidago chilensis (Arnica) was prescribed in the form of mouthwashes of freshly prepared tea at room temperature twice a day, its ingestion being prohibited. Patients received sachets with 0.2 g of dried Arnica leaves (corresponding to a concentration below which identified in the cytotoxicity assay), to be infused in 200 mL of boiling water for 10 min.

For the prevention of oral mucositis, three to five sessions of laser therapy per week were performed, one per day, at a dose of two Joules per point, with a 660 nm red laser, with a power of 100 mW, for 20 seconds of irradiation time, at equidistant points of two centimeters. And, for the treatment of oral mucositis: three to five sessions were performed, one a day, at a dose of three Joules per point, with a 660 nm red laser, with a power of 100 mW, for 30 seconds of irradiation time, in equidistant points of two centimeters.

Statistical analysis

IBM SPSS 20.0® (San Francisco, CA, USA) and Graphpad Prism® (San Diego, CA, USA) programs were used. Statistical tests were applied: nonlinear regression, chi-square, Kolmogorov-Smirnov, Levene analysis of variance, Mann Whitney, Kruskal-Wasllis and Dunn's post-test, Two-way ANOVA. Differences were considered significant when $p<0.05$.

3. Results

Arnica Cytotoxicity in SCC-4 Cells

The cytotoxicity index of the aqueous extract of *Solidago chilensis* (Arnica) in cells of the SCC-4 lineage determined was IC_{50}=90.74 μg/mL (R^2= 0.93).

Casuistry Characterization

Mean age was similar in groups L, A, LA, ML and MLA [x(5)=7,044, p>0.05Also, the proportion of female and male patients was similar between the studied groups ($\chi 2$ = 5.739, p>0.05), Table 1.

Regarding the type of cancer treatment, the distribution of cases treated with laser therapy, Arnica and laser therapy

associated with Arnica for the prevention of oral mucositis was similar (χ^2 = 4.914, p>0.05), Table 1.

Table 1. Distribution of patients submitted to head and neck radiotherapy and/or high toxicity chemotherapy studied, according to gender, age and cancer treatment.

	L	A	LA
Age (years)	51,7±16,4	59,7±10,5	54,5±4,3
Gender (%)			
Female	38,9	54,1	25
Male	61,1	45,9	75
Oncologic Treatment (%)			
CT↓	5,5	29,2	0
CT↑ and/or RT	94,5	70,8	100

(L) Laser therapy, (A) Arnica and (LA) Laser therapy associated with Arnica for oral mucositis prevention. (CT↓) Low toxicity chemotherapy and (CT↑ and/or RT) High toxicity chemotherapy and/or Radiotherapy.
Source: Authors

It is important to note that the medium age, the percentage of female and male genders and the type of cancer treatment were similar in the groups in this study.

Evaluation of the use of Arnica for the prevention of oral mucositis

As expected, patients undergoing chemotherapy of low toxicity in groups L (n=1) and A (n=7) did not develop oral mucositis.

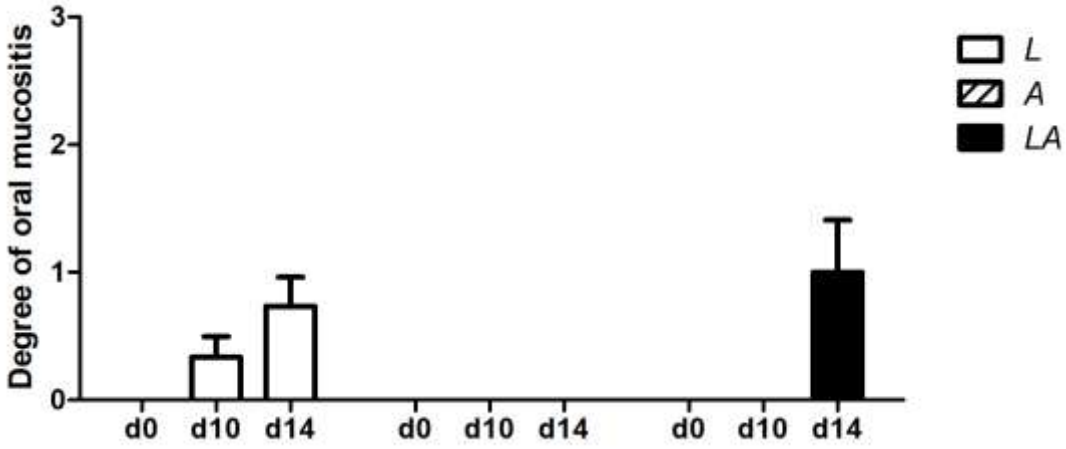
Interestingly, patients who used Arnica mouthwash for prevention did not develop oral mucositis over 14 days. Only one (5.9%) patient who used a mouthwash with Arnica tea who underwent chemotherapy Cisplatin (high toxicity) and head and neck radiotherapy developed oral mucositis after 34 days of follow-up.

Seven (38.9%) patients were diagnosed with oral mucositis on the 10th (median grade 0, min 0 - max 2) and 14th (median grade 0, min 0 - max 2) days of preventive treatment with laser therapy. Among patients in group L, 70.6% manifested oral mucositis between the first and 27th day of follow-up.

And, three (75%) patients developed oral mucositis only on the 14th (median grade 1, min 0 - max 2) day of preventive treatment with laser therapy associated with the use of Arnica. However, 100% of cases in the LA group had oral mucositis between the 15th and 20th day of follow-up.

The development of oral mucositis was significantly associated with the type of treatment used to prevent oral mucositis in this study: L, A and LA (χ^2 = 24.72, p<0.0001). And, the degree of oral mucositis in the cases submitted to head and neck radiotherapy and/or high toxicity chemotherapy and studied had a significant interaction with the type of preventive treatment with laser therapy associated or not with the use of Arnica [F(2) = 9.545, p<0.0001] and with the course of time of 14 days [F(2) = 11.995, p<0.0001], (Figure 1).

Figure 1. Evaluation of the effect of *Solidago chilensis* on the degree of oral mucositis in patients undergoing head and neck radiotherapy and/or high toxicity chemotherapy. At the beginning, 10th and 14th days of preventive treatment with low-level laser therapy (L), Arnica tea mouthwash (A) and laser therapy associated with Arnica tea mouthwash (LA). Two-way-ANOVA: degree of oral mucositis *vs* type of preventive treatment, p<0.0001; grade of oral mucositis *vs* time course, p<0.0001.



Source: Authors.

It is important to note that no patient that used Arnica mouthwash for prevention developed oral mucositis within 14 days.

4. Discussion

This study demonstrated which the use of *Solidago chilensis* (Arnica) as a preventive treatment for oral mucositis in patients undergoing high toxicity chemotherapy and/or head and neck radiotherapy is very promising, considering which its use seems to prevent the occurrence of disease in many cases or even delay its onset. However, Arnica's association with laser therapy has not added benefits for the treatment of oral mucositis. The use of herbal medicines has low cost, easy access to these plants, and almost no adverse effects (Santos et al., 2011). Although the use of other herbal medicines for the treatment of mucositis has been described (Meyer-Hamme et al., 2013; Yarom et al., 2013), this is the first clinical trial with Arnica for the prevention and treatment of oral mucositis.

One of the most common causes of mortality worldwide is cancer (Bray et al., 2018). Its treatment with head and neck chemotherapy and/or radiotherapy triggers many chemical changes in the oral mucosa, releasing reactive oxygen species, which activate transcription factors capable of stimulating the production and release of inflammatory cytokines, causing a clinically evident lesion, very painful and susceptible to secondary infections (Sonis, 2007). Therefore, it is very important to study new therapies for the prevention and treatment of oral mucositis.

In clinical dental practice, prevention and treatment with low-level laser therapy has shown promising efficacy in the control of oral mucositis, however, in most health services, this therapy is still difficult to access for many patients (Zadik et al., 2019). Thus, the use of mouthwashes with Arnica tea would be easy to handle and apply by the patients themselves at home. Different types of Arnica reduce inflammatory processes and stimulate repair effects (Ernst, 2003). Extracts of *Solidago microglossus* (Brazilian Arnica) *e Porophyllum ruderale* (Paulista Arnica), were biocompatible with fibroblasts from mouth ulcers within 24 h (Martins et al., 2009).

Ethanol and methanol solvents are the most used for the preparation of plant extracts (Rady et al., 2018). In this study,

the use of aqueous Arnica extract was chosen, considering which water is a solvent which does not affect the integrity of oral cells. To assess the cytotoxicity of an extract, cell viability testing can be performed with vital dyes, which cross the plasma membrane and concentrate in viable cell lysosomes (Borenfreund et al., 1988; Triglia et al., 1991). What makes it possible to calculate the IC_{50} and, the smaller the IC_{50}, the more active a compound is (Neubig et al., 2003). In this study, through the incorporation assay of neutral red, a vital dye, the IC_{50} of 90.74 μg/mL of Solidago microglossus was determined in SCC-4 cells treated for 24 h, in order to use a tea concentration of Arnica biocompatible with the oral mucosa.

Considering which risk factors such as age and gender have been compared with the variability in the occurrence of oral mucositis in cancer patients (Scully et al., 2006; Sonis, 1998), it was important which the medium age and the percentage of female and male genders were similar in the groups in this study. Young patients present mucositis, probably, due to the decrease in cell replication which occurs in the elderly patients (Porock, 2002) and, possibly, because of the complications in the tissue repair (Suresh et al., 2010). The female gender can be an independent risk factor and a predictor for oral mucositis in protocols with high chemotherapy doses (Vokurka et al., 2006), appearing to be more susceptible to this complication after chemotherapy treatment compared to males (Sonis et al., 2004).

In this study, only patients who have submitted cancer treatment with high toxicity chemotherapy associated or not with head and neck radiotherapy developed oral mucositis. The relationship between the type of chemotherapy and the occurrence of oral mucositis is well known (Sonis, 2009). Also, radiotherapy, when used directly in the head and neck regions, is related to the risk of occurrence of oral mucositis, especially when combined with chemotherapy (Scully et al., 2006).

The development and degree of oral mucositis in the cases submitted to head and neck radiotherapy and/or high toxicity chemotherapy studied was associated with the type of preventive treatment used: laser therapy, Arnica and laser therapy associated with Arnica. The results obtained in this study demonstrated which the prescription of Arnica mouthwash can be important for the prevention of oral mucositis in patients undergoing cancer treatment. Arnica has been widely used as it has antiseptic, analgesic, healing and anti-inflammatory properties (Malpezzi-Marinho et al., 2019). The aqueous extracts of the leaves of *S. chilensis* (Brazilian Arnica) demonstrated an important anti-inflammatory effect in a murine pleurisy model, inhibiting leukocytes in the inflammatory processes caused by carrageenan; and the aqueous extract of the roots and their fractions decreased the release of inflammatory mediators to the inflammation site and which its activity is related not only to the inhibition of pro-inflammatory mediators, but also to the inhibition of leukocyte infiltration (Goulart et al., 2007).

Possibly, the only case of development of oral mucositis seen in this study, after more than one month of Arnica use, was due to the time of oncological treatment. The chemotherapy with Cisplatin (high toxicity) and head and neck radiotherapy led to the development of oral mucositis only after 34 days of follow-up. The dosage and frequency of chemotherapy may have an effect on the occurrence and severity of oral mucositis, especially, which are highly toxic chemotherapy drugs, also the dosage of radiotherapy and its combination with chemotherapy increases toxicity to the body, aggravating oral mucositis (Sonis, 2009).

In an average of 16 days of cancer treatment, some patients who received preventive treatment with laser therapy developed oral mucositis between the first and 27th day of follow-up. Factors related to the individual can interfere with the occurrence and intensity of oral mucositis, in addition to the type of cancer treatment (Barasch & Peterson, 2003; Epstein & Schubert, 1999; Huber & Terezhalmy, 2005; Kostler et al., 2001). Oral mucositis usually occurs from 7 to 14 days after the use of chemotherapy and lasts for about two to three weeks (Katranci et al., 2012), the one induced by radiotherapy can appear after 3 to 4 weeks of treatment and its evolution is increasing if the radiotherapy is not suspended (Öhrn et al., 2001).

In a double-blind, randomized study, Cowen et al. used as preventive treatment, the HeNe laser (632.8 nm, 60 mW, and 1.5 J/cm2), daily for five consecutive days in 30 patients who received chemotherapy treatment prior to bone marrow transplantation. They observed which daily laser application reduced the intensity, severity and length of mucositis, in addition

to pain and the need for morphine administration (Cowen et al., 1997). In another prospective randomized, double-blind study, Bensadoun et al. related the prevention of mucositis with the use of low-level laser in patients treated with radiotherapy to the head and neck. The authors concluded which low-level laser irradiation is able to reduce the severity and duration of oral mucositis associated with radiotherapy (Bensadoun et al., 1999).

Although patients who received laser therapy associated or not with the use of Arnica had a similar degree of oral mucositis at the beginning and during the treatment phase of this study, the analysis of variance showed an interaction between the severity of the disease and the therapy used. However, the results did not show the interaction of the degree of oral mucositis over the time studied. Treatment with low-level laser therapy has an analgesic and anti-inflammatory effect, in addition to reduce edema, minimizing pain and symptoms of biostimulation; however, laser therapy does not have a direct curative effect and effectively favors tissue repair in the injured region through cell biostimulation (Lins et al., 2010).

In a triple-blind, randomized, controlled study, Gautam et al. used low-level laser therapy for prevention and treatment of oral mucositis in 221 patients with head and neck cancer submitted to antineoplastic treatment with chemotherapy and radiotherapy. The results showed which there was a significant reduction in the incidence of severe oral mucositis, associated pain, dysphagia and use of opioid analgesics for these patients treated with laser therapy (Gautam et al., 2012).

The adverse effects of the association of herbal medicines with laser therapy are not well understood. But the results of this study strongly suggest which laser therapy combined with Arnica did not maintain the beneficial effects of using Arnica and laser therapy alone for the prevention of oral mucositis.

5. Conclusion

The results obtained suggest which the use of Solidago chilensis tea (Arnica) is a promising therapy for the prevention of oral mucositis in cancer patients.

Future studies could assess the profile of cytokines present in the saliva of patients treated with Arnica's solution mouthwashes.

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