Revista Odonto Ciência
Journal of Dental Science

ORIGINAL ARTICLE

Rev Odonto Cienc 2013; 28(4)
http://revistaseletronicas.pucrs.br/ojs/index.php/fo

Open Access

Evaluation of the effectiveness of *Matricaria recutita* Linn. in the prevention and control of radiation-induced oral mucositis

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Abstract

Objective: To investigate the effectiveness of *Matricaria recutita* Linn. (chamomile) in the prevention and control of radiation-induced oral mucositis.

Methods: The sample consisted of 22 patients who were divided into three groups: group I (experimental) (n=7), patients were treated with 3% chamomile gel throughout the radiotherapy course; group II (positive control) (n=7), the treatment was carried out using 1% chlorhexidine gluconate gel only at the onset of mucositis until regression of symptoms; and group III (experimental) (n=8), patients with mucositis were treated with 3% chamomile gel following the same protocol described for group II.

Results: The results showed there were no statistically significant differences between the three groups ($P>0.05$). However, descriptive data indicated that group II was found to show the fastest clinical improvement in oral treatment, whereas group III took the longest period to show clinical improvement of mucositis.

Conclusion: Chamomile had no prophylactic effect on the onset of oral mucositis, but it was proven to be effective in decreasing the severity of this condition during treatment in most patients.

Keywords: Head and neck neoplasms; radiotherapy; mucositis; phytotherapy; chamomile

Avaliação da efetividade de *Matricaria recutita* Linn. na prevenção e controle da mucosite bucal radio-induzida

Resumo

Objetivo: Avaliar a eficácia da *Matricaria recutita* Linn. (Camomila) na prevenção e controle da mucosite oral radioinduzida.

Métodos: A amostra foi composta por 22 pacientes que foram divididos em três grupos. No grupo I (experimental) (n=7), os pacientes foram tratados com o gel de camomila a 3% durante todo o tratamento radioterápico; o grupo II (controle positivo) (n=7) fez o uso do gel de gluconato de clorexidina a 1% somente ao surgir a mucosite, até cessar a sintomatologia e o grupo III (experimental) (n=8) tratou a mucosite com gel de camomila a 3%, utilizando o mesmo protocolo proposto para o grupo II.

Resultados: Os resultados não apontaram diferenças estatisticamente significativas entre os três grupos com ($P>0,05$). Porém, os dados descritivos indicam que o grupo II apresentou melhora clínica da mucosite oral em menor tempo de tratamento, enquanto no grupo III a melhora clínica da mucosite ocorreu em um período maior quando comparado aos demais grupos.

Conclusão: A camomila não apresentou efeito profilático para o surgimento da mucosite oral, no entanto, mostrou-se eficaz em relação à diminuição da severidade no decorrer do tratamento na maioria dos pacientes.

Palavras-chave: Neoplasias de cabeça e pescoço; câncer bucal; radioterapia; mucosite oral; camomila

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Received: October 26, 2012
Accepted: November 5, 2013

Conflict of Interests: The authors state that there are no financial and personal conflicts of interest that could have inappropriately influenced their work.

ISSN: 1980-6523

Introduction

Radiotherapy, whether alone or combined with surgery and chemotherapy, remains the main and most effective treatment for malignant head and neck neoplasms. Similarly to chemotherapy, the ionizing radiation does not differentiate neoplastic cells from normal ones. Among the various side effects that manifest in the oral cavity and associated structures are: dry mouth, dysgeusia, radiation caries, candidiasis, osteoradionecrosis, progressive loss of periodontal attachment and oral mucositis, all of which affecting the patients' quality of life [1-3].

Oral mucositis is the most common acute complication and major dose-limiting factor for head and neck radiotherapy. Due to the high rate of cell turnover and low radioresistance, the mucosa cells of the oral cavity, pharynx and larynx quickly respond to the toxic effects of radiation. This complication can be described as an inflammation of the oral mucosa induced by chemotherapy and radiotherapy and represents a distinct stomatitis [2,4].

Mucositis is considered a common acute and debilitating side effect of radiotherapy in the oral cavity, because it impairs the swallowing of solids and sometimes liquids, limits speech and chewing, and exposes the patient to infections by opportunistic microorganisms, thus reducing the quality of life of the irradiated patients [5,6]. In addition, severe mucositis may require a premature complete or partial interruption of radiotherapy, increasing the risk of tumor cell proliferation and making it difficult to control the cancer [7].

Despite the efforts, researchers have difficulty in classifying methods for the prevention of mucositis. Treatment can be symptomatic or palliative: topical anaesthetics, anti-inflammatories and systemic analgesic drugs are used to relieve discomfort, and antimicrobial agents are administered to prevent infections. There has been no consensus on any substance or method, in terms of efficacy and safety, for the control of acute oral toxicity [8,9].

The extract of chamomile flowers (*Matricaria recutita* Linn) has been widely used in traditional medicine owing to its important therapeutic properties. *In vitro* and *in vivo* studies have demonstrated its antioxidant, antimicrobial, anti-inflammatory, hypocolesteremic, antigenotoxic and antiplatelet aggregation activity. This medicinal plant has been used to treat mucositis in radiation- and chemo-induced patients in order to provide relief and comfort, and has often helped to avoid the interruption of the antineoplastic treatment [5,10].

In light of these findings and because there are hardly any reports in the literature, the objective of this study was to evaluate the effectiveness of chamomile in the prevention and control of oral changes resulting from anticancer treatments, in order to provide a better quality of life for patients with head and neck cancer.

Methods

This study was conducted in accordance with the Declaration of Helsinki in 1975, which was revised in 1983 [11] and approved by the Research Ethics Committee at the University. A written informed consent was obtained from all participants enrolled in our research.

A clinical, single-blinded trial was carried out with intensive direct observation of patients diagnosed with head and neck malignant neoplasms. The patients underwent treatment in the period between May 2010 and May 2011 in the stomatology department at Dr. Napoleão Laureano Hospital (a reference unit for cancer treatment – located in the city of João Pessoa, PB, Brazil) and in the radiotherapy department at Dr. Ulisses Pinto Oncology Center of the Paraíba Charitable Foundation – FAP (in the city of Campina Grande, PB, Brazil). The sample consisted of 28 patients of both genders, over 18 years of age, who underwent external radiotherapy for the treatment of head and neck (except the larynx) malignant neoplasms, with an exclusive or concurrent indication of chemotherapy. At least, half of the mucosal area of the oral cavity had to be exposed to the irradiation and received a Karnofsky Performance Status (KSP)> 70 [12].

Prior to the execution of this study, the patients' oral health was assessed by an intraoral examination, using the Lockhart and Clark's criteria [13] to verify the presence of caries, periodontal health status, oral hygiene and use (or not) of prostheses (Table 1). A panoramic radiograph was requested to assess dental condition, following the protocol of care proposed by the hospitals.

Table 1. Grading of Mucositis.

Grade	Changes
0	No change
1	Erythema, asymptomatic lesions
2	Erythema, ulcers, pain and ability to take solid food
3	Erythema, ulcers, severe pain and only liquid nutrition
4	Confluent ulcers, severe pain and patients with enteral or parenteral support

The subjects included in our study were divided into three groups: Group I (experimental), seven patients treated with 3% chamomile gel (Dilecta Compounding Pharmacy) during radiotherapy; Group II (positive control), seven patients treated with 1% chlorhexidine gluconate gel (Dilecta© Compounding Pharmacy) from the onset of mucositis until one week after regression of symptoms, or until the end of treatment; and Group III (experimental), eight patients treated with 3% Chamomile gel from the onset of mucositis until one week after regression of symptoms, or until the end of treatment.

Extra and intraoral physical examinations were carried out weekly during the entire period on which the patient had

been irradiated until a week after the treatment. During these examinations, the onset and grading of oral mucositis were assessed, taking into account the World Health Organization (WHO) criteria for acute toxicity, which are adopted by various institutions, including those taking part in our study [14].

The data were analyzed with SPSS (Statistical Package for Social Sciences) for Windows, version 15.0 using descriptive and inferential statistics. For the descriptive procedures, frequencies and percentages, measures of central tendency (mean and median) and variability (standard deviation and amplitude) were presented. The procedures of statistical inference were performed using the Kruskal-Wallis test, which estimates whether there are differences between groups.

Results

The sample consisted of 68.2% (n=15) males and 31.8% (n=7) females, with a mean age of 65.9 years (median=70.0, SD=15.2), ranging from 18 to 86 years. Most of the sample (63.6%/n=14) were non-Caucasians, with 81.8% (n=18) retired; 9.1% (n=2) farmers; 4.55% (n=1) public servants; and 4.55% (n=1) students.

Regarding the patient's systemic health, 68.18% (n=15) had a Karnofsky Functional Performance (KFP) of 90 (normal, with minor complaints) and 31.82 (n=7) had a KFP of 80 (normal, some symptoms) at the time of initial clinical examination (Table 2).

Table 2. Distribution of patients regarding the Karnofsky Functional Performance employed – João Pessoa and Campina Grande/PB – 2010-2011.

Karnofsky	n	%
90	15	68.18
80	7	31.82
Total	22	100.00

Regarding the stomatological profile of the patients, 45.45% (n=10) were edentulous; 18.2% (n=4) were caries-free; 4.55% (n=1) had discrete caries lesions; 22.7 % (n=5) had apparent caries lesions, and 9.1% (n=2) had extensive widespread caries lesions. The majority (72.7%, n=16) did not wear prosthesis. Regarding oral hygiene, 13.6% (n=3) had good hygiene (little biofilm and no calculus); 18.2% (n=4) had regular hygiene (moderate biofilm and visible calculus); 22.7% (n=5) had poor oral hygiene, and the others were edentulous. With respect to the patients' periodontal statuses, one subject had clinically healthy gingiva, six had gingivitis and five had significant bone loss.

As for the location of the tumor, the tongue was the most common site of the primary lesion (36.3%, n=8), followed by the floor of the mouth (18.2%, n=4) and hard palate (18.2%, n=4).

Most of the sample (95.45%) developed mucositis during radiotherapy; this fact indicates that, in most patients, mucositis occurred after a dose of 2160 cGy, which corresponds on average to 12 sessions of radiotherapy.

In group I, the patients used chamomile gel since the beginning of radiotherapy, so they were evaluated as soon as the treatment started, as shown in Figure 1. Most individuals in this group developed mucositis grades 1, 2 and 3. In groups II and III, the evaluation of the mucositis grading was carried out after its onset.

As a way to estimate the prophylactic action of chamomile gel at inhibiting mucositis, group I (which received the substance during the treatment) was compared by means of the Kruskal-Wallis test with groups II and III, regarding the onset of this complication during the anticancer treatment and dose accumulated of radiotherapy. The results showed no significant difference between groups (P=0.330), as expressed in Table 3.

Table 3. Comparison between the groups control and experimental concerning the onset of mucositis – João Pessoa and Campina Grande/PB – 2010-2011.

Groups	M dose (SD) Kruskall-Wallis	
I	2143.33 cGy (331.16)	
II	2531.43 cGy (615.56)	$\chi^2 = 2.215$ $P = 0.330$
III	2090.00 cGy (412.38)	

Group I		Weeks of Treatment									
		1 st *	2 nd	3 rd	4 th	5 th	6.	7.	8.	9.	> 10%
Patients	A	WHO 0	WHO 0	WHO 2	A WHO	WHO 0	WHO 0				
	2	WHO 0	WHO 0	WHO 3	WHO 3	WHO 3	WHO 2	WHO 0			
	3	WHO 0	WHO 2	WHO 2	WHO 2	WHO 3	WHO 3	WHO 3	WHO 3		
	4	WHO 0	WHO 3	WHO 3	WHO 2	A WHO	A WHO	WHO 0			
	5	WHO 0	WHO 0	WHO 0	WHO 0	WHO 0					
	6	WHO 0	WHO 3	WHO 2	WHO 2	A WHO	A WHO				

Fig. 1. Distribution of patients in Group I (experimental) and clinical evaluation during treatment with the use of chamomile.

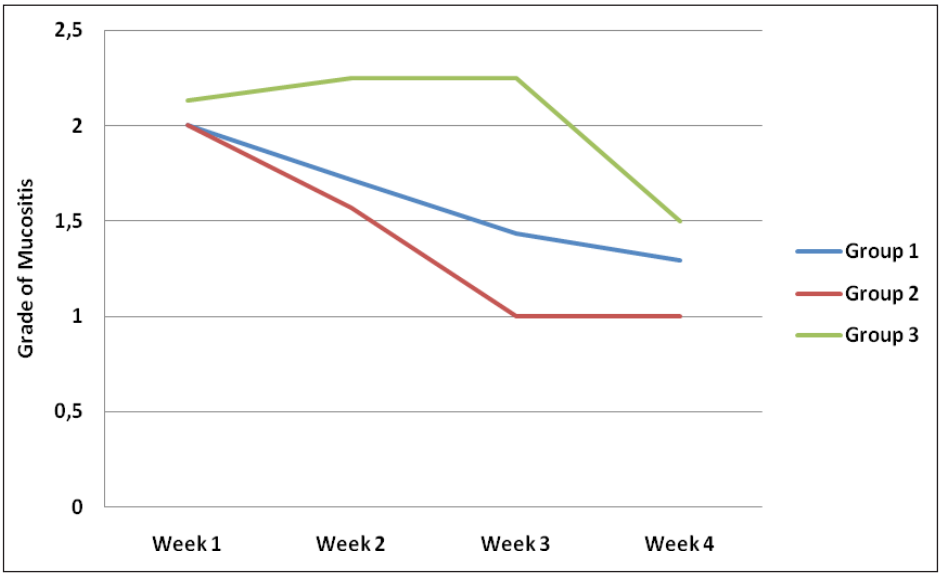

Fig. 2. Mucositis healing in the control and experimental groups.

In order to evaluate the repair of mucositis in response to the substances used in the study, the mucositis grading was compared between the three groups using the Kruskal-Wallis test. The findings showed no statistically significant difference between groups at any time of the evaluation course: 1st week (χ^2=0.054, *P*=0.973); 2nd week (χ^2=1.635, *P*=0.442); 3rd week (χ^2=4.526, *P*=0.104); and 4th week (χ^2=0.727, *P*=0.695). However, the descriptive data (Fig. 2) indicated that group III had the highest mucositis grading at all times evaluated. Group I had intermediate degrees of mucositis, and group II had the lowest degree, which suggests that there was a protective effect of the chlorhexidine gluconate.

Discussion

In our study, the majority of participants were male, which was also observed by Lima et al. [15]. However, a study by Weijers et al. [16] evaluating the epidemiological profile of patients with head and neck cancer in the Netherlands between the years 1980-1984 and 2000-2004, noted that the proportion of affected men over women declined from a 1:8 ratio to 1:2. The authors believed that the increase in the number of female smokers may be related to the decline in the proportion.

Regarding age, the patients who participated in the survey had an average age of 65.9 years, with most of them over 60 years. This profile is similar to that found by Lima et al. and Weijers et al. [15,16]. However, it differs from the data obtained by Suresh et al. [17], who observed a mean age of 34 years. Yet, that study was conducted in India and according to the author it is consistent with national trends.

There was a predominance of non-Caucasians in our study. This finding disagrees with the data obtained by Durazzo et al. [18], who found a prevalence of 80.6% of Caucasian patients with head and neck cancer. Such disagreement can probably be explained by differences in the prevalence of races across the country.

With regard to the anatomical site, the tongue was the most prevalent site of occurrence of malignancies; this corroborates with reports in the literature [16,18].

Some of the factors that may influence the onset of mucositis are: anatomical site; patient's general health; nutritional status; oral hygiene; presence of comorbidities; age and individual susceptibility [17]. In this study, there was no association between patients' oral hygiene with the onset and grading of mucositis. Nevertheless, it is worth noting that a large proportion of the participants were edentulous and this may have been a factor that influenced the correlation between oral health and mucositis.

Mucositis is the most prevalent side effect of the anticancer treatment, accounting for more than 90% of patients receiving radiotherapy to treat head and neck tumors [8,19]. This percent was observed in this study, and the onset was established at doses ranging from 14.4 Gy (Gray) and 36 Gy. In the majority (14 patients) of cases, it started from 21.6 Gy, confirming some reports in the literature [5,20,21].

The modification of the oral microbiota, particularly bacterial-induced radiation, is an important factor for the development of infections. This has also been implicated in the development of mucositis. Hence, an antiseptic such as chlorhexidine can help prevent these conditions and lessen the intensity of clinical oral mucositis. Some studies have reported its efficacy against this complication of the anticancer treatment [22,23], and that its antimicrobial effect would be primarily responsible for the decrease in the mucositis grading. The findings of our study corroborate with such statement, because the patients who used this medication showed less severe and lower mucositis grades over the course of radiotherapy, as well as stabilization of symptomatology in a considerably small time compared to the experimental groups.

The effectiveness of chamomile for the treatment and relief of oral mucositis symptoms in patients undergoing anticancer treatment has been reported in the literature [24]. The effect of topical chamomile in the treatment of oral mucositis induced by 5-fluoracil (5-FU) in hamsters was investigated, and results showed that the group treated with chamomile exhibited a lesser degree of mucositis throughout the evaluation period in comparison to the control and corticoid groups [25]. The anti-inflammatory, antimicrobial and healing activities of this plant can be directly linked to the therapeutic action of chamomile face to the mucositis lesions due to the presence of essential oils, rich in azulene, Matricine, α-bisabolol and a large concentration of flavonoids and other phenolic constituents present in chamomile [26].

Patients who used the chamomile gel after the onset of mucositis reported a reduced discomfort thereafter. In addition, the examiner noted a reduction in the severity of signs. These findings highlight the anti-inflammatory properties of this medicinal plant. However, data from this study do not allow estimating a prophylactic action of chamomile on mucositis. The variation in the mean radiation dose applied for the three groups of patients did not show significant differences, since the patients were given equivalent doses for the emergence of mucositis. The standard deviation of the first group showed a lower variability comparing the three groups, suggesting that there is less variation in response to this substance. Also, it is important to point out that only one patient from group I did not have mucositis at any time of radiotherapy.

Within the shortcomings of this study, it may be concluded that the 3% chamomile gel showed anti-inflammatory efficacy on oral mucositis, reducing discomfort and severity of the signs and symptoms of this complication during the anticancer treatment.

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