

Evaluation of the Impact of Oral Hygiene and Chamomile Tea in the Development of Oral Mucositis: Pilot Study

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Avaliação do Impacto da Higiene Oral Associada ao Uso do Chá de Camomila no Desenvolvimento de Mucosite Oral: Estudo-Piloto

Evaluación del Impacto de la Higiene Oral y el Té de Manzanilla en el Desarrollo de la Mucositis Oral: Estudio Piloto

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Abstract

Introduction: The oral mucositis (OM) represents a frequent inflammatory condition in cancer patients, and poor oral hygiene has been related as a predisposing factor for its onset. Chamomile tea has been studied as an adjunctive therapy in the management of OM due to its analgesic and anti-inflammatory properties. **Objective:** The objective of this study was to evaluate the influence of chamomile tea associated with a rigorous oral hygiene in the OM prevention. **Method:** Randomized pilot clinical study, with 35 patients assigned to two groups. The case-group underwent oral hygiene control associated with the use of chamomile tea before starting the first cycle of chemotherapy, while the control group, there were no previous guidelines and prescriptions. Data about sociodemographic characteristics, the type of neoplasm and the chemotherapy scheme proposed were collected. The variables OM, salivary flow and pain associated to the oral cavity were evaluated, and statistical analysis was performed with significance level $p < 0.05$. **Results:** It was observed that the majority of the patients had a mean age of 50 years, breast (57%) was the most prevalent tumor site and cyclophosphamide (52%), the most frequently used drug in this sample, no statistically significant result was observed in the two groups for OM, salivary flow and pain variables ($p > 0.05$). **Conclusion:** These data suggest that the use of chamomile tea and the accuracy of oral hygiene were not sufficient to prevent OM. **Key words:** Stomatitis; Chamomile; Plants, Medicinal; Oral Hygiene; Neoplasms.

Resumo

Introdução: A mucosite oral (MO) representa uma condição inflamatória frequente em pacientes oncológicos e uma higiene oral insatisfatória tem sido relacionada como fator predisponente para o seu surgimento. O chá de camomila vem sendo estudado como terapia adjuvante no manejo da MO em razão das suas propriedades analgésicas e anti-inflamatórias. **Objetivo:** Avaliar a influência do chá de camomila associada a uma rigorosa higiene oral na prevenção de MO. **Método:** Trata-se de um estudo-piloto clínico randomizado, no qual 35 pacientes foram alocados em dois grupos. O grupo-caso foi submetido ao controle de higiene oral associado ao uso do chá de camomila antes de iniciar o primeiro ciclo de quimioterapia; no grupo-controle, não houve orientações e prescrições prévias. Foram coletados dados referentes às características sociodemográficas, à neoplasia em questão e ao tipo de tratamento quimioterápico proposto. Foram avaliadas as variáveis MO, fluxo salivar e dor associada à cavidade oral, e realizada análise estatística com nível de significância $p < 0,05$. **Resultados:** Observou-se que a maioria dos pacientes apresentava-se na quinta década de vida, a localização do tumor mais prevalente foi a mama (57%) e a droga mais utilizada por esses pacientes foi a ciclofosfamida (52%). Nesta amostra, não foi observado resultado estatisticamente significativo entre os grupos, no que diz respeito às variáveis MO, fluxo salivar e dor ($p > 0,05$). **Conclusão:** Os dados sugerem que o uso do chá de camomila e o rigor na higiene oral não foram suficientes para a prevenção da MO.

Palavras-chave: Estomatite; Camomila; Plantas Medicinais; Higiene Bucal; Neoplasias.

Resumen

Introducción: La mucositis oral (MO) representa una afección inflamatoria frecuente en pacientes con cáncer, y la mala higiene bucal se ha relacionado como un factor predisponente para su aparición. El té de manzanilla se ha estudiado como una terapia adjuvante en el tratamiento de la OM debido a sus propiedades analgésicas y antiinflamatorias. **Objetivo:** El objetivo de este estudio fue evaluar la influencia del té de manzanilla asociado con una higiene oral rigurosa en la prevención de la MO. **Método:** Fue un estudio clínico piloto aleatorizado, en el que treinta y cinco pacientes fueron asignados en dos grupos. El grupo de casos se sometió a un control de higiene oral asociado con el uso de té de manzanilla antes de comenzar el primer ciclo de quimioterapia, mientras que en el grupo de control, no había pautas ni recetas previas. Se recopilaban datos sobre las características sociodemográficas, el tipo de neoplasia y el esquema de quimioterapia propuesto. Se evaluaron las variables MO, flujo salival y dolor asociado a la cavidad oral, y se realizó un análisis estadístico con nivel de significancia $p < 0,05$. **Resultados:** Se observó que la mayoría de los pacientes tenían una edad media de 50 años, el sitio del tumor más prevalente era la mama (57%) y el fármaco utilizado con mayor frecuencia era la ciclofosfamida (52%). En esta muestra, no se observaron resultados estadísticamente significativos entre los grupos con respecto a las variables MO, flujo salival y dolor ($p > 0,05$). **Conclusión:** Estos datos sugieren que el uso de té de manzanilla y la precisión de la higiene oral no fueron suficientes para prevenir la MO.

Palabras clave: Estomatitis; Manzanilla; Plantas Medicinales; Higiene Bucal; Neoplasias.

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Supporting information: The data that support the findings of this study are openly available in Mendeley Data at <https://data.mendeley.com/datasets/gwbj34yjc/1>. [reference doi: 10.17632/gwbj34yjc.1]



INTRODUCTION

Cancer is the second leading cause of death for diseases worldwide, and about 70% of cancer patients will receive anti-neoplastic chemotherapy during treatment¹. Chemotherapy works on cells that have high mitotic activity but its action is not exclusive in tumor cells. It also affects normal labile cells, as oral mucosa keratinocytes, which can lead to undesirable side effects such as oral mucositis and opportunistic infections².

The term oral mucositis (OM) emerged in the late 1980s to describe chemo and/or radiotherapy-induced oral mucosal inflammation in the head and neck region³. Its onset occurs in average up to the second week after administration of the antineoplastic drugs⁴. The OM results from the direct or indirect action of cytotoxic drugs, and its characteristics are inflammation and ulceration of the mucosa. It becomes swollen, erythematous and friable, resulting in pain, discomfort, dysphagia and systemic weakness¹. Evidence of dehydration, malnutrition and oral hygiene deficiency has been commonly associated with the OM⁵⁻⁷. The more severe grades of this condition may compromise oncologic therapy, with reduced chemotherapy dosage and/or change in the treatment plan. In more severe cases, treatment may be discontinued and directly affect patient survival⁷.

Usually, these lesions develop on the floor of the mouth, lip mucosa, lateral border of the tongue, buccal mucosa and soft palate⁸. Intense pain interferes with the patients' feeding, which may lead to the need for parenteral/enteral nutrition or even discontinuation of oncological treatment, as already mentioned⁹. In addition, mucosal ulcers serve as gateways for microorganisms, which may promote bacteremia, sepsis, and increased systemic infections¹⁰.

Oral keratinocytes undergo rapid cell renewal, usually every 7 to 14 days, which makes these cells susceptible to the cytotoxic therapy's effects^{11,12}. Both chemotherapy and radiotherapy can interfere with epithelial cell maturation and growth and induce changes in their life cycle¹³.

There are studies that describe the use of chamomile tea, laser therapy and mouthwash associated with oral hygiene instructions as palliative care used in the OM approach¹⁴⁻¹⁶. Also known as *Matricaria recutita*, chamomile has been studied because of its medicinal properties, and used as an adjunct to the prevention of OM due to its analgesic and anti-inflammatory effect, as it is capable of inhibiting the production of cyclooxygenase-2¹⁴. It is recommended that the patient uses the frozen chamomile tea, thus combining its anti-inflammatory effect with cryotherapy. This, in turn, promotes vasoconstriction and thus decreases blood flow in the oral cavity¹⁷. Basic oral hygiene as a protocol for the prevention of OM in cancer patients has also been the

object of study in the literature, because its efficacy in the prevention of this condition is already well established, as it reduces the patients' morbidity¹⁸.

The present study aims to evaluate the impact of the adoption of oral hygiene instructions associated with the utilization of chamomile tea in patients with solid malignancies submitted to chemotherapeutic agents known as cytotoxic agents.

METHOD

The study was submitted to the Institutional Review Board of Irmã Dulce's Social Works and approved with the protocol number CAAE no. 46909315.1.0000.0047. All patients were informed about the proposal and the purpose of the treatment, as well as the possible risks and benefits of the study, and signed the Informed Consent Form, where they stated that they understood the purpose of the study and the proposed treatment, pursuant to Resolution 466/12 of the National Health Council (Brazil). All procedures performed in studies involving human participants comply with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This was a pilot randomized clinical study whose population sample included patients with solid malignancies who had not yet begun chemotherapy treatment, through open demand, from the High Complexity Oncology Unit in Irmã Dulce's Social Works (OSID).

Participants were individuals with a minimum age of eighteen years at the beginning of the treatment who had not initiated the first cycle of chemotherapy, with average monthly income of R\$ 1,000.00 reais and level of education between the 1st and 2nd grades. Patients with any type of malignant tumor were included in the study, provided they used known cytotoxic drugs, namely: Capecitabine, Carboplatin, Cyclophosphamide, Cisplatin, Docetaxel, Doxorubicin, Fluorouracil, Oxaliplatin and Paclitaxel.

Patients with diabetes mellitus, immunologically mediated disease and systemic arterial hypertension were not included in the study.

The charts were the source to obtain data about the location of the neoplasm, the proposed treatment, the type of drug, the dose and the number of sessions the patients underwent. A questionnaire (attached) collected the socio-economic and cultural profile of the population: age, sex, systemic condition and socioeconomic situation.

In addition, an intraoral physical examination with artificial light and wooden spatula was performed, examining the entire oral cavity to determine possible oral alterations, especially mucositis.

Patients were assigned to two study groups, according to their chart number, where the even medical record was from the case group and the odd record from the control group. The control group consisted of individuals enrolled according to the criteria of inclusion and exclusion of the study, who did not receive oral hygiene orientation and did not use chamomile tea. The case group included a population with the same profile outlined in the control group, but this group did neither undergo a strict control of oral hygiene or used the cold chamomile tea. Chamomile tea was prescribed four times a day, in the form of a mouthwash, for 1 minute, and patients were guided not to swallow it. The patient was advised to maintain the tea refrigerated at a standard temperature of 15-17° C. There was no determination as to the brand of choice, it was only required to use options available in sachet form, and the preparation should follow the manufacturer's guidelines. For oral hygiene, the patient was instructed to brush 3 times a day (after the main meals) and to use a new dental brush when starting chemotherapy, with soft and uniform bristles and low abrasive toothpaste.

To register the appearance of the first lesions, the participants attended the Dental Service for weekly evaluations until the 14th day after the first cycle of chemotherapy, since this period presents a higher risk for the development of OM. In cases of OM, the evolution of tissue repair was compared using standardized photographic records, based in the reference scale of the mucositis World Health Organization¹⁹.

The saliva of the patients participating in this study was collected to determine the salivary flow on the 1st day of chemotherapy, in addition to the 7th and 14th days after starting the chemotherapy treatment. Patients were instructed to chew a 4cm² portion of parafilm (Bemis NA, Wisconsin, USA) during a 5-minute period, expelling saliva produced in a Becker graduated glass. Salivary flow values lower than 0.2 mL of saliva/minute were considered as salivary hypofunction, according to the study of Eisbruch et al.²⁰.

Information about the variables analyzed was saved in a standard Excel spreadsheet. After obtaining the data, it was performed the normality test. The non-parametric Friedman test was used to compare different study periods and the Mann-Whitney test to compare the groups and the Fisher's exact test for proportions comparisons. The level of significance was set at $p < 0.05$.

RESULTS

Thirty-five patients participated in this study, among which 21 were in the case group and 14 in the control group. Table 1 shows the sociodemographic data of the sample as well as the main locations of the neoplasms. The

median age was similar for both groups and most patients were in the fifth decade of life. There were more smokers and alcoholics in the control group, but this difference was not statistically significant ($p > 0.05$). About 57.1% of the participants presented breast cancer diagnosis in the two groups studied. Ovarian and colon cancer were the next most prevalent types.

Table 1. Socio-demographic characteristics of the study population, OSID, Salvador, Bahia, Brazil, 2019

Variables	Case		Control		p-value
	n	%	n	%	
Age (years)					
Median	59	52.0-	58	48.3-	0.606
(q1-q3)		68.0		66.5	
Smokers	7	33.3	3	21.4	0.704
Alcoholics	13	61.9	9	64.3	0.886
Location					0.249
Breast	12	57.1	8	57.1	
Ovarian	3	14.3	-	-	
Colon	2	9.5	1	7.1	
Pancreas	1	4.8	-	-	
Uterus	1	4.8	-	-	
Prostate	1	4.8	-	-	
Lung	1	4.8	-	-	
Testicle	-	-	1	7.1	
Uterine Lap	-	-	2	14.3	
Rectum	-	-	1	7.1	
Esophagus	-	-	1	7.1	

Fisher exact test; Mann-Whitney test. $p < 0.05$.

The most commonly used antineoplastic drug in both groups was cyclophosphamide (52.4% in the case group and 50.0% in the control group), followed by carboplatin (14.3% in each group) and fluorouracil (9.5% in the case group and 14.3% in the control group); there was no statistical significance in the distribution of chemotherapy types among the groups ($p > 0.05$); (Table 2).

Table 3 shows the variables OM and salivary flow throughout the study period. There was no statistically significant difference between the groups about the development of OM and reduction of salivary flow over time ($p > 0.05$). Both groups presented a mean of high salivary flow during the three analyzed periods, and were not classified as salivary hypofunction. However, three patients developed OM in the control group on the 14th day of analysis (21.42%), whereas in the treatment group, no signs of this inflammatory condition were evident in any of the analyzed periods.

Table 2. Profile of antineoplastic drugs used in patients' chemotherapy protocol, OSID, Salvador, Bahia, Brazil, 2019

Variables	Case		Control		p-value
	n	%	n	%	
Antineoplastic drug					0.983
Cyclophosphamide	11	52.4	7	50.0	
Carboplatin	3	14.3	2	14.3	
Fluorouracil	2	9.5	2	14.3	
Cisplatin	2	9.5	2	14.3	
Capecitabine	1	4.8	-	-	
Paclitaxel	1	4.8	-	-	
Docetaxel	1	4.8	-	-	
Oxaliplatin	-	-	1	7.1	

Fisher exact test; Mann-Whitney test. $p < 0.05$.

DISCUSSION

In Brazil, an estimated 600.000 new cases of cancer per year are anticipated for 2018-2019²¹. In this study, a high prevalence of cancer diagnosis was observed at the end of the fifth decade of life, which corroborates other studies where the mean age of patients was between the fifth and sixth decade of life^{22,23,12}. It was found that breast cancer was the most frequent type of neoplasm in the sample studied. This data ratifies the estimate of the National Cancer Institute José Alencar Gomes da Silva²¹ that predicts breast cancers the most prevalent form of neoplasm in Brazil, excluding non-melanoma skin cancers²¹.

Colon cancer was the second most common type in the study population and was described as one of the most prevalent types in the world population, the third most malignant type of cancer in the United States²⁴, and is classified among the six most prevalent types of cancer in Brazil²⁵. Some studies have shown that this high index can be attributed to lifestyle changes in large cities, where people exercise less, have a diet rich in fat, are more obese,

and tobacco and alcohol consumption is also higher²⁵.

There are many chemotherapeutic protocols that are used for the treatment of solid malignant tumors. It is known that not all chemotherapeutic agents are equally stomatotoxic or cause the same effects on oral tissues to the point of inducing OM. The development of OM depends on the immunological response of each patient, as well as factors related to cancer therapy, such as number of sessions, association of different drugs, among other variables². In the present study, cytotoxic drugs for the oral cavity were selected because they increase the predisposition to the development of mucositis as described at Curra et al.². However, it is important to point out that the groups differed in some types of chemotherapy agents as well as in tumor classification, and these aspects should be considered as limitations of the present study. In fact, our results have to be analyzed with caution since the sample size was small, considering the fact that this research was presented as a pilot study.

Patients with head and neck neoplasms, according to reports, are more susceptible to the development of OM than those with solid tumors at other sites¹⁵. This may be related to the protocol of cancer treatment that advocates the association of radio to chemotherapy. In addition, some drugs known to be stomatotoxic are widely used in the therapeutic approach of this type of cancer, which may induce clinical manifestations of severe hyposalivation. According to Sasada et al.¹⁶, there seems to be a positive relation between the reduction of salivary flow and the development of OM. For this reason, the relation between these two variables was investigated in the present study. However, statistical analysis did not show a significant relation between them ($p > 0.05$).

The chemotherapy drugs most associated with the development of OM reported in the literature are Fluorouracil (5-FU), Cyclophosphamide and Cisplatin²⁶. In a study conducted by Curra et al.², it was shown that administration of 5-FU and other derivatives of platinum

Table 3. Evolution of OM and salivary flow in the study periods, OSID, Salvador, Bahia, Brazil, 2019

Variables	Group	Evolution of the period			p-value
		1 st day Md (q1-q3)	7 th day Md (q1-q3)	14 th day Md (q1-q3)	
Oral Mucositis	Case	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000
	Control	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-3.0)	0.050
	p-value	1.000	1.000	0.293	
Salivary flow	Case	1.26(0.64-1.88)	0.88(0.63-1.75)	1.08(0.68-1.72)	0.137
	Control	1.1(0.8-2.270)	1.1(0.76-1.93)	1.0(0.54-2.42)	0.679
	p-value	0.702	0.516	0.727	

Non-parametric Friedman test $p < 0.05$

(cisplatin, carboplatin and oxaliplatin) aggravated the incidence and severity of OM from one cycle to the next². In the present study, no statistically significant result was noticed in the development of mucositis for both groups. It is likely that the sample size interfered with this result. However, even in the case of a pilot study with a small number of patients, the development of OM was observed only in the control group that did not receive instructions about their oral hygiene and the use of chamomile. Additionally, according to Sonis¹³, patients who undergo the first cycle of chemotherapy have a low probability of developing OM (about 20%), which may also justify the result observed in the present study, since the development of this condition was observed in 21.42% of patients who were not submitted to preventive measures.

Recently, the literature has strongly emphasized the analysis of the effectiveness of palliative care in reducing the oral cavity side effects derived from antineoplastic therapy¹⁴⁻¹⁶. This care, which consists of a strict oral hygiene control by the dental surgeon, who integrates the multidisciplinary health team, has been described and so was the use of chamomile tea. Braga et al.⁵ carried out a study with 40 patients divided in two groups, where the group that used 1% chamomile tea mouthwash associated with the oral hygiene instruction presented a reduction in the incidence of OM of 30% compared to 90% of the control group⁵. In an earlier study developed by Fidler et al.²⁷, with 164 patients assigned to two groups, where one was submitted to daily mouthwash with chamomile tea, and the other to a placebo saline solution, there were no sign of OM in any of the patients. Thus, the authors did not find statistically significant differences between the groups studied, in which the patients performed mouthwashes three times a day during fourteen days. In the present study, a similar result was found, although three patients in the control group had OM. There is still no consensus in the literature about the use of chamomile tea, so further studies are needed to establish its therapeutic potential in this target population. In particular, the concentration of the active principle and the different trademarks are relevant variables that should be considered.

A study by Vanlancker et al.⁶ on oral hygiene showed that both the number of bacterial cells and their composition interfere with the epithelial healing in OM. Another study evaluated the healing of wounds *in vitro* with different types of keratinocytes with and without the presence of the oral microbiota and confirmed that when it was present, there was a reduction in epithelial healing capacity²⁸. The guidelines of clinical practice for patients with mucositis recommended by the Multinational Association of Supportive Care in Cancer

and International Society of Oral Oncology (MASCC/ISOO)²⁹, include oral hygiene as a preventive method to avoid OM. Patients were also advised to brush with soft (infant) bristles to avoid trauma to the oral tissue. In a study by Djuric et al.³⁰, a group of 34 patients admitted to the hospital for induction remission therapy for acute leukemia were divided in two groups. One group underwent adjustment of the mouth area before starting the chemotherapy treatment, through teeth scaling and root planning, restorations of decayed teeth or with poor restorations, and adaptation of removable prostheses. Soft-bristled brushes and guidelines on how to perform oral hygiene were also provided. The control group did not receive pre-chemotherapy dental care, nor did oral hygiene instructions during treatment. There was no statistically significant result in this study, but the group receiving dental treatment developed less severe and less painful oral complications compared to the control group. These data showed that a dental adequacy prior to and during treatment initiation may be beneficial to patients.

Low-power laser therapy is another adjuvant treatment for OM that has been effective and is gaining prominence. When applied to soft tissue, the laser energy is transformed into heat and photochemical, photophysical, and photobiological effects⁹. Antunes et al.⁷ and Antunes et al.³¹ reported satisfactory results with the use of a prophylactic laser^{7,31}, pain relief⁷ and survival improvement in patients submitted to chemoradiotherapy in the head and neck region³¹, which can contribute to the reduction of treatment costs and possible hospitalization of the patient.

This type of study strengthens the need to include a dental surgeon in the multidisciplinary team in the highly complex units. The participation of this professional would be a great gain for both group of patients and the health service. Simple and low-cost preventive measures that are able to grant a better quality of life to cancer patients during treatment, and consequently reduce complications that would generate a higher hospital cost, are fundamental for the improvement of the clinical condition of this population.

CONCLUSION

In the present study, no statistically significant differences were observed between the group that received oral hygiene guidelines and used chamomile tea in relation to the group that did not undergo this approach. However, the introduction of preventive treatments such as the use of chamomile tea associated with cryotherapy and regular oral hygiene instructions is a simple, low-cost, preventive approach. This has been the objective of a recent research and needs to be better studied in order to facilitate the

establishment of protocols to control the disorders of the stomatognathic system in the population of individuals submitted to chemotherapy.

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CONFLICT OF INTEREST

We have no conflict of interest to declare.

AUTHOR'S CONTRIBUTION

The authors contributed equally in all the study phases and approved the final version to be published.

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