Prevention of Oral Mucositis in Patients undergoing Chemotherapy

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Prevenção da Mucosite Oral em Pacientes submetidos à Quimioterapia

Prevención de la Mucositis Oral en Pacientes sometidos a la Quimioterapia

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Abstract

Introduction: The chemotherapy is one of the cancer possible treatments and use chemotherapeutic drugs as 5-fluorouracil (5-FU), major cause of oral mucositis. This complication is the most common cause of pain. There is still no specific protocol for the prevention of this complication, but there are substances used empirically and palliative. **Objective:** Assessing the degree of mucositis during the 10 days after each chemotherapy cycle using the self-perception of each patient and the pain level reported with the use of the two substances studied: mallow tea and 0,12% chlorhexidine. **Method:** The selected patients were randomly randomized to perform mouthwash with 10 ml of the test substance, 3 times a day, during the infusion time of chemotherapy. In each accompanied cycle one of the studied substances were used. During the 10 days after chemotherapy, patients answered a questionnaire with closed questions about their pain and self-perception of their oral mucosa. **Results:** in cycles where mallow tea was used, self-perception of patients seems to be better with your oral mucositis is grade 1 and 2. However, in cycles where 0,12% chlorhexidine was used, patients experienced less pain. **Conclusion:** In both cycles that was used at 0.12% chlorhexidine was used as those where the mauve tea, most of the patients reported oral mucositis present. However, when used mauve tea was obtained mucositis in minor degrees. The 0.12% chlorhexidine it appeared to have less pain symptoms, although the difference was small when compared to the two substances.

Key words: Mucositis; Prevention & control; Chlorhexidine; Malva.

Resumo

Introdução: A quimioterapia é uma das formas de tratar o câncer, na qual utilizam-se drogas como o 5-fluorouracil (5-FU), maior causador da mucosite oral. Essa complicação é a causa mais comum de dor. **Objetivo.** Avaliar o grau de mucosite oral durante os dez dias após cada ciclo de quimioterapia, segundo a autopercepção de cada paciente e o nível de dor relatada com o uso das duas substâncias estudo: chá de malva e clorexidina 0,12%. **Método.** Os pacientes foram randomizados por sorteio para a realização de bochechos com 10 ml da substância determinada, três vezes ao dia, durante o período de infusão da quimioterapia. Em cada ciclo, utilizou-se uma das substâncias. Durante os dez dias após a quimioterapia, os pacientes responderam a um questionário com perguntas fechadas sobre a sua dor e a autopercepção da sua mucosa oral. **Resultados.** Nos ciclos utilizando o chá de malva, a autopercepção do paciente pareceu ser melhor, com sua mucosite oral sendo de graus 1 e 2. Contudo, nos ciclos utilizando clorexidina 0,12%, os pacientes apresentaram menos dor. **Conclusão.** Tanto nos ciclos em que foi utilizado a clorexidina 0,12% quanto naqueles onde foi utilizado o chá de malva, a maioria dos pacientes referiu apresentar mucosite oral. Porém, quando utilizado o chá de malva, a frequência de mucosite foi em menores graus. A clorexidina 0,12% pareceu apresentar menos sintomatologia dolorosa, apesar da diferença, comparando as duas substâncias, ter sido pequena.

Palavras-chave: Mucosite; Prevenção & Controle; Clorexidina; Malva.

Resumen

Introducción: La quimioterapia es una forma de tratamiento de cáncer y se utilizan drogas como el 5-fluorouracilo (5-FU), mayor causante de la mucositis oral. Aún no hay un protocolo específico para la prevención de esta complicación. **Objetivo:** Evaluar el grado de mucositis oral durante los 10 días después de cada ciclo de quimioterapia según la auto-percepción de cada paciente y el nivel de dolor relatado con el uso de las dos sustancias estudio: té de malva y clorexidina 0,12%. **Método:** Los pacientes fueron aleatorizados por sorteo para la realización de enjuague con 10ml de la sustancia determinada, 3 veces al día, durante el período de infusión de la quimioterapia. En cada ciclo se utilizó una de las sustancias. Durante los 10 días después de la quimioterapia los pacientes respondieron a un cuestionario con preguntas cerradas sobre su dolor y la autopercepción de su mucosa oral. **Resultados:** En los ciclos utilizando el té de malva la auto-percepción del paciente pareció ser mejor, con su mucositis oral siendo de grado 1 y 2. En los ciclos utilizando clorexidina 0,12% los pacientes presentaron menos dolor. **Conclusión:** Tanto en los ciclos en que se utilizó la clorexidina 0,12% como en aquellos donde se utilizó el té de malva, la mayoría de los pacientes refirió presentar mucositis oral. Sin embargo, cuando se utilizó el té de malva la frecuencia de mucositis fue en menores grados. La clorexidina 0,12% pareció presentar menos sintomatología dolorosa, a pesar de la diferencia comparando las dos sustancias haber sido pequeña.

Palabras clave: Mucositis; Prevención & control; Clorhexidina; Malva.

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INTRODUCTION

Cancer is one of the leading diseases affecting people worldwide. One of the treatment modalities is chemotherapy, which uses toxic agents such as 5-fluorouracil (5-FU), one of the drugs that causes the most damage to rapidly proliferating cells such as those of the oral mucosa[1,2].

The patient's pain and severity of the oral mucositis can compromise the chemotherapy dosages and regimen, negatively impacting the patient's prognosis and survival[2,3,4].

Several studies have analyzed chlorhexidine 0.12% as an alternative for the prevention and treatment of oral mucositis, due to its antifungal and antimicrobial properties. These properties have also been identified in herbal substances such as malva tea[5,6,7,8,9]. Once oral mucositis has been diagnosed, the standard treatment is low-level laser therapy[10].

The current study thus aimed to assess the degree of oral mucositis in the ten days following each cycle of chemotherapy, based on the patients' self-rated pain level comparing the two substances.

METHOD

This was a randomized clinical trial in which the patients were not aware of which substance they were using after each cycle.

The study was approved by the Institutional Review Board of Hospital da Cidade de Passo Fundo, Rio Grande do Sul State, Brazil, under case review number 236.127.

Patients were selected by the researchers at the Oncology Service of Hospital da Cidade de Passo Fundo from October 2013 to April 2014.

Inclusion criteria were: patients 18 years or older of both sexes with a diagnosis of cancer, undergoing chemotherapy with four days of infusion of 5-FU, and who agreed to participate by signing a free and informed consent form. Exclusion criteria were: patients undergoing adjuvant radiotherapy, smokers, or consumers of alcohol during treatment.

Patients were randomly selected to receive the first substance. In each cycle they received one of two substances, chlorhexidine 0.12% or malva tea, alternatingly, for prophylaxis of oral mucositis, during the four days of chemotherapy infusion. Randomization used small brown envelopes containing a slip of paper with a circle (blue for chlorhexidine 0.12% and orange for malva tea). After randomization, patients were allocated to receive the first substance. Patients were unaware of the substances they were receiving, except that they were a mouthwash and a tea. The intervention took place in all the chemotherapy cycles. On a daily basis during the chemotherapy infusion, the researchers took vials containing 30 ml of the substance for the mouthwashes, with a small 10 ml cup, to be filled three times a day for the mouthwash, thus totaling 30 ml per day.

All patients were instructed on the procedures: a) mouthwash three times a day (morning, afternoon, and evening) during the chemotherapy infusion period, using 10 ml of the respective substance for 1 minute, after which the material was discarded; b) completion of a diary for ten days after the end of each chemotherapy cycle.

The diary was completed at home and contained closed questions on the patient's level of pain according to a visual analog scale (VAS)[11] and self-rated condition of the oral mucosa, assessed in comparison to color photographs illustrating the degrees of oral mucositis. Patients examined their mucosa and compared it to the photograph that it most resembled. Patients received a new diary at the end of each chemotherapy cycle.

Characterization of the study sample used descriptive statistics and percentages to analyze and compare the variables' frequencies between the groups. Student's t-test was used to compare the outcome variables between the groups. All the analyses used the Bioestat 5.0. statistical package, with significance set at $p \leq 0.05$.

RESULTS

The study sample included seven patients, of whom 85.7% were men, with a mean age of 62.1±13.1 years [48-85], white (85.7%), 50% alcohol consumers, 57.1% non-smokers, and 42.8% former smokers. Among the latter, 28.5% had smoked for more than 15 years. In relation to histological type, 57.1% of the individuals presented adenocarcinoma and 42.8% squamous cell carcinoma, with gastric tumors as the most prevalent site.

The seven patients underwent a total of 18 cycles of chemotherapy each, accompanied by the researchers. All the patients' cycles involved 5-FU infusion associated with cisplatin. Chlorhexidine prophylaxis was used in ten cycles and malva tea in eight, according to the randomization.

As shown in Table 1, no significant differences were seen between the groups in relation to age, duration of smoking habit, and pain level.

As for patients' self-rated degree of oral mucositis, when chlorhexidine 0.12% was used as the mouthwash, the mucositis varied between grades 1 and 2 (Table 2). The highest mean level of self-reported pain was 2.6 on day 7 post-chemotherapy, followed by 2.2 on days 6 and 8 (Table 3).

Table 1. Comparison of age, duration of smoking habit, self-reported pain, and oral mucositis grade on the follow-up days comparing chlorhexidine (n=10) and malva tea (n=8) as prophylaxis

Variable	Group	Mean	Standard deviation	p
Age	Chlorhexidine	63.4	13.0	0.26
	Malva tea	65.8	15.8	
Duration of smoking	Chlorhexidine	2.7	2	0.26
	Malva tea	2.1	1.8	
Pain, Day 1	Chlorhexidine	1	2	1.00
	Malva tea	1	1.2	
Pain, Day 2	Chlorhexidine	1.6	2.5	0.86
	Malva tea	1.4	1.6	
Pain, Day 3	Chlorhexidine	1.6	2.5	0.71
	Malva tea	2	2	
Pain, Day 4	Chlorhexidine	2	3.1	0.86
	Malva tea	2.3	2.8	
Pain, Day 5	Chlorhexidine	1.9	2.8	0.58
	Malva tea	2.8	3.4	
Pain, Day 6	Chlorhexidine	2.2	2.5	0.67
	Malva tea	2.9	3.5	
Pain, Day 7	Chlorhexidine	1.9	3.4	0.70
	Malva tea	2.4	3.3	
Pain, Day 8	Chlorhexidine	2.2	3.3	0.97
	Malva tea	2.3	2.3	
Pain, Day 9	Chlorhexidine	1.8	2.2	0.94
	Malva tea	1.9	2.3	
Pain, Day 10	Chlorhexidine	1.9	2.5	0.93
	Malva tea	2	2.4	
Mean pain	Chlorhexidine	1.6	2.2	0.64
	Malva tea	2.1	2.3	
Mean grade oral mucositis	Chlorhexidine	1.6	0.3	0.76
	Malva tea	1.5	0.7	

For patients using malva tea as the mouthwash, their self-rated oral mucositis varied between grades 1 and 2 on most of the days, in addition to grade 3 in 50% of the patients on day 8 after chemotherapy infusion (Table 2). The highest mean self-reported pain levels were 2.9 on day 6 and 2.8 on day 5 post-chemotherapy (Table 3).

DISCUSSION

Numerous studies have proposed to verify the most effective methods for the prevention and treatment of oral mucositis. There is still no specific protocol for the prevention of this complication, and several substances have been used empirically and palliatively. Such studies are important, since they can potentially lead to a specific and effective protocol for the prevention of oral mucositis[12,13].

One of the most widely cited methods for the prevention and treatment of oral mucositis is chlorhexidine digluconate 0.12%, used as a mouthwash[5,14]. Chlorhexidine was thus included in the current study due to its antifungal, antimicrobial, and anti-inflammatory properties[6,7,8].

In addition to chlorhexidine 0.12%, the study also used malva tea. Although there are no published studies in the literature reporting the use of malva tea for the prevention of oral mucositis, it is considered a herbal remedy and nutraceutical with anti-inflammatory and antiseptic properties, especially in the oral cavity, considering its external use in the form of a mouthwash[8,9]. Beside the above-mentioned properties, *in vitro* studies have shown that *Malva sylvestris* L (malva or mallow) has an antimicrobial and anti-adherent effect on microorganisms in the oral cavity and an antifungal impact on four species of *Candida*[15], in addition to being readily available at a lower cost than other mouthwash methods. These characteristics made malva tea the target of investigation in this study, besides the fact that it has similar properties to those of chlorhexidine 0.12%.

In both types of prophylaxis, cycles with chlorhexidine or malva tea, the oral lesions were less severe, suggesting the importance of these substances in studies aimed at

Table 2. Frequency (%) of patient-rated oral mucositis on days post-chemotherapy

	Malva tea				Chlorhexidine 0.12%			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Day 1	100	0	0	0	88.9	11.1	0	0
Day 2	100	0	0	0	55.6	33.3	11.1	0
Day 3	100	0	0	0	55.6	44.4	0	0
Day 4	50.0	50.0	0	0	25.0	62.5	12.5	0
Day 5	50.0	50.0	0	0	37.5	37.5	12.5	12.5
Day 6	50.0	50.0	0	0	33.3	33.3	22.2	11.1
Day 7	50.0	50.0	0	0	37.5	50.0	0	12.5
Day 8	50.0	0	50.0	0	50.0	37.5	12.5	0
Day 9	66.7	0	33.3	0	62.5	37.5	0	0
Day 10	66.7	33.3	0	0	62.5	25.0	12.5	0

Table 3. Patient-reported pain on the ten days following chemotherapy cycles comparing malva tea and chlorhexidine 0.12% as prophylaxis

	Malva tea		Chlorhexidine 0.12%	
	Mean	SD	Mean	SD
Day 1	1	1.2	1	2
Day 2	1.4	1.6	1.6	2.5
Day 3	2	2	1.6	2.5
Day 4	2.3	2.8	2	3.1
Day 5	2.8	3.4	1.9	2.8
Day 6	2.9	3.5	2.2	2.5
Day 7	2.4	3.3	2.6	3.4
Day 8	2.3	3	2.2	3.3
Day 9	1.9	2.3	1.8	2.2
Day 10	2	2.4	1.9	2.5

establishing protocols for the prevention of oral mucositis.

A double-blind study by Mallick et al.[5] assessed 70 patients who used prophylactic mouthwashes during their chemotherapy. The results suggested that although patients who did daily mouthwashes with chlorhexidine digluconate 0.12% presented oral lesions, there was a significant reduction in the incidence and severity of mucositis when compared to the group that did not use the mouthwash solution. The patients that used chlorhexidine also took longer to present symptoms on their oral mucosa. However, the authors did not report which chemotherapy had been used. A similar study was conducted in 17 children 2 to 12 years of age undergoing chemotherapy, who used chlorhexidine digluconate 0.12% as a mouthwash twice a day and developed low-grade oral mucositis[16]. These data are corroborated by the findings in our study.

Although chlorhexidine has shown positive results in numerous studies[5,14,17,18], it has some characteristics like a stinging and astringent flavor[14], besides side effects that limit its use, such as altered taste, darkened teeth, and oral cavity irritation and sores [19] and a burning sensation[20]. On the other hand, in our study there was no report of such side effects by the patients that used this substance prophylactically.

As for patients' self-rated mucositis, among individuals that used malva tea there was no report of grade 4 oral mucositis on any of the ten days of follow-up. Meanwhile, in the cycles in which chlorhexidine 0.12% was used, a small percentage of patients reported grade 4 mucositis on days 5, 6, and 7.

As for patients' self-reported pain in the ten days after chemotherapy, although it was not significant, the cycles in which chlorhexidine was used appeared to display fewer painful symptoms. However, with both substances, the maximum mean self-reported pain occurred on days 6 and 7 (grade 2.8 with malva tea and 2.6 with chlorhexidine 0.12%). This is consistent with the findings by Elyasi et al.[14], who assessed an experimental group that used chlorhexidine 0.2% compared to a control group, showing that the experimental group experienced less pain. However, the concentration of chlorhexidine was higher than in our study. Another conflicting detail was that in addition to chlorhexidine, the patients also used mouthwash with a sodium chloride solution and a protocol of rigorous oral hygiene, practiced by 90% of the patients.

As for the timing of the acute phase of oral mucositis, the data are conflicting, since some authors report that it occurs between days 7 and 10 post-chemotherapy[13], while others have reported it between days 3 and 5[4]. In our study, the peak levels, consistent with the patients' self-reported pain, occurred between days 5 and 7 with both prophylactic substances.

After oral mucositis has developed, the treatment is symptomatic, depending on the grade and the patient's

pain level, which is subjective and varies from person to person. When necessary, it is recommended to use topical anesthetics and opioid analgesics to relieve the pain[3,21]. No patients in the current study reported using these substances for pain relief in the ten days of follow-up (according to the patients' diaries).

Pain affects the patient's survival, since it can influence oropharyngeal functions such as normal eating, swallowing, drinking, and speaking [21]. Our study found that although pain and oral mucositis had been present, during the follow-up visits before each cycle of chemotherapy the patients did not report major difficulties in performing these oral functions, thus suggesting the effectiveness of chlorhexidine 0.12% and malva tea in reducing the symptoms of oral mucositis.

The patients' self-report format used in this study poses a potential limitation, since it was examiner-dependent, that is, depending totally on the patient's own perception. In order to attenuate this limitation, patients should always be instructed to perform the method calmly and carefully.

CONCLUSION

In chemotherapy cycles with either chlorhexidine 0.12% or malva tea as prophylaxis, most patients only reported oral mucositis grades 1 and 2. However, in cycles where chlorhexidine was used, a small percentage reported grade 4 oral mucositis. There was no statistical difference in painful symptoms between the two substances.

CONTRIBUTIONS

Francielli Valduga and Elenusa Oltramari contributed to the study conception, data collection, and writing of the final text. Letícia Tainá de Oliveira Lemes contributed to writing the article. Carlos Eduardo de Mattos worked in the data collection. Letícia Stefenon and Carolina Barreto Mozzini contributed to the study conception, methodology, and final version of the article.

CONFLICT OF INTEREST:

None.

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