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Efficacy of Sucralfate Mouth Wash in Prevention of 5-fluorouracil Induced Oral Mucositis: A Prospective, Randomized, Double-Blind, Controlled Trial

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ABSTRACT

Sucralfate has been used for the prevention and treatment of radiotherapy- and chemotherapy-induced stomatitis and mucositis in a number of studies, but the results are contradictory. To answer such discrepancies, the present study was designed to evaluate the efficacy of sucralfate mouthwash in prevention of 5-fluorouracil (5-FU)-induced oral mucositis in patients with gastrointestinal malignancies. Patients with gastrointestinal cancers receiving 5-FU-based chemotherapy regimens were included in this randomized, blinded, controlled trial and were randomly allocated to either sucralfate mouthwash (every 6 h) or placebo. The patients were visited at fifth and tenth day of trial; the presence and severity of oral mucositis and the intensity of pain were assessed. The patients receiving sucralfate experienced lower frequency and severity of mucositis (76% vs. 38.5%, $P = 0.005$ and 84 vs. 38.5%, $P < 0.001$, respectively) and less intense pain (2.5 ± 2.2 vs. 5.08 ± 3.82, $P = 0.004$ and 1.33 ± 0.86 vs. 4.12 ± 3.5, $P = 0.001$, respectively) compared with the placebo group both at day 5 and day 10. Within the sucralfate group, a decrease in frequency and severity of mucositis was observed throughout the trial period, while in the placebo group no such effect was observed. Sucralfate mouthwash reduced the frequency and severity of 5-FU-induced oral mucositis in patients with gastrointestinal malignancies compared with placebo, indicating its efficacy in the prevention of chemotherapy-induced mucositis.

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Introduction

Chemotherapy is a commonly used approach for the treatment of malignant neoplasms. Mucositis is a frequent and painful debilitating complication of chemotherapy, which occurs in 40–76% of patients treated, respectively, with standard and high-dose chemotherapy (1,2). Oral mucositis is defined as inflammation and ulceration of the mouth mucosa with pseudomembrane formation, which can be caused by two major mechanisms: direct stomatotoxicity resulting from the direct action of the antineoplastic agent on oral mucosa and indirect stomatotoxicity resulting from myelosupression caused by chemotherapy. The oral mucosa has high mitotic, cell renewal, and epithelial maturation rates, which make it vulnerable to the side effects of chemotherapy. The chemotherapeutic agents reduce the rate of epithelial cell renewal, leading to localized or diffuse mucosal ulcers and inflammation (3–6).

The pain and discomfort caused by oral mucositis may hinder adequate nutrition or even cause an interruption of medication or changes in the drug regimen. Patients with severe mucositis often require dose reductions, treatment delays, or even chemotherapy discontinuation, resulting in possible decreased response rates and increased mortality (5). Furthermore, since the mouth harbors many bacteria, oral ulcers may become a portal for systemic invasion by bacteria, which may lead to potentially fatal systemic infections in myelosuppressed patients. All of these conditions may increase hospital stay, cause excess costs for supportive care and hospitalization, and change the quality of life or even threaten the survival of patients (7,8). Hence, the prevention and treatment of chemotherapy-induced oral mucositis is of great importance, both clinically and economically.

5-Fluorouracil (5-FU) is an antimetabolite of the pyrimidine analog type, with a broad spectrum of activity against solid tumors (of the gastrointestinal tract, pancreas, ovary, liver, brain, breast, etc.), alone or in combination with other chemotherapeutic agents, and is still a

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mainstay in chemotherapy (9). It is among the antineoplastic agents associated with a high incidence of mucositis. About 40% of 5-FU recipients face oral mucositis, 10–15% of which is of grades 3 and 4 (2,10). Several pharmacological agents have been tried for the prevention and/or treatment of 5-FU-induced mucositis, such as allopurinol, transforming growth factor β3, chamomile mouthwash, and oral glutamine, but the results are not still satisfactory (11–15).

Sucralfate is a basic aluminum salt of sucrose octasulfate, which is widely used in the treatment of peptic ulcers due to its cytoprotective action that protects the wound from mechanical damages. In addition to its cytoprotective action in gastrointestinal ulcers, it has been demonstrated that sucralfate prevents the release of inflammatory cytokines from damaged epithelial cells and stimulates angiogenesis and fibroblast proliferation, which is of crucial importance for the generation of granulation tissue and wound-healing processes (16–20). Sucralfate increases both epidermal growth factor and basic fibroblast growth factor (bFGF) concentration in the wound. It binds with bFGF and stabilizes it in a manner similar to that of heparin. Stabilized bFGF stimulates the formation of small blood vessels and activates cell division of fibroblast and epidermal cells (18–21).Therefore, sucralfate is supposed to accelerate the healing and reduce the pain in different ulcerative conditions. It has been also found that sucralfate possesses antibacterial activity (22, 23).

Sucralfate mouthwash or oral suspension has been tried for pain reduction and wound healing in several oral inflammatory or ulcerative conditions, including oral aphthae, oral ulceration of Behcet disease, tonsillectomy, oral CO_2 laser surgery, and also in radiation-induced mucositis (24–33). Sucralfate mouthwash has also been tried in the prevention or treatment of chemotherapy-induced oral and gastrointestinal mucositis (34–40). However, the results are contradictory and its clinical importance is still questionable. Furthermore, most of the studies included patients with leukemia receiving different chemotherapy regimens, and patients with other types of malignancies were rarely covered in the studies.

Thus, the authors decided to conduct a randomized, placebo-controlled trial to evaluate the efficacy of sucralfate mouthwash in the prevention of 5-FU-induced oral mucositis in patients with gastrointestinal malignancies receiving 5-FU-based chemotherapy regimens.

Materials and methods

Preparation of the mouthwash

Sucralfate suspensionwas prepared from the following materials (amounts are calculated for 100 mg of suspension): sucralfate powder (15 g), glycerin (30 g), xanthane (0.175 g), polysorbate 80 (0.75 g), methyl paraben (0.025 g), sodium saccharin (0.05 g), and water (54 g) by the following procedure: Methyl paraben was dissolved in ethanol and mixed with water. Appropriate amount of xanthane was added to this solution and allowed to hydrate overnight. Sucralfate powder was levigated with glycerin, followed by addition of polysorbate 80. This mixture was mixed with xanthane solution and stirred at 300 rpm for 1 h. Finally, sodium saccharin was added to the suspension as sweetener. Placebo suspension was prepared from the same materials and by the same method but without sucralfate powder. The final preparations were filled in 250-ml bottles and labeled.

Sucralfate quantification in the mouthwash

The amount of sucralfate in the mouthwash suspension was determined by comparing the aluminum content of the mouthwash with the aluminum content of 1 g of sucralfate powder. Aluminum assay was performed according to the United States Pharmacopeia XXXI by volumetric titration using zinc sulfate solution (41). The measurements were done in triplicate and the amounts were reported as mean $\pm$ SD.

Physicochemical and microbiological control tests

The chemical stability tests were carried out at 50°C, 60°C, 70°C, and 80°C. The sucralfate content of the suspension was determined at 24 h, 48 h, and 72 h and compared with the initial content. The physical stability tests included the measurement of *F* value (sedimentation factor), resuspension factor at 90° angle, viscosity, and flow. The microbiological limit tests were carried out according to the United States Pharmacopeia XXXI (41). The suspension was examined for the presence of aerobic microorganisms (bacteria and fungi) using soybean casein digest broth, soybean casein digest agar, and Sabouraud dextrose agar mediums. The sucralfate suspension was found to be physicochemically stable, and no evidence of microbial or fungal growth was observed at the test conditions.

Trial procedure

This study was a prospective, randomized, double-blind, placebo-controlled trial carried out between November 2011 and June 2012 in Imam Khomeini Educational Hospital, Sari, Mazandaran province, Iran. Patients above 18 yr of either sex receiving chemotherapy regimens containing 5-FU and calcium folinate were included in the study. The exclusion criteria were

preexisting oral mucositis, sucralfate intolerance, and irregular use of the mouthwash. The patients were randomly divided into two groups receiving either the sucralfate mouthwash or placebo through simple randomization procedure by a computer-generated list of random numbers. Both mouthwash suspensions were identical in color, taste, and consistency and were filled in similar bottles. The bottles were labeled with randomization codes A and B, corresponding to sucralfate and placebo, respectively, that prevented the identification of the allocation group. The randomization procedure was performed by an individual who was not involved in the trial procedure. Neither the investigators nor the patients were aware of the codes until the end of the trial.

The patients received the mouthwash right after the termination of chemotherapy and were recommended to use 10 ml of the mouthwash every 6 h for 10 days. The patients were instructed to rinse their mouth with the suspension for at least 5 min, but not to swallow the mouthwash. They were also advised to use the mouthwash 30 min after meals to ensure prolonged exposure of the mouthwash to the mucosal membranes.

The primary outcomes were pain intensity and mucositis grade. The patients were visited at days 5 and 10 after commencement of the trial and the oral mucosa was carefully inspected by the oncologist physician and any evidence of mucositis was recorded. The mucositis grade was assessed using World Health Organization grading system as follows: grade 0 = absence of mucositis; grade I (mild) = oral soreness and erythema; grade II (moderate) = oral erythema, ulcers, solid diet tolerated; grade III (severe) = oral ulcers, liquid diet only; grade IV (life threatening) = oral alimentation impossible. The pain intensity was self-assessed by the patients using a visual analog scale, with zero denoting absence of pain and 10 denoting unendurable pain, and recorded on days 5 and 10.

All patients underwent inspection of oral mucosa, dental evaluation, and hematological test prior to initiation of the trial; their white blood cells count, serum hemoglobin, serum creatinine, and blood urea nitrogen were measured in order to eliminate the confounding effect of preliminary predisposing conditions on the incidence of mucositis.

This trial was carried out according to the Declaration of Helsinki and the guidelines for human studies of the Mazandaran University of Medical Sciences. The study was approved by the Medical Research Ethics Committee of Mazandaran University of Medical Sciences and informed written consent was obtained from all of the patients before their recruitment in the study. The present trial was registered at the Iranian Registry of Clinical Trials with the registration code IRCT201107053014N4 (the full trial protocol could be accessed online at www.irct.ir).

Data analysis

The study sample size was calculated assuming a reference proportion of 76%, a 40% decrease in the incidence of oral mucositis, considering a confidence interval of 95% and a statistical power of 80% ($\alpha = 5\%$, two tails, and $\beta = 0.20$). The statistical analysis of the data was performed using SPSS software package version 18 (SPSS for windows, version 18, SPSS Inc., Chicago, IL). Quantitative data were analyzed with independent sample *t*-test, and pain intensity data and mucositis grade data were analyzed using nonparametric Mann–Whitney test. Values of $P < 0.05$ were considered to denote a statistically significant difference.

Results

Of the 52 patients included in the trial, one patient from group A discontinued intervention on the second day due to the bad taste of the mouthwash, leaving a total of 51 patients (35 males and 16 females) between 23 and 78 yr of age, who were divided to two groups: group A (25 patients) received sucralfate mouthwash while group B (26 patients) received placebo. Full details of the age, gender distribution, basal hematological test values (prior to commencing the trial), distribution of different types of cancer among the patients, and the chemotherapy regimens administered to the patients are represented in Table 1. As it could be observed, there was no significant difference in mean age between different study groups. The study population was predominantly composed of men (68.62%), which was more reflected in group B. There was no statistically significant difference in hematologic values between groups. The most frequent cancer types among patients were gastric and colon cancers accounting for approximately 72% of the patients, and the most frequently used chemotherapy regimens were regimens numbers 1 and 2 received by almost 78% of the patients (the full details of chemotherapy regimens could be found in Table 2). The majority of patients in both groups (84%) received 5-FU in doses of 750 mg or higher per chemotherapy cycle. As it could be depicted from Table 1, there was no difference in the distribution of cancer type, chemotherapy regimen type, and 5-FU dosage per chemotherapy cycle between the two study groups.

Table 1. Basal characteristics of the patients and frequencies of different cancer types and chemotherapy regimens.

Parameter		Group A ($N = 25$)	Group B ($N = 26$)	P value
Mean age (yr)		56.3	57.2	0.47
Male/female		15/10	20/6	—
Laboratory test values (mean ± SD)	WBC[a] ($10^3/mm^3$)	6.31 ± 3.28	5.14 ± 2.1	0.15
	Hb[b] (g/dl)	10.8 ± 1.82	11.75 ± 1.72	0.063
	BUN[c] (mg/dl)	21.14 ± 9.2	17.48 ± 4.39	0.13
	Cr[d] (mg/dl)	0.983 ± 0.2	1.06 ± 0.22	0.3
Type of cancer	Gastric	9	10	—
	Esophageal	5	5	—
	Colon	9	9	—
	Rectal	2	2	—
Chemotherapy regimen	1	12	12	—
	2	8	8	—
	3	1	1	—
	4	1	2	—
	5	2	2	—
	6	1	1	—
5-FU dose per chemotherapy cycle	600 mg	4	4	
	750 mg	14	14	
	1500 mg	7	8	

[a]White blood cell
[b]Serum hemoglobin
[c]Blood urea nitrogen
[d]Serum creatinine.

The severity of mucositis and intensity of mucositis-associated pain in different study groups at different time points throughout the trial are presented in Table 3. The majority of patients in group A had no signs of mucositis (grade 0) both in the fifth and tenth day. However, in group B, on the fifth day the majority of patients had a moderate mucositis (grade 2) and on the tenth day the majority of patients suffered from moderate to severe mucositis (grades 2–3) as is evident from their respective modes, and a significant difference in the severity of mucositis was observed between the two groups both at days 5 and 10 ($P_1 = 0.005$, $P_2 < 0.001$, respectively). These results suggest the effectiveness of sucralfate in the prophylaxis of oral mucositis. The results of the pain assessment during the trial show a significantly less pain intensity in group A compared with group B at the fifth and tenth day of trial which accords with the results of mucositis severity assessment, which further confirms the role of sucralfate in the prophylaxis of oral mucositis, leading to a reduction in mucositis-associated pain.

Table 2. Chemotherapy regimens used in the trial.

Regimen	Chemotherapeutic agents
1	5-FU, Calcium Folinate[1], Oxaliplatin
2	5-FU,Docetaxel[2], Cisplatin
3	5-FU, Cetuximab[3], Cisplatin, Docetaxel
4	5-FU, Oxaliplatin, Calcium Folinate, Capecitabine[4]
5	5-FU, Irinotecan, Calcium Folinate
6	5-FU, Cisplatin, Epirubicin
7	5-FU, Docetaxel, Oxaliplatin

[1]Leucoverin®,[2]Taxotere®,[3]Erbitux®,[4]Xeloda®,[5]Adriamycin®.

Table 3. Severity of mucositis and intensity of mucositis-associated pain in different study groups.

Outcome	Time point	Allocation group: Group A ($N = 25$)	Allocation group: Group B ($N = 26$)	Z score	P value
Pain intensity (mean ± SD)	Day 5	2.5 ± 2.2	5.08 ± 3.82	2.853	0.004
	Day 10	1.33 ± 0.86	4.12 ± 3.5	3.31	0.001
Mucositis severity (mode)	Day 5	0	2.5	2.82	0.005
	Day 10	0	2	3.72	<0.001

For a better demonstration of the distribution of different grades of mucositis in patients of either group and the changes in the severity of mucositis over time, the number of patients from each group suffering from different grades of mucositis at different time points is illustrated in Fig. 1. Fig. 2 demonstrates the changes in the grade of mucositis among patients within each group

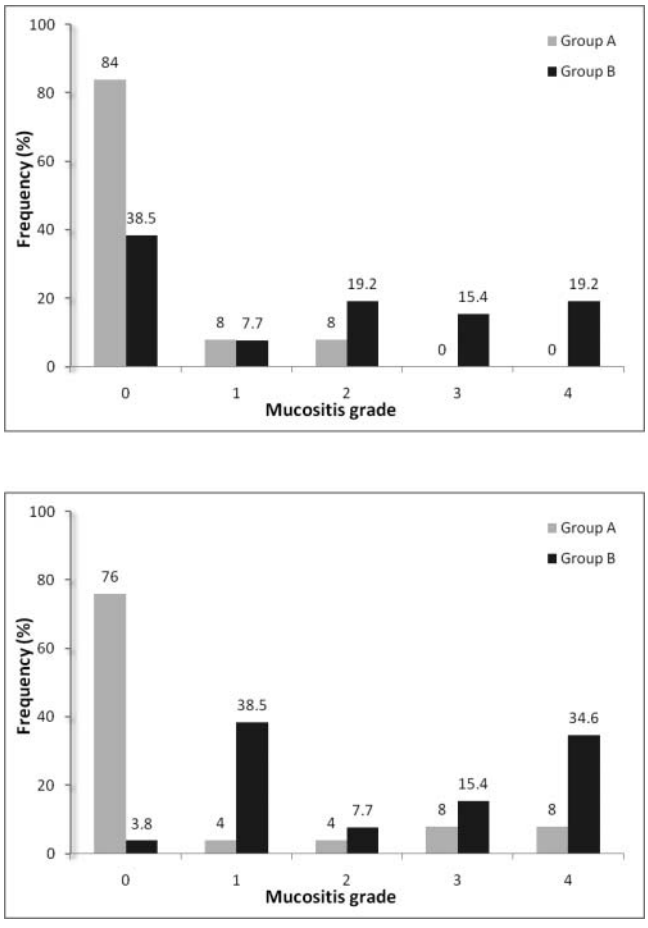

Figure 1. Severity of mucositis in the two study groups at day 5 (A) and day 10 (B) (grade 0 = no objective findings; 1 = soreness and erythema; 2 = ulcers, ability to eat solids; 3 = ulcers, ability to eat liquids; 4 = ulcers, nothing by mouth).

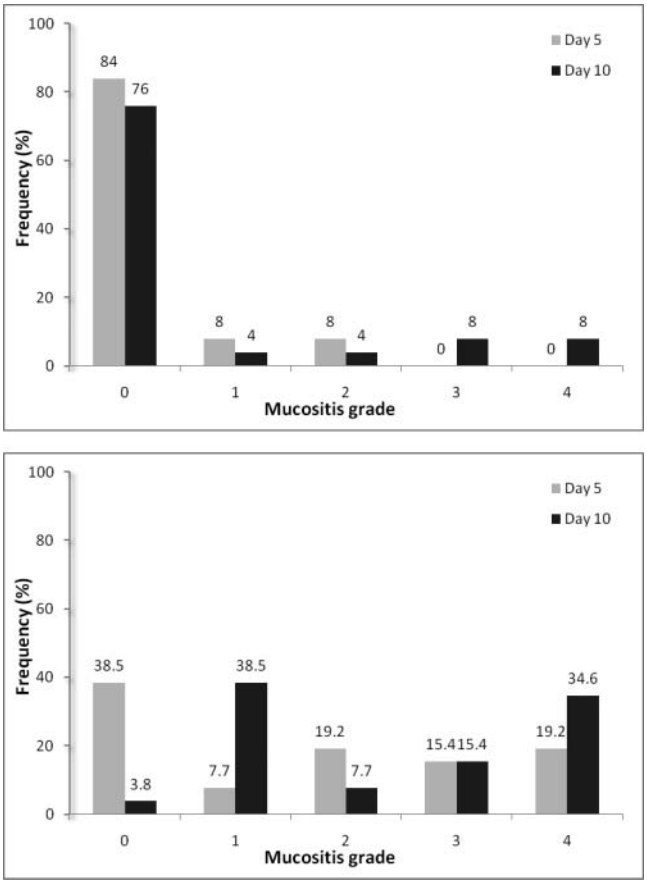

Figure 2. Changes in severity of mucositis within group A (A) and group B (B) over time (grade 0 = no objective findings; 1 = soreness and erythema; 2 = ulcers, ability to eat solids; 3 = ulcers, ability to eat liquids; 4 = ulcers, nothing by mouth).

over time. As it could be inferred from Fig. 1, at day 5, the number of patients without mucositis in group A was almost twice more than group B, and the overall frequency of oral mucositis was 37.5% lower in group A. In addition, the number of patients having grade-3 and -4 mucositis was to a great extent less in this group compared with group B. At the tenth day, only a small proportion of the patients in group A had mild to moderate mucositis and no patients with severe or life-threatening mucositis (grades 3 and 4) were found in this group, while in group B the number of patients with grade-1 and -2 mucositis was considerably more than group A and there were still some patients suffering from severe and life-threatening mucositis. The overall frequency of mucositis was 45.5% less in group A at day 10.

Figure 2A, shows the changes in the mucositis grade within group A over time. As it could be observed, there was an increase in the number of patients without mucositis and patients with grade-2 mucositis from day 5 to day 10, while the number of patients with grade-3 and -4 mucositis reduced to zero. In group B (Fig. 2B), from day 5 to day 10, the number of patients without mucositis and number of patients with grade-3 mucositis did not change, while there was a marked reduction in the number of patients with grade-1 and -4 mucositis and a considerable increase in the number of patients with grade-2 mucositis.

Discussion

There is limited information on the efficacy of sucralfate in prevention and treatment of chemotherapy-induced oral mucositis and the available data are somehow contradictory. Ferraro et al. (34) and Solomon et al. (35) studied the effectiveness of oral sucralfate in the treatment of stomatitis and mucositis in order but neither study assessed its efficacy in the prevention of mucositis. Loprinzi et al. (36) studied the effectiveness of oral sucralfate solution in the treatment of stomatitis in patients receiving FU-based chemotherapy and did not find any significant difference in severity or duration of stomatitis between the two arms. Their study did not evaluate sucralfate for prophylaxis either. In a pilot study by Chiara et al. (37), the efficacy of sucralfate gel in the treatment of chemotherapy-induced stomatitis was assessed in 40 patients, and no significant advantage was found for sucralfate in comparison with placebo. Although objective response was observed in the majority of patients, the between-group difference was not significant. Similarly, no significant difference in pain intensity was observed between the two groups. Once again, in this study sucralfate was not administered as a prophylactic procedure, but only as a therapeutic procedure in patients who developed stomatitis.

In a study carried out by Shenep et al. (38), the efficacy of oral sucralfate suspension in prevention and treatment of chemotherapy-induced mucositis was evaluated and a reduction both in pain and frequency of mucositis by sucralfate was found. Since their study was designed to detect differences greater than 40% between the two arms, the effect of sucralfate was considered insignificant. However, 5-FU was not included in the chemotherapy regimens considered for the study.

In a study by Nottage et al. (39), the effectiveness of sucralfate mouthwash in prevention and treatment of 5-FU-induced mucositis in patients with colorectal cancer receiving chemotherapy with 5-FU and leucovorin was studied during their first cycle of chemotherapy. Their study did not reveal any statistically significant difference in the severity or duration of mucositis between the two treatment groups, and the majority of patients in either groups reported varying degrees of mucositis with 24% of patients reporting severe mucositis (grades 3 and 4).

However, since the formulation and the drug content of the sucralfate mouthwash was not mentioned in the article, it is not possible to conclude whether the lack of efficacy of sucralfate observed in the study is due to the inability of sucralfate to prevent or cure mucositis or the result of insufficient drug dosing.

Furthermore, since the study was closed early, as declared by the authors, due to some technical problems, the required sample size was not reached and only about half of the required patients were included in the study (80 instead of 158 originally intended). Hence, as mentioned by the authors, it is possible that the result is a false-negative one, due to lack of power, confounding, or unbalanced patient groups. It is possible that a difference between treatment groups might have been found if more patients had been accrued, as was initially planned in the protocol.

On the other hand, in a study by Castagna et al. (40), the preventive administration of sucralfate appeared to efficiently diminish the severe oral and intestinal mucositis in patients treated with high-dose chemotherapy before bone marrow transplantation. Although the incidence of mucositis of any grade was similar in both groups, the proportion of patients with grade-3 or -4 oral mucositis was significantly lower in the sucralfate group. In addition, the occurrence of diarrhea was significantly less in the sucralfate group, and sucralfate treatment improved the recovery of enteral alimentation.

Due to the lack of sufficient evidence for the efficacy of sucralfate for prophylaxis of chemotherapy-induced mucositis, the authors conducted the present study to evaluate the efficacy of sucralfate mouthwash in prevention of chemotherapy-induced oral mucositis in patients with gastrointestinal malignancies receiving chemotherapy regimens based on 5-FU and calcium folinate, with or without other potentially mucositis-inducing chemotherapeutic agents. The mentioned settings were considered for this trial according to the high prevalence of gastrointestinal cancers in the Mazandaran province of Iran, and the widespread use of 5-FU in chemotherapy regimens for gastrointestinal malignancies. Although patients receiving different chemotherapy regimens were included in this study, this variability in therapeutic regimens was not considered a confounding factor due to the equal distribution of patients receiving each type of chemotherapy regimens in the two groups.

Our results showed a considerable difference both in the frequency and the severity of mucositis between the two groups in favor of sucralfate throughout the trial. At the end of the trial (day 10), there was a marked reduction in both the frequency and severity of oral mucositis in the sucralfate group compared with placebo group which strongly confirms the efficacy of sucralfate in the prevention of chemotherapy-induced oral mucositis. In addition, there was a decrease in the overall frequency of mucositis and a shift from severe mucositis to moderate mucositis within the sucralfate group throughout the trial, which indicates an acceleration in healing of mucositis caused by sucralfate. In other words, some of the patients who had developed oral mucositis at the beginning of trial did heal after five additional days of receiving sucralfate mouthwash, suggesting the active role of sucralfate not only in the prophylaxis but also in the treatment of oral mucositis, resulting in a reduction in severity and overall frequency of mucositis. Although there were some severe to moderate mucositis shifts in the placebo group suggesting self-remission can undermine the above mentioned claim, there was also some exacerbation of mucositis in this group, while similar exacerbation was not observed in the sucralfate group. The lower intensities of pain reported by the patients in the sucralfate group compared with the placebo group throughout the trial, and within the sucralfate group over time, provide further support for this claim. However, since the study was aimed and designed to evaluate the prophylactic potential of sucralfate for mucositis, the available data are not enough for drawing any conclusions about the possible therapeutic effects of sucralfate in oral mucositis.

These observations clearly signify the mucoprotective effect of sucralfate and its ability to protect the oral mucosa from the cytotoxic effects of chemotherapeutic agents, specifically 5-FU. The difference between the results obtained from the present study with literature data might be in part due to the difference in the chemotherapy regimens and doses, as well as the type and stage of cancer. Furthermore, variations in individual response to chemotherapy or pharmacogenetics and ethnic or racial factors may also play a role. However, this study was a short-term trial including just one cycle of scheduled chemotherapy program. The benefits of long-term administration of sucralfate for the prophylaxis of 5-FU-induced oral mucositis are still of questionable clinical importance and require further studies with long-term follow-up.

Conclusion

Taking into account all the above, it could be concluded that sucralfate, in the form of mouthwash, is more effective than placebo in the prophylaxis of 5-FU-induced oral mucositis and could be regarded as a means for prophylaxis of 5-FU-induced oral mucositis. However, the long-term benefits of sucralfate mouthwash for such purpose were not investigated in this study.

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Conflicts of interest

The authors declare that they have no conflicts of interest and have full control of all primary data and agree to allow the journal to review their data if requested.

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