

Short Communication

The role of sucralfate oral suspension in prevention of radiation induced mucositis

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Abstract

BACKGROUND: Mucositis is one of the most common complications of radiotherapy in head and neck cancers. The aim of this study was to evaluate sucralfate mouthwash in prevention of radiation induced mucositis.

METHODS: A clinical randomized trial performed on 52 patients with head and neck cancers in Sayyed-Al-Shohada Hospital of Isfahan University of Medical Sciences. These patients randomly assigned in 2 groups of 26 patients. Placebo and sucralfate was used for control and experimental patients respectively, from the beginning of radiotherapy. Patients were visited weekly until the end of treatment. Grade of the mucositis was evaluated according to WHO grading scale.

RESULTS: Sucralfate significantly reduced the mean grade of mucositis in weeks one to four (with P-values of 0.02, 0.02, 0.001 and 0.004, respectively). Development of grade3 mucositis was also lower in sucralfate group (P-value = 0.0001). But, time interval between radiotherapy and appearance of mucositis was not statistically different in the two groups (P-value = 0.9)

CONCLUSIONS: This study indicated that using oral suspension of sucralfate reduced the grade of radiation-induced mucositis, but did not prevent or delay it.

KEYWORDS: Mucositis, radiotherapy, sucralfate, head and neck cancers.

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Head and neck cancers constitute a common group of malignancies and interestingly, majority of them are potentially curable. Radiotherapy plays an important role in the definite treatment of these cancers. Oral mucositis is the most common complication observed in patients receiving radiotherapy or chemoradiation.

In addition to patient discomfort, this complication makes some reduction in the necessary dosage of therapeutic radiation.¹ Mucositis appears in form of painful lesions with dysphagia and odynophagia in a severe way that negatively affects quality of life in patients and also causes malnutrition and weight loss. In

some cases even termination of the therapy is a necessity.² Previous studies have shown that 80% of patients under radiotherapy with or without chemotherapy suffer from mucositis.³

Therapeutic strategies for mucositis are categorized in two groups, direct and indirect cytoprotectants. Sucralfate, gelclair, prostaglandins, NSAIDs, corticosteroids, cryotherapy, laser, vitamins and antioxidants belong to direct cytoprotectants. Hematopoietic growth factors, antimicrobial agents, and pharmacologic regulators are examples of indirect cytoprotectants.⁴

In recent years many studies examined different cytoprotectants.⁴ Some studies showed

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the anti-inflammatory effects of benzydamine oral solution.^{4,5} Corticosteroids on its own or in combination with other agents have been studied and it seems that they can reduce the pain and discomfort of radiation induced mucositis.⁴

In the recent years coating agents like the sucralfate were suggested for the prevention and treatment of mucosal reactions. Since sucralfate protects ulcerated epithelium by coating, liberates protective prostaglandins and increases the local availability of protective factors, this drug might directly interact with the pathogenesis of radiation induced mucositis⁶. Most of the studies on sucralfate in this field have been performed on oral ingestion of this agent and there are only a few studies about local application of sucralfate (mouthwash). Epstein showed that prophylactic oral rinsing with sucralfate solution did not prevent oral ulcerative mucositis but reduced the experience of pain during radiation therapy.⁷ A randomized, double-blind, placebo-controlled study using clinical and histopathological evaluation of oral mucositis suggested that sucralfate might be recommended in the prevention of oral mucositis induced by radiation therapy in patients with head and neck malignancies.⁸ In another study, decrease in the salivary lactoferrin and albumin levels suggested that sucralfate has a slight protective effect on the oral mucosa.⁹ Cengiz study on 28 patients showed that patients under sucralfate therapy experienced less mucositis than the control group.¹⁰ However, Saarilahti compared the effects of sucralfate oral suspension with GM-CSF oral solution in 19 and 21 patients, respectively and GM-CSF showed better effects than sucralfate.¹¹ Results of another randomized clinical trial demonstrated no difference between sucralfate and salt & soda mouthwash.¹² Meanwhile, a German study concluded that application of sucralfate during radiotherapy of head and neck cancer reveals only limited benefits for radiation induced mucositis.⁶ Finally, Stokman compared local application of eight different agents and did not find any advantage for sucralfate over other agents.¹³

As it is obvious, the clinical efficacy of sucralfate mouthwash for head and neck cancer patients is not consistent across studies. Considering the fact that sucralfate is a cheap and safe drug and there is not any report of serious side effects in aforementioned studies, this study investigated the effects of sucralfate oral suspension in prevention and reduction of radiation induced mucositis.

Methods

This was a double blind randomized clinical trial on 52 patients with head and neck cancers, who were referred to Sayyed-al-shohada hospital for radiotherapy from March 2007 to August 2007. The patients were randomly assigned into two groups. Control group (26 patients) received placebo and experimental group (26 patients) received sucralfate mouthwash. Sucralfate suspensions were administered from the beginning of radiation therapy (15^{cc} of 10% suspension: 10mg/100cc, 4 times a day).

Patients, who received at least 40 Gy radiations to at least two or more sites of oropharynx, oral cavity, soft or hard palate, hypopharynx, and nasopharynx, entered the study. All the patients were treated with conventional radiotherapy, 2Gy/fraction, one fraction per day and five fractions per week to a total dose of 55-60 Gy. Patients who were taking antibiotics, receiving 5-flouracil concomitantly with radiotherapy and those with Karnofsky performance status under 70 were excluded from the study. During the treatment, two physicians examined the patients together weekly and recorded mucositis gradeing based on WHO grading system (table1). When grade 3 mucositis appeared, the sucralfate was discontinued and the patient was treated by routine drug therapy in hospital (combination of antacid, diphenhydramine and lidocaine ± tetracycline).

Finally, the data were collected and analyzed by SPSS software. Mann-Whitney U test was used for comparing the grade of mucositis between the two groups. For evaluation of the time of response or non-response, the period

between the beginning of radiotherapy and the appearance of mucositis as well as the appearance of grade 3 mucositis were considered. Two-Sample Kolmogorov-Smirnov Test was used to (evaluate the normal distribution of variables).

Results

Of 52 Patients, 25% were male and 75% were female. The age of patients ranged from 18 to 69 years; 14.3% of patients were ≤ 39 years, 40.4% in age group 40-59 years and 41.3% were ≥ 60 years. The patients educational level was as follows: 65.4% illiterate, 19.2% had primary and guidance school education, and 15.4% had secondary school and higher education. Given American Joint Committee on Cancer (AJCC) staging system, 3.8% of patients had stage I cancers, 36% stage II cancers, 30.8% stage III cancers and 28.8% stage IV cancers. Squamous cell carcinoma (SCC) was the most common pathologic subtype of cancers (66%) followed by adenocarcinoma (23%). Table 2 compares gender, age and total dose of radiotherapy between control and experimental groups.

In control group, the grade of mucositis within 4 weeks of evaluation was 1.19, 2.42, 3.56 and 4, respectively. In experimental group, mean grade in weeks 1 to 4 were 1, 2, 2.81 and 3.05, respectively. Overall the mean grade in control and experimental groups were

2.8 and 2.2, respectively. Mann-Whitney U test showed that within 4 weeks of evaluation, severities of mucositis in experimental group was significantly less than those in control group, with P values of 0.02, 0.02, 0.001 and 0.004, respectively (table 3).

Using two-sample Kolmogorov-Smirnov test, the relative frequency of grade 3 mucositis in experimental group was significantly less than that in control group (100% in control group vs 57.7%) in experimental group, P-value = 0.0001 (table 4).

The time period between the beginning of radiotherapy and the appearance of mucositis was not statistically different in the two groups (P = 0.9).

Table 1. WHO grading system for radiation induced mucositis.

Grade	Definition
Grade 0	Without any mucosal change
Grade 1	Sore throat, erythema
Grade 2	Erythema, ulcer, able to swallow solid food
Grade 3	Ulcer, only liquid food
Grade 4	Unable to swallow

The overall percentage of mucositis (all grades) in experimental and control groups was 92.3% and 100%, respectively. Approximately, 40% of patients in sucralfate group could finish radiation therapy without any needs to routine drugs (mixture of AlMg, lidocaine and diphenhydramine) in our study.

Table 2. Distribution of age, gender and total dose of radiation between experimental and control groups.

Variable	Group	Experiment	Control	P-value
Age (Means ± SD) years		54.15 ± 14	53.46 ± 14.47	> 0.05
Gender (Male/Female)		73.1% /26.9%	76.9% /23.1%	> 0.05
Total dose of radiation (Mean ± SD) Gy		58.15 ± 3.22	57.62 ± 3.53	> 0.05

Table 3. Comparison of mean grade of mucositis between experimental and control groups in weeks 1-4.

a.Group	Week	Week 1	Week 2	Week 3	Week 4
Experimental (Means ± SD)		1 ± 0	2 ± 0.63	2.81 ± 0.84	3.05 ± 1.07
Control (Means ± SD)		1.19 ± 0.40	2.42 ± 0.57	3.56 ± .50	4 ± 0
P-value		0.02	0.02	0.001	0.004

Table 4. Frequency of grade 3 mucositis in experimental and control groups.

Group	Week	Week 2	Week 3	Week 4	Total
Experimental	Frequency	0	5	10	15
	Percentage	0%	19.2%	38.5%	57.5%
Control	Frequency	1	14	11	26
	Percentage	3.9%	53.9%	42.2%	100%

P-value= 0.0001

Discussion

In our study sucralfate mouthwash decreased the mean grade of radiation-induced mucositis in weeks one to four of the treatment. Meanwhile, grade 3 mucositis in experimental group was significantly less than that in control group. Although sucralfate did not prevent or delay the development of mucositis, a considerable number of patients in sucralfate group could complete their radiation treatment without any need for routine drug therapy in our study. These results are consistent with Cengiz study that reported less mucositis in patients using sucralfate mouthwash.¹⁰

There is also an indirect evidence from a randomized double blind study that sucralfate has a mild protective effect in radiation induced mucositis.⁹ In a study by Pfeiffer, sucralfate showed a significant decrease in mucositis grading, edema and erythema in comparison with placebo.⁴ On the other hand, Epstein could not derive a benefit for sucralfate in prevention of mucositis, but his statistical model was designed to detect more than 40% reduction in mucositis grade, which is the possible reason for this conclusion.⁷ Interestingly, all the above-mentioned studies reported less pain and less use of analgesics with the use of

sucralfate.^{4,7,9,10} Dodd found no difference between sucralfate and salt & soda mouthwashes in terms of developing duration and severity of mucositis.¹² Even though it was a randomized study, only 30 patients completed the intervention and the small number of patients could be the reason for this result. Another study concluded that GM-CSF oral solution had better effects than sucralfate¹¹ but this needs confirmatory results from future trials.

Unfortunately, we did not compare parameters such as pain, use of analgesics and time to healing between experimental and control groups. It is recommended to consider these parameters in future studies.

Overall, given the promising results of sucralfate in decreasing the grade of mucositis and its safety, it can be considered as an option for radiation induced mucositis and a matter for further studies, but it must be in mind that despite its useful effect, sucralfate mouthwash can not prevent or delay the development of radiation induced mucositis. Well-designed double blind randomized clinical trials with larger number of patients comparing sucralfate mouthwash with other available agents or their combinations are recommended.

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