Effect of cryotherapy on oral mucositis in patients with head and neck cancers receiving radiotherapy

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ABSTRACT

Background: Mucositis is an important adverse effect of cancer treatment. The aim of this study was to investigate the effect of ice cubes on oral mucositis following head and neck radiotherapy. ***Materials and Methods:*** A randomized controlled trial was conducted on 40 head and neck cancer patients who underwent radiotherapy. The patients were randomly divided into two experimental and control groups of 20 each. The patients in the experimental group received instructions for sucking ice cubes before and after each radiotherapy session for five minutes during the study period. Oral examinations were performed on the 1st, 7th, and 14th days of the study. Pain severity and mucositis were evaluated by a checklist and self-reported assessment by the patients at the above-mentioned intervals. ***Results:*** As time passed, the mean of pain intensity in the control group significantly increased ($p<0.001$), whereas the experimental group showed no significant difference during the study period ($p>0.05$). Patients' self-assessment in the control group showed significantly higher oral discomfort during the study period ($p=0.012$). In contrast, self-assessment of patients in the experimental group exhibited no significant changes during the study ($p>0.05$). ***Conclusion:*** Although no significant difference was observed in mucositis intensity between the experimental and control groups, patients using ice cubes during radiotherapy sessions felt more comfort in their oral cavity.

Keywords: *Radiotherapy, mucositis, pain, cryotherapy, ice.*

INTRODUCTION

Nowadays, head and neck cancers have become a major field of attention especially among the dental society. Annual worldwide incidence rate is more than half a million cases [(1)]. One of the common acute adverse effects of cancer treatment is mucositis, which is manifested in 80% of patients with head and neck cancers undergoing radiotherapy and a considerable number of patients receiving chemotherapy. Mucositis is defined as a painful inflammation and ulceration of mucous membranes. Severe pain may cause trouble for the patient in speaking, eating, or even mouth opening [(2,3)].

Treatment of mucositis is mainly based on supportive therapies, i.e., oral hygiene, consumption of adequate liquids, and application of mouth washes. Patients are recommended to avoid alcohol, citrus fruits, and hot foods. Related studies have introduced various substances and agents as effective medications for inhibiting or limiting signs and symptoms of mucositis. In this regard,

cryotherapy has been introduced as an effective therapy, but the evidence that it prevents mucositis is still inadequate and unreliable [4].

Cryotherapy is a treatment modality based on the application of low temperatures on a body part. The purpose of this treatment is to reduce inflammation, cellular metabolism, pain and spasm and increase vasoconstriction and cellular survival [5]. Several studies have assessed the effect of oral cryotherapy on development of mucositis. A Cochrane systematic review in 2002 reported that among six prophylactic agents, ice chips were the only effective agent in prevention of oral mucositis. However, the authors added that due to the limited number of studies and subjects and their special conditions, this is not strong and reliable evidence [4]. Another study revealed that cryotherapy decreases development of mucositis by 50% in patients receiving chemotherapy agents [6].

To our knowledge, although cryotherapy has shown some positive effects in preventing mucositis, there are still some shortcomings for this method such as vague method of ice chip application, limited number of supporting studies (which are predominantly designed on chemotherapy), and lack of investigation in patients undergoing radiotherapy. Therefore, this study was conducted to evaluate the effect of cryotherapy with a certain procedure on the incidence and severity of mucositis in patients undergoing radiotherapy.

MATERIALS AND METHODS

In this randomized controlled trial 40 patients with head and neck cancers undergoing radiotherapy were enrolled. All the cases were randomly selected from patients in the Department of Oncology, Shafa Hospital in Kerman. The patients were informed of the research process and their contribution to developing treatment modalities for mucositis. Informed consent was obtained from all the participants before the study. The study protocol was approved by EC and it was registered in the Iranian Registry of Clinical Trials (IRCT), with registration ID of IRCT201107127015N1.

Clinical examinations were performed by two dentists who were calibrated for oral mucositis grading.

Inclusion criteria included (I) partial or complete exposure of head and neck to radiation; (II) receiving a minimum dose of 2500 –3000 cGy in each radiotherapy session; (III) starting radiotherapy sessions at the beginning of the study and continuing constantly during the next two weeks. Exclusion criteria included (I) existence of oral mucositis; (II) existence of systemic diseases or taking any type of medication affecting the oral condition, especially periodontal tissues; (III) patients under 15 and over 55 years of age. The type of radiation was conventional X-ray with a linear energy of 9 MV photons. Data collection forms contained information about patient's name, contact information, age, sex, education level, smoking rate, history of systemic diseases and medications.

The participants were divided into experimental and control groups using block randomization technique with the formula of AABB, ABAB, ABBA, BBAA, BABA, and BAAB. The control group patients received instructions for standard oral care (use of a soft toothbrush with nonabrasive toothpaste and dental floss twice a day). The experimental group patients were instructed for standard oral care plus sucking ice cubes before and after each radiotherapy session for five minutes during the study period. Each patient participated in the study for two weeks to be considered as a complete study case.

Table 1. Physician-judged mucositis grading.

Grade	Definition
0 (none)	No toxicity
1 (mild)	Painless ulcers, erythema, or mild soreness
2 (moderate)	Painful erythema, edema, or ulcers but can eat
3 (severe)	Painful erythema, edema, or ulcers and cannot eat
4 (intravenous feeding)	Requires parenteral or enteral support

Oral mucositis was assessed on the 1st, 7th, and 14th days of the study using two approaches: Physician-judged mucositis grading and Patient-judged mucositis grading, which are described in tables 1 and 2 [7].

Sample size was calculated to detect a 40% difference in treatment effect considering an alpha error of 0.05 and beta of 0.20. To compare quantitative data between the two groups, Student's t-test or Mann-Whitney U test were used. Chi-squared test was used to compare categorical data between the two groups. Friedman's test was used to compare pain scores between different time intervals. Statistical significance was defined at $p<0.05$.

RESULTS

Out of 40 patients of this study, 23 (57.5%) were male. Average ages of the patients in the control and experimental groups were 49.1±15.4 and 42.9±14.9 years, respectively.

The patients in the control and experimental groups had no significant differences in age, sex, education level, and smoking rate. All the 40 patients completed the two-week study period and had no lapse during the study. Average received radiation doses was 5387 cGy during their radiotherapy. Among all the cancer types observed in this study (oral cavity, salivary glands, lymphoma, brain, larynx, oropharynx, and ear), the most frequent carcinoma was of the larynx (28.2%).

According to table 3, while the increase of pain severity in the control group was statistically significant (p<001), changes in the experimental group were not (p=0.155). Evaluation of Physician-judged mucositis grading revealed that in both the control and experimental groups, mucositis significantly increased during the study period. Assessment of patient-judged mucositis grading showed a significant increase in the controls (p=0.003), while the increase in the experimental group was not statistically significant (p=0.598) (table 3).

DISCUSSION

Mucositis and candidiasis are the most studied side-effects of cancer therapies. Various prophylactic agents have been investigated and advocated to treat these side-effects [4]. The current study showed that cryotherapy can reduce pain severity and symptoms of mucositis in patients with head and neck cancer, undergoing radiotherapy, but it

Table 2. Patient-judged mucositis grading.

Grade	Definition
0 (none)	None
1 (mild)	Mild discomfort
2 (moderate)	Definite discomfort but able to eat solid foods
3 (severe)	Marked discomfort that interferes with eating solid foods
4 (intravenous feeding)	Marked discomfort that prevents taking fluid or food by mouth, thus requiring intravenous feeding

Table 3. Pain severity (mean ± SE) and mucositis grading during the study period.

Variable	Group	1st day	7th day	14th day	p value
Pain severity	experimental	2.22±0.43	2.95±0.42	2.7±0.38	0.155
	control	0.55±0.28	2.00±0.51	2.85±0.58	<0.001
Physician-judged mucositis grading	experimental	0.55±0.15	1.10±0.12	0.95±0.13	<0.05
	control	0.50±0.17	0.85±0.18	1.2±0.20	<0.001
Patient-judged mucositis grading	experimental	0.60±0.15	0.75±0.16	0.60±0.15	0.598
	control	0.30±0.16	0.90±0.25	0.95±0.23	<0.01

was not effective in improving signs of mucositis. However, these findings are all based on a randomized controlled trial with a sample size of 40 patients, who were not blind about their treatment. In 2003, reviewing the side-effects of radiotherapy and chemotherapy introduced ice chips and benzydamie as the most effective agents for prophylaxis of mucositis [8].

A Cochrane systematic review in 2002 assessed the articles on mucositis and oral candidiasis. According to this report, among 6 prophylactic agents for mucositis, ice chips were the only effective factor. However, the authors pointed out that evidence of mucositis prevention for ice chips is weak and unreliable [4]. In another study on 60 patients, the effect of cryotherapy on mucositis in patients receiving chemotherapy was evaluated. Similar to the results of the present study, mucositis severity based on patients' opinion was significantly lower subsequent to the use of ice chips; however, according to dentists' opinion the results were different. They reported that based on dentists' opinion, mucositis severity in the intervention group was significantly lower than that in the controls [7].

In this study, based on previous studies, cryotherapy was applied by asking patients to hold ice cubes in their mouth for five minutes before and after each radiotherapy session during a two-week period. One of the shortcomings is that there is not a definite approach for applying cryotherapy in the oral cavity, which leads to inconsistencies and complicates the comparison of different studies. Therefore, there is a need for the establishment of a detailed method for the application of cryotherapy in the oral cavity. Moreover, larger sample sizes and longer study periods will assist in achieving more reliable results.

In conclusion, although clinicians could not find any improvements in the signs of oral mucositis subsequent to the use of ice cubes, patients reported significantly less pain and symptoms of mucositis.

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