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RESEARCH ARTICLE

Efficacy of Topical and Systemic Vitamin E in Preventing Chemotherapy-Induced Oral Mucositis

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Abstract

Background: There is still no consensus regarding the optimum treatment of chemotherapy-induced oral mucositis and its management is still mainly supportive. Vitamin E has been shown to be effective in reducing the symptoms of oral mucositis.
Objectives: Aim of this study was to assess the efficacy of prophylactic systemic and topical vitamin E in reducing the signs and symptoms of oral mucositis in patients receiving chemotherapy.
Patients and Methods: We conducted a placebo-controlled randomized clinical trial among 76 patients with a hematologic malignancy treated with chemotherapy. Patients were randomly assigned into three groups: supplementation with vitamin E paste (group 1) and 200 mg/d vitamin E pills (group 2). Group 3 received placebo paste, identical in appearance and taste to the vit E paste, but consisting of the vehicle only. Patients were advised to use the administered medication from two days before each cycle of chemotherapy till at least 20 days after completion of each cycle. Oral exam was performed 10-14 days after each cycle of chemotherapy.
Results: Patients in group 2 and 3 did not show any difference in degree of mucositis or severity of pain. However, after the second cycle, patients who were treated with topical vitamin E showed significantly less oral pain, and had fewer cases of severe mucositis compared to groups 2 and 3.
Conclusions: Topical vitamin E could be beneficial in reducing the severity of oral mucositis, but no therapeutic gain would be achieved by using systemic vitamin E in this regard.

Keywords: *Vitamin E; Chemotherapy; Oral Mucositis*

1. Background

Chemotherapy-induced oral mucositis is an important cause of patient discomfort during cancer therapy. Despite the use of a variety of preventive measures and development of various medications as well as targeted therapeutic interventions, its management is still mainly supportive (1). The incidence and severity of oral mucositis is influenced by the type of administered treatment and by the patient-related factors. In patients who receive conventional chemotherapy, oral mucositis can develop in 40%, and this can be increased to up to 70% in patients undergoing conditioning therapy for bone marrow transplantation (2). Mucosal toxicity during chemotherapy depends on various factors including type of antineoplastic agent, therapeutic regimen, duration of treatment and dose intensity, concomitant medication, and previous mucosatoxic treatments (2, 3). Mucositis may appear as early as three days after exposure to chemotherapy but more typically within five to seven days (4). Until today, a consensus on the prophylaxis and therapy of anticancer therapy-related mucositis has not yet been obtained. Many studies describe the use of various drugs as a therapeutic or preventive measure in patients diagnosed with mucositis; for many, however, the recommendations for using drugs are based on scientific evidence of low level of credibility due to low number of studied patients, heterogeneous groups, and simultaneous administration of several drugs (5). Vitamin E is an antioxidant agent which may limit tissue damage from free oxygen radicals and, thus, may reduce the severity of mucositis during cancer treatments (6).

2. Objectives

The purpose of this study was to assess the efficacy of prophylactic systemic and topical vitamin E in reducing the signs and symptoms of oral mucositis in patients receiving chemotherapy.

3. Patients and Methods

We conducted a randomized placebo-controlled clinical trial on patients undergoing chemotherapy for a hematologic malignancy.

Inclusion criteria were as follows: At least 18 years of age, diagnosis of a hematologic cancer (leukemia or lymphoma), and non-smoker and non-alcoholic. Patients who were supposed to receive head and neck radiotherapy as part of their treatment were excluded from the study. Besides, patients who were taking anticoagulant therapy were excluded, as some studies have shown that vitamin E may increase the bleeding tendency (7).

All patients were advised to follow the provided instructions including maintaining optimum oral hygiene, brushing teeth at least twice a day with a soft toothbrush, and using fluoridated toothpaste. They were also advised to avoid hard or spicy food as well as very hot or very cold food and beverages. The trial started with 76 patients who were allocated randomly (by block randomization) into three groups (26 patients in group 1, 24 in group 2, and 26 in group 3). Patients in group 1 were prescribed topical vitamin E twice a day (after breakfast and before sleep), group 2 received vitamin E pills twice a day (200 mg), and patients in the third group received placebo paste. All patients were studied for 4 chemotherapy cycles, and the highest grade of mucositis after each cycle was recorded for each patient. In case of occurrence of severe mucositis, patients were treated accordingly (e.g. magic solution, benzydamine, opiods, etc) until alleviating the symptoms.

Liquid form of vitamin E is actually oil, which is easily washed away by saliva. In order to overcome this problem, based on previous experience (8), we formulated a semi-solid white paste containing vitamin E with acceptable consolidation and good adherence to mucous membranes. For each day of the study, patients in group 1 were provided with two tubes of paste, each of them containing 1 g of vitamin E. Patients in groups 1 and 2 were instructed to use their medication since two days before till at least 20 days after completion of each cycle of chemotherapy.

Oral mucosa in all groups routinely was examined by dentists (who were blinded) between 10 to 14 days following the completion of each cycle of chemotherapy. However, patients were advised to attend at any other time in case of development of severe mucositis.

In each visit, oral mucosa was examined and a score was given to it based on the degree of mucositis using a 5-point scale based on the World Health Organization (WHO) oral mucositis grading scale (Table 1). Furthermore, the severity of pain was measured using visual analogue scale (VAS) which was scaled from 0 to 10 (0 = no pain, 10 = worst imaginable pain). To assess the severity of pain, ANOVA was used. Then, in order to compare the groups, Tukey's test and Mann-Whitney U test were used. To assess the quality of pain, Kruskal-Wallis test was used. The results were analyzed using SPSS software version 18.

4. Results

The characteristics of patients in different groups of the study are shown in Table 2, and the results of the study after the second cycle of chemotherapy are shown in Table 3.

After the second cycle of chemotherapy, 10 patients were excluded from the study due to various reasons (death, severe mucositis, noncompliance, etc). The results of the study after the third cycle of chemotherapy are shown in Table 4. After the third cycle, the other 15 patients were excluded from the study because of above-mentioned reasons. And the results of the study after the fourth cycle of chemotherapy are shown in Table 5.

Table 1. WHO Oral Mucositis Grading Scale

Grade	Description
0, none	None
Grade I, mild	Mild soreness, mild dysphagia, solid diet possible
Grade II, moderate	Moderate soreness, moderate dysphagia, soft or liquid diet possible
Grade III, severe	Severe pain, severe dysphagia, liquids only
Grade IV, life-threatening	Oral alimentation impossible

Table 2. Characteristics of Patients in Different Groups

	Group 1	Group 2	Group 3	P Value
Number of patients	26	24	26	NS
Gender				NS
Male	14	12	15	
Female	12	12	11	
Age, y [a]	30.81 ± 5.7	32.28 ± 10.92	29.18 ± 8.8	NS

[a] Values are presented as mean ± SD.

Table 3. Results of the Study After the Second Cycle of Chemotherapy [a]

Variables	Group 1	Group 2	Group 3	P Value
Number of patients	26	24	26	NS
Percentage of grade III or IV mucositis, %				
After 1st cycle	7.6	8.3	7.6	NS
After 2nd cycle	11.5	12.5	15.3	NS
Mean VAS score				
After 1st cycle	1.2	1.3	1	NS
After 2nd cycle	2	1.9	2.2	NS

[a] Abbreviation: VAS, visual analogue scale.

Table 4. Results of the Study After the Third Cycle of Chemotherapy

	Group 1	Group 2	Group 3	P Value
Number of patients	23	21	22	NS
Percentage of grade III or IV mucositis, %	21.7	33.3	31.8	0.01
Mean VAS score	2.43	3.8	4.4	0.05

Table 5. Results of the Study After the Fourth Cycle of Chemotherapy [a]

	Group 1	Group 2	Group 3	P Value
Number of patients	19	16	14	NS
Percentage of grade III or IV mucositis, %	26.3	43.7	42.8	0.01
Mean VAS score	2.9	4.33	4.86	0.001

[a] Abbreviation: VAS, visual analogue scale.

As it is shown, up to the second cycle of chemotherapy there was no difference between the groups either in the severity of mucositis or in the VAS score. However, after the third cycle, the number of patients with grade III or IV mucositis was significantly higher in groups 2 and 3 compared to group 1. The same trend turned out to be true for VAS score, as after the third cycle, patients in groups 2 and 3 reported higher VAS scores compared to the patients in group 1. No statistically significant difference was found in mucositis or VAS scores between groups 2 and 3. The trial was stopped after the fourth cycle of chemotherapy because continuing it was not considered ethical and afterwards all the patients were provided with vitamin E pastes, and in some cases, other treatment modalities were used to alleviate their symptoms.

5. Discussion

Chemotherapy-induced oral mucositis is a prominent cause of patient discomfort during cancer therapy. Oral mucositis can cause oral pain, poor nutrition, delays in administration of chemotherapy or reductions in the doses of chemotherapy drugs, increased length of inpatient stays, and even life threatening infections (9). Both patient and treatment-related factors influence the severity of mucositis, and incidence as well as severity may vary from patient to patient. Oral complications remain as the major source of illness despite the use of a variety of agents to prevent them, and despite development of various medications as well as targeted therapeutic interventions; however, its management is still mainly supportive and includes nutritional support, pain control, oral decontamination, palliation of dry mouth, and management of oral bleeding (1).

Patients who most frequently develop severe courses of oral mucositis are patients with head and neck cancer who receive chemotherapy simultaneous with radiotherapy.

In patients who receive conventional chemotherapy, oral mucositis develops in 40%, and this can be increased up to 70% in patients undergoing conditioning therapy for bone marrow transplantation (2). The pathogenesis of chemotherapy-induced oral mucositis is thought to involve direct mucosal injury, inducing apoptosis, toxic effect of releasing of inflammatory mediators, loss of protective salivary constituents, and therapy induced neutropenia (2, 10). Mucosal toxicity during chemotherapy depends on various factors including type of antineoplastic agent, therapeutic regimen, duration of treatment and dose intensity, concomitant medication, and previous mucosatoxic treatments. It is estimated that there is an increased risk of mucositis development with bolus and continuous infusions compared to the prolonged or repetitive administration of lower doses of cytotoxic agents (2, 3). Methotrexate, doxorubicin, 5-fluorouracil, bleomycin, vinblastine, docetaxel, and paclitaxel are some examples of chemotherapeutic agents that are more commonly associated with oral mucositis. The risk of mucositis is exacerbated when these agents are given in high doses, in frequent repetitive schedules, or in combination with radiation (4). Mucositis may appear as early as three days after exposure to chemotherapy but more typically within five to seven days. Progression to ulcerative mucositis typically occurs

within seven days after the start of chemotherapy. Uncomplicated by infection, mucositis typically heals completely within two to four weeks (4). Although a variety of new approaches to oral mucositis have been taken, a single efficacious intervention or agent for the prophylaxis or management of chemotherapy-induced oral mucositis has not yet been identified and management of oral mucositis is still mainly supportive and includes nutritional support, pain control, oral decontamination, palliation of dry mouth, and management of oral bleeding (1). Vitamin E is an antioxidant agent which may limit tissue damage from free oxygen radicals and thus, may reduce the severity of mucositis during cancer treatments (6). Chemotherapy generates free radical species, which require antioxidants to be neutralized. Vitamin E acts on a cellular level by protecting the cell membrane and preventing peroxidation. Studies have found vitamin E to be effective when it is applied topically twice per day. Vitamin E is considered to have a very low toxicity, and is generally well-tolerated. It is not mutagenic, teratogenic nor carcinogenic. Humans show few side effects following supplemental doses below 2100 mg of alpha-tocopherol per day for a few weeks to a few months. While high dose systemic doses of vitamin E may increase the bleeding tendency, there are no data depicting such a side effect for its topical use (7, 11). Topical use of vitamin E has been suggested to be able to fight free radicals generated during anticancer therapy, and stabilize the membranous potential (2, 5). In a randomized clinical trial including patients who had experienced chemotherapy-induced oral mucositis, the topical application of vitamin E was found to have a significantly superior activity compared with application of placebo (12). However, Ghoreishi (13) who studied the influence of vitamin E supplementation on the frequency, intensity and severity of mucositis in patients after bone marrow transplantation, did not confirm its prophylactic and therapeutic activity (5, 13). El-Housseiny et al. (14) in their study on 80 patients evaluated the effectiveness of systemic as well as topical application of vitamin E in the treatment of chemotherapy-induced oral mucositis. They concluded that while no significant improvement was observed by using systemic vitamin E, its topical application was an effective measure for the treatment of chemotherapy-induced oral mucositis (14). The present study also showed that applying topical vitamin E can be an effective method in alleviating the signs and symptoms of chemotherapy-induced oral mucositis, and similar to the previous studies, no therapeutic benefit was achieved by prescribing systemic vitamin E (14). Furthermore, there is controversy on the safety of antioxidant consumption during chemotherapy. Some experts believe that antioxidants may directly oppose the mechanisms of conventional cancer treatment, as many cancer treatments aim to destroy cancer cells by causing oxidative damage (15-18).

Because of these controversies and the fact that systemic vitamin E has not shown any therapeutic benefit in different studies, its prescription does not seem to be justified.

5.1. Limitations

The most important limitation of this and other similar studies is the fact that patent's compliance cannot be evaluated accurately, and therefore, we had to trust the patients and their families regarding the way and timing of using their prescribed medication. Furthermore, mainly because of cultural habit of taking over the counter and especially herbal medication by the patients, we were not able to make sure that the patients had not actually used any medication (for their mucositis) other than the prescribed ones.

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