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ORIGINAL ARTICLE

Effects of Topical Vitamin E Mouthwash in Preventing Oral Mucositis in Allogenic Hematopoietic Stem Cell Transplant Patients: A Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Oral mucositis is considered a frequent complication of conditioning regimen in patients undergoing hematopoietic stem cell transplantation (HSCT). Mucositis develops due to direct and indirect damage to the epithelial cells and production of reactive oxygen species (ROS). Vitamin E has shown positive effects in reducing production of ROS or improving its elimination. The aim of this study was to evaluate the effects of vitamin E mouthwash in lowering the incidence and severity of acute mucositis in patients undergoing allogenic HSCT.

Methods: The current study was designed as a double bind, placebo controlled randomized clinical trial. Eighty patients were randomized in a 1 to 1 method to receive either placebo or vitamin E mouthwash. Patients in vitamin E group received 400 International Units of vitamin E in form of mouthwash twice daily and placebo group received a mouthwash with equal composition but without vitamin E, starting the day of the chemotherapy initiation and continuing it for 14 days.

Results: Vitamin E mouthwash effectively reduced the duration of oral mucositis compared to placebo (P-value 0.02). The difference between placebo and vitamin E groups in terms of mucositis severity did not reach statistical significance (P=0.35). No difference in length of hospital stay was observed (P=0.46).

Conclusion: Vitamin E mouthwash could effectively reduce the duration of oral mucositis in allogenic HSCT patients. Further studies are required to show the effects of topical vitamin E in preventing the development of oral mucositis.

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Introduction

Oral mucositis (OM) is considered a frequent consequence of chemotherapy with variable incidence rates in different patients and disease settings. The incidence of severe forms of OM in patients undergoing HSCT has been reported to be about 30 to 60 percent. Even though, it might occur in nearly one hundred percent of patients when it is accounted for all grades of OM.[1, 2]

The development of chemotherapy-induced mucosal damage begins with the injury to the nuclear and

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non-nuclear materials of the mucosal cells by chemotherapeutic agents. The result is production of ROS and inflammatory mediators such as nuclear factor-kB (NF-kB), tumor necrosis factor α (TNF-α), Interleukin-6 (IL6) and Interleukin-1β (IL-1β). This would initiate an inflammatory cascade involving macrophages and matrix metalloproteinases (MMP) which results in mucosal ulceration.[3] Damage begins shortly after the insult to the epithelium. Mucosal changes in the oral cavity might be of clinical significance in about four days after chemotherapy initiation, although no obvious mucosal lesion might be present at early stages.[4] In patients undergoing HSCT, development of OM mostly occurs in the first 30 days after transplantation.[5]

Alkylating agents and antimetabolites have been reported to cause more severe OM compared to other agents. OM incidence has been reported to be higher in males, patients with lower Body Mass Index and those with a higher burden of oral cavity microbial colonization.[6] Reactivation of herpes simplex virus, overgrowth of fungal microflora of oral cavity which could disseminate in case of mucosal ulceration and increased incidence of alpha-hemolytic streptococcal bacteremia could be the common infectious complications of OM.[7-11] Oral intake of the patients could also be affected by OM and complicate the hospitalization and recovery courses.[12] Late complications of OM could include xerostomia and pain.[13]

To date, prophylactic and therapeutic options for OM have been limited. Most interventions are directed at lowering mucosal delivery of the chemotherapy by using local cold remedies and improving oral hygiene.[14] The effects of different medical mouthwashes have been doubtful so far.[15] Palifermin has been the only approved treatment for oral mucositis in patients undergoing autologous HSCT patients so far.[16]

Early studies which included limited numbers of patients have shown positive effects for topical vitamin E oil in the treatment of OM.[17] These effects have been further evaluated in clinical trials and meta-analyses studies and a positive effect for vitamin E in management of OM have been suggested.[18] Supplementation with vitamin E has shown positive effects in reducing disease-induced ROS production in cancer patients.[19] It is also shown that vitamin E can effectively prevent the production of ROS induced by chemotherapy.[20] Systemic supplementation of vitamin E could not yield a clinically significant result in lowering the incidence or severity of OM. It has been suggested that poor absorption of vitamin E and low concentration in areas of OM could be one possible reason for this observation.[21]

Considering the positive effects of vitamin E in management of OM and the information about its effects in counteracting ROSs, this study was designed to evaluate the effectiveness of topical vitamin E in lowering the incidence as well as the severity of OM in patients undergoing allogeneic HSCT.

Materials and Methods

Study Design

The current study was designed as a double blind, placebo-controlled randomized clinical trial. The study was performed between August 2018- July 2019. The study protocol was reviewed and approved by the ethics committee of Tehran University of Medical Sciences with the approval code of IR.TUMS.TIPS.REC.1397017. The study protocol was also registered in the Iranian Registry of Clinical Trials with registration number of IRCT20180416039325N1. All the patients were asked to sign an informed consent before enrollment into the study.

Study Population

Adult patients who were diagnosed with acute myeloid leukemia or acute lymphoblastic leukemia and were assigned to undergo allogeneic HSCT were considered eligible to be enrolled in the study. They received conditioning regimen with combination of busulfan 0.8 mg/kg every 6 hours intravenously for a total of 16 doses beginning 7 days before HSC transfusion, followed by cyclophosphamide 60 mg/kg intravenously daily for two doses (Bu/Cy regimen).

All patients received an immunosuppressive regimen consisting of methotrexate and cyclosporine in the following order: cyclosporine 1.5mg/kg intravenously; 3 days prior to HSCT to 7 days after transfusion continued by a dose of 3mg/kg until the patient could receive oral medication and then 6 mg/kg orally to reach a trough level of 100-300 microgram/ml along with methotrexate 10 mg/m^2 day 1, and 6 mg/m^2 on days 3, 6 and 11 after HSC transfusion.

All patients had been completed dental evaluation before the proedure. Routine oral care consisting of mouthwash with normal saline and chlorhexidine 0.2% every 8 hours was provided per protocol for all patients.

Patients with active OM or active bleeding at the time of the admission, history of vitamin E allergy or any kind of hypersensitivity reactions to it or who were receiving drugs that had interaction with vitamin E were excluded from the study.

All patients received pneumocystis jiroveci prophylaxis with trimethoprim-sulfamethoxazole, fungal prophylaxis with fluconazole and viral prophylaxis with acyclovir. The number of patients in each group was 40, with a Confidence Interval of 95% and a statistical power of 80%, based on previous studies which had demonstrated about 40% reduction in the incidence of OM.[22]

Placebo and Medication Mouthwash Preparation

The pharmaceutical science department of faculty of pharmacy prepared topical solutions for mouthwash in sealed; amber, light-resistant containers specifically coded for each patient. The placebo mouthwash compound was consisted of 175 ml of distilled water, 175 ml of pharmaceutical-grade glycerin, 17.5 ml of polysorbate 20, 1750 mg of sodium benzoate and 130 mg of aspartame. Topical solution of vitamin E for mouthwash contained 14800 IU vitamin E oil (Merck Pharmaceuticals), providing 400 IU vitamin E per 10 ml of mouthwash. Vitamin E and glycerin solutions have been shown to be compatible and stable in previous studies.[23, 24] Based on

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recommendations of National Health Service, the product was considered to have a shelf life of 28 days.[25]

Study Groups and Procedure

Forty patients were enrolled in each group of the study. Patients in each group were given instructions to administer 10 ml of mouthwash twice daily, hold the mouthwash for as long as they could and not to swallow it. In case the patients were supposed to use other mouthwashes, the study mouth wash was scheduled to be used last, so the persistence of the mouthwash in the oral cavity be assured. Patients were instructed not to eat or drink anything for at least an hour after mouthwash application and after that swish the oral cavity with water and spit if they wanted to consume foods or beverages. The duration of the mouthwash application was scheduled to begin on the day of the initiation of chemotherapy and end 7 days after stem cell transfusion (14 days).[26] The researchers, nurses, and patients were blinded in this study and only the compounding pharmaceutical expert was aware of the product composition. The blocked randomization procedure was carried out using a random number table.

Study Outcomes and Data Collection

Primary outcome of the study was to evaluate the effects of topical vitamin E in lowering the incidence and severity of oral OM in patients undergoing allogeneic HSCT.

Patients underwent daily examination of oral cavity and grading of OM were recorded in specified forms. The grading of OM severity was assigned using National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (NCI CTCEA v5) which is shown in Table 1.[27]

Statistical Analysis

The analysis was carried out using SPSS software version 23. Two samples independent t-test was used to compare continuous data. In order to analyze the qualitative and non-parametric data, the Pearson's Chi-Square test was employed. A P-value of less than 0.05 considered significant. Data with normal distribution are reported as mean and Standard Deviation (SD), whereas data without normal distribution are reported as median with Inter Quartile Range (IQR).

Results

Demographic and Baseline Characteristics

Overall, 80 patients were enrolled in this study. Four of the patients in the placebo group did not complete the study because of death or intolerance. Meanwhile, 5 in the vitamin E group were not included in the final analysis because of death, noncompliance, infection or heart failure. There was no significant difference in demographic data and laboratory tests between the case and the placebo group. Flow diagram of the study can be observed in Figure 1.

Outcomes of the Study

The incidence of OM observed in this study was 100%. Vitamin E mouthwash significantly reduced the duration of OM in the patients (P=0.02), but the difference in other outcomes did not reach a statistical significance. The topical solution of vitamin E could not lower the

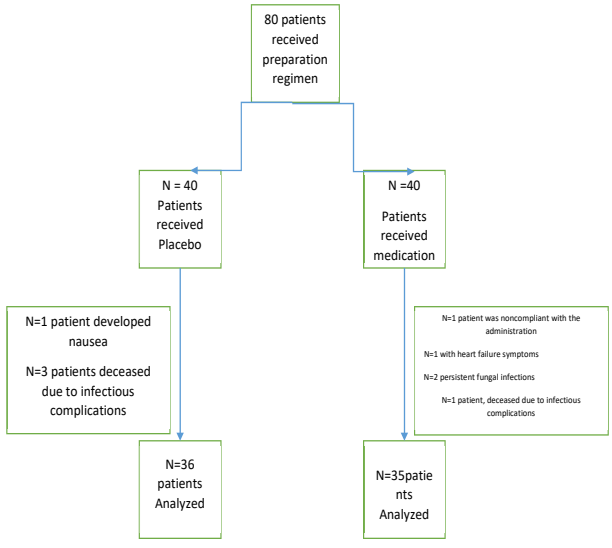


Figure 1: Flow diagram of the study

Table 1: NCI-CTC classification of oral mucositis seveirty

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oral mucositis	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain, interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Table 2: Comparison of mucositis onset, duration and grade in patients who received placebo or vitamin E mouthwash

Finding	Groups	Group A (mean and SD or median and IR)	Group B (mean and SD or median and IR)	P value
OM duration (days) [Median(IQR)]		7 (4)	6 (3)	0.02
Onset of OM development after stem cell transfusion		6.69 (4.28)	6.8 (3.63)	0.91
Onset of OM development after chemotherapy initiation		13.69)4.28(	13.80)3.63)	0.91
Highest grade of mucositis	Grade1 (%)	17 (47.2%)	23 (65.7%)	0.35
	Grade2 (%)	16 (44.4%)	10 (28.6%)	
	Grade3 (%)	2 (5.6%)	2 (5.7%)	
	Grade4 (%)	1 (2.8%)	0 (0%)	

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occurrence of different grades of OM (P=0.35).

Table 2 shows the statistical data on the mucositis in patients who received placebo or vitamin E mouthwash.

Discussion

To the best of our knowledge, this is the first placebo-controlled, double-blind clinical trial to evaluate the prophylactic effects of topical vitamin E on OM in HSCT patients. The results of the study showed that topical vitamin E decreased the duration of OM, but not the severity or incidence of occurrence of OM when compared to placebo.

All the patients involved in this study experienced OM. This rate of OM is in agreement with reports of previous studies. In a study by Vokurka et al. including a diverse population of patients, the incidence of OM with Bu/Cy conditioning regimen reported to be 100 percent. The severe types of involvement occurred in about 40 percent of the patients, and the duration of mucosal involvement in this study was reported to be about 11 days. The onset of OM in this study was 12 days after initiation of conditioning regimen which was almost similar to the findings of our study of about 13 days.[28] The study included patients with different base-line hematologic malignancies. Total duration of mucosal involvement in the current study was shorter than what is reported in the abovementioned study. This contrast could be explained due to the diversity of the patient population in the former study.

Another study also reported that the incidence of grade 2 or higher OM in patients receiving conditioning chemotherapy with Bu/Cy regimen was about 50 percent, although no patient with ALL was included in this study and the number of patients involved was limited.[29] The rate of grade 2 or higher OM development in the current study was somehow close to this range with about 34 and 53 percent of patients experiencing this type of involvement in vitamin E and placebo groups, respectively. Another study in patients with chronic myelogenous leukemia who received Bu/Cy conditioning regimen for HSCT reported OM of grade 2 or higher in 50% of the patients.[30]

As stated earlier, ROS production and the following cascade play the central role in the development and progression of OM and vitamin E is of proven benefit in restoring the effects of the enzyme Super Oxide dismutase (SOD) which is responsible for ROS elimination.[3] This beneficial effects of vitamin E initiated the idea for the prophylactic use of systemic vitamin E in radiotherapy-induced OM.[31]

The prophylactic efficacy of vitamin E has been evaluated in only one clinical trial to date. In a study by Arash Azizi et al., the effects of the topical paste of vitamin E was compared with systemic vitamin E and topical placebo. The results of the study showed that topical paste of vitamin E in three cycles of chemotherapy significantly lowered the incidence of severe forms of OM; however, the effects were not significant during the first two chemotherapy cycles.[22] It could be proposed that topical use of the vitamin E might be a good option for localized lesions, but in order to prevent development of OM development, it must be applied to all surfaces of the oral cavity. In contrast, our study was placebo-controlled, and patients were evaluated daily by the researcher.

Vitamin E could not lower the occurrence of OM in patients included in our study. One theoretical reason could be the characteristics of the topical formulation used in our study. Although the formulation was designed for optimal solubility and was stable, it might not have been able to sustain a high concentration of vitamin E in the mucosa for a prolonged duration. In studies that evaluated the effects of vitamin E in the treatment of OM, the oil forms were used and applied directly to lesions.[32] So the high concentration of vitamin E might be necessary for a reduction in the severity of OM, and it might have not been achieved with the formulation utilized in our study. The low concentration of vitamin E in the site of OM, has been suggested as the reason of failure for systemic forms of vitamin E in the prevention of OM patients.[21]

In fact, previous studies in patients undergoing radiotherapy have shown beneficial effects of topical vitamin E in preventing OM. In a study by Ferreira et al. fifty-four patients with oral cancers received topical vitamin E oil 400 milligrams before radiotherapy sessions. Vitamin E significantly reduced the development of OM in this subset of patients.[33] Although this study was placebo-controlled and resulted in beneficial effects, the method of application might not be useful in patients undergoing chemotherapy.-

Our study assessed comparatively the effect of topical vitamin E and placebo only in a specific subset of patients undergoing HSCT. It is prudent to evaluate the effects of prophylactic topical vitamin E in other kinds of malignancies receiving different chemotherapy regimens and or conditioning regimens. Meanwhile, duration of follow-up could be extended to evaluate for chronic mucosal sequels such as xerostomia.

Conclusion

The results of the current study demonstrate a positive effect for prophylactic topical vitamin E in shortening the duration of OM in allogeneic HSCT patients. Further studies are required to clarify any solid role for routine vitamin E application in this group of patients.

Conflict of Interest: None declared.

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