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Original Research Article

The efficacy of erythropoietin mouthwash in prevention of oral mucositis in patients undergoing autologous hematopoietic SCT: a double-blind, randomized, placebo-controlled trial

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Abstract

Oral mucositis (OM) as a complication of high-dose chemotherapy is frequently occurred in hematopoietic stem cell transplantation (HSCT) settings. Erythropoietin (EPO) has anti-inflammatory, antioxidant and wound-healing properties and therefore could have an important role in the prevention of OM. We conducted a double-blind, randomized, placebo-controlled trial to evaluate the EPO mouthwash effect on OM incidence and severity in 80 patients with non-Hodgkin's lymphoma, Hodgkin disease (HD) or multiple myeloma, undergoing autologous hematopoietic stem cell transplantation. Patients received either EPO mouthwash (50 IU/ml, 15 ml four times a day) ($n = 40$) or placebo ($n = 40$) from the starting day of high-dose chemotherapy until day +14 after transplantation or until the day of discharge from the hospital, whichever occurred first. OM was evaluated daily for 21 days after transplantation or until resolution of OM according to World Health Organization oral toxicity scale. The incidence of OM (grades 1–4) in the EPO mouthwash group and control group was significantly different (27.5% vs 77.5%, $p < 0.001$). The mean ± SD of two other parameters of OM including maximum intensity OM score (0.60 ± 1.06 vs 1.67 ± 1.27) and average intensity OM score (0.47 ± 0.80 vs 1.28 ± 0.86) was significantly lower in the intervention group ($p < 0.001$). Moreover, the mean ± SD duration of OM was also significantly shorter among the EPO mouthwash recipients (1.92 ± 3.42 days vs 5.42 ± 3.86 days, $P < 0.001$). Also, the duration of neutropenic fever was significantly shorter in the intervention group (2.12 ± 2.42 days vs 3.95 ± 4.01 days, $p = 0.016$). It is concluded that EPO mouthwash can reduce the incidence and duration of OM.

Keywords: **EPO mouthwash; oral mucositis; high-dose chemotherapy; hematopoietic SCT**

Introduction

Administration of high-dose chemotherapy (HDC) as part of the conditioning regimens prior to hematopoietic stem cell transplantation (HSCT) has a direct cytotoxic effect on the oral epithelium resulting in injury or disruption of the mucosal barrier [1].

Oral mucositis (OM) as one of the most debilitating side effects of HSCT usually characterized as painful, diffuse ulcerative lesions and is more likely to occur with certain chemotherapy drugs and more intensive protocols [2–4]. A number of treatment factors have been shown to influence the duration and severity of mucositis, including the site and dose of radiation, and the type and dose of cytotoxic agents [5–7]. Serious clinical consequences of OM include pain, increased risk of infection, impaired nutritional intake and extended hospitalization [8]. Mucosal damage is a multi-step process and results from damage to epithelial cells ranging from mild inflammation to extensive ulceration and begins to resolve at about the time of neutrophil recovery following HSCT [9,10]. The current management of OM is primarily palliative and supportive [11].

Although different agents have been evaluated in the prevention or treatment of OM following HDC, the effective therapy remains unclear [12]. Palifermin is the only approved agent to decrease the incidence and duration of severe mucositis associated with myelotoxic chemotherapy [13].

It seems that the main initiating factor of mucositis is the generation of oxidative stress and reactive oxygen species (ROS) during chemotherapy or radiation. Furthermore, following the initiation of OM by ROS, activation of nuclear factor kappa B as a main player and increasing levels of pro-inflammatory cytokines including IL-1β, IL-2, IL-6 and TNF-α seems to have a role in development of OM [14–18]. Therefore, the use of antioxidant and anti-inflammatory agents could be effective in reducing the incidence or severity of this side effect. It is indicated in several studies that antioxidant agents have some benefits in prevention of OM induced by chemotherapy and/or radiation therapy [19–22].

Erythropoietin (EPO), as a hematopoietic factor, produced mainly in the kidney via an oxygen-sensing mechanism and enhances red blood cell production by stimulating the proliferation of erythroid progenitors in the bone marrow [23,24]. Recombinant human EPO is therapeutically applied for the treatment of anaemia [25].

Moreover, EPO exerts anti-inflammatory effects by inhibiting NF- kappa B-dependent formation of pro-inflammatory cytokines such as TNF-α, IL-1 β, IL-6, IL-12 and IL-23 sub-units as well as intercellular adhesion molecule-1 and thus reducing local and circulating levels of these disease related cytokines [26,27]. Also, EPO treatment decreases production of ROS in neutrophils, which may improve innate immune responses against invading bacteria [28]. Furthermore, recent studies have considered EPO as a potent anti-inflammatory cytokine in inflammatory disorders and infectious diseases such as chemical tissue damage, Salmonella infection, trauma, myocardial infarction and chronic uremic inflammation in patients on maintenance hemodialysis [26,29–31].

As an antioxidant, EPO reduces ROS, membrane lipid peroxides and external phosphatidyl serine and enhances glutathione content, Superoxide dismutase and catalase activity of blood cells in patients undergoing hemodialysis [32,33]. EPO is a highly sialidated glycoprotein and contains more basic than acidic amino acids and many charged residues that may have mediated its scavenging activity for ROS [34,35].

In one animal wound-healing model, topical treatment of the wounds of diabetic rats with EPO-containing creams decreased the extent of apoptosis and the areas of the open wound in a dose-dependent manner [36].

However, there are no randomized studies addressing the effect of EPO mouthwash on incidence and severity of HDC-induced OM in patients undergoing autologous HSCT. Therefore, we performed a prospective, double-blind, randomized trial comparing EPO mouthwash with placebo for prevention of OM in this setting.

Patients and methods

We performed a double-blind, randomized, placebo-controlled clinical trial from February 2014 to March 2015 in the Hematology–Oncology and Stem Cell Transplantation Research Center (Shariati Hospital), Tehran University of Medical Sciences, Tehran, Iran. The study protocol was reviewed and approved by the Ethics Committee of the institution, and written informed consent was obtained from all patients before enrollment (Trial registration ID: IRCT2015042518842N8).

Patients

A total of 80 adult patients with non-Hodgkin's lymphoma (NHL), Hodgkin disease (HD) or multiple myeloma (MM), undergoing autologous HSCT, were enrolled in the study by the principal investigator. All patients had adequate cardiac, pulmonary, renal and hepatic function, as determined by the institutional protocol and were at least 18 years old. Subjects who had a Karnofsky performance status <70% or participated in another study using an unlicensed product were excluded from the study. Demographic parameters including age, sex, weight, height, BMI, type of disease and complete remission rate were recorded for each patient. Baseline characteristics of patients are shown in Table 1. Chemotherapy regimen and supportive care were administered according to the institutional clinical protocol. Conditioning regimens that were used included high-dose melphalan (100 mg/m^2 i.v. daily for 2 days) for patients with MM and the high-dose combination chemotherapy (carboplatin 750 mg/m^2 i.v. daily for 2 days, etoposide 300 mg/m^2 i.v. daily for 2 days, cytarabine 300 mg/m^2/dose i.v. two doses in each day for 2 days and melphalan 140 mg/m^2 i.v. for 1 day) for patients with NHL and HD. All patients who undergo autologous transplant received peripheral hematopoietic stem cells 1 day after completion of chemotherapy. A complete orodental examination was performed for all patients in order to detect and eliminate existing sources of infection, such as caries and periodontal disease. All enrolled patients received a similar protocol for prevention of OM, which included oral hygiene care in addition to 20 drops of nystatin every 3 h, mouthwashes containing 10 ml chlorhexidine 0.02% plus 10 ml diluted povidone iodine every 3 h. Fungal, viral and Pneumocystis jiroveci prophylaxis consisted of fluconazole, acyclovir and trimethoprim/sulfamethoxazole respectively.

Study design

Patients were randomly allocated to EPO mouthwash or control group in a blocked randomization schedule. Recombinant human EPO was kindly supplied by Pooyesh Darou Factory, Tehran, Iran, 10 000 IU/ml Ampoules. The

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Table 1. Baseline characteristics of patients

Characteristic	*EPO mouthwash group (n = 40)*	*Control group (n = 40)*	*p-value*
Male sex, *n* (%)	22 (55%)	19 (47.5%)	0.262
Age (year)	43.37 ± 13.67[a]	45.07 ± 16.26	0.614
Weight (kg)	75.24 ± 15.00	75.92 ± 15.32	0.842
Height (cm)	165.15 ± 9.99	163.75 ± 8.29	0.497
BMI (kg/m^2)	27.60 ± 5.05	28.49 ± 4.97	0.427
Disease type, *n* (%)			
NHL	10 (25)	10 (25)	
HD	9 (22.5)	9 (22.5)	1.000
MM	21 (52.5)	21 (52.5)	
Disease status before transplantation, *n* (%)			
CR_1	22 (55.0)	25 (62.5)	
CR_2	15 (37.5)	12 (30.0)	0.474
CR_3	3 (7.5)	1 (2.5)	

Abbreviation: CR, complete remission.
[a]Mean ± SD.

study group received 50 IU/ml EPO mouthwash in an aqueous vehicle. The control group received mouthwash vehicle (without EPO). The constituents of the mouthwash vehicle were sodium benzoate, sodium citrate, citric acid, sodium hydroxide, sugar and distilled water. Both patient randomization and drug preparation were performed in the pharmaceutical laboratory of Pharmacy Department. The drug or placebo mouthwash was supplied in a glass bottle and stored at 4°C. There were no differences in colour, flavour, taste or container of the study drug and the placebo. The mouthwashes were administered four times a day, 15 ml each time by the patients themselves from the starting day of conditioning regimen (day 1) to 14 days after transplantation or until the day of discharge from the hospital, whichever occurred first. All patients were expected to remain hospitalized until neutrophil recovery. Once the solution had been taken, oral intake was not permitted 1 h after administration. Both treatment groups received identical oral hygiene instructions such as tooth brushing after each meal and rinsing of the oral cavity.

The study sample size ($n = 80$, 40 participants were required in each study group) was calculated assuming a 30% decrease in the incidence of grade 2–4 OM, considering a confidence interval of 95% and a statistical power of 80% [8,21].

Primary outcomes

OM incidence, severity and duration were evaluated as primary study outcomes using five-grade World Health Organization (WHO) oral toxicity scale (grade 0: none; grade 1: soreness ± erythema; grade 2: erythema, ulcer and patient can swallow solid food; grade 3: ulcer with extensive erythema and patient cannot swallow solid food; grade 4: mucositis to the extent that alimentation is not possible) [37]. Patient assessment under supervision of the attending physician began from the starting day of conditioning regimen (day 1) and continued on a daily basis to 21 days after transplantation or until resolution of OM by a single clinical pharmacist trained for this study. The study participants, the attending physician and the outcome assessor were all blind to the treatment assignment.

Secondary outcomes

Several hematological indices were assessed including the duration of ANC under 500 cells/mm^3; neutrophil and platelet engraftment time (the time point after transplantation at which a patient can maintain a sustained ANC of >500 cells/mm^3 and a sustained platelet count of at least 20 000/mm^3 lasting for three consecutive days without transfusions) during hospital stay were measured. The incidence and duration of fever and length of hospital stay were also recorded during hospitalization. Moreover, the number of platelet and packed cell units transfused during hospitalization was documented.

Statistical analysis

Continuous variables were reported as mean ± SD and categorical data as percentage. Continuous and categorical data were compared between the two groups with independent sample *t*-test and chi-square test (or Fisher's exact test for dichotomous data) respectively. A p-value <0.05 was considered statistically significant, and a p-value between 0.05 and 0.08 was accepted as marginally significant.

Results

A total of 80 eligible patients were enrolled and completed the study. The demographic and baseline characteristics of the patients were comparable between study

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groups (Table 1). The use of parenteral opioid analgesics during OM presentation was not significantly different between study groups (1/40 patients in the EPO mouthwash group vs 3/40 patients in the control group, $p = 0.61$).

The incidence of OM (grades 1–4) in the EPO mouthwash group and control group was significantly different (27.5% vs 77.5%, $p < 0.001$). The differences between Mean daily WHO grades of OM were significant from the day 7 until day 13 after administration of HDC in study groups (Figure 1). There was also a significant decrease in the incidence of OM grades 2–4 in EPO mouthwash group compared with control group ($p = 0.003$). Four patients in the control group experienced OM grade 4, whereas none of the patients in the EPO mouthwash group developed this grade of OM. However, the lower incidence of severe OM (grades 3 and 4) in the EPO mouthwash group was marginally significant ($p = 0.077$). The frequency of OM grades in the study groups is illustrated in Figure 2. The mean ± SD of two other parameters of OM including maximum intensity OM score (0.60 ± 1.06 vs 1.67 ± 1.27) and average intensity OM score (0.47 ± 0.80 vs 1.28 ± 0.86) was significantly lower in the intervention group ($p < 0.001$). The mean ± SD duration of OM was also significantly shorter among the EPO mouthwash recipients (1.92 ± 3.42 days vs 5.42 ± 3.86 days, $p < 0.001$). There was no difference in the starting day of OM between two groups. The effect of EPO mouthwash on OM is summarized in Table 2.

All patients in this study had successful engraftment with no effect of EPO mouthwash on hematological recovery. No difference was observed between two groups regarding the duration of neutropenia as well as neutrophil and platelet engraftment time. Fever >38.3°C was observed in 70 (87.5%) patients during neutropenic phase. The duration of neutropenic fever was significantly shorter in the intervention group (2.12 ± 2.42 days vs 3.95 ± 4.01 days, $p = 0.016$) (Table 3). Packed cell and platelet transfusion requirements did not differ between two groups ($p = 0.16$ and 0.37 respectively). Finally, no statistically significant difference with regard to the length of hospital stay was observed between two groups (22.52 ± 5.28 days in EPO mouthwash group and 25.47 ± 14.49 days in control group, $p = 0.23$).

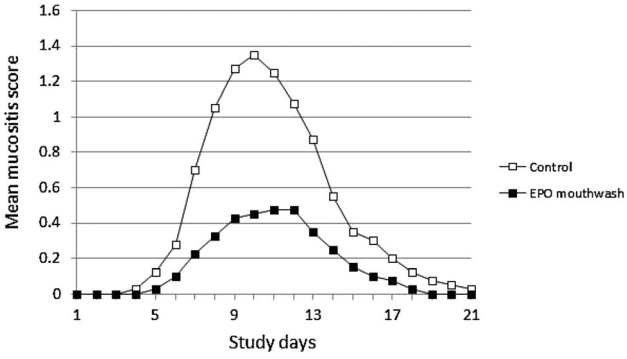

Figure 1. Mean daily WHO grade of OM in study groups. Each symbol shows the mean WHO grade of oral mucositis for patients in the EPO mouthwash (black squares) and control (white squares) groups on each day of study

Discussion

Different strategies have been used for prevention of chemotherapy-induced OM as the mainstay in managing this complication [38]. Among different agents only keratinocyte growth factor (palifermin) and cryotherapy have shown some advantages in preventing OM. As formerly mentioned, Palifermin is the only drug approved by the US Food and Drug Administration to decrease the incidence and duration of mucositis in patients with hematologic malignancies who receive high doses of chemotherapy and radiation therapy followed by HSCT [39]. Other agents such as aloe vera, amifostine, intravenous glutamine, granulocyte colony-stimulating factor, honey and laser have shown weaker evidence of benefit [3]. To the best of our knowledge, no previous clinical trial has investigated the effect of EPO mouthwash during cancer chemotherapy.

The result of the present study indicated that EPO mouthwash can significantly reduce the incidence of OM as well as average and maximum intensity score of OM in adult patients undergoing autologous HSCT. As formerly mentioned, EPO has been considered a pleiotropic glycoprotein hormone with a variety of anti-inflammatory, antioxidative and wound-healing effects, which are mediated by different mechanisms such as reduction of oxygen radical concentration, induction of lipoperoxidation, expression of intercellular adhesion molecule, infiltration of leukocytes into the tissues as well as inhibiting the production of pro-inflammatory cytokines including IL-2, IL-6, IL-8, IFN-γ, and TNF-α [40]. Amifostine, an antioxidant and cytoprotective agent, has been assessed in several trials for prevention and treatment of OM, but the results are inconclusive to establish a guideline to use amifostine in this setting [3,8,41]. In one review article, it was concluded that aloe vera mouthwash with anti-inflammatory, immunomodulation and scavenging free radicals properties and beneficial effects for wound healing, mucous membrane protection and treatment of oral ulcers can prevent radiation-induced mucositis in patients with head and neck cancers [42]. Another study demonstrated significant reduction in the incidence, severity and duration of OM induced by conditioning regimens followed by HSCT with using mouthwash containing *Camelia Sinensis* leaf extract as an antioxidant agent [43].

Another positive finding of our study was a trend toward a reduction in the incidence of severe OM (grades 3 and 4) as demonstrated by marginally significant p value. Perhaps having not enough number of patients with grades 3 and 4 OM to show significant difference between two groups

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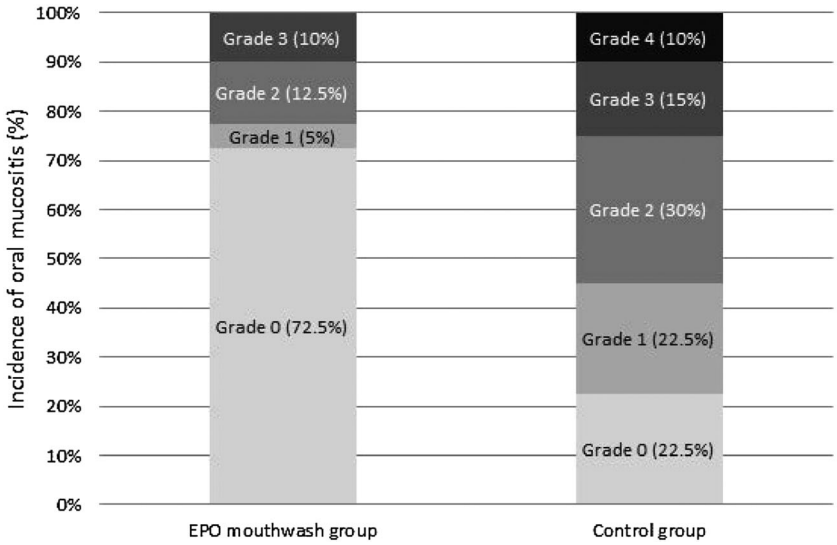

Figure 2. Incidence of oral mucositis in EPO mouthwash and control groups according to WHO grading scale

Table 2. Effect of EPO mouthwash on oral mucositis

Variables	*EPO mouthwash group (n = 40)*	*Control group (n = 40)*	*p-value*
Oral mucositis incidence	11(27.5%)	31(77.5%)	<0.001
Incidence of grades 2–4	10(25.0%)	23(57.5%)	0.003
Incidence of severe oral mucositis (grades 3 and 4)	4(10.0%)	10(25.0%)	0.077
Maximum intensity oral mucositis score	0.60 ± 1.06[a]	1.67 ± 1.27	<0.001
Average intensity oral mucositis score	0.47 ± 0.80	1.28 ± 0.86	<0.001
Duration of oral mucositis (days)	1.92 ± 3.42	5.42 ± 3.86	<0.001
Time to onset of oral mucositis after HSCT [3] (days)	4.64 ± 1.80	4.81 ± 2.17	0.82

Abbreviation: EPO, erythropoietin; HSCT, hematopoietic SCT.
[a]Values are shown as mean ± SD.

Table 3. Neutrophil and platelet engraftment

Variables	*EPO mouthwash group (n = 40)*	*Control group (n = 40)*	*p-value*
Duration of neutropenia[a]	8.50 ± 2.89[b]	9.12 ± 3.80	0.56
Duration of neutropenic fever[c]	2.12 ± 2.42	3.95 ± 4.01	0.016
Neutrophil engraftment time[d]	11.90 ± 2.64	12.30 ± 3.55	0.88
Platelet engraftment time[e]	13.47 ± 3.53	14.00 ± 3.69	0.39
Transfusion requirements			
No. of packed cell units transfused	0.52 ± 1.60	0.6 ± 1.17	0.16
No. of platelet units transfused	7.37 ± 9.46	7.57 ± 8.10	0.37

Abbreviation: EPO, erythropoietin.
[a]Duration of neutrophil count <500 cells/mm^3 in days.
[b]All numbers reported in mean ± SD.
[c]Duration of temperature >38.3°C in days.
[d]Absolute neutrophil count >500 cells/mm^3 for three consecutive days without transfusions—days after transplant.
[e]Platelet count >20 000/mm^3 lasting for three consecutive days without transfusions—days after transplant.

was the main reason that the *p* value became marginally significant. In one study, the therapeutic safety and efficacy of phenylbutyrate 5% mouthwash as a cytoprotective antitumor histone deacetylase inhibitor and chemical chaperone were evaluated for treating OM during radiotherapy or chemoradiotherapy in patients with head-and-neck cancer. The result of the study suggested a significant decreased incidence of severe OM (grades 3 and 4) in the intervention group [44]. Similar results were obtained by Jahangard-Rafsanjani *et al*. [21] and Moslehi *et al*. [45] on the efficacy of selenium and N-acetyl cysteine for the prevention of OM respectively.

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In addition, we noted that no patient in the EPO mouthwash group developed grade 4 OM, the most intolerable form of OM. These findings are in line with the findings of the study performed by Jahangard-Rafsanjani *et al*. [21] and Moslehi *et al*. [45]. In accordance with the reduction of the incidence of grade 4 OM, our results with EPO mouthwash is comparable with palifermin [13].

In our study, the overall duration of OM was also significantly shorter in the EPO mouthwash group, which is in agreement with the result of the study performed by Moslehi *et al*. [45] whereas in Jahangard-Rafsanjani *et al*.'s [21] study, only the mean duration of severe OM (grades 3 and 4) was significantly lower in the selenium group. However, none of the agents could alter time to onset of OM.

Hematological indices, such as duration of neutropenia, neutrophil and platelet engraftment time as well as length of hospital stay, were similar in both treatment arms of the present study. These results are comparable with studies performed by Thieblemont *et al*. [8], Jahangard-Rafsanjani *et al*. [21] and Moslehi *et al*. [45] evaluating the effect of amifostine, selenium and N-acetyl cysteine on OM in HSCT settings. On the other hand, there were significant differences in the incidence of neutropenic fever between the two groups, which are in contrast with the results of the clinical trials performed by Jahangard-Rafsanjani *et al*. [21] and Moslehi *et al*. [45].

The present study was the first randomized, placebo-controlled clinical trial to measure the efficacy of EPO mouthwash for the prevention of OM in patients undergoing HSCT. According to this fact, the EPO mouthwash administration protocol in our study may require further justification. We chose the dose of EPO mouthwash on the basis of a published patent of topical pharmaceutical preparation of EPO for the treatment of eye disorders and injuries [46] as an optimal dose of EPO mouthwash has not been determined in literature.

Administration protocol of EPO mouthwash was designed on the basis of development of chemotherapy-induced mucosal damage within 1 week of chemotherapy administration and reaching its highest severity within 2 weeks [14].

A double-blind, randomized, controlled study design was used to maximize the internal validity of our results. Outcome assessment was carried out by one clinician, which eliminated the risk of inter-rater variability. However, it was a limitation of our study that EPO mouthwash administration might be affected by patients' low compliance. Not to evaluate gastrointestinal mucositis was another limitation of our study.

In conclusion, the results of our study indicated that EPO mouthwash because of a clinically meaningful effect could be introduced as an outstanding agent for prevention of OM. As this study was the first experience of EPO mouthwash administration in HSCT setting, further prospective clinical trials with large study populations are warranted to establish the optimal dose and appropriate duration of administration for the prevention of OM.

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Conflict of interest

The authors have no conflict of interests to report.

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