BRIEF ARTICLE

The Lollipop with Strawberry Aroma May Be Promising in Reduction of Infusion-Related Nausea and Vomiting during the Infusion of Cryopreserved Peripheral Blood Stem Cells

Evren Ozdemir, Kiymet Akgedik, Sadiye Akdogan, Emin Kansu

Nausea and vomiting during the infusion of cryopreserved peripheral blood stem cells (PBSC) are common. The aim of this study was to explore the effect of lollipop with strawberry aroma on the infusion-related nausea and vomiting of cryopreserved autologous PBSCs. We compared 2 groups of adult patients receiving lollipop with strawberry aroma during cryopreserved PBSC infusions or not to assess the incidences of nausea and vomiting occurring during infusions. All patients received granisetron 3 mg i.v. twice a day, and lorazepam 1 mg every 4 hours orally for prophylaxis of the nausea and vomiting during conditioning phase and infusion day. Before infusion, all patients were premedicated with pheniramine maleate 45.5 mg i.v. and paracetamol 500 mg orally. The patients had no evidence of nausea or vomiting prior to cryopreserved PBSC infusions. The patients with ongoing nausea or vomiting owing to conditioning regimens and/or receiving additional antiemetics were excluded from the study. One hundred fifty-eight patients who consecutively underwent autologous stem cell transplantation for malignancy were included in the study. The first 110 patients (median age: 42.5, range: 17-75) were observed for the infusion related adverse effects only. The consecutive 48 patients (median age: 48, range: 18-80) were given a lollipop with strawberry aroma during cryopreserved PBSC infusions and observed for the infusion-related adverse effects. The 2 groups were comparable with respect to age, sex, diagnosis, stem cell collection methods, conditioning regimens administered, total mononuclear cell dose infused, number of total nucleated cells (TNCs) infused, number of $CD34^+$ cells infused, number of bags infused, total volume infused, amount of dimethylsulfoxide (DMSO), and infusion rate. Patients who received a lollipop with a strawberry aroma during infusions had significantly less nausea (6.3%, n = 3 versus 21.8%, n = 24, $P = .02$) and vomiting (2%, n = 1 versus 13.6%, n = 15, $P = .04$) than the ones who did not (observation only group). Other infusion-related adverse events were as follows; hypoxia, cough, dyspnea, abdominal cramping, tachycardia, hiccup, fever, chills, chest pain, hypotension, hypertension, agitation, sore throat, and arrhythmia. Incidences of each of these adverse events were <5% in both groups and were comparable. The use of a lollipop with a strawberry aroma during infusion of cryopreserved autologous PBSCs may be promising in reduction of infusion-related nausea and vomiting, with an easy administration at a very cheap cost.

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INTRODUCTION

Infusion-related toxicities of cryopreserved autologous peripheral stem cells (PBSC) are common [1-5]. Adverse events (AE), of either cardiovascular or noncardiovascular type, can occur after infusion of cryopreserved PBSC containing dimethylsulfoxide (DMSO) and are mostly attributed to the amount of DMSO infused. Among these AEs, nausea, vomiting, dyspnea, hypertension, hypotension, bradycardia, abdominal cramping, flushing, headache, fever, chills, and chest tightness are the most reported ones [1-5]. In some series, an overall incidence of noncardiovascular AEs was up to 70% [1-3].

From the Hacettepe University Institute of Oncology, Stem Cell Transplantation Unit, Ankara, Turkey.

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Correspondence and reprint requests: Evren Ozdemir, MD, Hacettepe University Institute of Oncology, Stem Cell Transplantation Unit, Hacettepe, 06100 Ankara, Turkey (e-mail: dreozdemir@yahoo.com).

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Cryopreservation of stem cells after collection from peripheral blood or bone marrow for autologous transplantation necessitates protection with DMSO to allow for the storage of collected cells in a viable condition for a prolonged period. DMSO is the most widely used cryoprotectant in the preservation of PBSCs. It offers cryopreservation of cell function by crossing the cell membrane rapidly to stabilize the cell throughout the freezing process. Unfortunately, DMSO, when infused with the thawed cell suspension, may induce some complications and side effects. Among these, nausea and vomiting are probably the most frequent AEs observed [1-5]. Because DMSO has great ability to cross tissue membranes, it is rapidly absorbed from the skin and mucosal surfaces of the body. A noxious, garlic-like taste and odor occurs in patients' mouth and on their tongues within minutes of DMSO administration, and may last for several hours. The taste and odor are associated with the metabolites of DMSO. A small proportion of the infused DMSO is reduced to dimethyl sulfide (DMS), which is excreted through the skin, breath, feces, and urine for approximately 24 to 48 hours after administration. This excreted DMS is the product responsible for the characteristic malodor described as a "noxious, garlic-like odor" [6-8]. The stimuli of odor and taste is received by the peripheral receptors and carried through the olfactory nerve and gustatory branches of facial, glossopharyngeal, and vagal cranial nerve pathways to the central olfactory and taste pathways including the limbic and hypothalamic neural system [9]. It may be the involvement of the limbic and hypothalamic neural system in the processing of odor and taste that leads to a complex reaction involving many aspects of cognition and emotion [10]. A range of olfactory and gustatory sensory stimuli can cause a variety of complex psychophysiologic responses such as profound childhood memories, an awareness of danger, and nausea and vomiting [11]. Therefore, it is likely that malodor and taste caused by DMSO metabolites affect the central limbic-hypothalamic pathways triggering nausea and vomiting.

We set out with this study to explore the effect of lollipop with strawberry aroma on the infusion-related nausea and vomiting of cryopreserved autologous PBSCs.

METHODS

Patients

We evaluated the infusion-related nausea and vomiting of cryopreserved autologous PBSCs transplanted in 158 consecutive adult patients receiving high-dose (HD) chemotherapy and stem cell transplantation for malignancy at our institution. The first 110 patients were observed for the infusion related AEs only and were not given a lollipop during infusions. The consecutive 48 patients were allowed to suck a lollipop with a strawberry aroma on their tongues and buccal mucosa during infusions and observed for the infusion-related AEs. These patients started sucking lollipops right before infusions began and continued to suck lollipops throughout all infusions until the end of the last bag infused. We compared these 2 groups of adult patients receiving a lollipop with a strawberry aroma during cryopreserved PBCS infusions or not to assess the incidences of nausea and vomiting occurring during infusions among each group. The characteristics of the patients and HD chemotherapy schedules employed are shown in Table 1. The patients had no evidence of nausea or vomiting prior to cryopreserved PBSC infusions. The patients with ongoing nausea or vomiting owing to conditioning regimens and/or receiving additional antiemetics were excluded from the study. All patients gave an informed consent to participate in the study.

Table 1. Characteristics of the Study Subjects

	Lollipop with Strawberry Aroma during Cryopreserved PBSC Infusion		
	Yes	No	*P*
N (%)	48 (30.4%)	110 (69.4%)	
Age (median, range)	48 (18-80)	42.5 (17-75)	.074
Gender			
Female	17 (35.4%)	45 (40.9%)	.59
Male	31 (64.6%)	65 (59.1%)	
Diagnosis			
Multiple myeloma	20 (41.7%)	31 (28.2%)	.18
Hodgkin's lymphoma	11 (22.9%)	24 (21.8%)	
Non-Hodgkin's lymphoma	11 (22.9%)	44 (40.0%)	
Others	6 (12.5%)	11 (10.0%)	
Stem cell collection method			
Filgrastim only	20 (41.7%)	31 (28.2%)	.1
HD cyclophosphamide followed by filgrastim	28 (58.3%)	79 (71.8%)	
Conditioning Regimens			
Mitoxantrone-Melphalan	24 (50.0%)	72 (65.5%)	.18
Melphalan	20 (41.7%)	31 (28.2%)	
Carboplatin-Melphalan	4 (8.3%)	7 (6.3%)	
MNCs infused ($\times 10^{10}$/kg) (median, range)	4.6 (1.8-13.4)	4.4 (0.8-19)	.49
TNCs infused ($\times 10^{8}$/kg) (median, range)	6.4 (2.5-21.6)	6.15 (2.0-21.0)	.65
$CD34^{+}$ cells infused ($\times 10^{6}$/kg) (median, range)	8.2 (2.3-24.3)	6.8 (2-28)	.08
Patient weight (kg) (median, range)	73.5 (47-113)	70 (39-98)	.29
No of bags (aliquotes) infused			
>2	41 (85.4%)	99 (90.0%)	.42
2	7 (14.6%)	11 (10.0%)	
Nausea			
Yes	3 (6.3%)	24 (21.8%)	.02
No	45 (93.7%)	86 (78.2%)	
Vomiting			
Yes	1 (2%)	15 (13.6%)	.04
No	47 (98%)	95 (86.4%)	

HD indicates high dose; TNCs, total nucleated cells; MNCs, mononucleated cells.

Apheresis and Cryopreservation

In all cases, the hematopoietic cell (HPC) source was PBSC harvested by apheresis using a CS-3000 blood cell seperator. PBSCs were collected following mobilization with filgrastim alone for all myeloma patients or following HD cyclophosphamide (Cy) for the rest of the patients (Table 1). Cell suspensions were cryopreserved in 10% DMSO and autologous plasma, in aliquots of 60 mL (fixed volume). The maximum cellular concentration in suspensions was 1×10^8/mL. Total mononuclear cell dose, number of total nucleated cells (TNCs), and number of $CD34^+$ cells were calculated before freezing. Cryopreservation was performed with a controlled rate of freezing, and aliquots were stored in liquid nitrogen.

Thawing and Infusion

HPCs were thawed and infused 24 hours after completion of HD chemotherapy. All patients received granisetron 3 mg i.v. twice a day, lorazepam 1 mg every 4 hours orally for prophylaxis of the nausea and vomiting during conditioning phase and infusion day. Before infusion, all patients were premedicated with pheniramine maleate 45.5 mg i.v. and paracetamol 500 mg orally. The cryopreserved aliquots (bags) were rapidly thawed, and each bag was immediately infused without further manipulation within 5 to 10 minutes.

Data Collection and Statistical Analyses

Data on occurrence of AEs were collected prospectively. Type (fever, chills, nausea, vomiting, abdominal cramping, tachycardia, bradycardia, hypertension, hypotension, sore throat, chest pain, cough, and dyspnea) and number of AEs occurring at each infusion were recorded using a specifically designed worksheet. AEs were graded using NCI-CTC. In all cases, infusions, observation, and care of the patients during infusions were performed by the primary care physician.

Statistical analyses were performed using Prism Statistical Software (Graphpad, San Diego, CA) on Macintosh computers (Apple Computer, Cupertino, CA). Intergroup comparisons were performed using the *t*-test and the Mann-Whitney *U*-test for univariate parametric and nonparametric group analyses, respectively. Distribution of categoric variables was compared using a chi-square-test and Fisher's exact test. All *P* values were 2-tailed and considered significant if $<.05$.

RESULTS

Patients Characteristics

Forty-eight patients (median age: 48, range: 18-80) were given a lollipop with a strawberry aroma during cryopreserved PBSC infusions and 110 (median age: 42.5, range: 17-75) were not (observation only group). The 2 groups were comparable with respect to age, sex, diagnosis, stem cell collection methods, conditioning regimens administered, total mononuclear cell dose infused, number of TNCs infused, number of $CD34^+$ cells infused, and number of bags (Table 1). The number of bags accurately reflects the volume and amount of DMSO infused, because we used a fixed volume (60 mL) of aliquots and each bag contained the same volume and amount of DMSO. Infusion rate was similar in both groups and each bag was infused after thawing within 5 to 10 minutes. Patients receiving a lollipop were slightly older ($P = .074$).

Table 2. Other Adverse Effects Observed

	Lollipop with Strawberry Aroma during Cryopreserved PBSC Infusion		
	Yes	No	*P*
N (%)	48 (30.4%)	110 (69.4%)	
Hypoxia	2 (%4.1)	4 (%3.6)	NS
Cough	2 (%4.1)	4 (%3.6)	NS
Dyspnea	1 (%2)	3 (%2.7)	NS
Abdominal cramping	1 (%2)	3 (%2.7)	NS
Tachycardia	0 (%0)	3 (%2.7)	NS
Hiccup	1 (%2)	2 (%1.8)	NS
Fever	1 (%2)	2 (%1.8)	NS
Chills	1 (%2)	2 (%1.8)	NS
Chest pain	1 (%2)	2 (%1.8)	NS
Hypotension	0 (%0)	2 (%1.8)	NS
Hypertension	0 (%0)	2 (%1.8)	NS
Agitation	0 (%0)	2 (%1.8)	NS
Sore throat	0 (%0)	2 (%1.8)	NS
Arrhythmia	0 (%0)	1 (%1)	NS

PBSC indicates peripheral blood stem cells.

The Lollipop with a Strawberry Aroma Reduces Infusion-Related Nausea and Vomiting during the Infusion of Cryopreserved PBSCs

Patients who received a lollipop with a strawberry aroma during infusions had significantly less nausea (6.3%, n = 3 versus 21.8%, n = 24, $P = .02$) and vomiting (2%, n = 1 versus 13.6%, n = 15, $P = .04$) than the ones who did not (observation only group) (Table 1). All nausea and vomiting episodes were grade I-II according to the NCI-CTC.

Other infusion-related adverse events were as follows; hypoxia, cough, dyspnea, abdominal cramping, tachycardia, hiccup, fever, chills, chest pain, hypotension, hypertension, agitation, sore throat and arrhythmia (Table 2). Incidences of each of these adverse events were <5% in both groups and were comparable (Table 2). All AEs were grade I-II according to the NCI-CTC, except 2 patients each in both groups had grade III hypoxia necessitating bronchodilator and oxygen treatment. One patient in the observation only group had grade I premature ventricular complexes (PVCs) that disappeared after infusion without intervention.

DISCUSSION

Infusion of cryopreserved PBSC containing DMSO may trigger nausea and vomiting, likely owing to the malodor and taste caused by DMSO metabolites. In this study, we have chosen a lollipop with a strawberry aroma and allowed a group of patients to suck this lollipop on their tongues and buccal mucosa during infusions in an attempt to mask the noxious taste and odor associated with the metobolites of DMSO. Our findings show that this approach may reduce infusion-related nausea and vomiting. We think that a pleasant taste and odor owing to the lollipop with strawberry aroma replaces or masks the taste and malodor produced by DMSO metabolites, thus decreasing physical symptoms of nausea and vomiting. Moreover, it is also very easy to administer at very cheap cost compared to the other preventive methods such as depletion of DMSO before autografting.

Adverse events after HPC infusion have traditionally been associated with the amount of infused cryoprotectant, DMSO [2-4,12]. Gastrointestinal side effects appear to be strictly related to the number of bags reinfused, probably reflecting on the amount of DMSO infused [3,12] and to speed of reinfusion [12]. Noncardiovascular AEs may also be dependent on patient age [13]. In our study, study groups were comparable with respect to age, number of TNCs infused, number of bags (aliquots) infused, amount of DMSO, and infusion rate. Therefore, the effects of such factors on the study outcome is unlikely.

Depletion of DMSO before autografting is another method to decrease the DMSO amount infused, and may cause less complications and side effects; however, the procedure is cumbersome, takes 3 to 4 hours of laboratory work per patient, and may have a potential for PBSC loss during the procedure [14,15].

In conclusion, the use of a lollipop with a strawberry aroma during infusion of cryopreserved autologous PBSCs may be promising in reduction of infusion-related nausea and vomiting with an easy administration at a very cheap cost. However, our findings need to be tested in a larger randomized trial for a definitive conclusion. A prospective randomized study comparing the effects of lollipops with different aroma on the infusion-related nausea and vomiting of cryopreserved PBSCs is underway at our institution.

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