

Effects of cryotherapy in preventing oral mucositis in hematopoietic stem cell transplantation patients: Literature review



Ebru Baysal^{a,*}, Dilek Sari^b

^a Ege University College of Nursing, İzmir, 35100, Turkey

^b Department of Fundamentals Nursing, Ege University College of Nursing, İzmir, 35100, Turkey

1. Introduction

Hematopoietic stem cell transplantation is the implementation of collecting stem cells from the patient himself or another person with a compatible tissue group and giving them to the patient following a preparation regimen [1]. The most significant side effect of hematopoietic stem cell transplantation is oral mucositis (OM), which occurs particularly due to the toxicity of the preparation regimen [2]. Conditioning regimen results in localized or diffuse ulceration and inflammation by reducing the renewal rate of epithelium cells in oral mucosa [3,4]. Depending on the disease type and the preparation regimen applied, the incidence of OM is 35–75% in autologous transplantation patients while it is 75–100% in allogenic transplantation patients [2]. Total Body Irradiation (TBI) combined with Chemotherapy (CT) leads to a higher rate of mucositis than only CT alone. The severity of mucositis varies depending on the CT agents used and high-dose etoposide and melphalan cause more severe mucositis [3,5]. Oral Mucositis (OM) often develops 5–7 days after the chemotherapy and may continue until the 14th day of hematopoietic stem cell transplantation.

OM causes dehydration and malnutrition by inhibiting patients' eating. As a result of all these, life-threatening infections develop, patients' opioid analgesic and total parenteral nutrition (TPN) uses increase, hospital stays are extended and healthcare costs go up while their quality of life decreases [2–4,6]. Because of all these reasons, prevention and treatment of OM is quite important. Today, no standard OM protocols are available which are approved for efficiency in the prevention and treatment of OM in autologous or allogenic stem cell transplantation patients [4]. Cryotherapy is a complementary and alternative method, easy-to-apply treatment based on the application of ice chips before and during CT. Though its mechanism of action is not precisely known, it is thought that ice causes vasoconstriction in the veins and reduces the exposure of oral mucosa to toxic agents [7]. CT treatment causes a decrease in salivary pH value and results in xerostomia. It is important to keep the oral pH at alkaline level (7.0–7.5) in order to preserve and maintain the mouth health. In the study conducted by Karagözoğlu and Ulusoy (2005), it was determined that cryotherapy increases the oral pH of the patients and thus decreased the

development of xerostomia and oral mucositis [8]. The results of previous studies carried out on the patients who received hematopoietic stem cell transplantation showed that in patients receiving chemotherapy drugs with short half-lives such as melphalan and 5-Fu, oral cryotherapy application is an effective, side effect free, economic and easily accessible method in the prevention of OM development [4,9–12]. However, it is still a debatable issue whether oral cryotherapy can prevent the development of OM in patients who have hematological malignancies and who receive HSCT. The results of relevant randomized controlled trials (RCTs) show great variety and sample sizes are small. OM is still a serious problem for the patients receiving hematopoietic stem cell transplantation. It is necessary to use evidence based, effective methods in the prevention and the maintenance of OM in these patients. Therefore, this literature review was conducted aiming to determine the efficacy of cryotherapy in the prevention of oral mucositis (OM) in the patients receiving hematopoietic stem cell transplantation.

2. Methods

2.1. Search strategy and selection criteria

The study was carried out a comprehensive search of literature published from February 2013 to April 2018. Five electronic databases were searched, including MEDLINE[®], Ebscohost, PubMed, Google Scholar and Science Direct. The key words used to search included cryotherapy, oral mucositis, hematopoietic stem cell transplantation and oral care.

Experimental controlled clinical studies which have been published in the last five years in Turkish and English languages and have full texts available were chosen to be included in the examination.

2.2. Data collection

In the first place, an evaluation form was constructed, which included eligibility criteria for the studies to be involved in the study. In accordance with this form, database scan was independently performed

* Corresponding author. Tel.: +90 232 388 11 03; fax: +90 232 388 63 74.

E-mail addresses: ebru.baysal@ege.edu.tr (E. Baysal), dilsari@gmail.com (D. Sari).

Identification

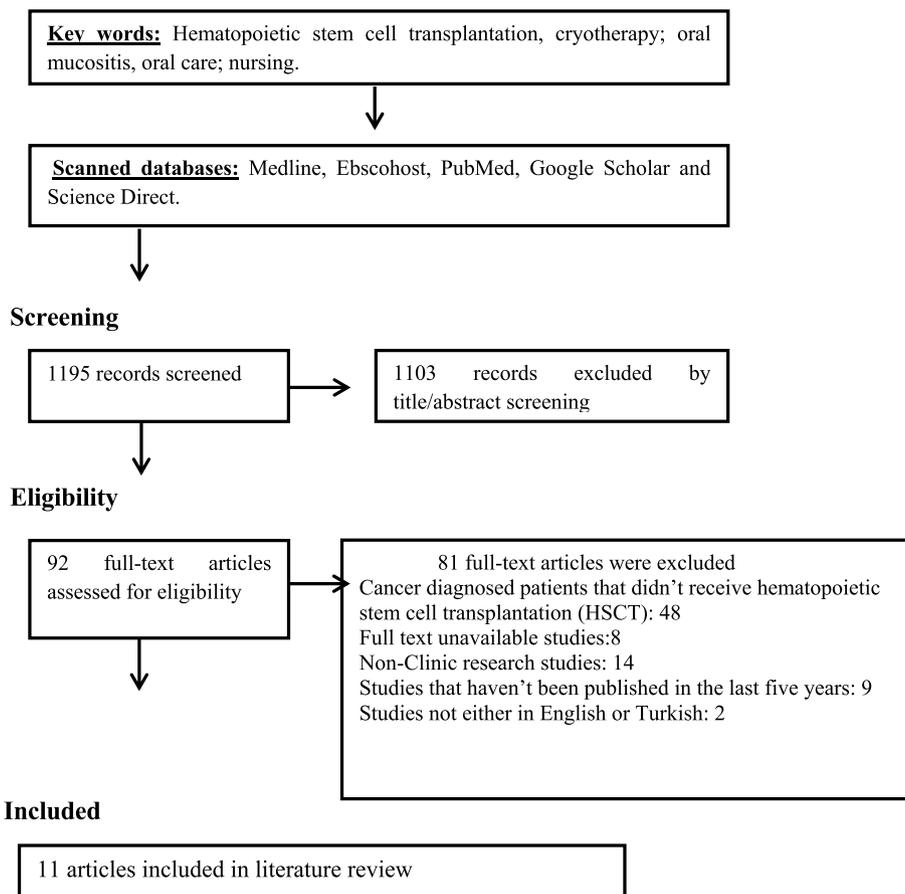


Fig. 1. Flowchart of study selection.

by two researchers. The studies which were found to meet the eligibility criteria by both of the researchers were included in the study. In the second phase, another form was constructed, in which overall information about the studies to be reviewed was documented including the author, the publishing year, the country, the design, the objective, sample size, and the population of the study as well as the oral mucositis evaluation form and the titles of the results of the studies. Based on this form, the studies were independently read and screened by two researchers separately and finally, the studies which were evaluated by both of the researchers were combined in one form.

Considering the eligibility criteria of the study, 1184 out of 1195 studies available were excluded. The reasons why those studies were excluded are; (i) they were not related to prevention of OM in HSCT patients, (ii) they were not original research study, (iii) unavailability of the full texts, (iv) studies that haven't been published in the last five years and (v) studies not either in English or Turkish. A total of 11 articles meeting the inclusion criteria made up the sample of the review (Fig. 1).

3. Results

A total of 1195 potentially relevant records were identified through database and manual searching, as delineated in Fig. 1. After screening the titles and abstracts, 1103 non-relevant studies were excluded. The full texts of the remaining 92 studies were assessed, and 81 studies were discarded because they did not meet our eligibility criteria. The excluded full-text studies, with the reasons for exclusion, are listed in Fig. 1.

The characteristics of the included studies are listed in Table 1. Two

studies were conducted in Japan, two in Sweden, two in Canada, two in Italy, one in Iran, one in Spain, one in the USA. Although all the studies were experimental, only 81.8% ($n = 9$) were randomized controlled studies. The sample sizes of the studies included in this study ranged from 24 to 140. Due to the hematologic or oncologic malignancies, samples of the studies were composed of adult patients who were given CT and/or RT before they receive HSCT. 36.3% ($n = 4$) of the studies were conducted on the patients receiving allogeneic stem cell transplantation [10,13,15] whereas 45.4% ($n = 5$) were carried out with the patients receiving autologous stem cell transplantation [3,9,11,12,16]. It was found that in 63.6% ($n = 7$) of the studies, patients were given a high dose melphalan infusion as the conditioning regimen [3,9–14].

It was also found that in order to determine OM levels of the patients, while in majority 54.5% ($n = 6$) of the studies WHO Oral Toxicity Scale was used [3,10,11,15–17] and in the other 4 studies, however, National Cancer Institute General Terminology Criteria for Adverse Events (NCI-CTCAE) was used [9,12–14].

The period of cryotherapy application was seen to vary between 40 min and 6 h depending on the preparation regimen in the studies. Three study compared oral cryotherapy to routine oral care, three studies compared oral cryotherapy to a normal saline rinse, one study compared oral cryotherapy to mouth rinses with oral nystatin-based protocols and three study compared oral cryotherapy to no treatment.

In the majority of the studies ($n = 9$), no adverse effects were observed in the patients against cryotherapy treatment and it was well tolerated by the patients. Only in a study carried by Mori et al. (2006) a slight amount of nausea and shivering was determined in the patients. 14 In another study conducted by Salvador et al. (2012), on the other hand, a slight amount of tooth sensitivity and shivering was seen

Table 1
Characteristics of the researchs included in the literature review.

Study and design	Purpose	Sample	Type of HSCT, conditioning regimens	Oral Mucositis Assessment Tool	Cryotherapy Group	Non- cryotherapy Group	Result
Aisa et al., 2005, Japan Randomized Controlled Clinic Trial	To assess the effect of oral cryotherapy to prevent oral mucositis resulted from high dose melphalan.	Sample size: 25 Experiment: 18 Control: 7	- Patients receiving allogeneic stem cell transplantation. -High dose melphalan (140 mg/m ²) + Fludarabine or Fludarabine plus other chemotherapy drugs and radiotherapy. -Patients with autologous stem cell transplantation -High dose melphalan (200 mg/m ²).	(NCI-CTCAE)	-Cryotherapy was initiated 15 min before the chemotherapy infusion and continued during and until 90 min after the end of the infusion, for a total of 120 min.	No information available	Cryotherapy was found to be effective in the prevention of oral mucositis in patients receiving high-dose melphalan before transplantation. Cryotherapy application significantly reduced the incidence of grade 3–4 oral mucositis, pain level, the use of narcotics and TPN. However, no significant differences were detected among the groups in terms of hospital stay length and weight loss.
Lilleby et al., 2006, ABD Prospective Randomized Controlled Clinic Trial	To compare the efficacy of cryotherapy versus saline mouth rinse in the prevention of grade 3–4 oral mucositis in the patients who had autologous HSCT.	Sample size: 40 Experiment: 21 Control: 19	- Patients with allogeneic stem cell transplantation. - High dose melphalan + fludarabine (group) -Other chemotherapy drugs and radiotherapy (group II).	(NCI-CTCAE)	-Cryotherapy was started 30 min before the infusion of melphalan and continued during (30 min) and until 6 h after the end the infusion.	Room temperature normal saline rinse	Cryotherapy application significantly reduced the incidence of grade 3–4 oral mucositis, pain level, the use of narcotics and TPN. However, no significant differences were detected among the groups in terms of hospital stay length and weight loss.
Mori, T. et al., 2006, Japan Non-Randomized Controlled Clinic Trial	To evaluate the effect of 60min.-120 min oral cryotherapy on the incidence of oral mucositis during high-dose mephalan infusion	Sample size: 35 Experiment: 17 Control: 18	- Patients with allogeneic stem cell transplantation. - High dose melphalan + fludarabine (group) -Other chemotherapy drugs and radiotherapy (group II).	(NCI-CTCAE)	-Cryotherapy was initiated 15 min before the melphalan infusion in experiment group 1 and administered during and until 30min after the end of the infusion, for a total of 60 min. -Cryotherapy was initiated 15 min before the melphalan infusion in experiment group 2 and administered during and until 90 min after the end of the infusion, for a total of 120 min.	No control groups	60-min cryotherapy administration in the prevention of oral mucositis in patients receiving conditioning regimen with a high-dose melphalan is as effective as 120-min administration. Besides, in the 60-min period, side effects as shivering and nausea were found to be less common.
Gori E. et al., 2007, Italy Prospective Randomized Controlled Clinic Trial	To assess the effect of oral cryotherapy on preventing severe oral mucositis following allogeneic stem cell transplantation.	Sample size:132 Experiment: 62 Control: 60	-Patients with allogeneic stem cell transplantation. -Conditioning regimen with low dose methotrexate (MTX).	WHO	-Cryotherapy was started at the same time with MTX infusion and administered for at least 1 h.	No information available	It was found that cryotherapy was not effective in reducing the severity of oral mucositis in patients receiving conditioning regimen with MTX before allogeneic stem cell transplantation.
Svanberg A et al., 2007, Sweden Randomized Controlled Clinic Trial	To assess the effect of oral cryotherapy on the preventing oral mucositis after autologous or allogeneic stem cell transplantation and on decreasing the use of intravenous (IV) opioid.	Sample size:78 Experiment: 39 Control: 39	-Patients with allogeneic or autologous stem cell transplantation. -Various conditioning regimens.	Oral Mucositis Assessment Scale (OMAS)	-Cryotherapy was started concurrently with the chemotherapy infusion and continued until the end of the infusion. The duration of cryotherapy application varies depending on the conditioning regimen and there is no standard time period.	Routine oral care	Cryotherapy was found to be an effective and well tolerated method in alleviating the severity of oral mucositis and reducing the duration of opioid use.
Svanberg A. et al., 2010, Sweden Randomized Controlled Clinic Trial	To investigate the effect of oral cryotherapy on the incidence and severity of oral mucositis, nutritional status and infection rate after myeloablative treatment.	Sample size: 78 Experiment: 39 Control: 39	-Patients with allogeneic or autologous stem cell transplantation -Various conditioning regimens	WHO	Cryotherapy was started 5 min before the infusion continued during the treatment. The duration of cryotherapy application has varied depending on the conditioning regimen and there is no standard time period.	Routine oral care	It was found that oral cryotherapy in patients receiving autologous or allogeneic stem cell transplantation has reduced the frequency level of oral mucositis, hospital stay length of the patient, decreased the nutritional needs with TPN and relieved the pain but hasn't affected the infection rate.
Salvador P. et al., 2012, Canada	To assess the effect of oral care protocol and cryotherapy in		-Patients with allogeneic stem cell transplantation.	WHO	Cryotherapy was initiated 5 min before the melphalan infusion and	Routine oral care	Oral cryotherapy in patients receiving conditioning regimen <i>(continued on next page)</i>

Table 1 (continued)

Study and design	Purpose	Sample	Type of HSCT, conditioning regimens	Oral Mucositis Assessment Tool	Cryotherapy Group	Non- cryotherapy Group	Result
Prospective Randomized Controlled Clinic Trial	reducing oral mucositis severity in patients undergoing autologous HSCT.	Sample size: 46 Experiment: 23 Control: 23	- Conditioning regimen with high-dose melphalan (200 mg/m ²).		continued until the end of 60-min infusion.		with a high-dose melphalan is effective in reducing severity of oral mucositis and in relieving mucosal-related pain. Only in 4 patients, a small amount of dental sensitivity and shivering were observed, which did not require intervention.
Batlle M. et al., 2014, Spain Retrospective Controlled Cohort Study	Comparison of the effect of oral cryotherapy and saline on prevention of OM in autologous stem cell transplantation patients with multiple myeloma or lymphoid neoplasms	Sample size: 134 Experiment: 66 Control: 68	-Patients who received autologous stem cell transplantation - 78 patients who received conditioning regimen with high dose melphalan and 56 patients who had BEAM protocol.	WHO	Cryotherapy was initiated 10 min before the melphalan infusion and continued during and until 15 min after the end of the infusion, for a total of 40 min.	Room temperature normal saline rinse	It was determined that compared to saline mouth rinse, oral cryotherapy is more effective in preventing oral mucositis, and it is an economic and well tolerated method. The incidence of oral mucositis, severity and number of days of antibiotic use were found to be significantly lower in the cryotherapy group. Oral cryotherapy is more effective than saline rinse in prevention and reduction of severity of oral mucositis in patients receiving autologous stem cell transplantation.
Askarifar M. et al., 2016, Iran Single Blind Randomized Controlled Clinic Trial	To assess the effect of oral cryotherapy on the severity oral mucositis in patients receiving autologous stem cell transplantation	Sample size: 29 Experiment: 16 Control: 13	-Patients receiving autologous stem cell transplantation. -Various conditioning regimens.	WHO	Cryotherapy was initiated 5 min before the chemotherapy (CT) and administered during and until 5 min after the end of CT.	Room temperature normal saline rinse	Oral cryotherapy in multiple myeloma patients receiving conditioning regimen with melphalan before autologous stem cell transplantation is effective in patients' narcotic analgesic use, severity, incidence and duration of oral mucositis.
Chen et al., 2017, Canada Retrospective Randomized Controlled Clinic Trial	To assess the effect of oral cryotherapy on the severity oral mucositis in patients with autologous stem cell transplantation	Sample size: 140 Experiment: 70 Control: 70	- Patients receiving autologous stem cell transplantation -Conditioning regimen with high dose melphalan.	WHO	Cryotherapy was initiated 5 min before the melphalan infusion and continued during and until 30 min after the end of the infusion, for a total of 65 min.	No information available	Oral cryotherapy in multiple myeloma patients receiving conditioning regimen with melphalan before autologous stem cell transplantation is effective in patients' narcotic analgesic use, severity, incidence and duration of oral mucositis.
Marchesi et al., 2017, Italy Prospective Randomized Controlled Clinic Trial	To assess the effect of oral cryotherapy on the prevention of OM with grade 3–4.	Sample size: 72 Experiment: 36 Control: 36	- Patients receiving autologous stem cell transplantation - Conditioning regimen with high dose melphalan (200 mg/m ²)	(NCI-CTCAE)	Cryotherapy was initiated with high-dose melphalan infusion and continued till the end of 1-h infusion.	Mouth rinses with oral nystatin-based protocols	Cryotherapy application in multiple myeloma patients receiving conditioning regimen with melphalan before autologous stem cell transplantation significantly reduces the incidence of grade 3–4 oral mucositis, IPN support, antibiotics use and decreases the use of opioid analgesics due to febrile episodes.

in four patients, which didn't require an interruption of the cryotherapy treatment.¹⁰ In all of the studies (100%), it was found that OM develops at various different levels in the patients. In 81.8% (n = 9) of the studies included within the scope of the review, application of oral cryotherapy was found to be effective in preventing oral mucositis in patients who were given hematopoietic stem cell transplantation. It was determined that cryotherapy treatment generally had an effect on decreasing the incidence [3,9,11,13,14,16,17] and severity of oral mucositis [3,9–12,16–18] and in some studies, it reduced the length of hospital stay [17], the use of opioid [9–12,18] and need for TPN [9,12,17] as well.

4. Discussion and conclusion

When the literature is reviewed, it is seen that the number of studies supporting the administration of cryotherapy in the prevention of oral mucositis has been increasing [19,20]. Multinational Association of Supportive Care in Cancer (MASCC) and The International Society of Oral Oncology (ISOO) evidence based clinic implementation guide suggest cryotherapy application to prevent oral mucositis in patients who have high dose mephalan before HSCT (Evidence Level III). Only in two studies [9,15], cryotherapy application was determined to be inefficient in preventing oral mucositis. In most of the studies, thanks to cryotherapy application, positive results were obtained.

It was also determined that application of cryotherapy generally has a positive effect on reducing the incidence [3,9,11,13,14,16,17] and severity of oral mucositis [3,9–12,16–18] and in some studies, it was found that cryotherapy reduces the length of hospital stay [17], relieves the pain related to mucositis [9,10,17], help reduce the use of opioid [9–12,18] and need for TPN [9,12,17] as well. The results of various different previous studies carried out with different patient groups are similar with these findings. When the overall results of the study are evaluated, it is seen that the methods used in the stem cell transplant patients reduce several problems as swallowing and nutrition problems due to oral mucositis development [21], decrease the administration of total parenteral nutrition (TPN) [21–24], morphine, patient-controlled analgesia (PCA) [24,25] and shorten hospital length of stay [21,23,24]. Most importantly, it was determined that in the results of many studies, the incidence and severity of oral mucositis in the patients decreased and the healing time shortened [5,10,14,22,26–28].

In most of the studies included in the literature review, it was seen that WHO Oral Toxicity Scale was used to identify and classify oral mucositis [3,10,11,15–17]. Today, though there are various scales to assess oral mucositis, WHO Oral Toxicity Scale is often used in both adult and pediatric patients because of its simplicity and convenience in clinical use [6].

In nearly half of the studies, it was seen that infusion of melphalan was used as a conditioning regimen before hematopoietic stem cell transplantation. When drugs with short half-life were given as bolus, the cryotherapy application was found to be effective in decreasing incidence and severity of OM [11]. The half-life of melphalan ranges from 8 min to 2 h depending on the dose and individual metabolic changes [3,4]. Previous studies show that oral cryotherapy administration is effective in the prevention of OM development in the patients who take CT drugs with short half-life as melphalan and 5-Fu [4,9–12].

Most of the articles included in the literature review are randomized controlled studies. In this respect, it is possible to state that evidence level of these studies is high and their results are reliable. Only in two of the reviewed studies, a slight amount of tooth sensitivity, nausea and shivering was observed in a very small number of patients, which didn't require an interruption of the cryotherapy application [10,14]. Because no moderate-severe side effects were detected in the patients participated in the studies, it can be concluded that cryotherapy application is well tolerated method. Cryotherapy is often recommended because of its low side effect profile, easy tolerability and availability with its economic profile.

This literature review had some limitations to consider. First, the literature review included only 11 controlled clinic studies and the sample sizes of most of the studies included in the study were small. Second, because they do not have a double-blind study design, the methodological quality of all the reviewed studies was low and this might cause some bias against. Third, although this literature review showed that oral cryotherapy was effective in HSCT patients, it should be noted that most of the studies reviewed in the study were about high dose melphalan-based conditioning regimens. It is seen that oral cryotherapy is effective only for chemotherapeutic agents with short plasma half-lives and it is rather impossible to draw conclusions about its efficacy in other conditioning regimens.

In summary, as a result of the literature review, it can be concluded that cryotherapy is a method that can safely be used in the prevention of OM and control some symptoms related to oral mucositis in the patients receiving conditioning regimen because of HSCT. It is also seen that although there are many studies indicating that cryotherapy is an effective method in the prevention of OM before HSCT, the number of studies about evidence-based applications are limited. In order to prevent the infections and other negative effects that OM might cause in HSCT patients, more controlled clinic studies are needed to be conducted and in accordance with the results, standard mouth care guidelines should be developed and they should be transferred to the clinic environment.

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