

## The effect of three different solutions on preventing oral mucositis in cancer patients undergoing stem cell transplantation: a non-randomized controlled trial: A Turkish study

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### Abstract

**Objective:** To evaluate the effect of different solutions administered to patients undergoing stem cell transplantation on oral mucositis.

**Methods:** The non-randomised controlled trial was conducted at a Istanbul Medipol Mega university hospital in Turkey between May 2014 and June 2016, and comprised patients undergoing stem cell transplantation. They were divided into three groups. Group 1 had patients using chlorhexidine gluconate and benzydamine hydrochloride solution. Group 2 had those using calcium and phosphate solution. Group 3 patients were using black mulberry syrup. Data was collected using a structured questionnaire and the World Health Organisation mucositis assessment scale. Assessment was done on days 7, 14 and 21. Clinical significance of oral solutions was statistically determined.

**Results:** Of the 83 patients, 30(36%) were in group 1, 28(34%) in group 2, and 25(30%) in group 3. On day 7, there was no significant difference in terms of grades among the groups ( $p>0.05$ ). On day 14, grade 2 mucositis was seen in 2(8%) patents in group 3, 5(17.9%) in group 2 and 5(16.7%) in group 1; Grade 3 mucositis was seen in 2(6.7%) patients in group 1, but none in the other two groups. On day 21, grade 3 mucositis was present in 2(8.0%) in group 3, 2(7.1%) in group 2, and 4(13.3%) in group 1.

**Conclusion:** The use of black mulberry and calcium-phosphate solutions was found to be beneficial in preventing and treating oral mucositis.

**Keywords:** Stem cell transplantation, Oral mucositis, Nursing. (JPMA 69: 811; 2019)

### Introduction

Options of cancer treatment lead to oral mucositis at different frequencies. Chemotherapy particularly prevents proliferation and growth of malignant cells, as well as maturation and growth of epithelial cells of oral mucositis that have the ability to proliferate rapidly, and damages the primary mucosal barrier.<sup>1-3</sup> Pain develops due to damaged mucosal barrier, attenuation of epithelial cells, erythema, oedema, haemorrhage and ulcerations. These problems, resulting from mucositis, may also lead to changes in treatment, such as decreasing the dose, skipping the dose,<sup>2</sup> and may have a significant adverse effect on quality of life of patients. Delayed response to the treatment and conditions causing a life-threatening situation may develop.<sup>4</sup> Development and severity of mucositis may also vary from patient to patient. Because of this condition, dose reduction may be required for chemotherapy cycles, and the therapy may even be delayed. In addition, localised ulcerations occurring in the

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mouth may lead to systemic infections. Therefore, treatment of mucosal damage requires special attention, time and cost. Basic approaches related to the treatment are for pain relief and prevention of bacterial-fungal infectious complications.<sup>3</sup> Oral care to be provided by nurses is also considerably important. Nurses playing a primary role in patient care are responsible for oral care and prevention of mucositis. However, nurses need to have sufficient knowledge and ability to follow up on improvements in order to prevent the development of mucositis and to provide an effective care when it develops. Despite numerous studies on the prevention and treatment of oral mucositis, no agent has been indicated to be completely efficient that may be accepted as the standard treatment. Different oral care regimens have been applied and efficiency of the agents used to eliminate symptoms has varied. However, the use of these agents to relieve the symptoms and enhance patients' quality of life may yield beneficial results. That is why study results for the methods to be used for the prevention and treatment of oral mucositis are still needed. The number of studies evaluating oral mucositis in patients undergoing stem cell transplantation is substantially limited. The present study was planned to

evaluate efficiency of black mulberry syrup, calcium-phosphate solution, and chlorhexidine gluconate-benzylamine hydrochloride solution on the prevention and treatment of oral mucositis seen in patients undergoing stem cell transplantation.

**Patients and Methods**

The non-randomised controlled trial was conducted at a university hospital in Turkey between May 2014 and June 2016, and comprised patients undergoing stem cell transplantation at the Adult Bone Marrow Transplantation Unit.

Power analysis was utilised for calculating the sample size. Required minimum sample size with  $\alpha = 0.05$  and power of the test  $\beta = 0.20$  was calculated as 21 in each group. Those included were in-patients aged at least 18 years who had no communication problem, were using any of the agents leading to oral mucositis (alkylating agents such as busulfan, melphalan, cyclophosphamide that are used at high doses; antimetabolites such as methotrexate, 5-fluorouracil; antibiotics such as dactinomycin, adriamycin, bleomycin, and alkaloids such as vinblastine), and who had no oral mucositis and provided informed written consent. Patients who had allergy (according to patient's declaration and records), were substance abusers, and refused to participate in the study were excluded. Permission was obtained from the non-invasive clinical trials ethics committee and from the institutional ethics committee.

The subjects were divided into three groups, with group 1 having patients using chlorhexidine gluconate and benzylamine hydrochloride solution (Andorex), group 2 having patients using calcium and phosphate solution (Caphosol), and group 3 having patients using black

mulberry syrup.

Data was collected using a structured questionnaire developed on the basis of literature.<sup>1,5,6</sup> and the World Health Organisation (WHO) mucositis assessment scale.<sup>7</sup>

The questionnaire consisted of questions to assess personal characteristics of the patients and their characteristics regarding oral health and disease process. Personal characteristics included questions about gender, age, educational status, marital status and smoking. Oral health characteristics included questions about tooth brushing habit, frequency of brushing teeth, and if or not there was any decayed tooth. Disease-process characteristics included questions about diagnosis, chemotherapeutic agents used, type of stem cell transplantation, and the cycle of the chemotherapy. The questionnaire was applied by using face-to-face interview method and the answers given by patients were recorded.

The WHO scale is a diagnostic tool commonly used to identify especially toxicities caused by cytostatic agents in clinical trials. In this classification, anatomical changes of oral mucosa and severity of mucositis are scored 0-4, where 0 = no mucositis, 1 = mild, 2 = moderate, 3 = severe, and 4 = life-threatening mucositis.<sup>7</sup>

Routine treatments of the patients were changed under no circumstances during the study. The questionnaire and the WHO scale were applied to the patients at baseline. The patients were then informed about the solutions and how the solutions would be applied. The solutions used were ordered by the physician of the clinic and was supplied from the institutional pharmacy. The solution containing chlorhexidine gluconate and benzylamine hydrochloride was applied by having the patient gargle for two minutes and before spitting out

Group 1	Group 2	Group 3
The structured questionnaire including socio-demographic and disease-related characteristics Mucositis Assessment Scale of World Health Organisation (WHO) Patient Education		
-The application as gargling in 5ml disposable goblet and spitting out four times a day (after meals and before bedtime at night) every day one day before starting oral care - Avoiding oral intake for 15 minutes after gargling -Oral examination every day -Daily oral mucositis assessment and recording	Applying half of the single -use solution mixed in a glass as gargling and spitting out four times a day (after meals and before bedtime at night) every day one day before starting oral care and then applying the remaining half as gargling and spitting out by having the patient gargled for one minute then spitted out according to instructions - Avoiding oral intake for 15 minutes after gargling -Oral examination every day -Daily oral mucositis assessment and recording	-The application as gargling in 5ml disposable goblet and swallowing four times a day (after meals and before bedtime at night) every day one day before starting oral care - Avoiding oral intake for 15 minutes after gargling -Oral examination every day -Daily oral mucositis assessment and recording

Figure: Flow chart of the application.

according to manufacturers' instructions. Black mulberry syrup was applied by having the patient gargle for two minutes and then swallowing it. Half of solution containing calcium and phosphate was also applied by having the patient gargle for 1 minute before spitting out according to instructions, while the remaining half was applied in the same way. The application continued until the patients recovered from neutropenia. Oral mucosa of the patients was evaluated and recorded every day. However, data of days 7, 14 and 21 were evaluated because mucositis generally occurs one week after chemotherapy, reaches the peak point on the day 14, and recovery is noted on day 21.<sup>1,8</sup> (Figure).

For statistical analysis, chi-square test was applied to determine the clinical significance of the solutions.

**Results**

Of the 90 patients initially enrolled, 7(7.7%) were excluded; 2(2.2%) for incomplete information, 2(2.2%)

**Table-1:** Comparison of Results Regarding Socio-Demographic and Oral Health Characteristics of Patients.

Characteristics	Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	p χ <sup>2</sup>
<b>Gender</b>				
Female	14 (46.7)	11 (39.3)	13 (52)	0.645
Male	16 (53.3)	17 (60.7)	12 (48)	0.646
<b>Age (years)</b>				
18-32	7 (23.3)	7 (25)	4 (16)	
33-47	7 (23.3)	6 (21.4)	10 (40)	0.705
48-63	13 (43.3)	11 (39.3)	7 (28)	0.7
64-79	3 (10.1)	4 (14.3)	4 (16)	
<b>Marital Status</b>				
Single	6 (20)	5 (17.9)	4 (16)	0.928
Married	24 (80)	23 (82.1)	21 (84)	0.928
<b>Educational level</b>				
University	8 (26.7)	5 (17.9)	6 (24)	
High School	7 (23.3)	8 (28.6)	5 (20)	0.965
Primary Education	12 (40)	12 (42.9)	10 (40)	0.964
Illiterate	3 (10)	3 (10.7)	4 (16)	
<b>Smoking</b>				
Yes	5 (16.7)	9 (32.1)	8 (32)	0.923
No	25 (83.3)	19 (67.9)	17 (68)	0.311
<b>Teeth brushing habit</b>				
Yes	20 (66.7)	21 (75)	19 (76)	0.691
No	10 (33.3)	7 (25)	6 (24)	0.688
<b>Decayed tooth</b>				
Yes	7 (23.3)	3 (10.7)	5 (20.0)	0.417
No	23 (76.7)	25 (89.3)	20 (80.0)	0.439
<b>Frequency of brushing teeth</b>				
Once a day	8 (40.0)	9 (42.9)	12 (63.2)	0.319
Twice a day	11 (55.0)	12 (57.1)	6 (31.5)	0.408
Three times a day	1 (5.0)	-	1 (5.3)	
Total	30 (100.0)	28 (100.0)	25 (100.0)	

discontinued the treatment, and 3(3.3%) patients died. Of the 83 patients who completed the study, 38(45.7%) were females and 45(54.2%) were males. Overall, 30(36%) patients were in group 1, 28(34%) in group 2, and 25(30%) in group 3. There was no significant difference among the groups in terms of gender, age, marital status, smoking,

**Table-2:** Comparison of results regarding disease characteristics of the patients.

Characteristics	Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	p χ <sup>2</sup>
<b>Diagnosis</b>				
Leukaemia	13 (43.3)	13 (46.4)	8 (32)	
MDS*	1 (3.3)	1 (3.6)	2 (8)	0.759
MM*	7 (23.3)	8 (28.6)	10 (40)	0.748
Lymphoma	9 (30)	6 (21.4)	5 (20)	
<b>Treatment</b>				
ASCT*	17 (56.7)	15 (53.6)	10 (40)	0.433
OSCT*	13 (43.3)	13 (46.4)	15 (60)	0.435
<b>Chemotherapy received</b>				
Busulfan cyclophosphamide	6 (20)	6 (21.4)	6 (24)	0.878
BEAM*	6 (20)	5 (17.9)	6 (24)	0.897
TBI*	7 (23.3)	5 (17.9)	2 (8)	
Cyclophosphamide	7 (23.3)	8 (28.6)	9 (36)	
Melphalan	4 (13.3)	4 (14.3)	2 (8)	
Busulfan-Fuldarabin				
<b>Number of cycles</b>				
1-5 cycles	6 (20)	14 (50)	9 (36)	0.389
6-10 cycles	16 (53.3)	10 (35.7)	11 (44)	0.406
11-15 cycles	7 (23.3)	3 (10.7)	4 (16)	
16-20 cycles	1 (3.3)	1 (3.6)	1 (4)	
Total	30 (100.0)	28 (100.0)	25 (100.0)	

MDS\*(Myelodysplastic Syndrome), MM\*(Multiple Myeloma), ASCT\*(Allogeneic stem cell transplantation), OSCT\*(Autologous stem cell transplantation), BEAM\*(Carmustine, Etoposid, Ara-C, Melfalan), TBI\*(Total Body Irradiation).

**Table-3:** Development of mucositis in patients on the 7th, 14th,, 21st.

Characteristics	Group 1 n(%)	Group 2 n(%)	Group 3 n(%)	p χ <sup>2</sup>
<b>Mucositis</b>				
Grade 0	28 (93.3)	25 (89.3)	23 (92)	0.512
Grade 1	1 (3.3)	3 (10.7)	2 (8)	0.572
Grade 2	1 (3.3)	0 (0)	0 (0)	
Grade 0	11 (36.7)	16 (57.1)	13 (52)	0.244
Grade 1	12 (40)	7 (25)	10 (40)	0.308
Grade 2	5 (16.7)	5 (17.9)	2 (8)	
Grade 3	2(6.7)	0 (0)	0 (0)	
Grade 0	15 (50)	17 (60.7)	20 (80)	0.153
Grade 1	5 (16.7)	7 (25)	1 (4)	0.180
Grade 2	6 (20)	2 (7.1)	2 (8)	
Grade 3	4 (13.3)	2 (7.1)	2 (8)	
Total	30 (100.0)	28 (100.0)	25 (100.0)	

and educational level (Table-1) and with respect to oral health and disease characteristics (Table-2).

On day 7, there was no significant difference in terms of grades among the groups ( $p > 0.05$ ). On day 14, grade 2 mucositis was seen in 2(8%) patients in group 3, 5(17.9%) in group 2 and 5(16.7%) in group 1; Grade 3 mucositis was seen in 2(6.7%) patients in group 1, but none in the other two groups. On day 21, grade 3 mucositis was present in 2(8.0%) in group 3, 2(7.1%) in group 2, and 4(13.3%) in group 1. Although there was no significant difference among the groups, grade 3 mucositis was identified mostly in patients of group 1 ( $p > 0.05$ ) (Table-3).

### Discussion

Oral mucositis is one of the most frequent symptoms in cancer treatment or patients undergoing stem cell transplantation,<sup>9</sup> and this may influence long-term treatments negatively.<sup>10</sup> Mucositis occurs one week after the onset of treatment and recovers in about 21 days.<sup>11</sup> Therefore, oral mucosa needs to be protected as the treatment gets started. Prevention and treatment of mucositis may vary based on numerous factors. It is reported that gender especially may be an indicator for mucositis.<sup>12</sup> The present study revealed that mostly male patients had mucositis in the three groups. Some studies evaluated the correlation between mucositis and age and revealed that it occurred more in younger patients.<sup>13</sup> In the present study, on the other hand, it was observed that most of patients groups 1 and 2 were aged 48-63 years and patients in group 3 were aged 33-47 years. Smoking is one of the risk factors of mucositis development. A study on patients with head-neck cancer concluded that cigarette was an important factor in the development of mucositis. However, there was no significant difference for smoking in some studies.<sup>1,14</sup> It was determined in the present study that most of patients did not smoke and there was no significant difference among the groups in terms of smoking.

Oral and dental health assessment of patients has a great importance before starting the treatment.<sup>15</sup> Therefore, oral and dental health of patients included in the present study was checked by a dentist in the dental health outpatient clinic and data regarding oral health of the patients were recorded based on consultation notes of the dentist. Also, European Group for Blood and Marrow Transplantation<sup>16</sup> has suggested that dental examination be performed before starting the treatment for cancer patients. Teeth brushing habit is one of the factors influencing the occurrence of mucositis.<sup>16</sup> Teeth brushing habits of the patients were questioned before starting the study and 66.7% of group 1, 75% of group 2, and 76% of

group 3 were in the habit of teeth brushing. A great majority of those brushing teeth did so twice a day. It is recommended to brush teeth twice a day for effective oral hygiene.<sup>17</sup> A great majority of patients in the present study were observing sufficient oral hygiene before the treatment. However, oral hygiene was ensured with solutions and by using oral care sponges, because teeth brushing would have caused inconvenience due to bleeding, infection and mucositis during the neutropenic period as the treatment started.<sup>16</sup> Previous studies stated that frequency of oral care influenced oral health during chemotherapy and radiotherapy, and oral care provided once every 2-4 hours following radiotherapy reduced mucositis and the likelihood of infection. Oral care performed four times a day in patients undergoing chemotherapy was also observed to decrease incidence of infections by 50%.<sup>18</sup> In a study, a significant difference was found between oral care and incidence of mucositis.<sup>19</sup> In the present study, patients were provided with oral care after meals and before going to bed 4 times a day. Solutions were applied according to application procedures and it was found that mucositis was observed less in patients of groups 2 and 3 compared to group 1.

Several studies have revealed that chemotherapy medications used mostly in patients with haematological malignancy were alkylating agents, anti-metabolites, vinca alkaloids, and the patients experienced more grade 2 mucositis.<sup>20</sup> It was determined in the present study that most of the patients received alkylating agent therapy had grade 0 and grade 1 mucositis. This result was observed to be more positive in terms of mucositis.

Because mucositis occurs on day 7, touches the peak on day 14 and recovery is seen around day 21,<sup>1,20</sup> results of days 7, 14 and 21 from the data recorded every day during the present study were evaluated. Even though there was no statistically significant difference among the groups in terms of mucositis ( $p > 0.05$ ), mucositis was observed less in group 3 and group 2 patients compared to the patients in group 1. Solution containing calcium and phosphate is used to prevent development of mucositis in cancer patients undergoing radiotherapy or high-dose chemotherapy.<sup>21</sup> A study assessed risk factors, clinical outcomes and prophylaxis of mucositis following allogeneic stem cell transplantation in 91 cases and concluded that the solution containing calcium and phosphate did not change incidence of mucositis.<sup>8</sup> One study found that this solution did not show an additional effect in the study evaluating the effect of calcium and phosphate solution and mouthwash on mucositis in addition to oral cryotherapy in patients undergoing stem cell transplantation,<sup>22</sup> while another study revealed that

mouthwash performed with calcium and phosphate solution did not change frequency and duration of mucositis in patients with head-neck cancer who were undergoing radiotherapy.<sup>7</sup> In contrast, a study on patients undergoing stem cell transplantation observed that incidence, severity and duration of mucositis decreased in patients using calcium and phosphate solution, analgesic need reduced.<sup>21</sup>

Generally, chlorhexidine gluconate form is used for oral hygiene and health.<sup>23</sup> Benzylamine hydrochloride (0.15%) has an anti-inflammatory action. Solution (Andorex) containing chlorhexidine gluconate (0.12%) and benzylamine hydrochloride (0.15%) is stated to have both antiseptic and anti-inflammatory action.<sup>24</sup> It is known that chlorhexidine is not recommended in clinical practice guidelines to prevent and treat oral mucositis in patients undergoing radiotherapy, standard dose chemotherapy, or haematopoietic stem cell transplantation.<sup>10</sup> Moreover, it is hard to use because of its unpleasant taste and over time it may lead to colour change in teeth. However, despite all these negative aspects,, the use of chlorhexidine for mucositis treatment has been continued because it is a broad-spectrum antimicrobial and antiseptic agent.<sup>9,11</sup>

Black mulberry syrup is frequently used, particularly for mouth sores, in Turkish society. It is easy to use thanks to familiarity with its taste, and is economical because it can be cultivated in several regions of Turkey. Black mulberry syrup is used especially for the prevention of tonsillitis and treating mouth and dental injuries. It presents a good antifungal and strong antimicrobial activity thanks to its papyriflavonol A, kuraridin, saphoraflavanone D and saphoraisoflavanone A contents.<sup>25</sup> In a study, black mulberry molasses was determined to prevent occurrence of mucositis and decrease its severity.<sup>6</sup> In another study, the effect of three different solutions on food and oral mucositis was evaluated in patients undergoing chemotherapy. Intraoral pain and cotton mouth was not reported by patients using black mulberry syrup.<sup>1</sup> In the present study, grade 0 mucositis was determined to be the most frequent in three groups on days 7, 14 and 21. Grade 2 mucositis was observed on day 7 in group 1 patients, grade 2 mucositis was not seen in patients in group 2 and group 3. On day 14, mucositis grade 3 was found in group 1. The group that developed grade 2 mucositis at the lowest rate was the one using black mulberry syrup. On day 21, grade 2 and 3 mucositis was high in group 1. In group 3, grade 0 mucositis was observed to be most frequent. Even though there was no significant difference between the groups ( $p>0.05$ ), patients in group 1 were determined to be exposed to

mucositis for longer time compared to those using other solutions. In addition, compared to group 3 patients, other patients had difficulty while gargling and did not want to gargle. Since the solution containing calcium and phosphate was too salty, the patients had difficulty during the application. Another situation that needs to be considered is that the cost of this solution was also high. Patients using black mulberry syrup stated that they were satisfied with its taste, did not have nausea, and it was more economical.

The single-center orientation of the study and a small sample were the limitations of the current study. Large-scale, multi-centred studies are recommended.

## Conclusion

Grade 0 and grade 1 mucositis were more frequent in all three groups. Less mucositis was identified in patients using black mulberry syrup and calcium-phosphate solution. Mucositis is a multidimensional process, and a single agent should not be expected to succeed for protection and treatment.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Source of Funding:** None.

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