

Mouthwashes with Plain Water Prevent Oral Mucositis Secondary to Hematopoietic Stem Cell Transplantation in Hematological Cancer Patients: A Retrospective Study

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Abstract

Background Oral mucositis (OM) is a common adverse effect in hematological cancer patients who have received hematopoietic stem cell transplantation (HSCT). In this study, we compared mouthwash with nystatin, aloe vera or plain water in OM prevention.

Design A retrospective chart review was conducted in participants. The incidence, severity and duration of OM, duration of oral pain, and the use of antalgics were recorded.

Setting/participants Hematological cancer patients who had received HSCT from January 2014 to December 2020 in West China Hospital were included in this study.

Results A total of 150 patients were included in our retrospective analysis. The nystatin group had the highest incidence (100.0%) of OM, followed by the aloe vera group (44.8%), the plain water group had the lowest incidence of OM (20.0%), and the nystatin group had the highest severity and the longest duration of oral mucositis. The incidence, severity and duration of pain in the nystatin group were significantly higher than the aloe vera group and plain water group, and the use of analgesic drugs in the nystatin group was also significantly higher than the other two groups ($P < 0.05$).

Conclusions In our hospital setting, plain water mouthwash achieves great effect in OM prevention in hematological cancer patients who have received HSCT.

Introduction

Hematopoietic stem cell transplantation (HSCT) has been widely used in treatment of different hematological cancers, such as lymphoma, leukemia and multiple myeloma[1]. As estimated, approximately 80,000 patients receive HSCT annually in the world, and the survival rate after HSCT exceeds 80% [2]. In general, high-dose chemotherapy or radiotherapy in conditioning regimens before HSCT is necessary to suppress the immune system, destroy any residual tumor cells and make room in the bone marrow for implanted stem cells[3]. However, patients will suffer from autoimmune dysfunction, systemic or local skin and mucosal damage due to the systemic toxicity and side effects resulted from high-dose chemotherapy or radiotherapy [4, 5]. Pre-HSCT chemotherapy and radiotherapy can inhibit epithelial cell renewal and destroy the normal ecological environment of the oral cavity, therefore result in oral mucositis (OM). A previous study reported that approximately 80% patients had developed OM secondary to HSCT [6]. The symptoms of OM include pain, erythema, oedema, haemorrhage and ulcerations, all of which affect the patients' quality of life. In some rare cases, severe OM may occur and interfere post-HSCT anti-tumor therapy. Therefore, it is necessary to implement effective preventive managements to avoid OM in patients undergoing HSCT.

According to clinical practice guidelines of the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/ International Society for Oral Oncology (MASCC/ISOO) and European Society for Medical Oncology (ESMO)[7, 8], basic oral care (BOC) is recommended for cancer patients to prevent OM after all therapeutic modalities. Rinsing mouth is a key step of BOC. However, the choice of agents for mouthwash is not standardized, probably because of inadequate and/or conflicting evidences [7, 9]. In this study, we retrospectively reviewed the methods and agents used for mouthwash in patients who underwent HSCT, and identified the effect way to prevent post-HSCT OM.

Materials And Methods

Patients and study design

In this retrospective study, we reviewed medical charts of patients hospitalized in Department of Hematology, West China Hospital, Sichuan University, CHINA, from January 2014 to December 2020. The patients' demographic and clinical information were retrieved from the hospital medical information system. This retrospective study was approved by the Medical Ethics Committee, West China Hospital, Sichuan University (approval #: 2021/888). The inclusion criteria included: 1) patients were diagnosed with leukemia, myelodysplastic syndrome, multiple myeloma, or lymphoma according National Comprehensive Cancer Network (NCCN) clinical diagnosis and treatment guidelines; 2) the patients were ≥ 14 years old; 3) the patients were underwent HSCT; 4) the patients volunteered to participate in this study; 5) the patients received single agents mouthwash. The exclusion criteria included: 1) patients had incomplete data; or 2) patients had OM before HSCT. All patients who received HSCT in our hospital were asked to do mouthwash to prevent OM. The patient could choose from three different rinse solutions, nystatin (a polyene anti-fungal agent), aloe vera (a perennial plant belongs to the Liliaceae family) or plain water. In most cases, if not all of them, the patients stayed with one rinse solution throughout the post-HSCT recovery.

Oral mucositis measurement

The occurrence and severity of OM in patients were diagnosed by the World Health Organization oral toxicity scale[10]. In brief, Grade 0 means no mucositis; Grade I means erythema and soreness may include buccal scalloping with or without erythema; Grade II means erythema is obvious, the pain is aggravated, the ulcers are scattered, and require a semi-liquid diet; Grade III means the mucosal ulcer is more obvious than the Grade II, and only a liquid diet can be taken; Grade IV means severe pain, mucositis to the extent that alimentation is not possible, and food cannot be eaten. The symptom of oral pain was evaluated by Numerical Rating Scale (NRS) with a number from 0 to 10 to indicate the degree of pain, 0 means no pain, and 10 means the most painful [11]. Other related information, such as OM location and duration, was also recorded.

Statistic analysis

SPSS version 21.0 (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY) was used for data analysis. Descriptive statistics were used to describe all study variables including demographic and clinical data. One-way analysis of variance or a nonparametric test (Kruskal-Wallis test) for continuous variables (age, BMI, duration of OM, severity and duration of pain), and the chi-square test for categorical variables (sex, education, marital status, employment, diagnosis, treatment, incidence, severity and location of OM, incidence of pain and use of analgesics) were employed to compare the differences among three groups.

Results

The sociodemographic and clinical characteristics of the participants

As described earlier in Materials and Methods section, a total of 150 patients who received HSCT from 2014 to 2020 in West China Hospital, were included in this study. The patients were categorized into 3 groups based on

the different ways of mouthwashes. Specifically, 47 patients used nystatin, 58 patients used aloe vera, and 45 used plain water. Mouthwash methods were summarized in Table 1. Demographic characteristics of patients were summarized in Table 2. There were no significant difference among three groups of patients except patients received plain water mouthwash had slightly higher of BMI than the other groups.

Table 1
Mouthwash methods

	Nycostin Group	Aloe Vera Group	Plain Water Group
Frequency	Rinse mouth upon awakening, before sleeping and at least four times a day after brushing		
Method	Contain 10-20ml mouthwash, gargle, and spit out after 1min		
Mouthwash	Dissolving 10 nystatin tablets (500,000U) in 250 ml of saline	Add 30-40g of fresh aloe vera gel to 250 ml of water, boil it, and then refrigerate it at 2°C-8°C	30-40°C plain water

Table 2
Comparison of sociodemographic and clinical characteristics among three groups(N = 150)

Items	Nystatin Group (n = 47) [$\bar{x}\pm s/n(\%)$]	Aloe Vera Group (n = 58) [$\bar{x}\pm s/n(\%)$]	Plain Water Group (n = 45) [$\bar{x}\pm s/n(\%)$]	F/ χ^2	P
Age	35.64±12.24	35.50±12.34	40.89±14.56	2.641 ^a	0.075
Gender	28(59.6)	30(51.7)	22(48.9)	1.153 ^b	0.590
Male	19(40.4)	28(48.3)	23(51.1)		
Female					
Level of education	13(27.7)	14(24.1)	20(44.4)	5.628 ^b	0.232
Middle school or below	10(21.3)	15(25.9)	7(15.6)		
High school	24(51.1)	29(50.0)	18(40.0)		
Junior college or above					
Marital status	39(83.0)	40(69.0)	30(66.7)	3.732 ^b	0.160
Married	8(17.0)	18(31.0)	15(33.3)		
Single/Divorced					
Employment status	32(68.1)	38(65.5)	26(57.8)	3.723 ^b	0.453
Employed	3(6.4)	1(1.7)	4(8.9)		
Retired	12(25.5)	19(32.8)	15(33.3)		
Unemployed					
Diagnosis	34(72.3)	34(58.6)	26(57.8)	-5.356 ^b	0.503
Leukemia	2(4.3)	3(5.2)	2(4.4)		
MDS*	2(4.3)	8(13.8)	8(17.8)		
MM*	9(19.1)	13(22.4)	9(20.0)		
Lymphoma					
BMI*	20.67±1.41	21.19±2.01	22.19±2.83	6.045 ^a	0.003
Treatment	16(34.0)	24(41.4)	17(37.8)	0.595 ^b	0.775
ASCT*	31(66.0)	34(58.6)	28(62.2)		
OSCT*					

^a F value; ^b χ^2 ; MDS* (Myelodysplastic syndromes); MM*(Multiple myeloma); BMI*(Body Mass Index); ASCT* (Allogeneic stem cell transplantation); OSCT*(Autologous stem cell transplantation).

The preventive effect of three mouthwash on OM

There were statistically significant differences in the incidence, severity and duration of OM among the three groups ($p < 0.05$) (Table 3). The nystatin group had the highest incidence (100.0%) of OM, followed by the aloe vera group (44.8%), and the plain water group had the lowest incidence (20.0%) of OM. Furthermore, the nystatin group had the highest severity and the longest duration of OM. The OM of the participants occurred in multiple locations. There were significant differences in the incidence of OM in the lingual surface, upper jaw, lip, throat and other parts among three groups ($p < 0.05$).

Table 3
Comparison of OM occurrence among three groups(N = 150)

Items	Nystatin Group (n = 47) [M(P25,P75)/n% %]	Aloe Vera Group (n = 58) [M(P25,P75)/n% %]	Plain Water Group (n = 45) [M(P25,P75)/n% %]	χ^2/Z	P	Multiple- Comparison
Incidence	47(100.0)	26(44.8)	9(20.0)	77.108 ^a	< 0.001*	G1 > G2* G1 > G3* G2 > G3*
Severity	0(0.0)	32(55.2)	36(80.0)	96.726 ^a	< 0.001*	G1 > G2* G1 > G3*
Grade 0	18(38.3)	24(41.4)	4(8.9)			
Grade I	18(38.3)	2(3.4)	4(8.9)			
Grade II	7(14.9)	0(0.0)	1(2.2)			
Grade III	4(8.5)	0(0.0)	0(0.0)			
Grade IV						
Duration	13.00(6.00,18.00)	0.00(0.00,7.25)	0.00(0.00,0.00)	62.978 ^b	< 0.001*	G1 > G2* G1 > G3*
Position						
Lingual surface	24(51.1)	14(24.1)	3(6.7)	23.739 ^a	< 0.001*	G1 > G2* G1 > G3*
Upper jaw	17(36.2)	3(5.2)	0(0.0)	29.084 ^a	< 0.001*	G1 > G2* G1 > G3*
Lips	21(44.7)	0(0.0)	3(6.7)	41.241 ^a	< 0.001*	G1 > G2* G1 > G3*
Checks	8(17.0)	4(6.9)	2(4.4)	4.376 ^a	0.116	
Throat	36(76.6)	1(1.7)	4(8.9)	84.472 ^a	< 0.001*	G1 > G2* G1 > G3*
Gingiva	2(4.3)	0(0.0)	0(0.0)	2.951 ^a	0.185	
Apex linguae	8(17.0)	2(3.4)	4(8.9)	5.444 ^a	0.055	

^a χ^2 ; ^b Z value; * P < 0.05.

The oral pain among three groups

There were statistically significant differences of oral pain among three groups for the incidence, severity, and duration ($p < 0.05$) (Table 4). Nystatin group had the most severe oral pain with the incidence (93.6%), severity [3.00 (2.00, 4.00)] and duration [8.00 (3.00, 13.00)]. More nystatin group of patients had to use analgesic drugs than the other two groups of patients ($p < 0.05$) (Table 4).

Table 4: Comparison of oral pain among three groups (N=150)

Items	Nystatin Group (n=47) [M (P25, P75) /n (%)]	Aloe Vera Group (n=58) [M (P25, P75) /n (%)]	Plain Water Group (n=45) [M (P25, P75) /n (%)]	χ^2/Z	P	Multiple-Comparison
Incidence	44 (93.6)	36 (62.1)	26 (57.8)	20.056 ^a	<0.001*	G1>G2* G1>G3*
Severity	3.00 (2.00,4.00)	2.00 (0.00,2.00)	2.00 (0.00,3.00)	36.673 ^b	<0.001*	G1>G2* G1>G3*
Duration	8.00 (3.00,13.00)	0.50 (0.00,5.00)	2.00 (0.00,4.00)	24.282 ^b	<0.001*	G1>G2* G1>G3*
Use of analgesics						G1>G2*
No	28 (59.6)	54 (93.1)	42 (93.3)	22.748	<0.001*	G1>G3*
Yes	19 (40.4)	4 (6.9)	3 (6.7)			

^a χ^2 ; ^b Z value; * P<0.05.

Discussion

Basic oral care is recommended for cancer patients to prevent OM caused by anti-tumor therapies [7, 8, 12]. In this study, we retrospectively review three methods of mouthwashes, nystatin, aloe vera, or plain water, in OM prevention in patients treated with HSCT. Our result suggested that plain water mouthwash could efficiently prevent OM occurrence in patients secondary to HSCT, and reduce the OM severity. Rinse mouth with plain water is easy, costless and well-tolerated, all of which may promote patient's adherence to routine mouse care. Plain water rinse also reduces bacterial load in oral cavity and provide comfort. The mechanism of plain water rinse in OM prevention is still not fully demonstrated. One previous study suggested that plain water mouth rinse might promote oral cleanness, therefore reduce oral infection [13]. Roopashri's study showed that distilled water and other mouthwashes, such as benzydamine hydrochloride, chlorhexidine, and povidone iodine, had the same preventive effect on oral mucositis in cancer patients [14].

Compared with water, nystatin mouthwash could hardly prevent OM in our study. Nystatin belongs to polyene anti-fungal agent[15]. Oral candidiasis is the most common opportunistic fungal infection of oral mucosa, and nystatin is considered as the first-line agent to treat oral candidiasis[16]. In Cidon' study, nystatin mouthwash showed effective in oral candidiasis prevention [17]. However, another study also suggested that nystatin mouthwash, either alone or in combination with chlorhexidine, could not prevent OM in cancer patients [18]. Furthermore, an adverse effect of nystatin mouthwash was taste of the agent. Epstein et al.[15] found that the taste of nystatin during mouthwash might cause patient nausea and vomiting, thus decreasing the therapeutic compliance.

Aloe vera is a perennial plant which has ingredient of hydroxyanthraquinone derivatives that shows active in sterilizing, inflammation relieving, toxins breaking down, pain alleviating, wound healing and immune promoting[19, 20]. According to our result, aloe vera mouthwash showed effective in OM prevention. There were no severe OM (grade III or above) occurred in aloe vera group. Most patients with OM in this group healed within a week. Literature search returned controversial findings of aloe vera in OM prevention. A previous study showed that aloe vera had healing activity to different mucocutaneous problems[21]. While a meta-analysis found aloe vera mouthwash showed no superior effect on OM prevention, compared with other natural products, such as honey, chlorhexidine and curcumin. Further studies might be required to address the function of aloe vera in OM prevention.

The latest ESMO clinical practice guideline does not recommend any specific types of mouthwash in OM prevention, probably because of inadequate and/or conflicting clinical evidences[7]. The results of this study suggested that under the current medical conditions, hematological cancer patients who underwent HSCT could gain a benefit from plain water mouthwash in OM prevention.

Conclusion

We compared three different ways of mouthwashes, nystatin, aloe vera, and plain water, in preventing OM in hematological cancer patients secondary to HSCT. Plain water mouth wash effectively prevented occurrence and severity of OM in the patients.

Declarations

Authors' contributions: Conceptualization: all authors; Methodology: Chuanli Zhang, Fengjiao Chen, Xinwen Du; Formal analysis and investigation: Chuanli Zhang, Xinwen Du; Writing - original draft preparation: Xinwen Du; Writing - review and editing: Chuanli Zhang, Fengjiao chen, Yuhuan Zheng.

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Code availability: Not applicable.

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Consent to participate: Not applicable.

Consent for publication: Not applicable.

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