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A comparison of dioctahedral smectite and iodine glycerin cream with topical mouth rinse in treatment of chemotherapy induced oral mucositis: A pilot study

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A B S T R A C T

Purpose of the research: To compare the efficacy of dioctahedral smectite and iodine glycerin (DSIG) cream with topical mouth rinse (composed of saline, gentamicin and Vitamin B_{12}) in treatment of chemotherapy induced oral mucositis (OM).

Methods and sample: A total of 130 intensive chemotherapy or stem cells transplantation induced OM patients were recruited. Among these patients, 67 patients received topical mouth rinse and 63 patients received DSIG cream treatment. The OM would be treated on the OM appearance and sustained for 5 days. OM severity was measured daily using The American Oncology Nursing Society recommended Oral Assessment Guideline (OAG) score system.

Key results: Compared with topical mouth rinse treatment, a significant lower OAG score was observed in DSIG cream treated patients. Specifically, the OAG scores were respectively 12.1 ± 1.1, 12.0 ± 1.2, 11.3 ± 1.3 and 10.4 ± 1.3 from day 2 to day 5 in topical mouth rinse treatment subgroup. Correspondingly, the OAG scores were respectively 10.2 ± 1.0, 9.3 ± 0.9, 8.5 ± 0.6 and 8.0 ± 0.2 for DSIG cream treatment subset (all $P < 0.05$). Importantly, compared with topical mouth rinse treatment, the DSIG cream significantly shortened OM repair time (4.68 ± 0.98 vs. 8.76 ± 1.80 days, $P < 0.001$). After 5 days treatment, 54 patients (85.7%) obtained complete regression with an OAG score ≤ 8, and 7 patients (11.1%) had partial regression with an OAG score of 9–10 in DSIG cream treatment subgroup. However, only 2 patients (3.0%) obtained completed regression and 32 patients (47.8%) had partial regression in topical mouth rinse treatment cohort. Moreover, no serious side-effect was observed in both cohorts.

Conclusions: Compared with topical mouth rinse, DSIG cream significantly lowered the OAG score and shortened OM duration.

Introduction

Oral mucositis (OM), presenting as painful ulcerative and inflammatory disease in oral mucosa, is a common side effect during cancer treatment, such as hematopoietic stem cell transplantation and chemoradiotherapy (Vera-Llonch et al., 2007). Under physiological conditions, oral mucosa and normal saliva activity are two important barriers to prevent microorganism invasion (Geckili et al., 2012). Moreover, the high mitotic rate made the oral epithelia with rapid proliferation to repair the impaired mucosa (Wu et al., 2012). However, due to the direct toxic effect of cytoxic agents, including 5-Fluorouracil (5-FU), Methotrexate, Doxorubicin, Etoposide and Vinblastine, the normal physiological self-repair function in oral mucosa will be disturbed (Bensinger et al., 2008; Naidu et al., 2004; Ohbayashi et al., 2008; Svanberg et al., 2010). Indeed, the incidence of OM was ranged from 15% to 40% in patients receiving cytotoxic chemotherapy, and was from 70% to 90% in patients given bone marrow transplantation (Ohbayashi et al., 2008; Vokurka et al., 2011). In a multicenter study, the chemotherapy induced OM was reported to impair of the functions of eating (82.4%), swallowing (78.9%), drinking (75.4%), sleeping (71.9%) and talking (43.9%) (Cheng et al., 2012). Significantly, 39.0%

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of patients had at least two simultaneous symptoms, and 24.6% of patients had all five symptoms concurrently (Cheng et al., 2012). Moreover, OM might cause profound psychological distress and impair quality of life (Cheng et al., 2012; Kim et al., 2012). In particular conditions, the chemotherapy intensity will be reduced due to OM caused side effects, and subsequently compromise the efficacy of the cytotoxic agents (Naidu et al., 2004). Therefore, it is necessary to develop more clinical adaptable approaches to manage the chemotherapy induced OM.

A series of pharmacological and nonpharmacological approaches have been developed for decades to treat chemotherapy and or radiotherapy-induced OM. However, none of these methods proved to be completely effective to date (Worthington et al., 2011). In a recent phase III, randomized, double-blind trial, doxepin rinse significantly decreased the mouth and throat pain than placebo for radiochemotherapy induced OM. However, 17% of patients were discontinued the rinses due to the adverse effects of burning discomfort and increased drowsiness (Leenstra et al., 2014). Moreover, cryotherapy and laser therapy had been used to treat OM for decades. In a prospective clinical study, compared with laser therapy (InGaAlP, 660 nm, 40 mW, 6 J/cm^2) alone, cryotherapy (ice chips) plus laser therapy lowered the OM severity and reduced the OM duration for patients received hematopoietic stem-cell transplantation (de Paula Eduardo et al., 2014). Despite the favorable efficacy, the cryotherapy had been found to be discomfortable during the therapy with ice, such as chills and nausea (Aisa et al., 2005; Mori et al., 2006). Thus, more effective approaches that have less side effects should be eagerly pursued to anticancer therapy induced OM.

Dioctahedral smectite (DS), the natural adsorbent clay formed of sheet of aluminomagnesium silicate, is efficient to protect gastrointestinal mucosa (Mujawar et al., 2012). This natural clay functions to reduce microbe, enhances the intestinal barrier and prevents the mucosal damage (Liu et al., 2012). Moreover, the disruption of the intestinal barrier may be exacerbated by the release of pro-inflammatory cytokines TNF, and by the bacterial colonization (Logan et al., 2008; Ong et al., 2010). Non-antibiotic topical antiseptics, including of iodine solutions (Cooper, 2007), gentian violet (Vazquez, 1999) and silver coordination polymers (Gordon et al., 2010), are effective in treating mucosal ulcers and have strong antimicrobial efficacy. On metallic implant substrates, silver coordination polymers exhibited strong biofilm sugar-independent bactericidal activity and prevented murine Staphylococcus epidermidis implant infection (Gordon et al., 2010). In an in vivo study, treatment with povidone–iodine or chlorhexidine yielded at least a 4-log reduction in bacterial intensity for gastrointestine mucosa (Ryou et al., 2012). Importantly, oral cavity epithelial and gastrointestinal mucosas have the similar physiological property and pathological reaction to chemotherapy (Lalla et al., 2014a). Thus, the reagent that was effective to prevent gastrointestinal mucositis might be also useful to OM. However, the mixture of DS and non-antibiotic topical antiseptics in treating OM had not yet been tested.

In the present study, we compared the efficacy of dioctahedral smectite and iodine glycerin (DSIG) cream and topical mouth rinse to chemotherapy induced OM. The purposes of this paper were to evaluate the feasibility of DSIG cream to reduce the OM related symptoms, and test its potential in future clinical implication.

Patients and methods

Patients

Eligible inpatients were those with age 18 years or older, pathological confirmed malignant tumors or malignant hematological diseases, performance status score of 0–2, and had chemotherapy induced OM. From January 2009 to December 2009, 138 OM patients that received 5-Fluorouracil (5-FU), Methotrexate, Doxorubicin, Etoposide or Vinblastine contained chemotherapy were recruited at the Third Affiliated Hospital and Sun Yat-sen Memorial Hospital of Sun Yat-sen University. The chemotherapeutic regimens and treatment intensity were administrated as National Comprehensive Cancer Network (NCCN) clinical practice guideline recommended. As shown in Table 1, the chemotherapy protocol included R-CHOP for lymphoma, AC-T and EC-T for breast cancer, and FOLFIRI and MFOLFOX6 for colorectal cancer. Patients were excluded from this study with the following exclusion criteria: gingival ulcers, apicitis, oral cavity infection, malignant tumor of oral cavity, allergy to iodine and Eastern Cooperative Oncology Group Performance Status score greater than 2. The informed consent was obtained prior to chemotherapy, and the study was approved by the Clinical Ethics Review Committee in the Third Affiliated Hospital, Sun Yat-sen University.

OM evaluation

The severity of OM was evaluated by The American Oncology Nursing Society recommended Oral Assessment Guide (OAG) (Eilers et al., 1988). Briefly, the OAG consists of eight oral related functions or features, including of voice, ability to swallow, lips, saliva, tongue, mucous membrane, gingival and teeth. Based on the severity of each function or feature, each component of the score can be given a score between 1 and 3 with score of 3 is the worst. Eight components of scores were added to get an overall score. Therefore, the highest OAG score would be 24. Moreover, OAG score less than 8 was regarded as normal, and OAG score greater than or equal to 8 was viewed as OM.

Table 1
Patient characteristics.

Characteristics	No. patients (%)	Topical mouth rinse ($n = 67$)	DSIG mixture ($n = 63$)	*P* value
Age (yrs)				
<53	61 (46.9)	30	31	0.61
≥53	69 (53.1)	37	32	
Gender				
Male	94 (72.3)	49	45	0.83
Female	36 (27.7)	18	18	
Tumor types				
Lymphoma	48 (36.9)	24	24	0.96
Breast cancer	44 (33.9)	23	21	
Colorectal cancer	38 (29.2)	20	18	
Chemotherapy regimen				
R-CHOP	48 (36.9)	24	24	0.98
AC-T	30 (23.1)	15	15	
EC-T	14 (10.8)	8	6	
FOLFIRI	14 (10.8)	7	7	
mFOLFOX6	24 (18.4)	13	11	
Chemotherapy cycle				
R-CHOP (3 W/C × 6)	48 (36.9)	24	24	0.98
AC (3 W/C × 4)–T (3 W/C × 4)	30 (23.1)	15	15	
EC (3 W/C × 4)–T (3 W/C × 4)	14 (10.7)	8	6	
FOLFIRI (2 W/C × 12)	14 (10.7)	7	7	
mFOLFOX6 (2 W/C × 12)	24 (18.5)	13	11	
OAG score				
8–10	109 (83.8)	57	52	0.52
11–12	20 (15.4)	9	11	
≥13	1 (0.08)	1	0	
ECOG PS				
0–1	128 (98.5)	66	62	0.97
2	2 (1.5)	1	1	

OM, oral mucositis; OAG, Oral Assessment Guideline; ECOG PS, Eastern Cooperative Oncology Group Performance Status; W/C, week/cycle.

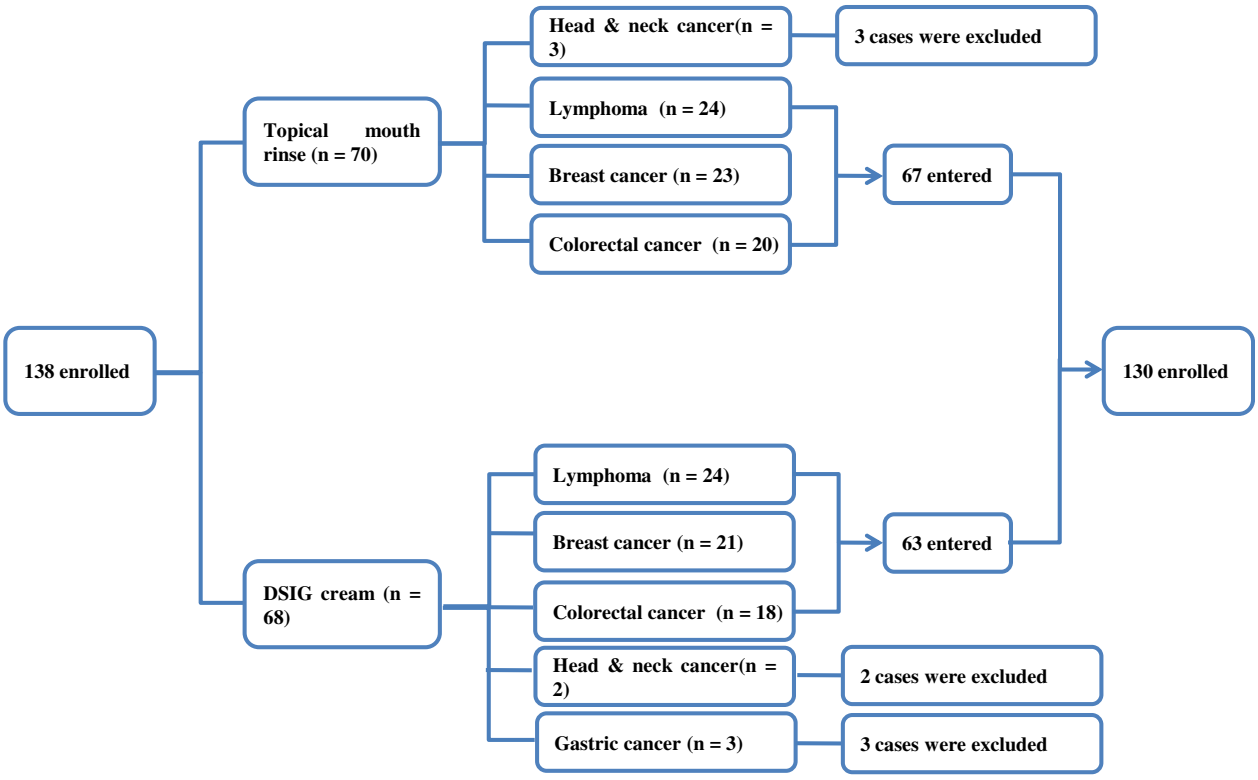

Fig. 1. Consort diagram.

Administration of interventions and assessment

All recruited patients were randomly assigned to topical mouth rinse or DSIG treatment subgroup. The intervention of all patients was administered by two trained nurses. These 2 nurses were aware of the treatment allocation for each patient due to the different properties between topical mouth rinse and DSIG cream. The nursing care started on the OM appearance and sustained for 5 days. The topical mouth rinse, composed of saline 400 ml, gentamicin 640000u and Vitamin B_{12} 500 mg, was used to rinse mouth four times daily. At each rinse, the topical mouth rinse would be gargling for one minute. The DSIG cream, consist of dioctahedral smectite (3 g) and iodine glycerin (10 ml), would be coated to oral mucosa once the OM was appeared. Similarly, the DSIG cream would be smeared four times daily, and each DSIG coating would last for 1 h with fasting.

The OM monitoring was started on the OM appearance and lasted for the whole treatment process. OM severity was measured daily with a light source using the OAG score system by two trained nurses. After 5 days topical mouth rinse or DSIG cream treatment, OM was assessed with the following criteria: complete regression (OAG score $\leq$8): mucosal hyperemia regression completely, pain and ulcer disappeared; partial regression (OAG score of 9–10): $\geq$50% of mucosal hyperemia and ulcer was regressed; progression (OAG score $\geq$11): mucosal hyperemia, ulcer or pain was deteriorated or sustained.

Statistical methods

The statistical analyses were performed using SPSS v. 17.0 (Chicago, IL) with the Manne–Whitney, Fisher's and Unpaired *t* test. The SPSS software was used to generate the random number under normal distribution. The patient number was calculated by setting the power to 80.0%. The OAG score were compared between the topical mouth rinse and DSIG cream treatment subgroups using

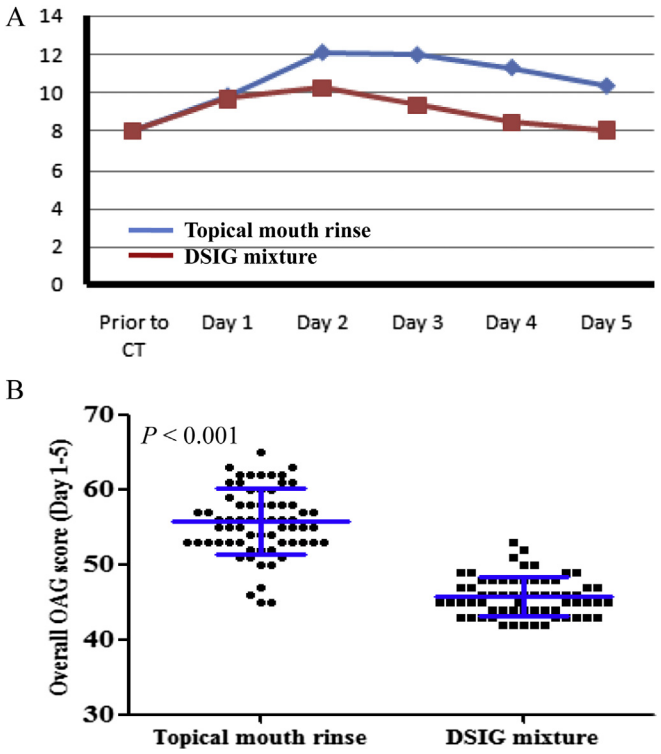

Fig. 2. The oral mucositis OAG score in topical mouth rinse and DSIG cream treatment subgroups. A. The average oral mucositis OAG scores were compared during OM treatment in both subgroups. B. The merged oral mucositis OAG scores, that combined day 0 to day 5 OM OAG scores, were compared between topical mouth rinse and DSIG cream treatment subgroups.

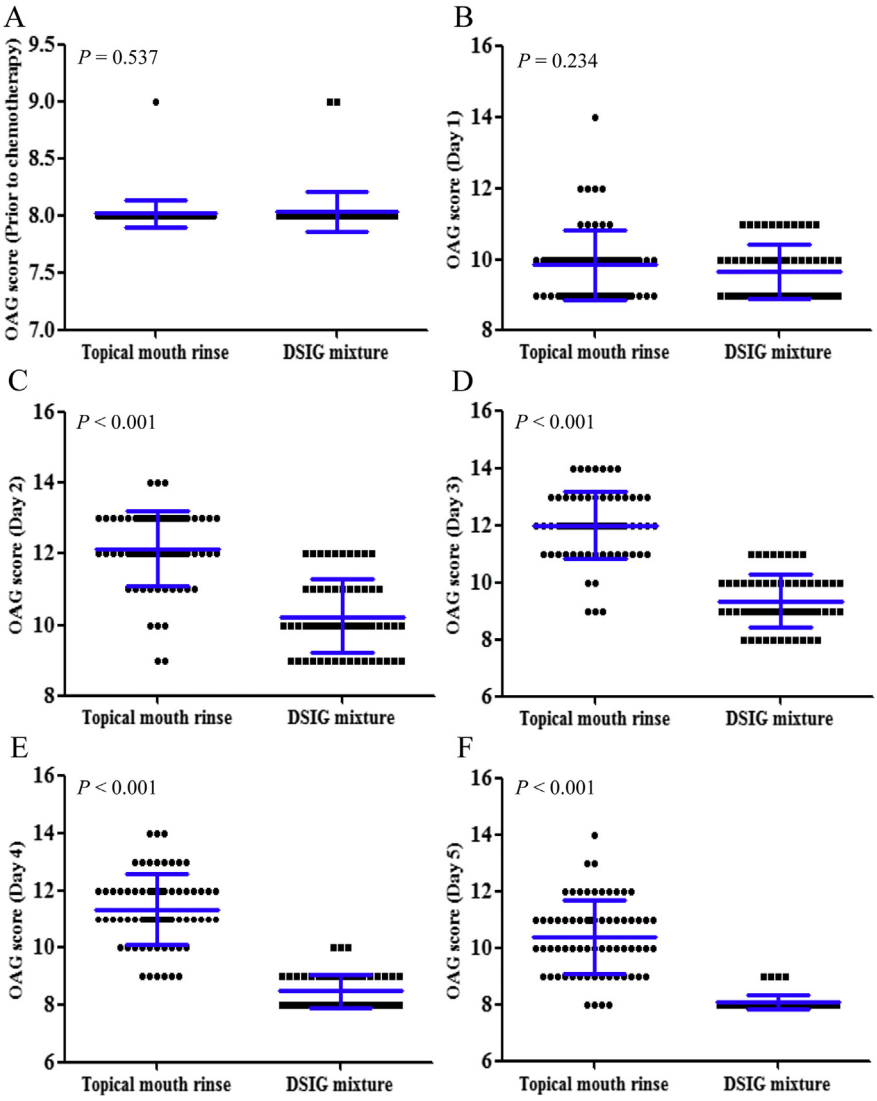

Fig. 3. The oral mucositis OAG scores were compared between topical mouth rinse and DSIG cream treatment subgroups. The oral mucositis OAG scores were compared at the time of prior to chemotherapy (A), day 1 (B), day 2 (C), day 3 (D), day 4 (E) and day 5 (F) using *t* test in both subgroups.

GraphPad Prism 5.0 (CA, USA). All *P* values quoted were two-sided and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

In this study, one hundred and thirty eight malignant patients were recruited, including of 5 patients with head and neck cancers, 44 patients with breast cancers, 3 patients with gastric cancers, 38 patients with colorectal cancers and 48 lymphoma patients. In OM treatment process, 8 patients were excluded due to 3 gastric cancer patients with poor compliance and 2 head and neck cancer patients with iodine allergy in DSIG subgroup, and 3 head and neck cancer patients with poor compliance in topical mouth rinse subset. Totally, 130 chemotherapy induced OM patients, including of 63 patients in DSIG treatment subgroup and 67 patients in topical mouth rinse subset, were recruited (Fig. 1). As shown in Table 1, a comparable age (range, 19–78; average 53.0; $P = 0.61$) and gender ($P = 0.83$) distribution was observed in both subgroups. Moreover, we also observed a balanced distribution of the tumor types and therapeutic protocols in both cohorts (with all $P > 0.05$). Significantly, prior to OM treatment, 83.8% patients (109/130) had an OAG score 8–10 (topical mouth rinse vs. DSIG cream: 57 vs. 52), and 15.4% patients (20/130) had an OAG score 11–12 (topical mouth rinse vs. DSIG cream: 9 vs. 11). Additionally, we only observed one patient developed an OAG ≥13 OM in topical mouth rinse subgroup.

OM assessment

After 5 days treatment, compared to topical mouth rinse subset, a significant OAG score downward trend was observed in the DSIG cream treatment subgroup (Fig. 2A). Accordingly, when combined the day 1–5 OAG score as overall score, the merged OAG score of topical mouth rinse subset (55.7 ± 4.4) was evidently higher than that of DSIG cream treatment subgroup (45.8 ± 2.6, $P < 0.001$; Fig. 2B). Specifically, these two cohorts had the similar OM OAG score at day 1 (topical mouth rinse vs. DSIG: 9.9 ± 1.0 vs. 9.7 ± 0.8, $P = 0.23$, Fig. 3A). From day 2 to day 5, the topical mouth rinse

subset had the higher OAG score (day 2–5, 12.1 ± 1.1, 12.0 ± 1.2, 11.3 ± 1.3, 10.4 ± 1.3, respectively) than that of DSIG cream treatment subgroup (10.2 ± 1.0, 9.3 ± 0.9, 8.5 ± 0.6, 8.0 ± 0.2, respectively; with all $P < 0.05$, Fig. 3B–F).

Importantly, compared with topical mouth rinse, the DSIG cream significantly shortened the OM repair time (4.68 ± 0.98 days vs. 8.76 ± 1.80 days, $P < 0.001$). At day 5 (Fig. 4A), we observed 54 patients (85.7%) obtained complete OM regression, 7 patients (11.1%) had partial regression and 2 patients (3.2%) developed OM progression in DSIG cream treatment cohort. However, we only observed 2 patients (3.0%) obtained completed OM regression and 32 patients (47.8%) had partial regression in topical mouth rinse treatment cohort (Fig. 4B). For the treatment related side effect, we observed 3 patients had the temporary and low-grade taste alteration in DSIG cream cohort.

Discussion

Mucosal damage is a devastating and debilitating complication of chemotherapy, and gives rises to significant adverse clinical impairment and psychological distress (Lalla et al., 2014b; Ottaviani et al., 2013). In this study, 130 chemotherapy induced OM patients were assigned to two cohorts: one group received DSIG cream treatment and the other group was given topical mouth rinse alone (Fig. 1). We found that the DSIG cream treatment had a higher therapeutic response (Fig. 2), lowered OAG score (Fig. 3) and shortened OM duration (Fig. 4), suggesting that DSIG cream might to be a useful method to treat chemotherapy induced OM.

The distinguish feature of DSIG cream is the high concentration of dioctahedral smectite and iodine glycerin. Dioctahedral smectite is the natural adsorbent clay of non-systemic specific aluminomagnesium silicate with cytoprotective actions on gastrointestinal mucosa (Martirosian et al., 1998; Yao-Zong et al., 2004). The mucosa protective action of dioctahedral smectite might be attributed to its barrier function (Chang et al., 2007). Due to the unbalanced charge distribution, dioctahedral smectite can specifically bind to strain *Escherichia coli* 31A (ES31A) (Bertin et al., 2000). Moreover, dioctahedral smectite might function as a barrier by shielding the OM from bacterial or fungal invasiveness, and releasing of pro-inflammatory cytokines (TNF-α) to repair the damaged mucosa (Mahraoui et al., 1997). Significantly, iodine glycerin is effective in inhibiting bacteria and fungi, especially for Candida albicans (Okuda et al., 1998). Indeed, our study confirmed that, compared with the routinely used mouth rinse, DSIG cream greatly shortened the OM repair duration (Figs. 2–4), suggesting that DSIG cream might to be clinical adaptable to chemotherapy induced OM.

Multivitamins had been reported to be functional in repairing OM and healing other type of wound, though the efficacy was controversial among the previous studies (Branda et al., 2004; El-Housseiny et al., 2007; Mills, 1988; Zhang et al., 1999). We had previously reported that Vitamin B12 plus gentamicin might be useful to prevent oral ulcer, relieve pain and promote OM repair for patients given hematopoietic stem cell transplantation (Zhang et al., 1999). In addition, application of 100 mg Vitamin E twice daily may effectively improve OM repair (El-Housseiny et al., 2007). In head and neck squamous cell carcinoma, beta-carotene, a source of Vitamin A, significantly inhibited chemotherapy induced OM, and obtained a 40% (8/20) OM complete remission as well as 15% (3/20) partial remission (Mills, 1988). Conversely, the correlation analysis showed that serological Vitamin B12 level was not the predictive factor to chemotherapy induced OM for breast cancer (Branda et al., 2004). It had been reported that mouth rinse might be a favorable preventive measure during the OM appearance and development (Lambrecht et al., 2013; Saunders et al., 2013). However, in our clinical practice, we found that mouth rinse was not to be sufficient once the chemotherapy induced OM was developed.

In a series of published clinical trials and meta-analysis, the mouth rinse showed a preventive function prior to OM appearance, whereas had limited treatment efficacy to chemotherapy induced

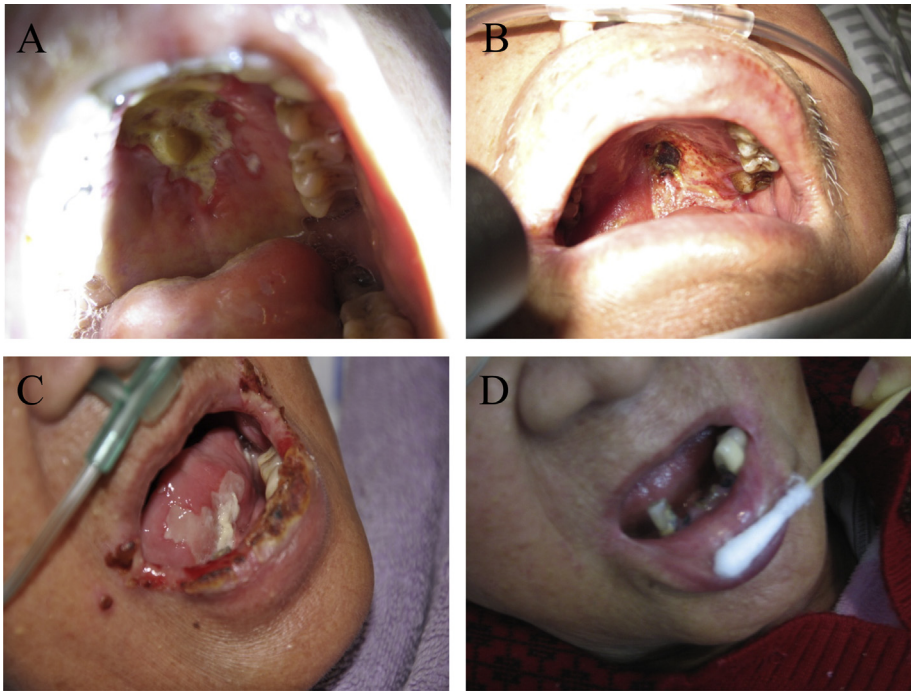

Fig. 4. The representative oral mucositis treated with topical mouth rinse or DSIG cream. A representative oral mucositis prior to (A) and after (B) the topical mouth rinse treatment were displayed. A. The oral mucositis on the palate was surrounded by erythema and multiple ulcers. B. After 5 days topical mouth rinse treatment, the oral mucositis was partial regressed with escharosis on the palate. A representative oral mucositis prior to (C) and after (D) the DSIG cream treatment were shown. C. The chemotherapy arisen serious ulcerations on lips and the base of tongue. D. The oral mucositis was completely regressed after 5 days DSIG cream treatment.

OM (Clarkson et al., 2010). Here, we further confirmed that the mouth rinse had a lower OM response rate (50.7%), whereas the DSIG cream had a favorable OM response rate (96.8%) and shortened the OM duration (Figs. 2 and 3). For the underlying mechanism, we supposed that the iodine glycerin adherent to the OM might function as an antifungal or antibacterial agent to kill disease-causing germs. Importantly, dioctahedral smectite would simultaneously construct a barrier to block the pathogenic bacteria reproduction, leading to a combined function to repair the damaged oral mucosa. However, we also observed several limitations of this pilot study. Firstly, the DSIG cream was made up freshly prior to every mouth smearing. Additionally, the mouth smearing was operated by the trained nurse to the inpatient cases. However, these made up and mouth smearing might be inconvenient for the OM patients at home. Secondly, we did not include the radiation induced OM patients in this study. Because the radiotherapy sustained a longer time than chemotherapy, the therapeutic response of OM might be varied between these two subgroups. Further investigations would be warranted in these points at our ongoing study.

In conclusion, our study confirmed that DSIG cream significantly reduced OM duration, relieved OM symptom. DSIG cream might to be a clinical adaptable approach to treat chemotherapy induced OM.

Conflict of interest

The authors declare no conflict of interest.

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