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Research article

Radiation-induced mucositis: A retrospective study of dexamethasone-lidocaine-vitamin B12 mouth rinse versus compound chlorhexidine mouthwash in nasopharyngeal carcinoma

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ABSTRACT

Oral mucositis causes substantial morbidity during head and neck radiotherapy, especially nasopharyngeal carcinoma. During radiotherapy, patients develop severe oral mucositis, which leads to oral pain and difficulty in eating and interruption of radiotherapy, affects the treatment effect and increase the probability of recurrence. Although we have explored various methods to reduce the mucosal damage caused by radiotherapy, these methods still cannot reduce pain caused by mucositis clinically. Therefore, the use of Dexamethasone-Lidocaine-Vitamin B12 Mouth rinse (DLVBM) proved its role in reducing oral mucosal pain, reducing the weight loss of patients, and completing radiotherapy according to the course of treatment. 133 patients with nasopharyngeal carcinoma who received radiotherapy (a total dose of 70 Gy) in our hospital from January to December 2020–2021 were selected. 67 patients received DLVBM treatment for mucositis reaction, and 66 patients received Compound chlorhexidine mouthwash (CCM) to deal with mucositis. Symptoms related to oral mucosal pain score and body weight, mucosal healing time were analyzed retrospectively. We found that patients with the DLVBM group significantly reduced oral pain and reduced weight loss. However, there was no significant difference about the mucosal healing time between the DLVBM group and CCM group. DLVBM may be moderately more effective in preventing radiation-induced mucositis and mucositis-related pain, and their use may lead to less frequent RT course interruptions from mucositis.

1. Introduction

Radiotherapy (RT)-induced mucositis is the most common and clinically significant acute adverse effect of radiotherapy for head-and-neck cancer. Symptoms can be severe, such as pain and difficulty eating. Additionally, Oral mucositis and Esophageal mucositis can lead to hospitalization. More than 90% of patients with head-and-neck cancers develop oral mucositis during radiotherapy, and mouth-washes and systemic analgesic agents are frequently used to treat the condition [1–4].

In radiotherapy of patients with nasopharyngeal carcinoma, the anatomical parts of nasopharynx, oropharynx, oral cavity, nasal cavity and lymph node drainage area should be irradiated, which can kill the tumor and cause damage to normal tissues or organs at

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the same time. The oropharynx and oral mucosa are most affected, often causing acute and chronic radioactive oral mucositis, with an incidence of up to 97% [5]. In this situation, patients usually exhibit with oral mucosal congestion, edema, flaky mucosal stomatitis, inflammatory or bloody secretions, ulcers and sore throat. Dysphagia, eating difficulties, poor nutritional status, and even secondary infection are commonly associated with these clinical signs. Severe oral mucositis can lead to interruption or suspension of treatment [6]. Therefore, the prevention and treatment of oral mucositis is very important in during radiotherapy for nasopharyngeal carcinoma.

Numerous clinical trials have evaluated different medications for radiation-related mucositis. Arora [7] used laser photobiomodulation to irradiate oral mucosa, which confirmed that laser application can effectively prevent radiation-induced oral mucositis. At present, there is no report of adverse reactions. Sio TT et al. confirmed that among patients undergoing head and neck radiotherapy, the use of doxepin mouthwash or diphenhydramine-lidocaine-antacid mouthwash vs placebo significantly reduced oral mucositis pain during the first 4 h after administration; however, the effect size was less than the minimal clinically important difference [8]. Anti-radiation drugs have a protective effect on oral mucosa. Intravenous amifostine can effectively reduce the severity of acute radiation oral mucositis [9]. Rovirosa A dipped recombinant human granulocyte colony stimulating factor mixture with a cotton swab and applied it to the ulcer, which has obvious effect in the treatment of radiation stomatitis [10]. Although we have explored various methods to reduce the mucosal damage caused by radiotherapy, these methods still cannot reduce pain caused by the radiation mucositis clinically.

Pain from radiotherapy- and chemoradiotherapy-induced oral mucositis is a substantial adverse effect of treatment for head and neck cancer. The treatment center alleviates the pain caused by oral and esophageal mucositis, so we configured a self-made mouthwash. The purpose of this pilot study was to compare the efficacy of Dexamethasone-Lidocaine-Vitamin B12 Mouth rinse Versus treatment of other mouthwashes in regard to these verity of mucositis, severity of mucositis-related pain, and time required to heal RT-induced mucositis in patients with NPC. An additional purpose was to monitor the weight loss that occurred in these NPC patients over the study period.

2. Material and method

2.1. Clinical data

133 patients with nasopharyngeal carcinoma who received radiotherapy in our hospital from January to December 2020–2021 were selected. All patients met the following criteria: squamous cell carcinoma was diagnosed by pathology; First radiotherapy; Have not used fluorouracil and other drugs that are easy to cause stomatitis; There was no obvious lesion in oral mucosa. All patients were treated at the Department of Radiotherapy, The First Affiliated Hospital of Wenzhou Medical University. The Ethical Committee approved the study protocol before enrolling any patients in the trial (Ethics number: KY2023-R017).

2.2. Therapeutic method

All patients received radical radiotherapy, Radical intensity-modulated radiotherapy for primary nasopharyngeal lesions and cervical metastatic lymph nodes Treatment (IMRT: 69.96Gy/2.12Gy/33F, 1 time/day, 5 times/week). The evaluation of radiotherapy plan for nasopharyngeal carcinoma is based on the international guidelines published on Int J Radiation Oncol Biol Phys in 2019 [11]. We instructed patients to take oral hygiene before starting radiotherapy. The treatment method of patients in DLVBM group: 4 ml dexamethasone solution (produced by Tianjin Jinyao Pharmaceutical Co., Ltd, 1 ml:5 mg), 20 ml lidocaine hydrochloride solution (produced by tianjin Jinyao Pharmaceutical Co., Ltd, 5 ml:0.1 g), 4 ml Vitamin B12 solution (produced by Zhejiang Ruixin Pharmaceutical Co., Ltd, 1 ml:0.5 mg) shaken with 250 ml normal saline, used before three meals and before going to bed respectively, and explained to the patients that take it orally for 3 min before swallowing it. The patients in the control group were treated with Compound chlorhexidine mouthwash. DLVBM were dispensed in hospitals. Compound chlorhexidine mouthwash is producing pharmaceutical preparation, which can be used directly according to the instructions. All patients received professional oral hygiene instruction from competent doctors and nurses. Clinical practice and previous literature suggest that the time of oral mucosal pain in the first 2–3 weeks of RT [12]. All patients followed our recommendation to use it from day 17 of radiotherapy until 2 weeks after the end of radiotherapy. During radiotherapy, patients were required to visit the supervising physician weekly. The follow-up included weekly weight changes after the start of radiotherapy, changes in pain sensations after the start of mouthwash, and time to remission of inflammation in the oral mucosa.

2.3. Outcome measures

Changes of body weight before and after radiotherapy: Record the weight at the beginning of radiotherapy, and record the weight again after radiotherapy, and analyze the weight loss after radiotherapy; Pain score before and after mouthwash use: we choose a time point before eating at noon to score the pain about 17 times of radiotherapy, and score the pain after using the mouthwash; Healing time of oral mucositis: Follow up the healing time of oral mucositis by telephone and outpatient after radiotherapy. The grading of oral mucositis was evaluated by the American Society of radiation oncology (RTOG): grade 0 had no change; Grade 1 hyperemia may be accompanied by mild pain; Grade 2 lamellar mucositis may be accompanied by moderate pain; Fibromucositis with grade 3 fusion may be accompanied by severe pain; Grade 4 ulcer, necrosis [13]. The time when the patient's oral mucositis recovers to Grade 0–1 is defined as Healing time of oral mucositis.

2.4. Data analysis

The statistical techniques used to evaluate for differences between the two mouthwash groups were t-tests and chi-square analyses, with a significance level (alpha) set at 0.05 (p value threshold).

3. Result

3.1. Pretreatment patient and tumor characteristic

The patients were evenly distributed among the study and control groups with respect to total radiation dose, gender, tumor localization, TNM classification, Chemotherapy program, cycles of chemotherapy, synchronous chemotherapy, Average body weight before and after radiotherapy and number of patients interrupted by radiotherapy. Men out numbered women, and The mean age in the DLVBM group was 52.8 ± 9.9 years and in the CCM group 53.7 ± 11.1 years (P = 0.62). The average weight in DLVBM group after radiotherapy was 59.04 ± 7.52 kg and in CCM group 53.7 ± 8.34 kg (P = 0.000), and the number of patients in the CCM group who interrupted radiotherapy due to oral pain caused by radiotherapy is more, there was statistical significance between the two groups (P = 0.046). The remaining clinical characteristics of the two groups were not statistically different, P value is greater than 0.05 (Table 1).

3.2. Body weight

All patients were weighed before and after radiotherapy. The mean weight loss of the patients after radiotherapy was 4.22 ± 3.53 kg in the DLVBM group and 8.15 ± 4.08 kg in the CCM group. The body weight significantly decreased in both groups during RT, the reduction range of the DLVBM group was lower than that of the CCM group, and difference was noted between the treatment groups in the average weight lost (P = 0.000) (Fig. 1).

3.3. Mucosal pain

All patients had varying degrees of oral mucosal pain in RT, which was confirmed by the use of VAS after the onset of pain sensation. Our results showed that there is no statistical difference between the two groups before use, but after using mouthwashes, the pain score of the DLVBM group is lower than that of the CCM group (The DLVBM group scored an average of 2.06 ± 0.94; the CCM group scored an average of 3.8 ± 1.49), which is statistically significant (p = 0.000), indicating that the drug effect of the DLVBM

Table 1
Pretreatment patient and tumor characteristics.

Variable	DLVBM	CCM	X or t value	p value
Gender				
Male	45	46		
Female	22	20	0.099	0.753
Age (y)				
≥50	41	39		
<50	26	27	0.061	0.804
Mean	52.8	53.7	−0.496	0.620
Tumor stage				
I/II stages	12	17		
III/IV stages	55	49	1.201	0.273
Radiation dose				
GTV	70Gy	70 Gy		
CTV	60 Gy	60 Gy	0	1
Chemotherapy program				
TP	39	37	0.892	0.64
GP	24	23		
No	4	7		
Cycles of chemotherapy				
0-2	14	18		
3-4	30	28		
5-6	23	21	0.66	0.719
synchronous chemotherapy				
Platinum	21	16		
Nitozumab	11	14		
No	30	36	1.458	0.482
Interruption of radiotherapy				
Yes	2	8		
No	65	58	3.991	0.046
Average body weight				
before radiotherapy	63.26	59.04	0.867	0.387
after radiotherapy	61.91	53.73	3.768	0.000

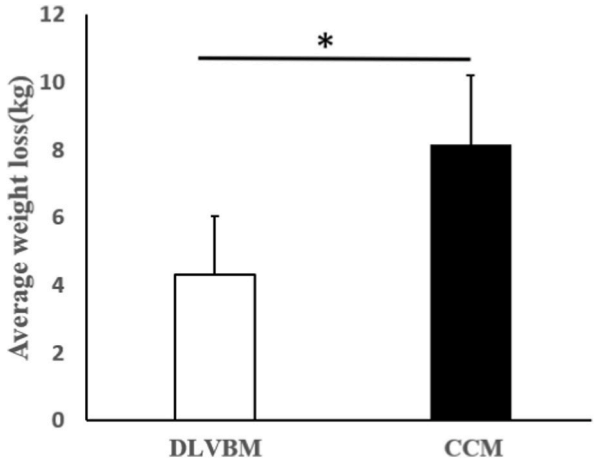

Fig. 1. The mean weight loss after radiotherapy in the Dexamethasone-Lidocaine-Vitamin B12 Mouth rinse group (DLVBM) and in the Compound chlorhexidine mouthwash group (CCM). The asterisk represents that the p value is less than 0.05.

group is better than that of the CCM group. We also did a paired sample T-test to compare for each sample (in each group) before and after mouthwashes, the pain scores of both groups were alleviated after drug use, there was statistical significance between the pain scores of two groups before and after drug use (DLVBM group: $P = 0.000$; CCM group: $P = 0.000$, see Fig. 2) (see Fig. 3).

3.4. Mucosal healing time

We continued to follow up the patients within a month after the end of radiotherapy by telephone and outpatient and recorded the healing time of the oral mucosa. No significant differences were found in the average number of days for the mucositis to heal between the two mouthwash groups ($P = 0.536$, $p > 0.05$). Mucosal healing time was an average of 17.14 ± 5.72 days in the DLVBM group, and an average of 16.56 ± 5.22 days in the CCM group.

4. Discussion

The anatomical location of nasopharyngeal carcinoma is very complex and sensitive to radiotherapy, so radiotherapy is the preferred treatment in clinic. Patients with late stage were treated with induction chemotherapy followed by concurrent chemo-radiotherapy, and patients with early stage were treated with concurrent chemoradiotherapy alone or even radiotherapy alone [14–16]. In recent years, with the continuous improvement of radiotherapy technology, more and more medical units have begun to use intensive radiotherapy technology (IMRT), which can maximize the radiation dose concentration in the tumor target area, effectively kill the tumor while reducing the damage to neighboring tissues. But despite our best efforts to protect normal tissue, radioactive oral mucositis still exists in most patients with nasopharyngeal cancer who receive radiation therapy [17–20]. Oral mucositis causes pain and difficulty in eating and swallowing. Severe mucositis may even cause treatment interruptions, which in turn, may have an adverse effect on the eventual locoregional cancer control rate and outcome [21]. At present, laser photobioregulation is

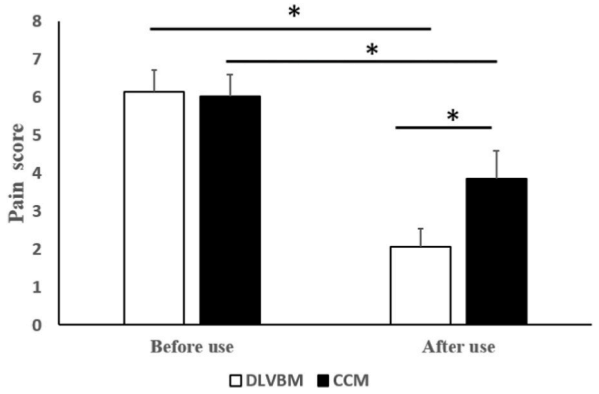

Fig. 2. The pain score before and after using the Dexamethasone-Lidocaine-Vitamin B12 Mouth rinse group (DLVBM) and the Compound chlorhexidine mouthwash group (CCM). The asterisk represents that the p value is less than 0.05.

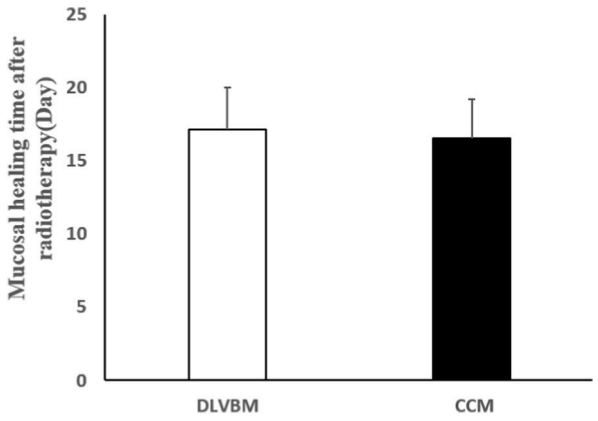

Fig. 3. The mucosal healing time after radiotherapy in the Dexamethasone-Lidocaine-Vitamin B12 Mouth rinse group (DLVBM) and the Compound chlorhexidine mouthwash group (CCM).

recommended for MASC prevention and treatment of oral mucositis, but this treatment is expensive and complicated, so it cannot be popularized in the population. Our study shows that dexamethasone-Lidocaine-vitamin B12 mouthwash is effective in alleviating radiation oral mucositis and may benefit radiotherapy patients.

As an amide local anesthetic commonly used in clinic, lidocaine is a sodium channel blocker [22]. By preventing the permeability of nerve cell membrane, blocking the Na+ and K+ exchange channels inside and outside the cell, inhibiting the conduction of nerve action potential and making nerve cells lose their excitability and conductivity, thus producing local anesthetic effect. At the same time, lidocaine has the characteristics of quick action, strong and lasting effect, strong penetration and large safety range, and no dilation of blood vessels and tissue almost no stimulation. Therefore, as the main component of mouthwash, it can effectively relieve the pain of oral mucositis and improve the tolerance of patients [23]. Dexamethasone is one of the glucocorticoids, which has many clinical applications. In the treatment of radioactive oral mucositis, it mainly plays an anti-inflammatory role. Dexamethasone can inhibit the aggregation of inflammatory cells, including macrophages and white blood cells at the site of inflammation, and inhibit phagocytosis, lysosomal enzyme release, and the synthesis and release of inflammatory chemical mediators, which can reduce and prevent the tissue response to inflammation, thereby reducing the expression of inflammation. At the same time, the short-term application of dexamethasone can also protect the ulcer surface, and can be used as a drug to promote the healing of ulcer, without obvious adverse reactions [24,25]. Vitamin B12, also known as cobalamin, is a red crystalline powder. It has two coenzyme forms of glutamine and methylglutamine. As a cofactor of methyltransferase, it is involved in the synthesis of methionine and thymine. To make the methyl receptor a methyl derivative (e.g., methionine, methyl homocysteine). Therefore, vitamin B12 can promote protein biosynthesis and thus promote the healing of oral mucosa. At the same time, previous studies have shown that oral microbial imbalance can aggravate the level of radioactive oral mucosa. Vitamin B12 plays an important role in microbial regulation. This may also be an important reason why the compound preparation can reduce radiation mucositis [26–29].

The results of the preset study strongly suggest that the mouth rine made of lidocaine, dexamethasone and vitamin B12 can reduce patients' eating pain, prevent oral infection and promote ulcer healing. In particular, gargling before going to bed can promote patients to sleep and improve sleep quality. Gargling before eating can increase patients' food intake and reduce patients' malnutrition. Through clinical observation, the self-made mouthwash is simple, safe and effective in relieving pain and inflammation. There is no adverse drug reaction in patients during use. From the above research results and previous research reports [8–10], the self-made mouthwash has a certain effect on mucositis caused by radiotherapy, alleviates patients' oral pain, increases patients' eating, and makes radiotherapy go smoothly without obvious side effects.

Although this study has been carefully designed and followed up, there are still some defects. First of all, there were only 133 patients enrolled in this study. As a control study, a small number of cases may lead to bias in results. Secondly, although we have conducted close follow-up of patients undergoing radiotherapy, the evaluation of mucosal inflammation is somewhat related to patients' subjective feelings, so there may be some deviation in the records. Finally, we should not limit the effect of compound preparation on oral mucositis after radiotherapy for single nasopharyngeal carcinoma, but should also add other head and neck tumors, so that the results will be more convincing.

Declarations

Author contribution statement

Raoying Xie: Conceived and designed the experiments; Wrote the paper.

Kejie Li; Xiaolin Ren: Performed the experiment; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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