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Original Article

Effects of a bioadhesive barrier-forming oral liquid on pain due to radiation-induced oral mucositis in patients with head and neck cancer: A randomized crossover, preliminary study

Sakiko Soutome [a], Souichi Yanamoto [b*], Yumiko Kawashita [a], Masako Yoshimatsu [c], Maho Murata [b], Yuka Kojima [d], Madoka Funahara [e], Masahiro Umeda [b], Toshiyuki Saito [a]

[a] *Department of Oral Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*
[b] *Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*
[c] *Oral Care Center, Nagasaki University Hospital, Nagasaki, Japan*
[d] *Department of Dentistry and Oral Surgery, Kansai Medical University Hospital, Osaka, Japan*
[e] *Kyushu Dental University School of Oral Health, Kitakyushu, Japan*

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Abstract *Background/purpose:* Bioadhesive barrier-forming oral liquid, is a recently developed medical material for the management of pain caused by oral mucositis associated with cancer radiotherapy or chemotherapy. The purpose of this study was to evaluate the effectiveness of this liquid in relieving pain resulting from radiation-induced oral mucositis in patients with head and neck cancer.
Materials and methods: This randomized, crossover trial investigated the analgesic effects of bioadhesive barrier-forming oral liquid using dexamethasone ointment as a control. Fifteen patients with mild or moderate pain due to radiation-induced oral mucositis were randomly assigned to two groups. Group A applied dexamethasone ointment once on day 1, had a wash-out period on day 2, and used bioadhesive barrier-forming oral liquid once on day 3. Conversely, group B used bioadhesive barrier-forming oral liquid on day 1, had a wash-out period on day 2, and applied dexamethasone ointment once on day 3. The effectiveness in relieving pain was compared between the two groups.

* Corresponding author. Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8588, Japan.
E-mail address: syana@nagasaki-u.ac.jp (S. Yanamoto).

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Results: One patient reported nausea immediately after the application of bioadhesive barrier-forming oral liquid and was therefore excluded from the analysis. Dexamethasone ointment and bioadhesive barrier-forming oral liquid relieved pain in 85.7% and 71.4% patients, respectively ($p = 0.682$). Nine patients wished to continue dexamethasone ointment after the study, while only five wished to continue bioadhesive barrier-forming oral liquid.
Conclusion: Our findings suggest that the analgesic effect of bioadhesive barrier-forming oral liquid is comparable or inferior to that of dexamethasone ointment in patients with radiation-induced oral mucositis. Further studies are needed to verify these findings.

Introduction

Although widely used for the treatment of head and neck cancer, radiotherapy (RT) induces several adverse events, including xerostomia, oral mucositis, taste disturbance, oral candidiasis, radiation-induced dental caries, and osteoradionecrosis. Oral mucositis is a serious early complication that can cause severe pain and difficulties in eating, which decreases the patients' quality of life and occasionally hinders the continuation of RT. However, effective methods for preventing radiation-induced oral mucositis have not yet been established.[1–3]

We previously conducted a randomized controlled trial to determine whether the application of a spacer, accompanied by administration of pilocarpine and topical dexamethasone ointment, were effective in preventing severe oral mucositis during RT for oral cancer.[4] Our results revealed that these measures significantly prevented severe oral mucositis during RT alone; however, no efficacy was observed during RT combined with cisplatin or cetuximab therapy. This indicated a continued need for an effective pain management strategy for patients receiving RT with bio- or chemotherapy.

Episil® (Solasia Pharma Inc., Tokyo, Japan), a bioadhesive barrier-forming oral liquid, was recently developed for the management of pain due to oral mucositis associated with cancer chemotherapy or RT.[5] Following its application to the oral mucosa, phospholipid and triglyceride lipid components spread and self-assemble with a trace volume of aqueous fluid at the mucosal surface to form a bioadhesive liquid crystalline lining that protects the sore and inflamed mucosa. However, because Episil® is not a drug but a medical material, no phase 3 clinical trials have been conducted. Therefore, its efficacy as an analgesic has not been established. Thus, we aimed to examine the analgesic effects of Episil® in a randomized crossover trial with dexamethasone ointment (Dexaltin® Oral Ointment 1 mg/g; Nihon Kayaku Co., Ltd, Tokyo Japan) as the control agent.

Materials and methods

Study design

This randomized, open-label, crossover trial was conducted as a specific clinical study in accordance with the Clinical Research Law enacted in April 2018 in Japan. Written informed consent was obtained from each participant. The study was performed in accordance with the 2013 Declaration of Helsinki and approved by the Clinical Research Review Board of the university. The study protocol was registered in the Japan Registry of Clinical Trials (jRCT) on March 3rd, 2019 (jRCTs072180039).

Patients

The study subjects were selected from patients diagnosed with head and neck cancer who received RT involving the oral cavity between March 2019 and March 2020. Patients judged to have poor cognition and those with hypersensitivity to the test drug/material were excluded.

Intervention

Patients with mild or moderate pain due to radiation-induced oral mucositis were enrolled and randomly assigned to two groups. Group A patients applied dexamethasone ointment once on the first day, had a wash-out period on the second day, and used Episil® once on the third day. Conversely, group B used Episil® on the first day, had a wash-out period on the second day, and applied dexamethasone ointment on the third day. Treatment was assigned using computer software, with the presence or absence of chemotherapy as the assignment factor.

Evaluated data

Data regarding age, sex, primary site, leukocyte count, lymphocyte count, hemoglobin, albumin, RT method (three-dimensional conformal radiation therapy/intensity-modulated radiation therapy [IMRT]), use of a combination of chemotherapy (CRT) or biotherapy (BRT), and analgesic effect were evaluated. Analgesic effects were classified according to the patients' subjective symptoms based on a 4 points Likert-like scale as follows: 1) marked improvement, 2) improvement, 3) unchanged, and 4) worsening. The analgesic effective rate was calculated as the percentage of the patients with marked improvement plus improvement in the total number of patients.

Endpoints

The primary endpoint of the study was the difference in the analgesic effect of Episil® and dexamethasone ointment. Where pain relief was achieved, the duration of the effect was recorded. The secondary endpoints were the drug/material that the patient wished to continue after the study and the incidence of adverse events related to the test drug/material.

Statistical analysis

All statistical analyses were performed using SPSS software (version 24.0; Japan IBM Co., Tokyo, Japan). The difference in analgesic effects between Episil® and dexamethasone ointment was analyzed by Fisher's exact test, while the difference in pain relief duration between groups was analyzed by the Mann—Whitney U test. In all analyses, two-tailed p-values of <0.05 were considered statistically significant.

Results

Patient characteristics

A total of fifteen patients were enrolled, with eight assigned to group A and seven to group B (Table 1). The primary site was the oropharynx in seven patients; oral cavity in five; and nasal cavity, hypopharynx, and nasopharynx in one each. All but one of the 15 patients underwent IMRT, and 11 patients received concurrent chemo- or biotherapy. On average, Episil® or dexamethasone ointment was applied 3.8 days (range, 0—13 days) after the onset of grade 2 oral mucositis.

Table 1 Characteristics of patients with radiation-induced oral mucositis.

Factor		Number of patients/mean value
Age	mean ± SD	66.9 ± 10.9
Sex	Male	11
	Female	4
Primary site	Oropharynx	7
	Oral cavity	5
	Nasal cavity	1
	Hypopharynx	1
	Nasopharynx	1
Leukocytes	Mean ± SD	5727 ± 2142
Lymphocytes	Mean ± SD	1769 ± 1096
Hemoglobin	Mean ± SD	12.4 ± 1.80
Albumin	Mean ± SD	3.60 ± 0.731
Method of RT	IMRT	14
	3D-CRT	1
Concurrent chemotherapy	RT alone	4
	CDDP	6
	CBCDA	1
	DeVIC	1
	Cet	3

Abbreviations: SD, standard deviation; RT, radiotherapy; IMRT, intensity modulated radiation therapy; CDDP, cisplatin; CBCDA, carboplatin; DeVIC, dexamethasone + etoposide + ifosfamide + carboplatin; Cet, Cetuximab.

Comparison of analgesic effects between Episil® and dexamethasone ointment

The analgesic effects of Episil® and dexamethasone ointment are summarized in Table 2. Application of dexamethasone ointment was associated with marked improvement in four patients, while an additional eight described some improvement. Pain levels were unchanged in two patients, and no patient experienced worsening pain following treatment. In comparison, a marked improvement in pain levels was observed for four patients in the Episil® group, while an additional six patients reported some improvement. No change was reported by three patients, and one patient reported worsening pain. Dexamethasone ointment and Episil® relieved pain in 85.7% and 71.4% patients (patients with marked improvement plus improvement/total number of patients), respectively, with no significant between-group difference ($p = 0.682$).

In patients showing some improvement or marked improvement, the effect lasted 103.3 ± 54.31 min after the application of Episil® and 62.73 ± 47.35 min after the application of dexamethasone ointment. Thus, Episil® had a slightly longer effect, although the difference was not statistically significant ($p = 0.336$).

Test drug/material that patients wished to continue after the study

From 14 patients, excluding one who could not use Episil® because of nausea, nine wished to continue dexamethasone ointment while five wished to continue Episil® after the study (Table 3).

Adverse events

One patient developed nausea immediately after the application of Episil®, which was immediately removed. The nausea disappeared shortly after removal, with no subsequent side effects. No other drug/material-related adverse events were observed.

Discussion

We conducted a randomized crossover study to determine whether Episil® is more effective than dexamethasone ointment in relieving pain associated with radiation-induced oral mucositis using a small number of patients for preliminary investigation. The results suggested that Episil® was less effective than dexamethasone ointment; however, there was no statistically significant difference between the two, possibly because of the small number of cases examined. The rate of oral mucositis in patients

Table 2 Comparison of analgesic effects between Episil® and dexamethasone ointment in patients with radiation-induced oral mucositis.

Pain-relieving effect	Group A (dexamethasone first)		Group B (Episil® first)		Total	
	Episil®	Dexamethasone	Episil®	Dexamethasone	Episil®	Dexamethasone
Marked improvement	4	3	0	1	4	4
Improvement	2	4	4	4	6	8
Unchanged	1	1	2	1	3	2
Worsening	1	0	0	0	1	0
Unknown (discontinuation of the test)	0	0	1	1	1	1

Table 3 Drug/material that patients with radiation-induced oral mucositis wished to continue after the study.

Test drug	Number of patients
Dexamethasone ointment	9
Episil®	5
Unknown (discontinuation of the test)	1

receiving RT for head and neck cancer is almost 100%. Thus far, none of the preventative measures that have been tried has demonstrated any efficacy.[1,2] The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines recommend several prophylactic and therapeutic measures during head and neck RT, such as the use of mouthwashes containing benzydamine, 2% morphine, or 0.5% doxepin; use of low-level laser therapy; and administration of systemic zinc supplements.[3] However, these treatments are not covered by public medical insurance in Japan; therefore, they are not widely administered.

In Japan, dexamethasone ointment or triamcinolone ointment has been widely used since the 1980s for the treatment of oral mucositis, including radiation-induced oral mucositis. In a phase 2 trial, Rugo et al. reported that prophylactic use of dexamethasone oral solution substantially reduced the incidence and severity of stomatitis in patients receiving everolimus and exemestane therapy.[6] A "prophylactic care bundle" that includes topical administration of dexamethasone ointment has been advocated for radiation-induced oral mucositis.[7] However, a subsequent randomized controlled trial confirmed that, although dexamethasone ointment had a preventive effect on oral mucositis in patients receiving RT alone, it had no effect when administered to patients undergoing CRT or BRT.[4]

Episil® is a bioadhesive barrier-forming oral liquid developed for the management of pain due to oral mucositis. Previous studies that investigated the analgesic effect of this liquid reported its effectiveness as an analgesic in patients undergoing RT or chemotherapy[5,8] (Table 4). Hadjieva et al.[5] tested the analgesic effects of Episil® and Episil®-benzydamine in patients showing moderate radiation-induced oral mucositis and found that the effects did not differ between the two materials. Meanwhile, Chen et al.[8] compared the analgesic effects of Episil® and Kangsu™ (Luye Pharmaceutical Co. Ltd, Nanjing, China), which is an oral rinse approved as a class II medical device for the treatment of oral mucositis (including RT- or chemotherapy-induced mucositis) in China. They found that the local analgesic effect of Episil® was significantly better than that of Kangsu™.[5,8] In Japan, medical insurance is applicable to spacers, pilocarpine, dexamethasone ointment, and various gargles for radiation-related oral adverse events; however, neither Episil®-benzydamine nor Kangsu™ are covered under this system.

Corticosteroids have excellent anti-inflammatory properties, and steroid ointments are widely used for various types of stomatitis. However, it has also been

Table 4 Previous clinical studies on the analgesic effects of Episil®.

Author (year)	Study design	Inclusion	No. of patients	Test material	Control material/drug	Outcome	Main results
Cheng et al.[8] (2018)	RCT	Chemotherapy or radiotherapy	60	CAM2028 (Episil®)	Oral rinse (Kangsu™)	Pain for 6 h	The local analgesic effect of CAM2028 was significantly better than that of Kangsu™.
Hadjieva et al.[5] (2014)	Crossover	Radiotherapy (grade 2 mucositis)	32	CAM2028 (Episil®)	CAM2028-benzydamine	Pain for 8 h	The analgesic effect did not differ between the two groups.

established that inadvertent use of steroids can result in infection, and there is a concern that the use of steroid ointment in cancer patients with reduced overall health could increase the risk of oral candidiasis. In an observational study of 326 patients with oral or oropharyngeal cancer, it was found that the risk factors for oral candidiasis were leukopenia and exacerbation of stomatitis, and that steroid ointment was not a risk factor.[9] For these reasons, we conducted a preliminary study to determine the efficacy of Episil® using dexamethasone ointment as the control treatment.

It is possible that Episil® only adheres to the mucosal surface and has no anti-inflammatory effects. Another reason for the reduced efficacy of Episil® may be that it was easily peeled off and difficult to apply over the site of mucositis for a longer duration. Our study focused on the use of Episil® for radiation-induced oral mucositis, a condition that occurs rapidly and spreads widely. Under these circumstances, accurate application of Episil® is difficult; however, it is expected to be effective against oral mucositis that occurs in a small area, such as everolimus-related oral mucositis.

In addition to efficacy, we also investigated the duration of pain relief. Hadjieva et al.[5] reported that the analgesic effects of Episil® persisted for up to 8 h. In this study, the effect of Episil® lasted for 103 min, slightly longer than the duration of effects of dexamethasone ointment (63 min). In order to clarify the duration of the effect of this material, additional investigations involving a larger number of cases are required. In adverse events, nausea to Episil® occurred in one case. This patient originally had a strong gag reflex, and it was speculated that he had nausea due to reflexes that occurred because the spray of Episil® was not properly sprayed on the affected area and reached the pharynx. Therefore, it was considered that this was not an adverse event such as drug allergy of Episil® itself, but a physical and technical problem.

This study has some limitations, because of which the results cannot be generalized to a larger population. First, this was a preliminary study, so the number of cases was small and adequate statistical analysis could not be performed. Second, because Episil® was applied directly by the patient, it was not possible to confirm whether the material was applied correctly. However, to the best of our knowledge, this study is the first to confirm the efficacy of this material using a steroid ointment as a control. In the future, we recommend consideration of this material as well as dexamethasone ointment for the treatment of oral mucositis caused by anticancer drugs or molecular targeted drugs for solid cancer.

In conclusion, our findings suggest that the analgesic effect of Episil® is comparable or inferior to that of dexamethasone ointment in patients with radiation-induced oral mucositis. Larger studies with longer follow-ups would be needed as larger sample sizes would be needed to prove the non-inferiority of Episil®.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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