Effects of bio-adhesive barrier-forming oral liquid (Episil®) on pain due to radiation-induced oral mucositis in patients with head and neck cancer: A randomized crossover trial

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Abstract

Background Bio-adhesive barrier-forming oral liquid (Episil®) is a recently developed medical device 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 material for the relief of pain resulting from radiation-induced oral mucositis in patients with head and neck cancer who are undergoing radiotherapy.

Methods This was a randomized, open-labeled, crossover trial investigating the pain relief effects of Episil® using dexamethasone ointment as a control. Fifteen patients who had mild or moderate pain due to radiation induced oral mucositis were randomly assigned to two groups: group A 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 day 1, followed by a wash-out period on day 2 and dexamethasone ointment on day 3. The effectiveness of the test drug/materials on the relief of pain was compared.

Results One patient reported nausea immediately after application of Episil® and was therefore excluded from the analysis of pain relief. Dexamethasone ointment relieved pain in 85.7% of patients compared to 71.4% with Episil® ($p = 0.682$). Nine patients wished to continue dexamethasone ointment after the study while only five wished to continue Episil®.

Conclusions Our findings suggest that the pain relief effect of Episil® is comparable to or less than that of dexamethasone ointment. Larger follow-up studies are needed to verify these findings.

Trial registration:

The study protocol was registered in the Japan Registry of Clinical Trials (jRCT) on March 3rd, 2019 (jRCTs072180039).

Background

Although widely used for the treatment of head and neck cancer, radiotherapy (RT) causes a range of 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 leading to difficulties in eating, which decreases the patients' quality of life and in some cases 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 were able to significantly prevent severe oral mucositis during RT alone; however, no efficacy was observed during RT combined with cisplatin or cetuximab therapy, demonstrating a continued need for an effective pain management treatment for use with combined RT and bio- or chemotherapy.

Bio-adhesive barrier-forming oral liquid (Episil®) was a recently developed medical device for the management of pain in oral mucositis associated with cancer chemotherapy or RT [5]. After application of the material 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 bio-adhesive liquid crystalline lining protecting the sore and inflamed mucosa. However, since Episil® is not a drug but a medical material, no phase 3 clinical trials have been conducted and therefore efficacy has not been established. The purpose of this study is to examine the pain relief effects of Episil® using a randomized crossover trial with dexamethasone ointment as control.

Methods

Study design

This is a randomized, open-labeled, crossover trial investigating the pain relief effects of Episil® (Solasia Pharma Inc., Tokyo, Japan), using dexamethasone ointment (Dexaltin® Oral Ointment 1 mg/g; Nihon Kayaku Co., Ltd, Tokyo Japan) as a control. This study 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. This study was performed in accordance with the 2013 Declaration of Helsinki and was approved by the Clinical Research Review Board at Nagasaki University (No. RB18-0014).

Patients

The study subjects were drawn from patients diagnosed with head and neck cancer who received RT in Nagasaki University Hospital or Kansai Medical University Hospital between March 2019 and March 2020, and whose oral cavity was contained in the radiation field. Patients judged to be lacking cognitive ability and those with hypersensitivity to the test drug/material were excluded.

Intervention

Patients who had mild or moderate pain due to radiation induced oral mucositis were enrolled and randomly assigned to two groups: Group A applied dexamethasone ointment once on the first day, had a second day as a wash out period, and used Episil® once on the third day. Group B conversely used Episil® on day 1, followed by a wash-out on day 2 and dexamethasone ointment on day 3. The treatment assignment was performed using computer software, and the assignment factor was the presence or absence of combination with chemotherapy.

Data examined

The data examined here includes age, sex, primary site, leukocyte count, lymphocyte count, hemoglobin, albumin, RT method (three-dimensional conformal radiation therapy (3D-CRT) / intensity modulated radiation therapy (IMRT)), combination of chemotherapy (CRT) or biotherapy (BRT), and pain relief effect. Pain relief effects were classified according to the patients' subjective symptoms into one of four categories: 1) marked improvement, 2) improvement, 3) unchanged, and 4) worsening.

Endpoints

The primary endpoint of the study was a comparison of the pain relief effects of Episil® and dexamethasone ointment. Where pain relief was achieved, the duration was recorded. The secondary endpoint was the drug/material that the patient wished to continue after the study, and the incidence of adverse events of 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 pain relief between Episil® and dexamethasone ointment was analyzed by Fisher's exact test. The difference in pain relief duration between the test drug/materials was analyzed by Mann-Whitney U test. In all analyses, two-tailed p values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of fifteen patients were enrolled, with 8 assigned to group A and 7 to group B (Table 1). The primary site in 7 patients was the oropharynx, while the oral cavity was the primary site in 5 patients, and nasal cavity, hypopharynx, and nasopharynx in one each. All but one of the 15 patients underwent intensity modulated radiation therapy (IMRT), and 11 patients had concurrent chemo- or biotherapy. On average, Episil® or the control substance was applied 3.8 days (range, 0–13 days) after the onset of grade 2 oral mucositis.

Comparison of pain relief effect of Episil® and dexamethasone ointment

The effects of Episil® versus the control ointment on pain relief are summarized in Table 2. Application of dexamethasone ointment was associated with marked improvement in 4 patients, while an additional 8 described some improvement. Pain levels were unchanged in 2 patients, and no patient experienced worsening pain following treatment. In comparison, a marked improvement of pain levels was reported in 4 patients following application of Episil®, while an additional 6 patients reported some improvement. No change was reported in 3 patients, and 1 patient reported worsening pain. The improvement ratio (marked improvement plus improvement / total patients) of dexamethasone ointment was 85.7%, while that of Episil® was 71.4%, although the difference was not statistically significant ($p = 0.682$).

Table 2
Comparison of pain relief effect between Episil® and Dexamethasone ointment

Pain relief 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

In patients showing some improvement or marked improvement of pain resulting from the test drug/material, the effect lasted 103.3 ± 54.31 minutes after application of Episil® and 62.73 ± 47.35 minutes after application of dexamethasone ointment. Episil® had a slightly longer duration of effect but was not significantly different ($p = 0.336$).

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

In 14 patients, excluding one who could not use Episil® due to nausea, 9 wished to continue dexamethasone ointment after the study and 5 wished to continue Episil® (Table 3).

Table 3
Test drug that the patient wished to continue

Test drug that the patient wishes to continue	Number of patients
Dexamethason ointment	9
Episil®	5
Unknown (discontinuation of the test)	1

Table 4 Clinical research on Episil®

Author (year)	Study design	Inclusion	Number of patients	Test material	Control material/drug	Outcome	Main results
Cheng Y (2018)	RCT	chemotherapy or radiotherapy	60	CAM2028 (Episil®)	Oral rinse (Kangsu™)	Pain for 6 hours	The local analgesic effect of CAM2028 was significantly better than that of Kangsu™.
Hadjieva (2014)	Crossover	radiotherapy (grade 2 mucositis)	32	CAM2028 (Episil®)	CAM2028-benzydamine	Pain for 8 hours	The pain relief effect did not differ between the two groups.

Adverse events

One patient was nauseated immediately after application of Episil® and the material was immediately removed. Nausea disappeared shortly after removal, with no subsequent side effects. This case was excluded from the analysis of pain relief effect. No other drug/material-related adverse events were found.

Discussion

Oral mucositis develops almost 100% when the head and neck cancer is treated with RT. 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 recommends several prophylactic and therapeutic measures during head and neck RT such as the use of mouthwashes containing benzydamine, 2% morphine, or 0.5% doxepin, the 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, and therefore are not widely administered.

In Japan, dexamethasone ointment or triamcinolone ointment have 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 with RT alone, there was no effect when administered to patients undergoing CRT or BRT [4].

Episil® is a bio-adhesive barrier-forming oral liquid developed for the management of pain in oral mucositis. Previous studies that investigated the pain relief effect of this material reported that Episil® demonstrated effectiveness as a pain reliever in patients undergoing RT or chemotherapy [5, 8] (Table 4). Hadjieva et al tested the pain relief effects of Episil® and Episil®-benzydamine in patients showing moderate radiation-induced oral mucositis, and the effects did not differ between the two materials [5], while Chen et al compared the pain relief effects of Episil® and Kangsu™ (Luye Pharmaceutical Co. Ltd, Nanjing, China), which is an oral rinse approved in China as a class II medical device for the treatment of various oral mucositis including RT- or chemotherapy-induced mucositis. They found that the local analgesic effect of Episil® was significantly better than that of Kangsu™. In Japan, medical insurance is applicable to spacers, pilocarpine, dexamethasone ointment, and various gargles in radiation-related oral adverse events, but neither Episil®-benzydamine or Kangsu™ are covered under this system.

Table 4
Clinical research on Episil®

Table 1 Patient characteristics		
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
Conccurent chemotherapy*	RT alone	4
	CDDP	6
	CBCDA	1
	DeVIC	1
	Cet	3
*RT: radiotherapy CDDP: cisplatin CBCDA: carboplatin DeVIC: dexamethasone, etoposide, ifosfamide, carboplatin		

Corticosteroids have excellent anti-inflammatory properties, and steroid ointments are widely used for various stomatitis. However, it has also been 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, we recently reported 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 a control treatment.

We conducted a randomized crossover study to determine whether Episil® is more effective than dexamethasone ointment in relieving pain associated with RT induced oral mucositis using a small number of patients for preliminary investigation. The results suggested that Episil® was less effective as an analgesic than dexamethasone ointment, however there was no statistically significant differences between the two test-drug/materials, likely due to the small number of cases examined here. 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 was difficult to accurately apply to the site of mucositis for a longer duration. Our study focused on the use of Episil® for RT induced oral mucositis, a condition that occurs rapidly and spreads widely. Under these circumstances it is therefore difficult to apply Episil® accurately; however, it is expected to be effective for 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 hours. In this study, the effect of Episil® lasted for 103 minutes, which was slightly longer than that of dexamethasone ointment (63 minutes), although there was no significant difference. In order to clarify the duration of the effect of this material, additional investigations are required involving a larger number of cases.

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

Conclusions

Our findings suggest that the pain relief effect of Episil® is comparable to or less than that of dexamethasone ointment. Larger follow-up studies are needed to verify these findings.

Declarations

Ethics approval and consent to participate: This study was performed in accordance with the 2013 Declaration of Helsinki and was approved by the Clinical Research Review Board at Nagasaki University (No. RB18-0014) and registered with the Japan Registry of Clinical Trials (jRCT) on March 3rd, 2019 (jRCTs072180039). Written informed consent was obtained from all participants included in the study. Details are available at the following address:

https://jrct.niph.go.jp/

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare no competing interests.

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Authors' contributions: All authors contributed to the study conception and design. Material preparation was performed by Sakiko Soutome, Souichi Yanamoto, Maho Murata, and Madoka Funahara. Data collection was performed by Yumiko Kawashita, Masako Yoshimatsu, and Yuka Kojima. Analysis were performed by Madoka Funahara and Masahiro Umeda. The first draft of the manuscript was written by Sakiko Soutome, Masahiro Umeda, and Toshiyuki Saito, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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References

1. Rodriguez-Caballero A, Torres-Lagares D, Robles-Garcia M, Pachon-Ibanez J, Gonzalez-Padilla D, Gutierrez-Perez JL. Cancer treatment-induced oral mucositis: a critical review. Int J Oral Maxillofac Surg. 2012;41:225–38.
2. Moslemi D, Nokhandani AM, Otaghsaraei MT, Moghadamnia Y, Kazemi S, Moghadamnia AA. Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A review of the current literature. Radiother Oncol. 2016;120:13–20.
3. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, McGuire DB, Migliorati C, Nicolatou-Galitis O, Peterson DE, Raber-Durlacher JE, Sonis ST, Elad S. Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO Clinical Practice Guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120:1453–61.
4. Kawashita Y, KoyamaY, Kurita H, Otsuru M, Ota Y, Okura M, Horie A, Sekiya H, Umeda M. Effectiveness of a comprehensive oral management protocol for the prevention of severe oral mucositis in patients receiving radiotherapy with or without chemotherapy for oral cancer: a multicenter, phase II, randomized controlled trial. Int J Oral Maxillofac Surg. 2019;48:857–64.
5. Hadjieva T, Cavallin-Ståhl E, Linden M, Tiberg F. Treatment of oral mucositis pain following radiation therapy for head-and-neck cancer using a bioadhesive barrier-forming lipid solution. Support Care Cancer 22. 2014;1557–62.
6. Rugo HS, Seneviratne L, Beck JT, Glaspy JA, Peguero JA, Pluard TJ, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol. 2017;18:654–62.
7. Kawashita Y, Hayashida S, Funahara M, Umeda M, Saito T. Prophylactic bundle for radiation-induced oral mucositis in oral or oropharyneal cancer patients. J Cancer Res Ther. 2014;2:9–13.
8. Cheng Y, Qin SK, Chen YP, Dong LH, Sun XD, Yu SY, et al. Local analgesic effect of a bioadhesive barrier-forming oral liquid in cancer patients with oral mucositis caused by chemotherapy and/or radiotherapy: a randomized multicenter, single-use, positive-controlled, open-label study. Onco Targets Ther. 2018;11:8555–64.
9. Nishii M, Soutome S, Kawakita A, Yutori H, Iwata E, Akashi M, et al. Factors associated with severe oral mucositis and candidiasis in patients undergoing radiotherapy for oral and oropharyngeal carcinomas: a retrospective multicenter study of 326 patients. Support Care Cancer. 2020;28:1069–75.

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