Clinical Investigation Of Use Of Episil® Oral Solution In Oral Mucositis During Radiotherapy For Head And Neck Cancer

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Abstract

Objective: Episil® is a bioadhesive barrier-forming oral liquid gel that has been used in recent years to relieve pain at the onset of oral mucositis (OM) associated with radiotherapy (RT) or chemoradiotherapy (CRT) in patients with head and neck cancer (HNC). We retrospectively analyzed the clinical effect of Episil® on OM in patients with HNC who underwent RT or CRT.

Patients and Methods: A total of 65 patients with HNC were treated with RT or CRT at our hospital between June 2018 and May 2020. Among the 65 tumors, 64 were histologically confirmed as squamous cell carcinomas, and one malignant lymphoma.

Results: The median total RT dose was 50 Gy (range, 30–70 Gy) and the completion rate of RT was 63/65 (97%). The median time to OM resolution was 47 (6–90) days and was significantly longer (53 [27–90] days) when the total RT dose was ³51 Gy ($p<0.001$). Episil® was used in 26 patients; among them, 10 of whom discontinued its use due to several factors including ineffective pain relief, usage difficulties, and taste intolerance. The median duration of use was 30 (1–52) days and was significantly longer (34.5 [10–52] days) ($p<0.001$) when patients experienced pain relief at treatment initiation.

Conclusion: Although Episil® has been shown to be effective in improving the pain of OM caused by RT of HNC patients. Episil® needs to be improved, and medical professionals are required to give careful attention to each individual patient.

1. Introduction

Oral mucositis (OM) is the primary complication of radiotherapy (RT) or chemoradiotherapy (CRT), causing decreased quality of life (QOL) in patients with head and neck cancer (HNC) [1–3]. Additionally, OM can cause decreased RT or CRT completion rate, leading to poor clinical outcomes in these patients [4]. The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) /International Society for Oral Oncology (ISOO) clinical practice guidelines[5, 6] recommend several prophylactic, therapeutic, and pain control methods for OM during RT or CRT, such as oral cryotherapy, human keratinocyte growth factor-1 (KGF-1/palifermin), low-level laser therapy (LLLT), patient-controlled analgesia (PCA) with morphine, benzydamine mouthwash, transdermal fentanyl, 2% morphine mouthwash, 0.5% doxepin mouthwash, and zinc supplements. Additionally, they recommend basic oral care (BOC), including a combination of tooth brushing, flossing, and mouth rinsing at least once daily (with alcohol-free, saline, sodium bicarbonate) to maintain oral hygiene [7]. However, in Japan, the following products are not approved for use and not covered by medical insurance: KGF-1/palifermin, LLLT, benzydamine mouthwash, transdermal fentanyl, 2% morphine mouthwash, and 0.5% doxepin mouthwash. In contrast, Episil® is the only bio adhesive barrier-forming oral liquid covered by medical insurance and available for use in Japan, to optimize oral health care of cancer patients since 2018. In Japan, dentists are prescribing Episil® in collaboration with physicians to manage pain experienced during OM in patients with cancer. Episil® is a lipid-based drug carrier system in the oral cavity, and

contains soybean lecithin and diolein. When it comes in contact with the oral mucosa, oil accumulates on the surface of the saliva and forms small spheres that rapidly join to form a thin gel skeleton arrangement, which creates a physical barrier. The lipid and ambient water components in the saliva undergo non-chemically mediated molecular self-assembly to form lipid films (Figure 1) [8].

Episil® should be rinsed around the mouth about 1 h before eating to form a protective layer over painful areas; additionally, topical analgesics may be co-administered to intensify the therapeutic effect. It should be noted that Episil® and topical analgesics should not be swallowed. Episil® adheres to ulcerative areas and within 5 min forms a protective membrane that acts as a mechanical barrier to relieve pain. Additional effects of bioadhesive lipid formation include lubrication, moisturization, and mechanical protection of the sore mucosa.

The current MASCC/ISOO guidelines do not mention the effectiveness of bio adhesive barrier-forming oral liquids. This is due to the insufficient evidence regarding the reduced severity of mucositis when these products are used; however, some of these oral care products provide comfort for patients [9]. The European Oral Care in Cancer Group [10] and UK Oral Mucositis in Cancer Group [11] suggest the usefulness of topical gel or film oral mucosal protectants, such as Caphosol®, Mugard®, Oralife®, Gelclair®, and Episil®, and recommend their use for mild to moderate OM.

A previous study reported that Episil® is an effective and safe product for pain relief caused by OM in patients with cancer [8, 12]. However, adverse reactions of Episil® have been noted, including nausea and difficulties in proper application at the OM site [13]. Clinically, we have experienced some benefits and difficulties when using Episil® for HNC patients; however, these experiences are rarely discussed in the literature.

For these reasons, more evidence is needed to support the use of Episil®. We aimed to examine the pain-relieving effects and patients' perceptions of Episil® during initiation of RT or CRT for HNC.

2. Patients And Methods

This study retrospectively examined the clinical data of 65 patients with HNC who underwent RT or CRT at our Hospital between June 2018 and May 2020. Among the 65 tumors, 64 were histologically confirmed as squamous cell carcinomas, and one malignant lymphoma.

All patients received RT involving three-dimensional conformal RT (3D-CRT) (46 patients) or intensity-modulated RT (IMRT) (19 patients). The overall therapeutic irradiation dose was 30–70 Gy (median, 50 Gy). The purpose of RT was post-operative irradiation. Two patients had their planned RT doses reduced and interrupted (30 Gy and 54 Gy) due to deterioration of their nutritional status. The original dose for a 30 Gy patient was 50 Gy, and the original dose for a 54 Gy patient was 60 Gy. RT was performed once per day (2 Gy) five times a week. In addition, 63 patients received concurrent chemotherapy; the regimens included either cisplatin (CDDP; 30 mg/m^2/w), tegafur-gimeracil-oteracil-potassium (TS-1®) (80 mg/m^2), or cetuximab (400 mg/m^2/w and 250 mg/m^2/w) (Table 2).

Prior to the start of RT, an oral care team comprising an oral surgeon and dental hygienist examined the oral cavity and administered oral hygiene care for patients with HNC. Simultaneously, patients were oriented regarding OM management, including instructions regarding tooth brushing, mouth washing, oral moisturizing, nutrition, and using Episil® during treatment.

During the treatment, daily assessment of OM severity was conducted regarding functional disorders, symptomatic aspects, and clinical examination according to Common terminology criteria for adverse events (CTCAE) version 4.0. OM severity was graded as follows: grade 1, asymptomatic or mild symptoms, intervention not indicated; grade 2, moderate pain, not interfering with oral intake, diet modification indicated; grade 3, severe pain, interfering with oral intake; grade 4, life-threatening consequences, urgent intervention indicated; grade 5, death.

When OM was first observed and patients started to experience pain, we prescribed our original mouthwash containing sodium gualenate hydrate, sodium bicarbonate, and 0.2% lidocaine (Xylocaine), which was gargled 6–8 times a day. We repeated the discussion regarding Episil® use, and left the decision of receiving it to the patients. Episil® was administered by one dentist (Y.K.), and patients were instructed to use it three times per day, at least 5–10 min before a meal. Patients experiencing difficulties using Episil® in this manner prompted the dental hygienist to explain methods of easier administration, as described earlier in the manuscript.

We assessed pain relief after RT according to the WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain [5]. To minimize the impact of confounding factors, we confirmed the timing of all pain medications, including opioids, and ensured the presence of at least a 2-h interval before starting Episil®. The pain-relieving effect of Episil® was confirmed by one dentist (Y.K.) within 6 h of its use in an interview with each patient by recording the patients' impressions of its use. Pain in the oral mucosa was assessed by a dentist (Y.K.) and noted in the medical records.

All statistical analyses were performed using the IBM SPSS version 22.0 (IBM, Armonk, NY, USA). The measurement data were expressed as the median, maximum (max), and minimum (min) values and were analyzed using the Mann–Whitney U test or Pearson's chi-square test. Statistical significance was set at $P<0.05$.

3. Results

3.1. **Patient characteristics**

Table 1 lists the patients' baseline characteristics. Among the 65 patients, 26 were included in the Episil® use group, and 39 were in the control group that did not use Episil®. No significant differences were observed regarding the baseline characteristics between groups. The wide range of irradiation doses (30–70 Gy) is due to the inclusion of both preoperative and postoperative irradiation. The median overall irradiation dose was 50 Gy; additionally, the most frequently delivered dose was 50 Gy in 28 patients,

followed by 60 Gy in 22 patients. The oral cavity was included in the irradiation area of 59 patients, and six patients were irradiated only neck region. Four patients were aware of pain due to oral mucositis in the pharyngeal mucosa even if irradiation was only to the neck, and used Episil®. No significant difference was observed regarding RT irradiation method or concurrent chemotherapy between the groups. Two patients who used Episil® , underwent dose reduction of RT due to pain from OM and deterioration in nutritional status, and the RT completion rate was 97% (63/65).

3.2. Oral mucositis

The overall median days to resolution of OM were 47 days (range, 6–90 days). The number of days to resolution of OM was not significantly related to Episil® usage or the highest previous grade of OM during RT (Table 2); however, it was related to the irradiation dose. Compared to a lower dose, a radiation dose higher than the median total irradiation dose (50 Gy) significantly lengthened the median healing time (39 days [range, 6–57 days] vs. 53 days [range, 27–90 days], respectively; P<0.001) (Table 2).

3.3. Pain-relieving effect, duration of use, and impressions of use of Episil®

Table 3 shows the pain-relieving effects of Episil® (n=26) confirmed within 6 h of its initial use. Among 26 patients, 16 experienced pain relief within 6 hours of Episil® use, while six reported no pain relief. No significant difference was observed regarding the pain-relieving effect of Episil® between patients with OM grade of 2 and 3.

The median duration of Episil® use was 30 days (range, 1–52 days). Patients who experienced pain relief at the start of Episil® use had significantly longer duration of Episil® use (>29 days) (Table 4). In contrast, if Episil® did not improve pain at the start of use, the duration of use was £7 days (P<0.001).

Table 5 shows patients' impressions of Episil® within the first 6 hours of use. Among 26 patients, ten complained of difficulty in continuing Episil® use. Notably, these were the same patients who did not experience pain relief with Episil® at the start of use. In addition to less relief of pain caused by OM (four patients), other reasons for difficulty of use of Episil® were inability to reach the painful area (three patients), dislike of the taste (two patients), and dislike of the smell (one patient).

4. Discussion

Episil® has been shown to relieve pain and improve malnutrition in patients with HNC [14]. This study showed that Episil® non-significantly caused pain-relief in patients with grade 2 and 3 OM (Table 3). Among the 26 patients who received Episil®, 16 experienced pain-relief, which is lower than that reported in a previous study [8]. There are few reports regarding the use of Episil® exclusively in patients with HNC; additionally, reports lack data on the factors associated with difficulty in its use. This study found that these factors included lack of pain relief, inability to reach the painful area, and dislike of the taste and smell. Problems related to taste and smell may be attributed to the oil and ethanol in the product.

Patients were instructed to gargle before using Episil®. Patients were asked regarding their awareness of xerostomia; however, no relationship was found between the presence of xerostomia and the pain-relieving effect of Episil® (data not shown). A patient-friendly and individualized manner of instruction is crucial when teaching patients regarding Episil® use. In Japan, dental hygienists are often responsible for instructing patients on the use of such products. For example, Kawano et al. reported the importance of developing a patient-friendly formulation while considering different aspects, such as spray shape [15, 16].

The present results showed that Episil® had no effect on the healing time of OM caused by RT, which is consistent with a previous report [17]. The dose delivered to the oral mucosa determines the degree of OM; however, concomitant chemotherapy may add to this effect [18]. In the present study, the first to show the duration of use of Episil®, the duration of use was shown to be over 30 days if it was effective in improving pain. The median healing time of OM using RT or CRT for HNCs was 45 days; additionally, Episil® was used for more than 30 days if it was effective in relieving pain. Currently, health insurance in Japan prohibits the use of Episil® for over 30 days; however, the results of this study suggest that the use of Episil® for longer periods should be allowed. We found that there are many problems associated with Episil® treatment. Episil® is usually used by spreading it in the oral cavity with the tongue; however, HNC patients have a wound in the oral cavity, which makes it difficult to apply it with the tongue and requires individualized treatment. In our university hospital, dental hygienists took the lead in the treatment, and we believe that this led to the prolonged use of Episil® and the sustained pain-relieving effect.

The method and site of RT and concomitant chemotherapy may affect patients' QOL. In particular, the impact of IMRT on patients' QOL is controversial. The meta-analysis of de Felis et al. found that IMRT is superior to 3D-CRT, in terms of xerostomia rates [19]. However, Oba et al. reported that IMRT caused mucositis to progress and significantly worsened the patient's QOL [20]. In our study, no difference was observed between the irradiation sites, methods, or chemotherapy. It is possible that the incidence and healing period of oral mucositis differs depending on chemotherapy. Further studies with a larger sample size are warranted to validate the findings of this study.

This study has some limitations. It was not a randomized controlled trial and the nutritional improvement with Episil® use was not evaluated, as has been reported previously [13]. Further prospective studies are necessary to determine the effect of Episil® on nutritional improvement.

5. Conclusions

Although Episil® has been shown to be effective in improving the pain of OM caused by RT of HNC patients. Episil® needs to be improved, and medical professionals are required to give careful attention to each individual patient.

Declarations

Conflicts of Interest: The authors declare no conflicts of interest.

Funding: This research received no external funding.

Informed Consent Statement: Patient consent was waived due to the retrospective study design

Author Contributions: Y.K. performed the following aspects of the study: conceptualization, methodology, software, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration, and funding acquisition. K.I. validated the data. S.T., I.T., H.N., and R.Y. curated the data. All authors have read and agreed to the published version of the manuscript.

Ethics Statement: The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Faculty of Dentistry of Tokyo Medical and Dental University. The requirement for written informed consent from each patient was waived because of the retrospective nature of the study (approval no. D2018-016).

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Tables

Table 1. Baseline characteristics of the Episil® use and control groups (n=65)

Characteristic	Use (n=26)	Control (n=39)	*P* value
Age (y) Median (min–max)	62.5 (41–83)	68 (22–90)	0.076
Irradiation total (Gy) Median (min–max)	54 (30–66)	50 (40–70)	0.897
Irradiation site			
Oral cavity	10	20	
Oral cavity + neck	10	16	
Oropharynx	0	1	
Oropharynx + neck	2	0	
Neck	4	2	
			0.371
Method of RT			
3D-CRT	16	30	
IMRT	10	9	
			0.367
Concurrent chemotherapy			
CDDP	11	21	
TS-1	13	14	
Cmab	1	3	
None	1	1	
			0.536

RT: radiotherapy; CDDP: cisplatin; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; TS-1: tegafur-gimeracil-oteracil-potassium; Cmab: cetuximab

Table 2. Relationship of various factors with days until resolution of OM (n=65)

	n	Days to Resolution of OM	*P* value
		Median (min–max)	
Total	65	47 (6–90)	
Episil®			
Use	26	43 (12–90)	
Control	39	49 (6–88)	0.312
Mucositis grade			
1	4	31 (24–39)	
2	21	37 (12–90)	
3	37	51 (6–88)	
4	3	49 (41–53)	
			0.407
Irradiation total (Gy)			
30–50	33	39 (6–57)	
51–70	32	53 (27–90)	
			<0.001
Irradiation site			
Oral cavity	30	46 (6–74)	
Oral cavity + neck	26	49 (12–90)	
Oropharynx	1	68	
Oropharynx + neck	2	53 (51–54)	
Neck	6	39 (27–40)	
			0.108
Method of RT			
3D-CRT	46	44 (6–88)	
IMRT	19	52 (12–90)	
			0.157
Concurrent chemotherapy			
CDDP	32	41 (6–90)	

TS-1	27	50 (20–74)	
Cmab	4	44 (24–88)	
None	2	42 (35–49)	
			0.765

OM: oral mucositis; RT: radiotherapy; CDDP: cisplatin; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; TS-1: tegafur-gimeracil-oteracil-potassium; Cmab: cetuximab

Table 3. Pain-relieving effect after using Episil® (n=26)

Pain-relieving effect	Mucositis Grade 2	Mucositis Grade 3	*P* value
Effective	7	9	
Not effective	6	4	
			0.536

Table 4. Pain-relieving effect and duration of using Episil® (n=26)

Pain-relieving effect	n	Days	*P* value
Not effective	10	1–7	
Effective	1	10	
Effective	15	³29	
			<0.001

Table 5. Impressions of Episil® use (n=26)

Impression	n	*P* value
Favorable	7	
Difficult to use	2	
Method of use needs improvement	7	
Impossible to use	10	
		0.236

Figures

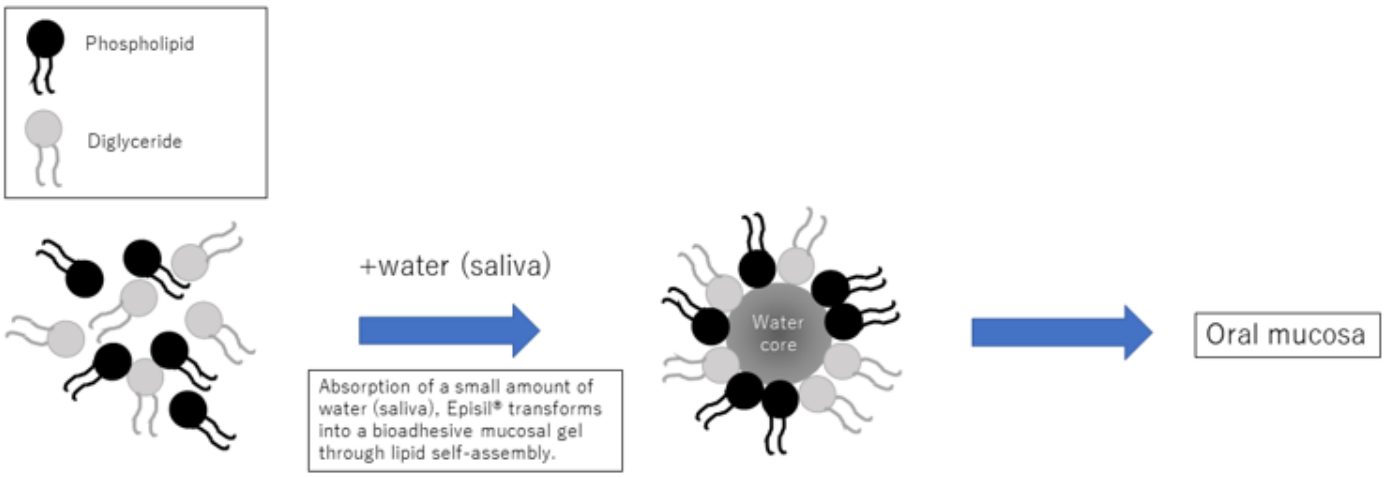

Figure 1

Mechanism of action of Episil®. When applied to the oral mucosa, the phospholipid (soybean phosphatidylcholine) and diglyceride (aprylic acid diglyceride) components self-assemble with trace amounts of water (saliva) to form a bioadhesive liquid lining that protects the oral mucosa. (Figure is modified from Hadjieva et al [8].)