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The Effect of Sucralfate on the Reduction of Radiation Esophagitis: Clinical and Laboratory Data

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Sucralfate에 의한 방사선 식도염 감소 효과: 임상 및 실험 결과

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목적: 이 전향적 연구는 sucralfate에 의한 방사선 식도염의 감소효과를 임상연구를 통해 규명하고 이의 기전을 밝히는 것을 목적으로 하였다.
대상 및 방법: 1995년 6월부터 1996년 6월까지 폐암 혹은 식도암으로 진단받고 완치 목적의 방사선치료를 받은 총 51명의 환자를 대상으로 하였다. 모든 환자를 sucralfate 투여군과 위약 대조군의 두 군으로 구분하였다. 방사선 식도염의 정도를 pain scale 및 내시경에 의한 육안소견으로 관찰하였고 기전 규명을 위해서 inducible nitric oxide synthase, myeloperoxidase, 및 lipid peroxidation을 측정하였다.
결과: Sucralfate 투여군에서 sucralfate에 의한 소화기계 장애는 미미하였고 입맛에 맞지 않아 투약을 중단하였던 한 명을 제외하고는 모든 환자가 방사선치료 종료 시까지 투약이 가능하였다. 증등도 이상의 방사선 식도염을 나타낸 빈도가 sucralfate 투여군에서 통계학적으로 유의하게 감소하였다(25% 대 74%)(p=0.001). 내시경으로 관찰한 식도 점막의 손상정도가 sucralfate 투여군에서는 모든 환자가 등급 1 이하였으나 위약 대조군에서는 80%가 등급 2 이상이었다. 방사선에 의한 oxygen metabolites의 생성이 sucralfate 투여군에서 통계학적으로 유의하게 감소하였다(p=0.001).
결론: 이 연구를 통해 sucralfate가 방사선 식도염을 효과적으로 감소시켜 방사선치료에 대한 순응도를 증가시킬 수 있음을 확인하였다. 또한 이러한 효과가 방사선에 의한 oxygen metabolites의 생성이 sucralfate에 의해 감소한 것에서 비롯될 수 있음을 실험적으로 관찰하였다.

Key Words: Radiation, Esophagitis, Sucralfate, Oxidative metabolites, Nitric oxide

INTRODUCTION

Radiotherapy is one of the most effective modalities in cancer management. However, there are side effects frequently encountered in daily patient care, such as diarrhea, mucositis, nausea, skin reactions and others. Particularly, esophagitis is a common acute compli-

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1996년도 제 38차 American Society for Therapeutic Radiation and Oncology (미국, Los Angeles) 석상에서 발표되었음.
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cation that develops by irradiation to thoracic area including the esophagus. During the radiation treatment of lung or esophageal cancers, a substantial portion of the esophagus is included in the radiation field and receives 30 to 60 Gy depending on the primary target volume.

Esophageal squamous epithelium has modest radiosensitivity which is similar to that of the oral mucosa. It is assumed that radiation-induced esophagitis is largely due to depletion of clonogenic epithelial cells. Histologically, acute radiation esophagitis is characterized by basal cell necrosis, submucosal edema, capillary dilation and swollen endothelial cells. Radiation therapy with over 30 Gy to the mediastinum causes symptoms like retrosternal burning and painful swallowing during or, in rare cases, even after the completion of radiation treatment. These symptoms may lead to reduction of nutritional intake and deterioration of performance status. Also, chemotherapy may enhance the radiation damage of the esophagus. The available management for esophagitis during radiation treatment is palliative and is of limited effectiveness. Management includes change of diet to soft or liquid one, avoiding irritating food, and taking topical anesthetic agents and systemic analgesics. Sometimes, patients require a treatment break due to severe irritation.

Sucralfate (Ulcermin^{R}, Choong Wae Pharma co., Seoul, Korea), sucrose sulfate-aluminum hydroxide complex, is an active ulcer healing drug and is produced by the reaction of sodium sucrose octasulfate with basic polyaluminum chloride. The known cytoprotective mechanisms of sucralfate are as follows; 1) antipeptic activity and absorption of bile acid(1), 2) increase of sodium bicarbonate secretion(2), 3) augmentation of mucous resistance by producing mucus secretion and by changing mucous components(3), 4) stimulation of prostaglandin secretion(4), 5) protection of blood vessels(5), 6) promotion of epithelial regeneration by protecting & stimulating mucosal proliferation zone(6), and 7) stimulation of growth factors such as EGF(7). Several studies on the reduction of esophageal irritation by taking this compound during radiation therapy have been reported(8,9).

The aim of this double-blind study is to evaluate effect of sucralfate on reduction of radiation-induced esophagitis in patients receiving thoracic irradiation for lung or esophageal cancers and to prove it via laboratory data.

MATERIALS AND METHODS

Patients with lung or esophageal cancers who were planned to receive thoracic irradiation for 6 weeks with a radical purpose were eligible for this prospective study. Ineligibility criteria were followings; previous radiation therapy to the chest, inability to take oral medications, or known intolerance to sucralfate. Between June 1995 and June 1996, 56 patients were enrolled onto the study. A signed informed consent was obtained from every patients and each candidate was assigned either to sucralfate group or to placebo group. These patients took 3 (TID) to 4 (QID) packages daily before each meal and right before radiation, starting on the first day of radiation treatment and continued while receiving radiation treatment. Sucralfate and placebo were supplied by Joogwae Pharmaceutical Corporation and their compositions are listed in Table 1.

Of the 56 patients, five patients were excluded from the study since they stopped receiving radiation therapy before total dose of 20 Gy; two due to poor general condition, one complaining of bad taste, and two due to refusal of further treatment. Other two patients didn't finish the planned radiation course due to deteriorating general condition, but they were still included in the study because more than 30 Gy of radiation was delivered to the esophageal area. There-

Table 1. Contents in Sucralfate and Placebo suspension (15 ml)

Sucralfate		Placebo	
Sucralfate	6.67 g	Corn starch	1000.0 mg
Crystalline cellurose	0.5 g	Agar-agar	15.0 mg
Hydroxyethyl cellurose	0.8 g	Microcrystalline cellurose	75.0 mg
D-sorbitol	10.5 g	Hydroxyethyl cellurose	135.0 mg
Sucrose	7.0 g	D-Sorbitol (70 %)	2145.0 mg
Ethanol	2.0 ml	D-Xylitol	600.0 mg
Methyl parahydroxybenzoate	0.08 g	Methyl paraben	12.0 mg
Prophyl parahydroxybenzoate	0.02 g	Propyl paraben	3.0 mg
		Sodium chloride	22.5 mg
		Lemon essence	15.6 mg
		Dimethicone	7.5 mg
		Water for injection	Q.S.

Table 2. Patients' characteristics

	Sucralfate (32 pts.)	Placebo (19 pts.)
Age (Median)	25~74 (61)	45~73 (63)
Male : Female	29 : 3	16 : 3
Disease site		
Lung	23	9
Esophagus	15	4
RT dose (Gy)		
(Median)	45~61.2 (59.4)	30~67.8 (54)
Length of irradiated		
esophagus (cm)	16	16
Lung (Median)	12~22 (15)	12~20 (15)
Esophagus (Median)	17~29 (19)	14~22 (19)
Chemotherapy*	24 (75%)	11 (58%)
Concurrent (L†/E‡)	24 (15§/9)	8 (4¶/4**)
Sequential (L/E)	0	3 (3/0)

*Concurrent chemotherapy during the radiation therapy was undertaken as follows; daily cisplatin, 6 mg/m^2/day, as a radiosensitizer in lung cancer patients and 2 cycles of 5-FU (1,000 mg/m^2/day for 3 days) and cisplatin (20 mg/m^2/day for 3 days) as a systemic chemotherapy in esophageal cancer patients. †Lung cancer, ‡Esophageal cancer, §2 patients: 1 cycle of cisplatin containing systemic chemotherapy and then daily cisplatin concurrently with the radiation as a radiosensitizer. 1 patient: daily cisplatin, ¶1 patient: daily cisplatin during the radiation therapy after induction chemotherapy with ifosfamide, cyclophosphamide, and etoposide, **1 patient: daily cisplatin

fore, 51 patients were available for the evaluation of sucralfate effect (32 and 19 paitents in sucralfate and placebo groups, respectively).

Most patients except two received between 55 to 60 Gy with 1.8~2 Gy per fraction. Patients' characteristics are presented in Table 2. Median length of irradiated esophagus was 16 cm in both of sucralfate and placebo groups (range 12~29 cm and 14~22 cm, respectively). Twenty four out of 32 patients and 8 out of 19 patients in sculralfate and placebo groups, respectively, received concurrent chemotherapy during the radiation therapy (daily cisplatin, 6 mg/m^2/day, as a radiosensitizer in lung cancer patients and 2 cycles of 5-FU (1,000 mg/m^2/day for 3 days) and cisplatin (20 mg/m^2/day for 3 days) as a systemic chemotherapy in esophageal cancer patients). Other 3 patients with lung cancer in placebo group received radiotherapy after induction chemotherapy.

Each week, the physician evaluated clinical symptoms using Radiation Therapy Oncology Group (RTOG) grading system for acute esophageal toxicity. The pain scale for evaluating degree of subjective symptom consisted of 6 faces which express the pain (Fig. 1) (10). The nurse asked the patient to choose a face which describes best how he or she was feeling at that

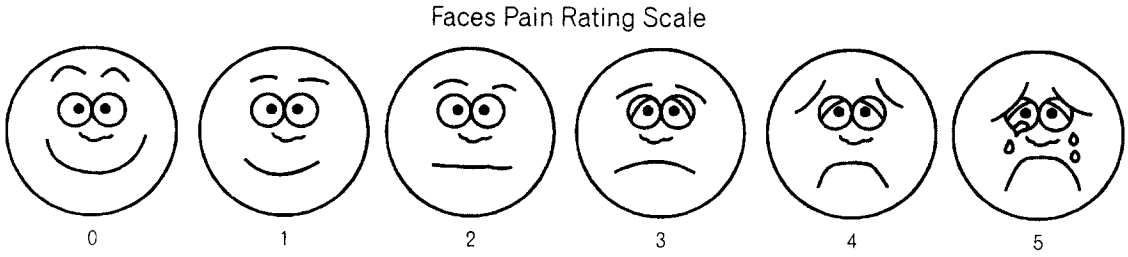

Fig. 1. Faces Pain Rating Scale. Explain to the person that each face is for a person who feels happy because he has no pain(hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling. (Wong D, Baker C. Pain in children: comparison of assessment scales. Pedia Nur 1988;14:9-17.)

Table 3. Endoscopic grade

Grade	Endoscopic finding
0	Null
1	Mild erythema without ulceration
2	Some erosion with friable, erythematous, edematous hemorrhagic mucosa
3	Linear ulceration with edematous, erythematous mucosa
4	Conglomerate ulceration without stenosis
5	Conglomerate ulceration with stenosis

time.

On the 3rd week of treatment by which time patients received about 20 Gy, 14 of the enrolled patients agreed to perform endoscopy and multiple biopsies from non-tumor sites were examined. Endoscopic grading system (Table 3) was used to assess the gross damage of the esophagus. From the tissue homogenization, we evaluated the amounts of reactive oxygen and nitrogen metabolites. Inducible NOS activity was monitored by the conversion of [^{14}C]-L-arginine to [^{14}C]-citrulline(11). NO is known to be related to pathogenesis of inflammatory bowel condition. MPO activity as a indicator of granulocyte (primarily neutrophil) infiltration into the tissue was measured spectroscopically using method of Krawisz et al(12). Concentrations of thiobarbituric acid reactive substance (TBA-RS) and chemiluminescence (CL) assay as an index of lipid peroxidation were estimated(13). The t-test and chi-square test was used to test for differences among groups. Results were considered statistically significant when $p<0.05$.

RESULTS

All the patients were able to take sucralfate without difficulties. Side effects with sucralfate were not frequent. Constipation was expected but was not a major problem for any of the patients. Only one patient who was excluded from the study complained of bad taste and nausea and refused to take medication after a few radiation treatments. Overall compliance to both treatment groups was very good.

Much less number of patients in sucralfate group experienced moderate to severe esophagitis (RTOG grade 2 or pain scale 4) than the placebo group throughout the radiation therapy (25% (8/32) *vs.* 74% (14/19), p=0.001)(Table 4). We performed subset analysis for evaluating the effect of intake frequency of sucralfate. The incidence was lower in QID subgroup (15.4% (2/13)) compared to that in TID subgroup (32% (6/19)) but difference was not statistically signi-

Table 4. Pain scales for subjective symptom of esophagitis

Grade	Sucralfate (N=32)			Placebo (N=19)		
	CTx*(+)	CTx (−)	Total	CTx (+)	CTx (−)	Total
0	4	−	4	−	−	−
1	−	−	−	−	1	1
2	4	2	6	1	−	1
3	11	3	14	3	−	3
4	5	3	8	3	8	11
5	−	−	−	1	2	3

*Concurrent chemotherapy

Table 5. Laboratory data

	Sucralfate	Placebo	p value
iNOS (nM/min/mg protein)*	0.15±0.10	0.12±0.08	0.594
MPO (U/mg protein)†	0.41±0.12	0.95±0.07	0.001
TBA-RS (nmol/mg protein)‡	2.11±1.09	5.94±0.34	0.001
CL (nmol/mg protien)§	1.57±0.50	5.30±0.67	0.001

*inducible nitric oxide synthase, †myeloperoxidase, ‡thiobarbituric acid reactive substance, §chemiluminescence assay

ficant.

Endoscopic examination confirmed that there was significantly less esophageal irritation with sucralfate treatment. Endoscopic grades in the sucralfate group (9 patients) were less than grade 1 in all patients. However, 80% of the placebo patients (5 patients) showed higher than grade 2.

The laboratory data with biopsied specimens confirmed that there were less oxidative metabolites in the irradiated tissues treated with sucralfate than the placebo group (p=0.001)(Table 5). But activity of iNOS was not reduced in sucralfate group (p=0.594).

DISCUSSION

The present study demonstrates an effective reduction of moderate to severe radiation induced esophagitis with prophylactic oral sucralfate during radiation therapy. There was a good compliance with sucralfate (dropout rate 3%); only one patient was unable to tolerate the bad taste. This is quite a contrast to the study carried out by McGinnis (dropout rate was 58%)(9). A gastrointestinal trouble such as constipation was not a major problem in taking the medication over the 6-week period.

Increased rate of esophagitis and more severe esophageal damage may develop in patients who receive chemotherapeutic agents concomitant with mediastinal radiotherapy. Chemotherapy is known to potentiate radiation injury in the esophagus(14,15). This effect is particularly common with doxorubicin but has also been described with bleomycin, dactinomycin, cyclophosphamide, fluorouracil, etoposide methotrexate, and cisplatin. Since over 50% of our patients received chemotherapy during the course of radiotherapy, high rate (74%) of RTOG grade 2 to 3 esophagitis in the

placebo group was as expected. However, even though there were more patients receiving concurrent chemo-radiotherapy in sucralfate group, prophylactic use of sucralfate was effective in reduction of incidence of moderate to severe esophagitis from radiation (25%). Also, we confirmed the protective effect of sucralfate on esophageal damage from radiation by endoscopic evaluation. Endoscopic grades were less than grade 1 in all the sucralfate group patients, and were more than grade 2 in 80% of the placebo group patients. Previously, there has been a few data dealing with the effects of sucralfate on oral and gastrointestinal mucosa(16~18). Beneficial effects of sucralfate in management of oral mucositis induced by chemotherapy and its usefulness in early relief of pain from radiation-induced esophagitis were also reported(8,19). On the other hand, some reported no benefit of prophylactic oral rinsing with sucralfate to prevent oral ulcerative mucositis(9,20,21). Oral mucosa may not be protected with sucralfate since drugs pass through the oral cavity so quickly. But using radioactively labelled sucralfate, Pfeiffer et al. reported that 20~30% was still bound to the oral mucosa lining 2.5 hours after sucralfate swishing which could be helpful in reducing the irritation from further damage(19). In the most recent data by McGinnis, 97 patients were enrolled for randomized trial to study the effect of sucralfate in patients receiving radiation to mediastinum(9). He found no beneficial effect with sucralfate. However, in that study patients received with higher dose per fraction of radiation (3 Gy per day) and also dropout rate due to symptoms of nausea, vomiting and/or an upset stomach was high (58%). We think that vomiting itself may lead to mechanical damage of esophageal mucosa and can augment the damage by radiation.

Histologically, acute radiation esophagitis is characterized by basal cell necrosis, submucosal edema, capillary dilatation, and swollen endothelial cells. After several weeks of radiation, superficial erosions occur owing to failure of regeneration and to blood vessel damage. Therefore, sucralfate can effectively reduce these radiation-induced damages by exerting its known protective action such as follows; 1) increment of epidermal growth factor binding to ulcerated areas, 2) protection of vascular integrity of the mucosa, 3) stimulation of cell restitution and cell proliferation. In addition, sucralfate seems to stimulate endogenous sulfhydryl compounds. True anti-oxidant effects of sucralfate have been shown in studies on its protection of gastric mucosa(8). Actually, most of radiation damages are due to hydroxyl radical, highly reactive oxygen free radical, produced by radiation. Our data showed that prophylactic sucralfate reduced the production of oxygen metabolites. We suggest that scavenging effect on oxidative metabolites, that are produced by radiation, may be one of the important action mechanisms of sucralfate.

One of early changes induced by irradiation is the development of an acute inflammatory reaction of mucosa. Main histologic feature of radiation-induced mucosal damage is similar to that seen in inflammatory bowel disease. Recently, NO which is a highly reactive nitrogen intermediate, has been actively studied in animal model of intestinal inflammation and in patients with inflammatory bowel disease(22, 23). A report from Konturek et al. suggested that activation of the NO system may be involved in the gastroprotective and hyperemic effects of sucralfate (24). NO is a mediator molecule produced by a variety of cell type and is synthesized from L-arginine via NOS, an enzyme that exists in three isoforms(25). The inducible subtype of NOS is associated with NO production in pathophysiological conditions. This present study evaluated whether the protective effect of sucralfate on radiation induced esophagitis involves NO pathway. The levels of iNOS expression were higher in both of placebo and sucralfate groups compared to normal control (data not shown) but were

not significantly different between these two study groups. Therefore, these results suggested that NO may contribute to induction of radiation damage to esophagus, but protective effect of sucralfate do not necessarily involve the NO-arginine pathway.

CONCLUSION

The data presented in this study demonstrate that prophylactic sucralfate can reduce the incidence of moderate to severe esophagitis during radiation therapy to mediastinum and makes easier for patients to tolerate the thoracic radiation treatment. Endoscopic evaluation of gross features also confirmed the above findings. The laboratory findings on the biopsy specimen suggested that sucralfate acts as a scavenger of highly reactive oxygen metabolites and is the effective drug in reducing radiation induced espophagitis.

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