Effects of Na-sucrose Octasulfate on Skin and Mucosa Reactions During Radiotherapy of Head and Neck Cancers

A Randomized Prospective Study

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Na sucrose octasulfate (Na SOS) was tested for ability to relieve radiation-induced acute skin and mucosal reactions in patients with head and neck cancer. Sixty patients were included in this prospective, double-blind, randomized study. Skin and mucosal reactions were scored using several variables. No statistically significant difference was found between the results with Na SOS and those with placebo for any of the variables, with the exception of skin desquamation, which showed a significant difference in the placebo group. The most likely explanation for this is that the Na SOS gel itself left behind a flaky layer that was difficult to distinguish from radiation-induced flaking. In conclusion, we cannot recommend Na SOS in the routine management of radiation-induced skin and mucosal reactions.

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Irradiation mucositis is an unavoidable but transient side effect of curative radiotherapy of head and neck cancer. It is defined as a reactive inflammatory-like process of the oral and oropharyngeal mucous membrane associated with erythema caused by vascular dilatation and the formation of pseudomembranes. In the worst cases ulceration may develop. Mucositis is invariably associated with pain, difficulties in eating and drinking, and thus limits food intake.

Like the mucous membranes, the skin is also vulnerable to radiotherapy. Both the outer layer (the epidermis) and the mucous membranes in the oral cavity/pharynx are all of ectodermal origin and similarly composed. The only difference is in the outermost layer of epidermis, the stratum corneum. The clinical manifestation of radiation damage to these tissues appears when the cell number is depleted to some critical value. The biological effects of mucosa irradiation have been investigated in mice, in which denudation is a result of continued loss of mature cells from the surface and a lack of recruitment of new cells from the stem cells in the basal epithelial layer.

To minimize discomfort during therapeutic irradiation of the oral cavity, intensive oral hygiene programs are recommended and pre-therapy examinations should be performed to exclude foci of infections, prevent mechanical irritations, and so on. The importance of the oral microbiological flora on mucositis is uncertain. Most authors agree that irradiation-induced mucositis is basically a tissue reaction, and hence difficult to prevent.

There have been very few reports of successful prevention of radiation-induced skin reactions and therefore the question of how to manage this problem in radiotherapy is an important one. Different types of topical ointments (wax, paraffin, aloe, almond, olive and herb oils) or corticosteroids have been used but there is no documentation of the effects.

Sucralfate is a persulfated disaccharide, sucrose-octasulfate (SOS), complexed with aluminium (Fig. 1). The drug was introduced as an anti-ulcer drug more than 20 years ago. The exact mode of action of sucralfate—or more precisely aluminium sucrose-octasulfate—is not fully understood. Regarding treatment of peptic ulcer, it has been shown that the drug has a high affinity to the ulcerated mucosal surface; the drug causes an increase in the level of prostaglandins, and binds basic fibroblast growth factor (bFGF), protecting it from acid degradation. Sucralfate is

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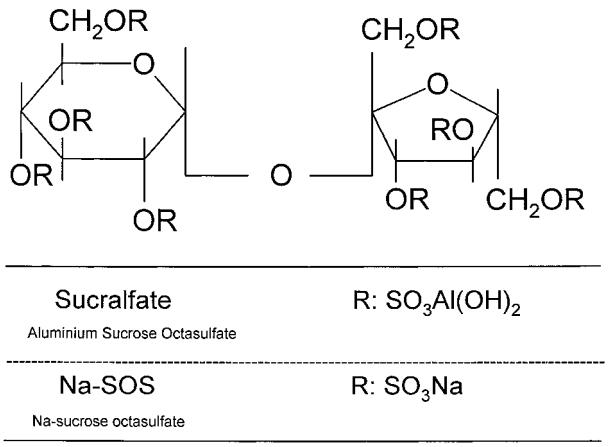

Fig. 1. Chemical structure of sucralfate (aluminium sucrose octasulfate) and Na-SOS (Na-sucrose octasulfate).

thus angiogenic, based on its affinity to bFGF, and increases blood flow. A comprehensive review of the pharmacodynamic properties and therapeutic use of sucralfate in peptic ulcer disease has been published by Folkman et al. (1).

Animal experiments also give the impression that sucralfate stimulates regenerative processes in the skin and accelerates wound healing. This effect is probably mediated by interaction with some of the natural growth factors of the skin (2, 3).

Some years ago the hypothesis was tested that sucralfate could be used topically on skin and mucous surfaces outside the gastrointestinal tract. Pfeiffer et al. (4, 5) performed two studies where the conclusions suggest that oral sucralfate mouth rinsing is a useful method in preventing and relieving chemotherapy- as well as irradiation-induced mucositis. Using radioactively labelled sucralfate, they found that 20–30% was still bound to the oral mucosal lining 2.5 h after mouth rinsing.

Maiche et al. (6) conducted a study with sucralfate cream in patients receiving radiotherapy to the chest wall. They found a clear and significant protective effect of active cream vs. vehicle control.

Whereas sucralfate is practically insoluble in water at pH 7, the sodium salt of SOS (Na-sucrose octasulphate (Fig. 1)) is readily soluble in water at neutral pH. By using the sodium salt in topical formulation, our working hypothesis was that we would obtain a higher concentration of the free and pharmacologically active molecule, at least in the mucous membranes.

Although some studies have demonstrated a beneficial effect of sucralfate on chemotherapy- and radiation-induced mucositis (4–6), other studies do not show any convincing effect (7–11). Thus we feel that the question of whether sucrose octasulfate can prevent/relieve radiation-induced mucositis is still unanswered.

The aim of our study, a combined randomized, double-blind vehicle-controlled right/left study, was to evaluate the protective effect of Na-SOS gel on radiation-induced skin damage in head and neck cancer. In the same group of patients, we also did a double-blind, placebo-controlled study on the effect of prophylactic oral rinsing with Na-SOS to prevent ulcerative mucositis.

Table 1

Distribution of TNM categories at start of treatment (SOS)

	N0	N1	N2	N3
Tx			1	1
T0		1	2	1
T1	3			
T2	9	3	2	
T3	1		1	
T4	1		4	

MATERIAL AND METHODS

Between September 1995 and June 1998, 60 patients (20 females and 40 males) with squamous cell carcinoma of the head and neck region were included in the study. All patients received radiotherapy encompassing the oral cavity and/or oropharynx. There was no age limit, but patients had to be suitable for follow-up. Written informed consent was obtained from all the patients. Those ineligible for inclusion were (i) patients with skin diseases directly affecting the irradiated fields, (ii) patients with allergic and other systemic skin diseases, even if not directly affecting irradiated fields and (iii) patients with mucous membrane diseases apart from the cancer. The local ethics committee approved the study.

The mean age of the patients was 60 years (range: 21–81 years). All patients were included in the analyses whether they complied with the treatment or not.

Site distribution was as follows (SOS/placebo): lip 1/1; oral tongue 12/7; gingiva 5/6; floor of mouth 1/4; oral cavity (unspecified) 4/5; oropharynx 2/1; nasopharynx 0/1; nasal vestibule 1/0; larynx 0/3 and unknown primary 4/2. TNM classifications are presented in Table 1 (SOS) and Table 2 (placebo).

Radiotherapy was given with megavoltage (4–6 MV) irradiation from a linear accelerator. Two upper opposing lateral portals with a separate anterior low-neck portal were used. The lateral fields were treated 5 days a week with a midplane dose of 2 Gy per fraction, to a total dose

Table 2

Distribution of TNM categories at start of treatment (placebo)

	N0	N1	N2	N3
T0			1	1
T1	6			1
T2	4		1	
T3	2	1	2	
T4	2	3	6	

of 50 to 70 Gy. The anterior field received 2 Gy at 3 cm depth and was treated up to 50 Gy.

The mean total dose was 59.7 Gy (range 20–72 Gy). The patient who received 20 Gy died from a heart attack after 5 fractions.

Each patient served as her/his own control. They were double-blindly randomized to apply Na-SOS gel and vehicle control, respectively, on one or the other side of the radiation field. The same patients were randomly allocated to receive either Na-SOS or placebo for the oral rinsing procedure.

Treatment with Na-SOS gel was started on day 1 of the radiotherapy course. The gel was applied twice a day during radiotherapy and for 2 weeks after cessation of therapy. Each patient was also instructed to perform oral rinsing 5 times a day, lasting for at least 2 min, and then to spit out the Na-SOS- or placebo suspension. In addition, the patients were instructed to devote special care to oral hygiene, with daily cleansing, removal of debris and rinsing with saline solution several times a day. The oral rinsing procedure also started on day 1 and continued for 14 days after radiotherapy had ended.

Assessments of the skin and mucosal reactions were made at the start and thereafter weekly during treatment. The final score was assessed 2 weeks after completed radiotherapy. For scoring of the mucosal reaction, a modified scoring system proposed by Van der Schueren (12) was used: Grade 0: none; Grade 1: slight erythema; Grade 2: pronounced erythema; Grade 3: spotted mucositis (patches smaller than 0.5 cm); Grade 4: confluent mucositis (patches larger than 0.5 cm).

Food intake was assessed by the WHO grading system (13): Grade 0: none; Grade 1: soreness; Grade 2: can eat solids; Grade 3: requires liquid diet only; Grade 4: alimentation not possible.

The appearance of the treated skin was judged according to an expansion of the EORTC/RTOG acute skin reaction scoring system (14). Erythema was graded as none (0), mild (1), moderate (2) and severe (3). Desquamation was graded in a scale of none (0), dryness of the skin (1), moderate flaking (2), severe flaking (3) or patchy moist desquamation (4).

Patients were also asked to rate their symptoms of itching and pain in their right and left treatment fields as none (0), mild (1), moderate (2) or severe (3).

The SPSS version 6.1 statistical software was used (SPSS Inc., Illinois, USA) and the drug was supplied by BM Research, Kirke Værløse, DK-3500 Værløse, Denmark.

RESULTS

Skin reaction

The percentages of patients in the two treatment groups reaching a high-grade score for skin erythema (grade 2–3), desquamation (grade 3–4), itching (grade 2–3) and pain (grade 2–3) versus time are shown in Figs. 2–5. The curves for skin erythema (Na-SOS and placebo) more or less overlap and peak at visit no. 6, which corresponds to a mean dose of 51.7 Gy. For skin desquamation, the Na-SOS curve peaks at visit no. 6, while the placebo curve peaks at visit no. 7. For itching, the skin reaction seems to be particularly severe at visit no. 8, while for pain, at visits no. 6 (Na-SOS) and no. 7 (placebo).

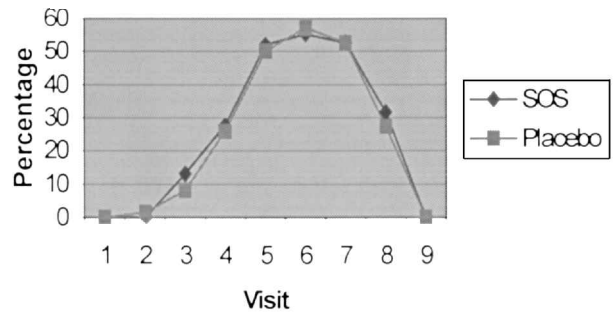

Fig. 2. Time course of percentage of patients with skin erythema grade 2–3 with and without Na-SOS.

To include all measurements in the statistical calculations, the curves were evaluated longitudinally by averaging the absolute values (grade) of skin reactions for all visits. From a statistical point of view, this is equivalent to calculating AUC (area under curve), the only difference is a proportional factor k = (number of visits) × (time between visits) = constant. The efficacy variables were analyzed using Wilcoxon's signed rank test. The results are summarized in Table 3.

Mucosal reaction

The mucosal reaction was evaluated objectively by scoring the oral/pharyngeal mucositis and subjectively by scoring the patients' ability to eat. While the patients served as their own control for skin reaction, they were divided in two groups for mucosal reaction, one for Na-SOS (n = 30) and one for placebo (n = 30). No significant difference was found between the two groups for the mean radiation dose, $D_{SOS} = 61.5$ Gy vs. $D_{placebo} = 57.9$ Gy ($p = 0.1126$, two-sided t-test). As distinct from the skin reaction, the

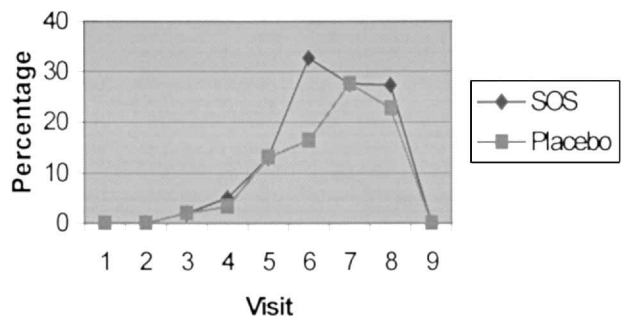

Fig. 3. Time course of percentage of patients with skin desquamation grade 3–4 with and without Na-SOS.

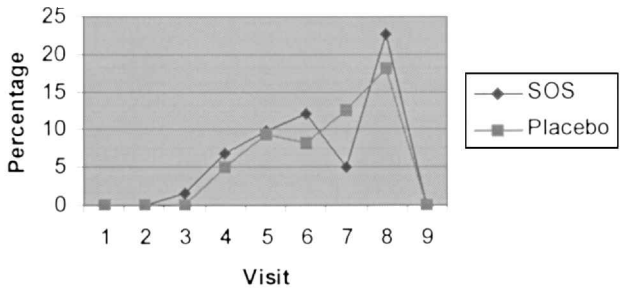

Fig. 4. Time course of percentage of patients with itching grade 2–3 with and without Na-SOS.

mucosal reaction for the two treatment groups differed with respect to point of time for visits as well as their number. The efficacy variables were therefore not evaluated longitudinally, but by their maximum value. The frequencies of maximum scores of current interest are shown in Figs. 6 and 7. Regarding mucositis and alimentation disability, the difference between Na-SOS and placebo did not reach statistical significance, $p = 0.0639$ and 0.5722, respectively (Mann–Whitney–Wilcoxon signed rank test).

DISCUSSION

Introduction of high voltage equipment for radiotherapy has drastically reduced the side effects in skin, usually the dose-limiting factor in the pre-accelerator era. Nevertheless, brisk skin reactions can still be observed in association with radiotherapy, particularly when using opposing lateral and tangential portals, frequently applied in the head and neck region.

Furthermore, virtually all patients who receive radiotherapy to the head and neck region develop oral/oropharyngeal complications. Mucositis is not only painful but it can also limit adequate nutritional intake and can decrease the willingness of patients to continue treatment. Mucositis diminishes quality of life and may result in clinical complications and prolongation of the treatment period, thereby reducing the probability of cure.

There are several studies, randomized and non-randomized, that have evaluated the possibility of reducing mucosal reaction during chemotherapy in general and radiotherapy of head and neck tumors in particular. For a comprehensive review, see Plevová (15), but the literature on skin reaction management is in much shorter supply. Whatever the reason for this, the bottom line is—we are still in search of the optimal regimen in the management of skin and mucosal radiation-induced damage.

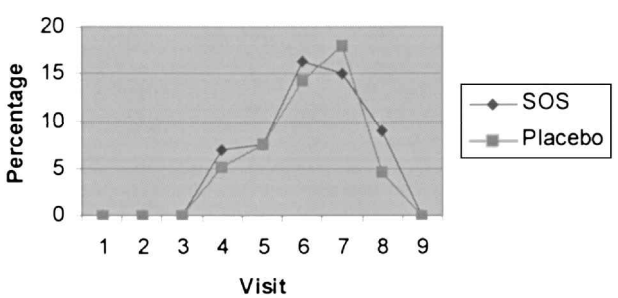

Fig. 5. Time course of percentage of patients with pain grade 2–3 with and without Na-SOS.

Table 3

Skin reactions, mean values (± SD) of all visits

Skin reaction	Na-SOS Mean ± SD	Placebo Mean ± SD	p-value (2-tailed)
Erythema	0.99 ± 0.48	0.94 ± 0.46	0.1335
Desquamation	0.82 ± 0.47	0.72 ± 0.46	0.0172
Itching	0.29 ± 0.27	0.29 ± 0.27	0.8546
Pain	0.21 ± 0.27	0.19 ± 0.27	0.2584

Anecdotal reports suggest a pronounced response to oral sucralfate in patients with chemo- and radiotherapy-induced mucositis (16), supported by results of several studies (4, 5, 17). However, no statistically significant reduction in mucositis was seen in other, randomized, double-blind studies (7–11). In the management of skin reaction during radiotherapy, we have only been able to find two reports on sucralfate. The acute radiation reaction of the skin was statistically significantly prevented by sucralfate cream in one study, while in the other there was no difference in effect between sucralfate in sorbolene and sorbolene alone (6, 18).

The purpose of the present study was to investigate whether it was possible to obtain a better effect by using the sodium salt of sucral octasulfate, which is thought to give a higher concentration of the free and pharmacologically active molecule, at least in mucous surfaces. Unfortunately, with the exception of skin desquamation, we were not able to find any difference between Na-SOS and placebo. For skin desquamation, there was a significant difference at the 5% level in favour of placebo. The most likely explanation for this is that the Na-SOS gel itself left behind a flaky layer that was difficult to distinguish from radiation-induced flaking.

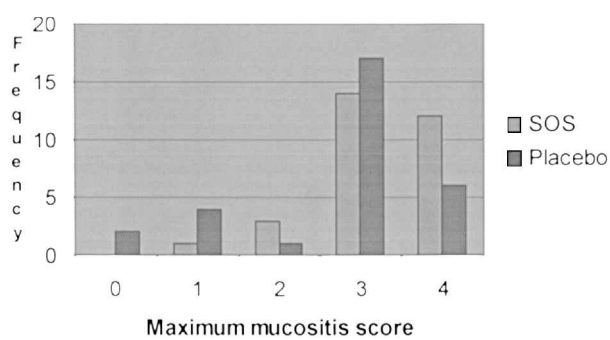

Fig. 6. Frequency of maximum mucositis score with and without Na-SOS.

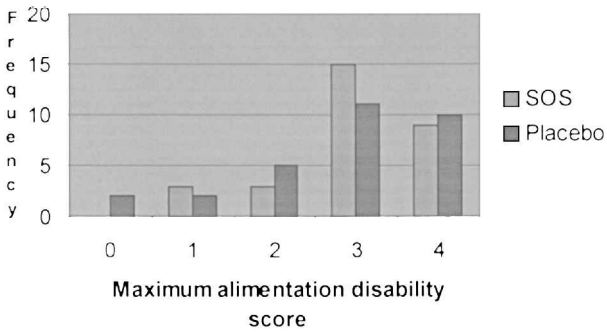

Fig. 7. Frequency of maximum alimentation disability score with and without Na-SOS.

In conclusion, on the basis of the present study, we cannot recommend Na-sucrose octasulfate in the routine management of irradiation-induced skin and mucosal reactions.

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