Different Saliva Substitutes for Treatment of Xerostomia Following Radiotherapy

A Prospective Crossover Study

Felix Momm[1], Natalja Jurievna Volegova-Neher[1], Jürgen Schulte-Mönting[2], Roland Guttenberger[1]

Background and Purpose: Xerostomia is an important chronic side effect of radiotherapy in the head and neck area. The authors investigated the efficacy of different artificial saliva compounds in patients with postirradiation xerostomia.
Patients and Methods: In 120 patients with xerostomia after radiotherapy for head and neck cancer, four different saliva substitute compounds (gel, carmellose spray, oil, mucin spray) were tested in a prospective crossover design. Xerostomia at baseline and under treatment with each compound was measured with a questionnaire approved in a pilot trial.
Results: All compounds significantly improved xerostomia when compared to baseline situation ($p < 0.0001$). The gel was rated best, the carmellose spray was rated worst by the patients, but the single compounds did not differ significantly in their effects. In spite of this result, most patients chose the carmellose spray as their favorite compound. This is due to its good taste and easy handling, which play an important role for the acceptance of the products. Big individual differences in the preference of the single compounds were found.
Conclusion: For most patients considerable relief from xerostomia can be reached by saliva substitutes. Thus, every patient with xerostomia should be given different artificial saliva compounds for a test period. This will help to find the individually best way to cope with the dry mouth.

Key Words: Xerostomia · Saliva substitutes · Radiotherapy · Supportive care · Head and neck cancer

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Unterschiedliche Speichelersatzpräparate zur Behandlung der Xerostomie nach Strahlentherapie im Kopf-Hals-Bereich. Eine prospektive Cross-over-Studie

Hintergrund und Ziel: Eine wichtige chronische Nebenwirkung der Strahlentherapie im Kopf-Hals-Bereich ist die Xerostomie. Die vorliegende Studie untersucht unterschiedliche Speichelersatzprodukte bezüglich ihrer Effektivität auf diese Mundtrockenheit.
Patienten und Methodik: An 120 Patienten mit einer Xerostomie nach Bestrahlung im Kopf-Hals-Bereich wurden vier unterschiedliche Speichelersatzprodukte (Gel, Carmellose-Spray, Öl, Mucin-Spray) in einem prospektiven Cross-over-Design getestet. Die Xerostomie vor Beginn der Studie und während der Behandlung mit den einzelnen Präparaten wurde mit einem Fragebogen ermittelt, der in einer Pilotstudie entwickelt worden war.
Ergebnisse: Alle Präparate verbesserten im Vergleich mit der Situation vor der Studie die Xerostomie signifikant ($p < 0{,}0001$). Das Gel wurde von den Patienten am besten, das Carmellose-Spray am schlechtesten bewertet, doch die verschiedenen Präparate unterschieden sich in ihrem Effekt nicht signifikant. Trotz dieses Ergebnisses wählten die meisten Patienten das Carmellose-Spray als ihr „Lieblingsprodukt" aus. Dies ist auf seinen guten Geschmack und seine gute Handhabbarkeit zurückzuführen, die für die Akzeptanz der Präparate eine wichtige Rolle spielen. Die Bevorzugung einzelner Produkte war individuell sehr unterschiedlich.
Schlussfolgerung: Bei den meisten Patienten kann durch Speichelersatzprodukte eine merkliche Besserung der Xerostomie erreicht werden. Jedem Patienten mit Mundtrockenheit sollten verschiedene dieser Präparate zum Testen zur Verfügung gestellt werden. Dies trägt dazu bei, die individuell beste Möglichkeit der Xerostomiebehandlung herauszufinden.

Schlüsselwörter: Xerostomie · Speichelersatzpräparate · Strahlentherapie · Supportive Therapie · Kopf-Hals-Tumoren

[1] Department of Radiotherapy, University Clinic Freiburg, Freiburg, Germany,
[2] Department of Medical Biometry and Statistics, University of Freiburg, Freiburg, Germany.

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Introduction

After radiotherapy in the head and neck region xerostomia is a regularly observed chronic side effect. The lack of saliva particularly disturbes eating, speaking, and sleeping. Thus, it is a most important reason for a loss of quality of life in irradiated patients [1, 2, 13–15, 28, 36]. The usual therapies for xerostomia are drinking large quantities, using chewing gum, candies, and/or artificial saliva [1, 9]. There are several strategies what to use as saliva substitute. Water-binding molecules such as sodium carboxymethylcellulose or mucin [1, 18, 20] are approved as well as oily liquids or gels [7, 30, 34, 35]. None of these has serious side effects and all have been investigated for a long time. But, to our knowledge, no study compared the most commonly used artificial saliva compounds in one group of patients. At the same time, we were frequently asked by our irradiated head and neck cancer patients how to cope with xerostomia. Therefore, we decided to conduct a crossover trial to compare the efficacy of four common artificial saliva products.

Patients and Methods

Patients

From August 2002 to April 2003, 120 patients were included in this prospective study. Inclusion criteria were time after radiotherapy > 4 weeks, Karnofsky index > 70, tumor in complete remission, age > 18 years, written informed consent, and subjective xerostomia after radiotherapy in the head and neck region (question "have you got problems with a dryness in your mouth?" answered with "yes"; all patients in our follow-up outpatient department were asked). Three patients dropped out of study: one patient died from other than study/tumor reasons, two patients were noncompliant. Therefore, further three patients were recruited according to protocol and a total number of 120 evaluable patients were reached. Patient characteristics are depicted in Table 1.

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristika.

Total number of patients (evaluable)	123 (120)
Age (range)	59 (29–89) years
Gender male : female	89 : 31
Mean radiation total dose (range)	60,0 (19,8–74,0) Gy
Mean time from radiotherapy (range)	1,001 (45–7,441) days
Patients with additional chemotherapy	32
Treatment of xerostomia before study	
Drinking much water/tea	114
Chewing gum	12
Mouth washes	13
Candies	18
Oil/fat	6
Saliva substitute (spray)	13
Tumor site	
Oropharynx	37
Hypopharynx	14
Oral cavity/tongue	25
Larynx	16
Nose	3
Salivary glands	2
Thyroidea	4
Cervical lymphatic nodes	13
Unknown primary	6
Histology	
Squamous cell carcinoma	100
Adenocarcinoma	5
Lymphoma	14
Other	1
Staging	
TX	2
T0	5
T1	17
T2	37
T3	24
T4	21
N0	19
N1	24
N2	55
N3	5
NX	3
M0	104
M1	2
Staging lymphoma (Ann Arbor)	
I	5
II	7
III	0
IV	2

Tested Compounds

Four different compounds were tested as saliva substitutes: (1) Aldiamed gel (Biomedica, Rodgau, Germany), containing *Aloe vera* (gel); (2) Glandosane® spray (cell pharm, Hannover, Germany), containing sodium carboxymethylcellulose (*carmellose*); (3) rape oil (oil pressed by Brändle, Germany, and filled in pump spray bottles at Freiburg University Clinic, Germany; *oil*); (4) Saliva medac spray (medac, Wedel, Germany), containing mucin extracted from pig stomach (*mucin*).

Study Process

The patients were numbered in order of inclusion in the study. All patients received all four compounds for 1 test week each (crossover design). The patients were told to use the compounds as often as they wanted. They were advised to stop using the product, if any problems occurred. The sequence of the compounds was defined by a randomization list composed by an independent statistician. At baseline and after every test week, the patients had to fill in a questionnaire about xerostomia. Thus, every patient had to pass five visits. In total, 600 questionnaires were evaluated.

Questionnaire

Patient characteristics such as age, sex, tumor site, tumor stage, and time interval from radiotherapy were recorded. Patients were asked how long and how often they had used the

particular compound, and the rest of the product was weighed to check the information (data not shown). All questions about xerostomia had to be answered using the German school mark scale (1–6, 1 = very good; 6 = poor) well known to our patients. The questionnaire was developed according to the WR-38 study [3, 31] and tested in a pilot trial [20]. The questions are listed in Table 2.

Table 2. Questionnaire.

Tabelle 2. Fragebogen.

Questions 1–8: baseline and after each week		
1	Please estimate your xerostomia in resting state (without eating, chewing, any saliva substitute)	1 = not dry 6 = very dry
2	Please estimate your difficulties with speaking	1 = no difficulties 6 = big difficulties
3	Please estimate your difficulties with eating, swallowing and chewing	1 = no difficulties 6 = big difficulties
4	Please estimate how often you need liquid to facilitate eating	1 = no liquid needed 6 = liquid for every bite
5	Please estimate how often you need a product against dryness of the mouth (saliva substitute, water, chewing gum, etc.) when not eating	1 = never or 1×/day 2 = 5×/day or less 3 = 10×/day or less 4 = 15×/day or less 5 = 20×/day or less 6 = more than 20×/day
6	Please estimate your difficulties with sleeping caused by dryness of the mouth	1 = no difficulties 6 = big difficulties
7	Please estimate your difficulties with taste	1 = no difficulties 6 = big difficulties
8	How viscous is your saliva?	1 = liquid 6 = highly viscous
Additional questions after each test week		
9	How do you mark the tested compound as saliva substitute? A: in general, B: in taste	1 = very good 6 = poor
10	Would you like to go on using the tested compound?	Yes/no
Additional question after all 4 test weeks		
11	After testing all four compounds: which compound would you prefer for further use?	

Study Endpoints

Primary endpoint was an equally added score of the items 1–8 in the study questionnaire. Secondary endpoints were all single items of the questionnaire and the two additional questions concerning the patients' satisfaction with the individual compounds. Additionally, we explored whether preference of compounds was dependent on subgroups in sequence of use, age, sex, and time from radiotherapy.

Evaluation was based on the questionnaires filled in by patients and controlled for completeness by one of the clinical authors.

Ethics

The trial was approved by the ethics committee of the University of Freiburg, Germany, and informed consent was obtained for each patient following the current revision of the Helsinki Declaration.

Statistics

The main tool for comparing the four (compounds) and five (including baseline) paired measurements, respectively, was the Friedman test, followed by pairwise Wilcoxon tests. Friedman's test is not sensitive neither to differences between strata nor to ceiling effects. Wilcoxon's test was applied in a modification stratified for the 24 sequences of application. No α-adjustment was applied, since the significance level of all differences to baseline would not be affected, and for the "no difference" statements between the compounds such a correction would not be appropriate.

However, for a more detailed look on possible predictive factors, use of repeated measures ANOVA was necessary. For this purpose, data were transformed by the function $log_{10}(64)–log_{10}(64–x)$ for the summary score and $log_{10}(8)–log_{10}(8–x)$ for single items, thus achieving a better fit to the requirements of the linear model. Age and time from radiotherapy were dichotomized at the median.

Results

The patients were randomized to 24 different sequences of use of the four tested compounds. Patients with different sequences scored their xerostomia differently ($p = 0.01$), but the sequence of their use had no influence on differences in rating of the compounds ($p = 0.84$). Preferences for a single compound could not be found for subgroups of age ($p = 0.66$), gender ($p = 0.34$), or time from radiotherapy ($p = 0.52$).

Median and quartiles of added scores of all eight xerostomia questions (Table 2) are depicted in Figure 1. The minimum of an added score can be 8 (8 × school mark 1, which is best), the maximum can be 48 (8 × school mark 6, which is worst). All tested compounds got better marks (31.0–32.7) than xerostomia management at baseline (35.1; Figure 1). This result is significant tested by Friedman test (baseline and each compound; Figure 1). The best compound was the gel with an average added score of 31. The difference between the gel as the best and the carmellose spray as the worst tested compound is not statistically significant.

The average marks given to the compounds for the single questions are depicted in Table 3. None of the compounds relieved patients' difficulties with eating, their need to drink while eating, or their impaired sense of taste. Patients perceived their saliva to be less viscous (0.2 marks on average) when using any of the tested compound. Xerostomia at rest or while speaking was diminished considerably by all compounds. Frequency of saliva substitute use and quality of sleep were influenced most positively by all tested compounds. Especially the gel showed best results by reducing frequency of use by 0.8 marks and improving quality of sleep by 1.0 mark on average. Levels of significance are given in Table 3.

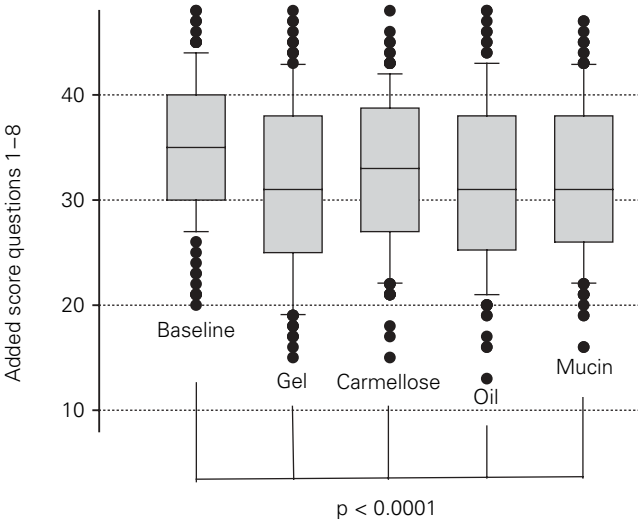

Figure 1. Results of added scores. Quartiles are depicted, p: Friedman test. Paired values make significant differences in spite of large standard deviations (see Discussion).

Abbildung 1. Ergebnisse der addierten Scores. Quartile, p: Friedman-Test. Gepaarte Werte ergeben signifikante Unterschiede trotz großer Standardabweichungen (s. Diskussion).

Table 3. Results – single questions.
Tabelle 3. Ergebnisse – einzelne Fragen.

Question	Baseline	Gel	Carmellose	Oil	Mucin
1 xerostomia*	4.5 ± 0.11	3.7 ± 0.11	3.8 ± 0.12	3.8 ± 0.12	3.8 ± 0.11
2 speaking*	5.2 ± 0.10	4.3 ± 0.11	4.4 ± 0.13	4.3 ± 0.13	4.3 ± 0.12
3 eating	3.3 ± 0.15	3.2 ± 0.15	3.3 ± 0.15	3.2 ± 0.15	3.2 ± 0.15
4 liquid	4.9 ± 0.13	5.0 ± 0.13	5.0 ± 0.13	4.9 ± 0.14	4.8 ± 0.14
5 frequency*#	4.9 ± 0.12	4.1 ± 0.14	4.6 ± 0.13	4.3 ± 0.13	4.4 ± 0.13
6 sleeping*§	4.4 ± 0.17	3.4 ± 0.17	3.9 ± 0.16	3.5 ± 0.17	3.7 ± 0.17
7 taste	2.8 ± 0.17	2.9 ± 0.17	2.8 ± 0.17	2.8 ± 0.16	2.8 ± 0.16
8 viscosity**	5.0 ± 0.13	4.8 ± 0.14	4.8 ± 0.14	4.8 ± 0.14	4.8 ± 0.14

Mean answers to single questions (± standard deviations)
Levels of significance:
*p < 0.0001 baseline versus every saliva substitute
**p < 0.02 baseline versus every saliva substitute
#p < 0.0001 gel versus carmellose, p = 0.014 gel versus mucin, p = 0.028 oil versus carmellose,
§p = 0.006 gel versus carmellose, p = 0.015 oil versus carmellose

When asked about the general effect of each compound, the patients marked the gel best with 3.5 and the oil worst with 4.0 on average (Table 4). The carmellose was marked best in taste (3.1). The oil was worst in taste with a score of 4.3 on average (Table 4). These results are confirmed by the patients choosing their favorite compound: gel, mucin, and carmellose were favorite of about 27% of patients each. The oil was chosen as favorite by 17.5%. About 55% of patients wanted to go on using the carmellose spray, whereas only 42% wanted to continue using the oil (Table 4).

Discussion

Radiotherapy affects the salivary glands and thus causes xerostomia. Initially, under radiation therapy an increased permeability of endothelial cells in the periductal capillaries is observed and causes an interstitial edema. The gland's channels are compressed leading to their progressive obstruction. By cell death and fibrotic conversion of the tissue, function is affected irreversibly in the sense of a "consequential late effect": saliva can be produced only in a small quantity [5].

Thus, many patients complain about severe xerostomia after radiation therapy: salivary gland tissue has a tolerated dose TD 100/5 of 50 Gy when the whole organ is irradiated. The TD 100/5 is the smallest radiation dose which will cause a clinically relevant and well-defined consequence of radiation with a probability of 100% in 5 years [5, 11]. An irreversible loss of function will be found even at doses of 40 Gy. However, limiting the planned dose to salivary glands to values < 40 Gy may jeopardize the efficacy of radiation therapy with curative intent. Up-to-date salivary glands' output after radiotherapy is about 10–15% of pretreatment values [5, 11].

When deciding to conduct this study we wondered whether we could recruit enough patients. But as mentioned above, xerostomia is a very annoying problem of patients after radiotherapy [1, 13–15, 36] for head and neck cancer, and we were able to recruit the planned 120 patients in a single institution within a period of 9 months.

Our results show a significant benefit of all tested compounds in xerostomia treatment when compared to baseline xerostomia management. As the data evaluated are paired, this significance occurs in spite of high standard deviations in patients scoring their xerostomia.

High standard deviations in rating the four tested compounds show that patients prefer different xerostomia treatment. This is caused by patients living different lifes and thus having different problems with xerostomia. Some patients, who have to talk much for their

Table 4. Results – favorites.
Tabelle 4. Ergebnisse – „Lieblingspräparate".

	Gel	Carmellose	Oil	Mucin
Favorite compound	34 (28.3%)	32 (26.7%)	21 (17.5%)	33 (27.5%)
Effect (school mark)	3.5 ± 0.15	3.6 ± 0.14	4.0 ± 0.17	3.6 ± 0.15
Taste (school mark)	3.3 ± 0.14	3.1 ± 0.13	4.3 ± 0.15	3.2 ± 0.14
Continue use	64 (53.3%)	66 (55.0%)	50 (41.7%)	62 (51.7%)

± standard deviation

job, benefit from a spray helping them quickly to cope with their speaking problems. Other patients prefer compounds with an effect lasting overnight and resulting in better sleep.

In the main questionnaire (questions 1–8), the carmellose spray received the worst marks, whereas most patients wanted to go on using it when asked after the test week. This can be explained by patients appreciating the product not because of enduring effects, but because of its good taste and its easy handling. As we were told in additional free text parts of the questionnaire (data not shown), many patients had considerable problems with the application of the compounds and especially with handling the gel. As depicted in Figure 1, the oil was as good as the other compounds in the main questionnaire, and by one patient it was even marked with the best result of all questionnaires. But when asked whether they wanted to go on using it, most patients rejected the oil because of its bad taste. High standard deviations in marks given for the oil (Table 4) also show, that patients had very different opinions about its effect and taste: best treatment of xerostomia seems to be very individual.

Considering sex, age [19] and radiation dose, it was not possible to identify groups of patients preferring one single product. Thus, the easiest way to improve xerostomia treatment seems to offer several compounds to test and to choose from. This way, patients can find their favorites and can even choose combinations, for example a spray at work and a gel at night. Improved xerostomia treatment will positively influence quality of life and may also promote dental health and prevent infections in the head and neck region.

Recently, great efforts were made to develop radioprotective medications to decrease side effects of radiotherapy. By systemic application of amifostine before every fraction, salivary gland function after therapy could be improved [27, 29, 32, 33]. The application of pilocarpine/carbacholine [4, 16, 17, 26], coumarin/troxerutine [10] and adrenergic substances [22] had some success as well.

Further, first studies exist about possibilities to relocate the salivary glands out of the radiation field by operation [8]. Dose reduction at the glands by modern treatment techniques such as three-dimensional treatment planning or intensity-modulated radiotherapy has a protective effect as well [6, 12, 21, 37]. In future, there will be a chance to replace the supportive care for xerostomia by prophylactic measures.

In spite of great efforts in the field of radioprotection of salivary glands, chronic xerostomia is still a considerable problem for quality of life and oral health in patients after radiotherapy for head and neck cancer [1, 13, 15, 23–25]. On the basis of the present study we suggest that every patient should be encouraged to test different artificial saliva compounds to find the individually best way to cope with xerostomia.

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Address for Correspondence
Felix Momm, MD
Department of Radiotherapy
University Clinic Freiburg
Robert-Koch-Straße 3
79106 Freiburg
Germany
Phone (+49/761) 270-9462, Fax -9582
e-mail: momm@mst1.ukl.uni-freiburg.de