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Randomized controlled trial of the effectiveness of three different oral moisturizers in palliative care patients

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Most patients in palliative care have problems with dry mouth caused by medication or as a direct result of their condition. Dry mouth may cause problems that affect the primary disease negatively and contribute to poorer quality of life in palliative patients. This randomized controlled trial compared the efficacy of three different oral moisturizers: 17% watery solution of glycerol; oxygenated glycerol triester (marketed as Aequasyal in Europe and as Aquoral in the USA); and a newly developed product, Salient. Of the three products, glycerol provided the best relief from xerostomia directly after application, but had no effect after 2 h. By contrast, the effects of Aequasyal and Salient were largely maintained over the same period. The findings for oral discomfort and pain and speech problems showed a similar pattern. Despite its poor effect after 2 h, patients preferred glycerol over Salient and Aequasyal, probably because of the unpleasant taste of Aequasyal and the consistency and mode of application of Salient. Within the limitations of this study, none of the three products tested was found to be clinically completely adequate. However, the glycerol solution was preferred by this group of patients, and its short-lived effect can be compensated for by frequent applications.

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Saliva plays a fundamental role in maintaining oral health. Healthy individuals produce resting (unstimulated) whole saliva at a rate of 0.3–0.4 ml min^{-1}. The subjective feeling of xerostomia is thought to occur when less saliva is secreted than the amount of water lost from the mouth by evaporation and by absorption through the oral mucosa (1). Mucin-rich resting saliva lubricates mucous membranes and teeth, and stimulated saliva plays an important role in mastication, speech, swallowing, and digestion. Constituents such as lactoferrin, peroxidase, and histatin contribute to salivary antimicrobial, antiviral, and antifungal properties (2). In individuals with failing salivation, these important properties of saliva in the oral cavity are reduced or absent, causing dry and sore mucous membranes, delayed wound healing, rapid development of caries and erosion, fungal infections of the mouth and throat, discomfort, pain, and problems using dentures (2). Dry mouth can also lead to swallowing difficulties, speech disturbances, loss of appetite, dehydration, and malnutrition, thus having a negative effect on diseases and contributing to reduced quality of life, particularly in life's final phase (3).

Palliative care is the active treatment and care for patients with incurable diseases and short life expectancy. Relief of the patient's physical pain and other distressing symptoms is central, together with measures aimed at relieving psychological, social, and spiritual/existential problems. The goal of palliative care is the best possible quality of life for patients and their families (4). In some guidelines, the palliative care patient population is defined to include patients with a life expectancy of <9–12 months. In reality, the palliative phase starts when it is recognized that the disease is incurable, and it ends when the patient dies. In Norway, palliative care patients with advanced disease may be transferred to a specialist palliative care unit, at either a hospital or a nursing home, when there is a wish or need for extended care. The term 'terminal' may be confused with the term 'palliative', but the former refers primarily to the last few hours or days before death (5). It is difficult to predict when death is likely to occur. However, by applying the World Health Organization (WHO) performance status scale, which ranges from grade 0 (the patient is fully active and able to carry on all predisease performance without restriction) to grade IV (the patient is completely disabled, cannot carry on any self-care and is totally confined to bed or chair) (6), the cause of the patient's decline can be described. About 95% of patients in palliative care in Norway are cancer patients (7).

Many patients in palliative care have received treatment or medications that may have adverse effects on oral health. In addition to radiation and chemotherapy to the head/neck, drugs with anticholinergic and/or sympathomimetic effects, opioids, glucocorticoids, and bisphosphonates may have an unfavourable impact on oral health (8). In the last phase of life, an opioid analgesic (morphine), a sedative (midazolam), an antiemetic (haloperidol), and an antisecretory agent (glycopyrrolate) are commonly given subcutaneously to relieve symptoms and may be combined (9). Other disease-related factors that may have adverse effects on oral health are dehydration, difficulties in chewing, impaired immune response, unfavourable changes in bacterial flora and secondary infections, anxiety and depression, impaired motor function, and an inability to self-care (10–12).

A range of different products are used in an effort to alleviate the symptoms of dry mouth. There are several commercially available mouthwashes and gels. In addition, there are many products that are used based on tradition and experience, such as tea, vegetable oil, and cream, and watery solutions of glycerol in different concentrations (13). A Cochrane review from 2011 concluded that there was no strong evidence that any topical therapy is completely effective for relieving the symptoms of dry mouth. However, one product, oxygenated glycerol triester (OGT), was shown to be somewhat more effective than an aqueous electrolyte solution (Saliveze) (14). The present paper reports findings from a randomized controlled trial (RCT) in which the efficacy of three moisturizers [17% watery solution of glycerol, OGT, and a newly developed product (Salient)] was compared.

The trial was designed to answer the following question: Do any of the three agents improve xerostomia, reduce pain and discomfort, and improve ability to talk in palliative care patients? The hypothesis was that there was no difference in efficacy between 17% glycerol, OGT, and Salient.

Material and methods

The study was designed as an RCT (Fig. 1) with a crossover design (Fig. 2), and was performed according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (15). All patients were treated with three oral-care products. A block randomization was applied for the sequences (1–6) in which the patients would receive the different products (Fig. 2). The project leader (GVS) generated the intervention sequences. The study was conducted by the Institute of Clinical Dentistry, Faculty of Medicine, University of Bergen, Norway.

A sample size of 30 individuals per product was calculated to be sufficient based on crude chi-square tests with dichotomous outcomes based on an expected 40% difference between two of the products. As no similar study with relevant effects was found, this was considered a clinically relevant effect. The calculations did not take into account the use of the full ordinal Likert scale in the analyses or the fact that all patients received all products in a crossover design.

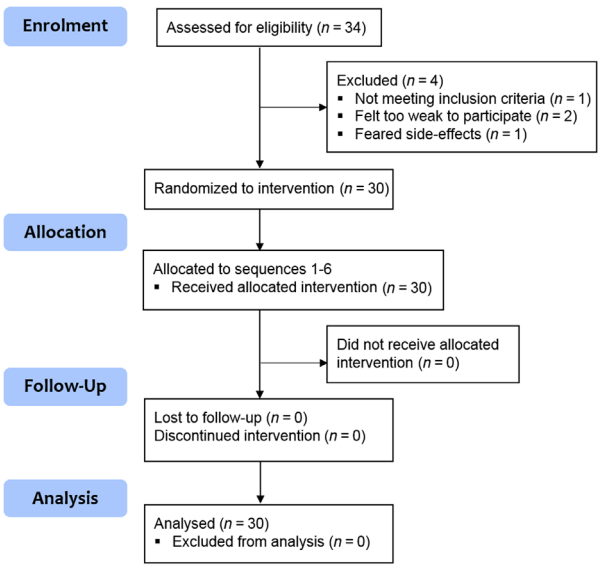

Fig. 1. Flow diagram of the different phases (enrolment, allocation, follow-up, and analysis) of the study [performed according to Consolidated Standards of Reporting Trials (CONSORT)].

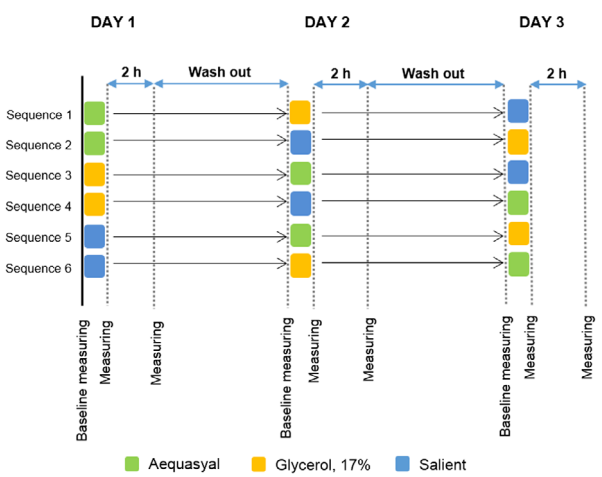

Fig. 2. Schematic diagram of the clinical intervention from baseline to the end.

Thirty patients were recruited from two palliative care units (at Haraldsplass Deaconess Hospital and the Red Cross Nursing Home, in Bergen, Norway) (Fig. 1). A nurse at each unit was in charge of enrolling patients who met the eligibility criteria. Of the 34 eligible patients who were enrolled, 30 were selected by the project leader GVS (Fig. 1).

Eligibility criteria for participants were: xerostomia (subjective feeling of dry mouth); in institutionalized palliative care; curative treatment of existing diseases completed or terminated; WHO performance status ≥III (corresponding to Karnofsky Performance Status Score of 30%–40% (i.e., only capable of limited self-care, confined to bed or chair more than 50% of wake time); cognitively functioning, capable of and willing to give written consent, capable of giving responses to a limited questionnaire; and expected to remain at the care centre for a minimum of 3 d. Patients who had

previously been treated with chemotherapy and/or radiotherapy to the head and neck region were excluded.

All participants received verbal and written information by the project leader on the purpose of the study, how it would be carried out in practice, and the potential benefits and side-effects of the products. The intervention started as soon as the consent form was accepted and signed.

The project leader assigned the participants to the interventions. The intervention was, in general, carried out after morning routine care and breakfast. Each product was applied at the same time of day to avoid the risk that diurnal variation in health status might influence the outcome.

If the patient agreed to participate, he/she answered a short questionnaire, which contained the primary outcome measures of subjective xerostomia, discomfort and pain, and speech problems. These measures were recorded on a 5-point ordinal Likert scale at three points in time: before the intervention; immediately after the intervention; and 2 h after the intervention (Fig. 2). In addition, evaluations of taste and application method of the products used were recorded on a 3-point ordinal scale. The actual wordings of all categories are shown in Figs. 3–6. After all products had been applied and procedures completed (2 h after the last intervention, normally on day 3), patient preference of the three products was recorded on a 4-point nominal scale on the same questionnaire. At the same time, the patients were asked to comment freely on the products and procedures. Demographic characteristics, medical history, and medications were registered in a personal and health information form (Table 1).

The products were presented in neutral containers without labels, ensuring that the patients were blinded as to their content. The dentist who carried out the intervention could not be similarly blinded because of the differences in application methods for the three products.

The three products compared in this study were: (i) a 17% watery solution of glycerol (not a patented compound; Sanivo Pharma, Oslo, Norway; Batch no. 17A121); (ii) Oxygenated glycerol triester (OGT) (Eisai SAS, Paris, France; Batch no. CH130); and (iii) Salient (Salient Pharma, Klampenborg, Denmark; Batch no. 715990). The tradename for OGT is Aquoral in the USA and Aequasyal in Europe (though so far not marketed in Scandinavia). The product is CE marked, and classified as a medical device, class I. Salient is a newly developed product, which is CE marked and classified as a medical device, class IA. Salient becomes commercially available in 2019; its main ingredients are polyethylene oxide and hydroxypropyl methylcellulose.

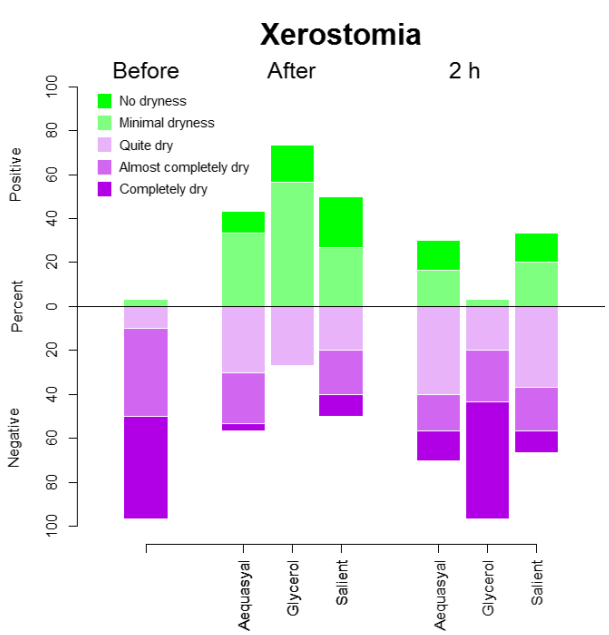

Fig. 3. Xerostomia at baseline, immediately after application of product, and 2 h later.

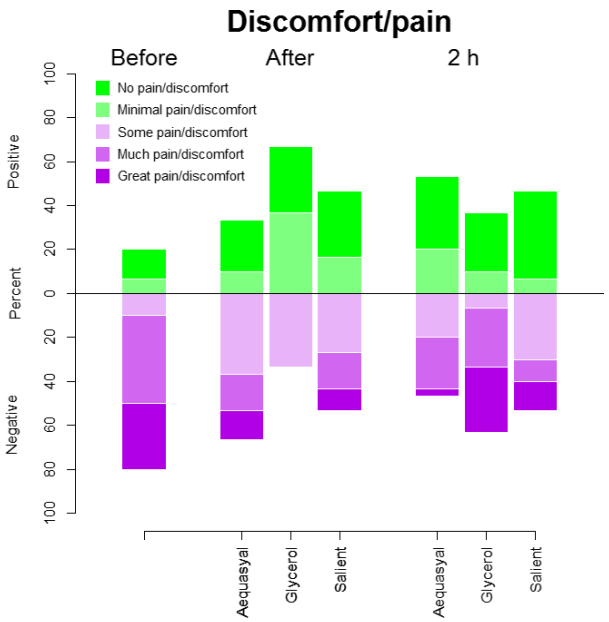

Fig. 4. Discomfort/pain at baseline, immediately after application of product, and 2 h later.

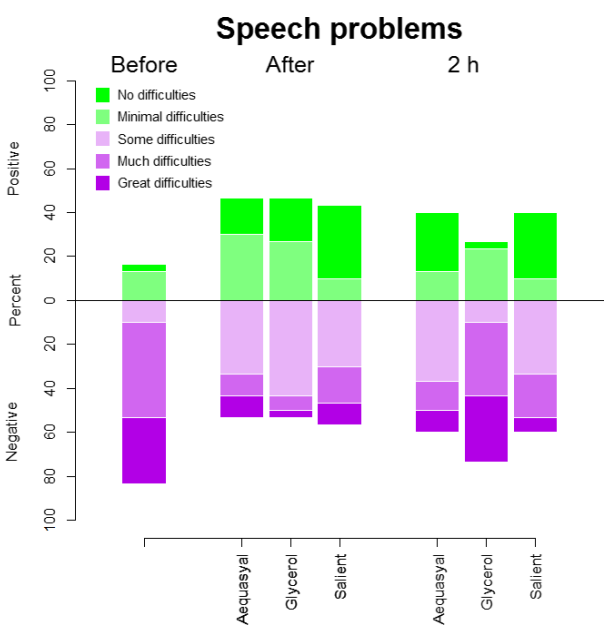

Fig. 5. Speech problems at baseline, immediately after application of product, and 2 h later.

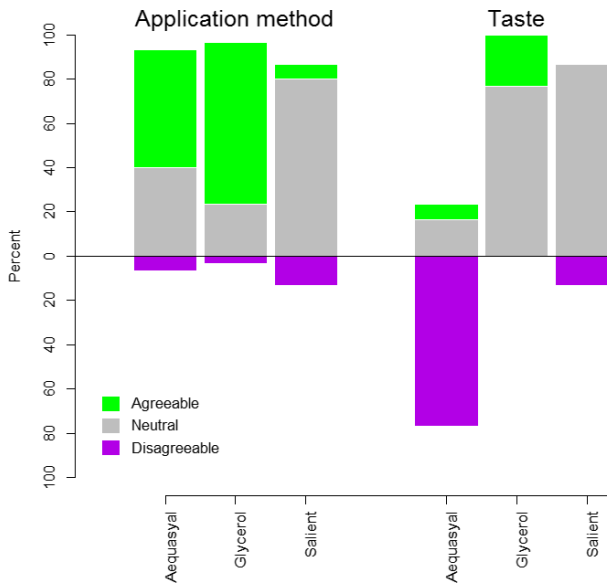

Fig. 6. Assessment of application method and taste.

A dentist (SFK) performed the procedure as follows. Initially, lips were lubricated with white Vaseline (petroleum jelly) and mucosa was cleaned with 0.3% saline solution. The actual product was then applied. Aequasyal was sprayed onto the mucosa; glycerol was applied with a soaked gauze pad on lockable tweezers; and Salient was dispensed to the patient on a spoon. The night following each application was considered a washout period, after which a new product could be applied. The total duration of the intervention was thus normally 3 d. However, the patient's condition or other treatments might necessitate a longer period.

The study was conducted in the period 1 March 2018 to 30 November 2018. The study was approved by the Regional Committee for Medical and Health Research Ethics, Northern Norway (REC North ref. no. 2016/2316), and registered at the Norwegian Social Science Data Services (NSD), and with ClinicalTrials.gov (ID: NCT03400969).

Statistical analyses

For categorical variables, percentages and frequencies were reported. To investigate any differences in the Likert scales between the three oral-care products analysed, marginal ordinal logistic regression with robust variance estimates was applied, adjusting *P*-values for correlation between the nine repeated observations for each individual. The ordinal logistic regression allows analyses of the ordered 5-point Likert scale between the oral care products for the three time points in one joint model. Changes from the baseline measures for each of the oral care products, and differences between the products immediately and 2 h after application, were reported as ORs. To study possible carry-over effects, differences between products at baseline the day after they were applied were analysed.

Ordinal regression, with robust variances, was also applied to analyse differences in the 3-point scales for taste and application method of the three products. The OR is interpreted as difference in risk (e.g., between products) for an 'increase' in one level of the Likert scale. To test whether the distribution of the preferred product was uniform for the three, a chi-square test was applied. The statistical analyses were performed using STATA (version 15; StataCorp, College Station, TX, USA). Values of $P < 0.05$ were considered statistically significant.

Table 1

Demographic and disease-related information for patients included in the trial

Patient characteristics	Description/categories	Number
Gender	Female/male	17/13
Age	Female patients: mean (range)	68 (51–81)
	Male patients: mean (range)	69 (37–88)
Actual disease, main diagnosis	Chronic obstructive pulmonary disease	2
	Cancer, locally advanced or metastatic	
	Gastrointestinal	12
	Pancreatic or bile duct	5
	Lung	3
	Gynecological	4
	Other (prostate cancer, Ewing sarcoma, multiple myeloma, malignant melanoma)	4
Additional diagnoses	Diabetes mellitus	3
	Chronic obstructive pulmonary disease	3
	Lung transplant rejection	1
	Syringomyelia	1
	Kidney failure	1
Medication	Non-opioid analgesics	21
	Opioid analgesics	23
	Corticosteroids	6
	Benzodiazepines	20
	Antiemetics	11
	Laxatives	15
	Antidiabetics	3
	Antidepressants	7
	Antihypertensives, diuretics	7
	Proton pump inhibitors	14
	Antibiotics, antifungals, antivirals	11
	Anticoagulants	9
	Antisecretory agents (airways and bowels)	5
Parenteral infusions	Intravenous nutrition	4
	Syringe driver for subcutaneous medication	15
World Health Organization performance status	III	12
	IV	18

Results

Demographic characteristics, medical history, and medications of the patient sample are shown in Table 1. Of the 30 patients, 17 (57%) were female (mean age = 68 yr) and 13 were male (mean age = 69 yr). The main diagnosis was cancer in 28 (93%) of the patients; 12 (40%) had WHO performance status III and 18 (60%) had status IV.

The effects of the products used on xerostomia are shown in Fig. 3 and Table 2. Relative to baseline

Table 2

Effect of the three oral care products on primary outcomes, immediately after application and 2 h later

Outcome	Immediately after		Two hours later	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Xerostomia				
A: Aequasyal	13.10 (6.15–27.90)^{B}	<0.001	8.79 (4.70–16.46)^{B}	<0.001
B: Glycerol	38.59 (18.73–79.48)^{A}	<0.001	0.93 (0.57–1.51)^{AC}	0.763
C: Salient	16.95 (7.19–39.97)	<0.001	9.76 (4.68–20.36)^{B}	<0.001
Discomfort/pain				
A: Aequasyal	3.35 (1.85–6.06)^{B}	<0.001	5.69 (3.20–10.12)^{b}	<0.001
B: Glycerol	8.39 (4.12–17.08)^{A}	<0.001	1.85 (1.00–3.45)^{ac}	0.051
C: Salient	4.70 (2.63–8.39)	<0.001	5.61 (3.15–10.02)^{b}	<0.001
Speech				
A: Aequasyal	4.89 (2.74–8.73)	<0.001	4.86 (2.51–9.40)^{B}	<0.001
B: Glycerol	6.07 (3.66–10.07)	<0.001	1.18 (0.73–1.89)^{AC}	0.496
C: Salient	5.45 (2.53–11.72)	<0.001	5.01 (2.66–9.42)^{B}	<0.001

Results represent odds ratio for a change in one level of the Likert scale over time in primary outcomes for the three oral care products. Statistically significant differences between products immediately after application, and 2 h later, are marked using superscript letters. Compared with product: A: $P < 0.01$, a: $P < 0.05$; B: $P < 0.01$, b: $P < 0.05$; C: $P < 0.01$, c: $P < 0.05$.

recordings, all products produced improvements immediately after the intervention. At this time, a higher number of respondents treated with glycerol reported no or minimal oral dryness (indicated by the green shades of the columns) compared with respondents treated with Aequasyal. Two hours after intervention, the effect of glycerol had decreased relative to the other two products (in fact, had reverted to baseline), whereas the effects of Aequasyal and Salient largely persisted.

The effects of the products on the occurrence of discomfort and pain are shown in Fig. 4 and Table 2. Relative to baseline recordings, all products produced improvements immediately after the intervention. At this time, a higher number of respondents treated with glycerol reported either no or only minimal discomfort or pain (indicated by the green shades of the columns) compared with respondents treated with Aequasyal. Two hours after the intervention, the effect of glycerol had dropped relative to the other two products and was no longer different from baseline, whereas the effects of Aequasyal and Salient largely persisted.

The effects of the products on the occurrence of speech problems are shown in Fig. 5 and Table 2. Relative to baseline recordings, all products showed pronounced improvements immediately after intervention. At this time, there were no significant differences between the products. Two hours after the intervention, the effect of glycerol had dropped by a larger amount than that of the two other products and was no longer different from baseline, whereas the effects of Aequasyal and Salient largely persisted.

No statistically significant carry-over effect was discovered for xerostomia, discomfort and pain, or speech problems (smallest $P = 0.13$).

Data on the application method of the moisturizers are shown in Fig. 6 and Table 3. Whereas 22 (73%) of the 30 patients reported that the application method of glycerol was agreeable, only a few felt that about Salient. Aequasyal occupied an intermediate position between glycerol and Salient.

Table 3

Difference in risk (e.g., between products) for a change in one level of the Likert scale

Variable	OR (95% CI)	*P*-value
Application method		
A: Aequasyal	1^{C}	<0.001*
B: Glycerol	2.52 (0.75–8.47)^{C}	0.135
C: Salient	0.13 (0.04–0.48)^{AB}	0.002
Taste		
A: Aequasyal	1^{BC}	<0.001*
B: Glycerol	125.56 (13.39–1,177.12)^{AC}	<0.001
C: Salient	15.04 (4.4–51.34)^{AB}	<0.001

Differences between products are marked using superscript. Compared with product: A: $P < 0.01$; B: $P < 0.01$; C: $P < 0.01$.
*Test of homogeneity.

The data for taste are shown in Fig. 6 and Table 3. Aequasyal was disliked by 23 (77%) of 30 patients. For the other products, most respondents reported a neutral taste. The majority of patients (19/30, 63%) preferred glycerol ($P < 0.001$). The corresponding numbers for Salient and Aequasyal were six (20%) of 30 and three (10%) of 30, respectively. Two of the patients preferred not to use any of the three products. There was no association between the preferred product and on which day the preferred product was applied ($P = 0.48$).

Open-ended comments

All patients commented on the treatment received. The remarks concerning xerostomia, taste, application method, and preferred product mirrored those reported above. The sticky, glutinous consistency of Salient was mentioned by 18 (60%) of 30 patients. In addition, 11

(37%) of 30 patients characterized the taste of Aequasyal as strange, strong, oily, rancid, nauseating, or disgusting. Others (4/30, 13%) were dissatisfied with the use of a small spoon when dispensing Salient, and an equal number of patients commented that the most important factor for their well-being was oral care in itself; that is, getting help with brushing their teeth and cleaning the mucosa.

Discussion

The main findings of this RCT study were that the 17% glycerol solution was the most effective moisturiser of the three products in the short term, but had no effect 2 h after application. Aequasyal and Salient had longer-lasting effects. A similar pattern was displayed for discomfort and pain and speech problems. The glycerol solution was preferred by the patients.

A problem with artificial saliva is that it is unable to provide sustained relief for any substantial period of time (14). Although all three products in this study had reduced effects after 2 h, only Salient and Aequasyal showed an improvement in xerostomia over baseline. Despite the fact that this provides an answer to the primary objective of the study (i.e., the three products did improve xerostomia, reduce pain and discomfort, and improve ability to talk), the two products with the most sustained effect on xerostomia were, in most cases, not the patients' preferred product. The findings for discomfort and pain and speech showed the same tendency: Aequasyal and Salient either had a negligible reduction or, in the case of Aequasyal, even an increased effect 2 h after application. Glycerol, on the other hand, even though it showed the most favourable effect immediately after application, had the least (or no) effect after 2 h.

Why the patients, perhaps surprisingly, still preferred glycerol is probably because of the disagreeable taste of Aequasyal and the unpleasant sticky consistency of Salient, reported by a majority of the respondents. This supposition is strengthened by the fact that no factors, other than the above, were mentioned in the open-ended comments.

When evaluating the possible clinical implications of these findings, the rationale for choice of products and selection of patients is of importance. Thus, Aequasyal was chosen because this was the only product, in a Cochrane Review from 2011 (14, 16), found to provide significant relief from dry mouth. According to the manufacturer, Aequasyal adheres to the oral mucosa, forming a lipid film that protects against mechanical trauma, and may help to reduce loss of moisture from the oral tissue and inflammation. A 17% watery glycerol solution was chosen because this concentration was recommended by 'helsebiblioteket.no', a public website run by the Norwegian health authorities that provides health-care professionals with recommendations based on available evidence (17). Glycerol in varying concentrations is used by 36% of Norwegian health institutions (13) and is inexpensive, easily available, and easy to apply. However, in some countries (including the USA, the Netherlands, Great Britain, and Singapore), its use is not recommended because of possible hydroscopic properties, which may result in desiccation of the mucous membranes (18). Salient was chosen because of the manufacturer's claim that the combination of the two main ingredients has a quality described as *spinnbarkeit*, best explained as 'spinnability' or 'stretchability', which appears to be of value in alleviating the symptoms of dry mouth. The ingredients of Salient are innocuous and commonly used in medications, cosmetics, and nutrients.

It has been argued that the effect on xerostomia of various saliva substitutes is related to the aetiology of the patient's health status (19, 20). This may be because salivary gland function is influenced by various factors and stimuli, which can cause changes in volume, flow, and composition (21). The reasons why palliative care patients were selected for this study are twofold: it was assumed that their need for oral care might be greater and/or different from less compromised patients; and that in such patients, possible differences between products might be more discernible.

That palliative care patients were used in this experiment had some implications for the study design. The frailness of the patients meant that it was necessary to affect their daily life as little as possible. Hence, only a few, carefully chosen, questions were asked.

Our ability to generalize from this study is limited. The study sample was relatively small and only a few variables were explored. Nevertheless, the sample size was still sufficient for adequate statistical analyses, and increasing the sample size would have been extremely demanding. Recruitment required cooperation of the nursing staff and the severely compromised patients, and the presence of the researcher at any one time. Another limitation is the assessment of only one dose of treatment. However, it would be difficult to conduct such a study on this group of patients if it interfered more with their daily life than the present study, considering their short remaining lifespan.

It is likely that the findings of the present study are generalizable to similar patients; that is, severely compromised patients. On the other hand, the conclusions drawn from the present select and special population are not valid for generalization to healthier patients. To do so, further research would be needed. Similarly, no conclusions can be drawn from the present study for products other than those tested.

To the best of our knowledge, studies comparing different saliva substitutes have never before been performed in palliative care patients, only in less compromised patients with dry mouth problems (19, 20, 22). However, Aequasyal was previously tested in an RCT study of psychotropic drug-induced xerostomia (16). In that sample, only two out of 37 patients found the taste disagreeable and none reported nausea. This may indicate that the palliative care patients perceive such products differently from healthier patients. Alternatively,

the psychological status for which they were treated or the drugs used might be of importance in this context.

It is useful to consider whether any of the three products could be improved. For Aequasyal, perhaps the taste problem might be solved chemically. The present 17% concentration of glycerol is not based on scientific evidence, but rather on tradition and long-term experience. A higher concentration, up to 30% (which may be used without desiccation of the mucosa) (23), might perhaps produce better sustainability of the effect. Finally, the way in which Salient was dispensed could perhaps be improved. Rather than use of a small spoon for application, which was disliked by some respondents, use of a spray could be investigated, and it might be possible to reduce the disagreeable feeling of stickiness by increasing the water content. In view of the limited clinical usefulness of the tested products in their present form, and the plethora of other oral-care agents that exist, it cannot be precluded that other products might show different properties and better clinical outcome. However, so far this does not appear to be supported by scientific evidence.

It is also useful to consider what properties would be ideal in a product used for oral care. Based on the present findings, a product with a non-nauseating pleasant taste, texture, and consistency appears paramount, but a low viscosity and an agreeable application method may also be important. However, only an in-depth qualitative investigation among palliative care patients might provide a comprehensive answer to this question.

Even though the findings clearly demonstrate significant differences among the three products, none had completely satisfactory clinical properties. However, the preferred product, glycerol, has the advantage of being immediately effective and well tolerated by the patients. It may be possible to compensate, to some extent, for the drawback of glycerol, namely the short-lived effect, by frequent applications or higher concentrations. Regardless, the findings of this study do not contribute radically to improving guidelines for palliative oral care.

Within the defined limitations of this study, we conclude that none of the three tested products was found to be clinically completely adequate. The 17% concentration of glycerol had the most positive effect immediately after application, but little or no effect 2 h thereafter. Aequasyal and Salient had a long-lasting effect, but were nevertheless not preferred by the patients – probably because of the disagreeable taste of the former and the unpleasant, sticky consistency of the latter. The need for better products and further research in order to improve oral care seems obvious. Of clinical relevance, the glycerol solution was preferred by this group of patients, and its short-lived effect can be compensated for by frequent applications.

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Conflicts of interest – None to declare.

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