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Randomized controlled and double-blinded study of Caphosol versus saline oral rinses in pediatric patients with cancer

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Abbreviations:

OM	Oral mucositis
WHO	World Health Organisation
ChIMES	Children's International Mucositis Evaluation Scale
SCT	Stem cell transplantation
OMAS	Oral Mucositis Assessment Scale
OAG	Oral Assessment Guide
MASCC	Multinational Association of Supportive Care in Cancer
ISOO	International Society of Oral Oncology
LOESS	Locally estimated scatterplot smoothing
AUC	Area under curve

Abstract

Background: Oral mucositis (OM) is a significant side-effect of cancer treatment. The purpose of this study was to compare topically administered Caphosol to saline oral rinses in the prevention of mucositis in pediatric cancer patients undergoing chemotherapy.

Procedure: A controlled, double-blinded and randomized clinical study recruited patients between 2 to 17.99 years of age who were diagnosed with a malignancy and were receiving either high-dose methotrexate, anthracycline or cisplatin chemotherapy (NCT0280733). All patients received two seven-day cycles of the mouth rinses, i.e. one cycle of Caphosol and one cycle of saline in a randomized order. Oral changes and symptoms were evaluated using the World Health Organisation (WHO) toxicity scale and the Children's International Mucositis Evaluation Scale (ChIMES) scale. The primary endpoint was the frequency and severity of OM and oral symptoms.

Results: A total of 56 patients were recruited to the study, of whom 45 were randomized, with a median age of 6.5 years (range 2.1 to 17.1 years). No cases of severe OM were observed. Grade ≥3 oral symptoms were present at least once in 6 (13%) patients during the Caphosol cycle and 13 (29%) patients during the saline cycle (p=0.12). The peak of symptom scores was evident at around day 4 to 7 after administration of the chemotherapy with no marked differences between the rinse solutions. Multivariable regression analysis did not indicate a benefit of using Caphosol over the saline solution.

Conclusions: Caphosol rinse was not superior to saline in preventing OM or associated symptoms.

Key words:
Caphosol, mucositis, prevention, randomized, saline

Introduction

Oral mucositis (OM) is a painful inflammation that is caused by mucosa-breaking cytotoxic drugs or local radiotherapy to the neck and head region in cancer patients.[1] Children with hematological malignancies such as acute leukemias, advanced lymphomas, bone sarcomas and those undergoing stem cell transplantation (SCT) are at higher risk for developing OM.[2] Drugs considered the most harmful to oral mucosa include anthracyclines (e.g. doxorubicin), methotrexate, etoposide, cytarabine, and cyclophosphamide.[3] OM has an incidence of approximately 20-40% in the adult population undergoing chemotherapy.[4] Some studies have suggested that oral mucosal side effects occur more frequently in children compared to adults with cancer and that the rate may be as high as 90% among children less than 12 years old.[5-7]

OM is characterized by generalized erythematous, erosive and ulcerative lesions.[8] Many of the normal defence mechanisms are compromised in patients undergoing cancer therapy, who are thus predisposed to higher risk for bacteremia, fungal infection and sepsis.[9] OM in cancer patients may necessitate the use of parenteral nutrition and can lead to infection, pain and discomfort for the patients.[10] Previous studies have shown that patients with OM have also increased risk for mood disturbances, anxiety and depression.[11] OM is a significant side effect of cancer treatment in pediatric oncology patients. Traditionally, several control measures have been undertaken to prevent and treat OM, such as rinses or gels combining antiseptic/anti-mycotic/anesthetizing agents. Recently, the use of the Caphosol (Jazz Pharmaceuticals plc) solution has gained popularity.[12] Caphosol is a super-saturated Ca(2+)/PO(4)(3-) containing mouth rinse that is suggested to enhance healing of the mucosal

signalling pathways resulting in reduced inflammation, and activation of mucosa healing and epithelial proliferation.[13]

Since there is little evidence about the effects of Caphosol solution as a preventive mouth rinse in pediatric oncology patients, we compared Caphosol to saline rinses as a mucositis preventive measure in a randomized and double-blinded trial.

METHODS

2.1 Study design and ethical permission

This was a multicenter, prospective, double-blinded, and randomized clinical trial. The study was registered with clinicaltrials.gov (NCT02807337) before enrollment of the first patient, activated in August 2016, and closed to enrollment in December 2019. The study was approved by The Regional Ethics Committee of Tampere University Hospital (n:o R16021). All patients and/or their parents provided written informed consent prior to participation. Every subject was given a study code number, and analyses were carried out without personal identification data.

2.2 Patients

Patients between the ages of 2-17.99 years who were diagnosed with a solid or hematological malignancy and who were receiving chemotherapeutic drugs were invited to participate in the study. Their chemotherapy regimen included one of the following drugs that are known to

expose to mucositis: high-dose methotrexate (≥1 g/m2), any anthracycline (doxorubicin, daunorubicin, idarubicin, mitoxantrone) or cisplatin, and at least two cycles of chemotherapy that included the above mentioned drugs. The interval between the two rinse cycles was at least 3 weeks to allow

proper mucosa healing between the chemotherapy courses. Patients were excluded from the study if they had mucositis at the start of the chemotherapeutic regimen or had received high dose chemotherapy with SCT. Also, patients undergoing the induction chemotherapy for acute leukemias were excluded during that period. The study was open in three university hospitals, but the main site (Tampere) recruited >95% of the patients.

2.3 Study protocol and intervention

The study was a double-blinded study; hence, the clinical researchers, research nurses, and patients/parents were unaware of which rinse solution was used (Caphosol or saline solution). They tasted very similar and were packaged in similar ampules to avoid anyone being able to guess the content. Since Caphosol consisted of two solutions (A and B) that were mixed immediately before use, we applied the same procedure to the saline solution to maintain blinding; that is, two vials of saline solution were mixed. Both Caphosol and saline ampules were relabeled by the hospital pharmacy and provided by the investigators. The treatment group allocation was based on randomization and was performed once for every participant by an independent pharmacist using an online service (http://www.jerrydallal.com/random/permute.

htm). The randomization code was opened after the trial was closed. During the second cycle, according to the crossover design, the patient used the other mouth rinse (Caphosol→saline, or saline→Caphosol). Blinding was maintained throughout the study.

Oral rinsing began the same day as the chemotherapeutic course, and rinsing was continued for consecutive 7 days four times per day (= one rinse cycle). If overt OM developed during the treatment, the patient was allowed to revert to routine mucositis procedures in the ward that included the use of Caphosol; in this case, the patient and the study team continued to remain blinded to the study rinse solution. The patients were recruited either by a dentist, trained nurse, or pediatric oncologist, and the initial evaluation of the oral health by a dentist, trained nurse, or pediatric oncologist was performed before the start of chemotherapy and at discharge from the hospital.

All patients were encouraged to comply with the routine hospital oral care protocol, which consists of brushing one's teeth with fluoridated toothpaste and a soft toothbrush twice per day. When that is not possible, rinsing or swabbing of the mouth twice per day with an alcohol-free chlorhexidine mouthwash is recommended. Regular (every 3 months) visits to the dental department were scheduled for patients' oral examinations.

2.4 Measurement of outcomes

The primary endpoint of the study was the frequency and severity of oral mucositis between the Caphosol and saline rinses following chemotherapy that has potential to harm mucosa. OM was assessed using the World Health Organization (WHO) Oral Toxicity Scale[14] before and after the chemotherapy course by a dentist, pediatric oncologist, or trained nurse. Examination focused on the integrity of mucosa in the soft palate, buccal region, ventral side of the tongue, and the floor

of the mouth by using a high-powered flashlight for illumination.

Patient-reported outcomes were assessed by using the Children's International Mucositis Evaluation Scale (ChIMES)[15] daily for 2 weeks (14 days). The printed questionnaires were handed out to the

patient's family at the ward prior to the onset of the chemotherapy course, and either the patients or their guardians filled in the questionnaires before returning them to the investigator.

2.5 Statistical methods

The statistical power of the study design was calculated a priori. For a three-fold difference (10% vs 30%) in symptoms between mouth rinse solutions, a total of 68 subjects needed to be randomized into two groups of similar size (n = 34) to reach a statistical power of 80% with a false positive rate of 5%. The study was closed before the full enrollment due to slow recruitment and a change in the Caphosol preparation (from solution to effervescent tablet).

We defined two binary variables based on the observed ChIMES variables. The first variable turned positive if any of the ChIMES Q1-Q4 scores was above 2, and the other turned positive if either of the Q5-Q6 scores was 1. Barplots and Chi-square *P*-values were calculated and plotted for the variables stratified by the administered rinse solution. The dependence effect caused by observations collected from the same patient was taken into account when analysing the data.

Intention-to-treat was used as the basis for all analyses. Statistical significance was defined as alpha < .05, and the R (v. 3.6.2) software environment was used in statistical analyses.

Three statistical approaches were taken to estimate the differences between Caphosol and saline cycles. First, we plotted a 14-day time series for each ChIMES variable with its arithmetic mean values and locally estimated scatterplot smoothing (LOESS).[16] For clearer and

smoother illustrations,we linearly interpolated the values between the means of two successive days.We also generated a composite outcome variable by aggregating all symptom-related ChIMES variables into a single variable with no specific weight.

Second, we calculated the area under curve (AUC) values for both rinsing periods and each ChIMES variable following the treatment cycle; the area was limited by the x-axis and the ChIMES curve. The individual AUCs were averaged, and the standard error of mean was calculated. The averages were compared with a *Z*-test, and for each AUC value, the standard error was reported. The reported *P*-values were corrected for multiple testing by using the Bonferroni method. The auc( ) function is from the R package PK (v. 1.3-4), along with the null-hypothesis testing function test( ).

Third, we fitted linear mixed-effects models to all ChIMES variables. This facilitated addressing the autocorrelation structure between values of successive days for each subject. As all ChIMES plots start from the origin, a statistically significant interaction between time and the administered rinsing solution was the statistic of interest.We also separately evaluated the magnitude and statistical significance of a given rinse solution. The time variable was included in models as a factor and the rank of the given treatment cycle as a binary variable. The modeling was done using R package “nlme” (v. 3.1-142) and its function lme( ).

We observed a moderate amount (0-16%) of missing values in the daily ChIMES questionnaires completed by patients/caretakers. We opted not to impute missing values by linear interpolation or by repeating the last known score as this would poorly represent the missing data. All statistical functions allowed missing data to the input tables.

3. RESULTS

3.1 Patient characteristics and use of oral rinses

A total of 56 participants met the inclusion criteria, of which 11 declined. Thus, 45 children and adolescents with a median age of 6.5 years (range 2.1-17.1 years; see Table 1) were randomized to

receive two 7-day cycles of mouth rinse in a randomized order at least 3weeks apart from the beginning of chemotherapy potentially harmful to oral mucosa.

Out of 45 randomized subjects, the majority were treated for hematological malignancies (n=28, 62%), and the most common chemotherapy agent was high-dose methotrexate (n=27, 60%, cycle 1 and n=27, 60%, cycle 2; Table 1). Thirteen (29%) patients discontinued the study due to the rinse's bad taste, severe nausea, and vomiting, or overall feeling of weakness (n = 6 [13%] during Caphosol and n = 7 [16%] during the saline cycle; Figure 1). On average, patients received more than or equal to three rinses per day for 7 days, and no difference in the mean number of rinse applications was observed between the cycles (Figure S1). Thirty-two patients completed the study with two full cycles of mouth rinsing, but analyses were performed for 45 subjects according to the intention-to-treat principle.

3.2 Assessment of oral mucositis

No cases of severe OM (WHO ≥ 4) were observed. Three study subjects had WHO scores of 1–3 at the end of the course (Figure 2), two of which were observed during saline and one during Caphosol rinse cycle.

3.3 Assessment of patient-reported oral symptoms

Oral symptoms of grade ≥ 3 (ChIMES questions 1–4) were reported by 13% (n = 6) and 29% (n = 13) of the study subjects during the Caphosol and saline cycles, respectively (P = .12; Figure 2). When judged by the use of pain medication (question 5) or the presence of oral lesions (question 6), 31% (n = 14) and 49% (n = 22) of the patients presented with oral symptoms during the Caphosol and saline cycles, respectively (P = .13). None of the differences reached statistical significance.

The level of oral symptoms in time was visualized by plotting the recorded scores on a curve according to the rinsing solution. As shown in Figure 3 (Caphosol red and saline blue), the overall level of symptoms was low and below the score of 1 in all instances (pain, swallowing, eating, and drinking). The shape of the curve showed that symptoms peaked at around days 4-7 after administration of the chemotherapy and the curves depicting the two rinse solutions were

nearly superimposable. Similarly, the application of pain medication or reporting of mouth lesions by the patient/caretakers showed no distinction between the rinse solutions.

We built a composite metric that joined the six ChIMES scores (questions 1-6): the curves for both rinse solutions were almost indistinguishable (Figure S2), indicating that there was no difference in oral symptoms according to which solution was used.

We next calculated AUC values for the ChIMES scores. As shown in Table 2, no statistically significant differences were observed for pain, eating, drinking, or use of pain medication between the rinse solutions. In contrast, during the Caphosol cycle, patients showed fewer problems with swallowing and a lower prevalence of oral lesions when Caphosol was administered as the second rinse after the saline. However, there was no benefit for Caphosol in a reverse setting in which subjects first received Caphosol followed by saline in the next cycle.

Finally, we applied a linear mixed-effects regression model to estimate the contribution of individual rinse solutions to the study endpoints (Table 3). No statistically significant interaction was observed between the time variable and the administered rinse, which suggests that there are no differences in the ChIMES scores between the rinse solutions.

4 DISCUSSION

In this randomized, controlled, and double-blinded study, we observed no difference between the studied groups and Caphosol did not provide any benefit compared with saline in pediatric patients undergoing conventional chemotherapy. Similarly, there was no clinically

meaningful difference between the two rinse solutions in the self reported ChIMES scores. This study does not support the routine use of Caphosol solution over saline for the prevention of OMor oral symptoms in children and adolescents undergoing conventional chemotherapy courses.

Several clinical studies have shown positive effects of Caphosol in the frequency, intensity, and duration of overt OM in adult patients undergoing chemotherapy treatment and SCT.[17-19] Favorable results were also reported in the adult population with head and neck cancer undergoing radiotherapy or radiochemotherapy.[20] A few randomized trials[13,21,22] have studied Caphosol in the context of mucositis prevention in adults and have reported no benefit. Scientific evidence of mucosa healing or preventive benefits of Caphosol in pediatric cancer patients is scanty. Raphael et al (2014)[23] reported the results of a double-blinded placebo-controlled study with 33 randomized patients (4-18 years old) who received either Caphosol or placebo rinses four times a day for the treatment of OM. However, Caphosol did not reduce the occurrence of overt OM. In another study with 220 pediatric patients undergoing myeloablative treatment, Treister et al (2017)[12] found that Caphosol did not prevent OM when compared with a placebo saline rinse. Their study population received more intensive and mucositis-promoting chemotherapy compared to ours, and therefore our results are better applicable in conventional chemotherapy settings.

Participants in our study were pediatric cancer patients undergoing conventional chemotherapy with a mean age of 6.5 years. The outcome analysis was based on the assessment of both health care professionals (WHO scale) and patient/caretakers (ChIMES). The overall compliance was good, and the ChIMES questionnaires were faithfully completed. Our study was designed so that each patient

served as their own control (crossover), and only the order of applied mouth rinse solution was randomized. This seeked to reduce the interindividual variability and to lessen the probability that duration of the given therapy would bias the results. The study was originally powered to detect an absolute difference of 20% in favor of Caphosol solution (10% vs 30% proportion of mucositis or oral symptoms).We did not observe any clinically significant reduction in the frequency or seriousness ofOMor related symptoms after the use ofCaphosol. Although the study was stopped before the full accrual, the results do not suggest that any clinically meaningful difference was left unobserved for this reason. Overall, our results are in line with earlier studies [12,23] and support the routine use of saline solution as a primary preventive measure as long as the patient can tolerate it.

In our study, 29% of patients discontinued the rinse application due to varied reasons. Based on the patient self-assessment reports, both rinses were tolerated similarly, although the saline rinse was reported to have a stronger taste.Our study, like the Jacobs et al (2013) study,[24]demonstrates that ChIMES questionnaire is a feasible metric of oral symptoms in pediatric patients when evaluating mucositis related symptoms. The second major finding of our study was the overall low prevalence of significant mucosal damage or related symptoms in chemotherapy-treated children: the majority of the patients had none or only mild findings or symptoms. Thismay indicate the success of the regular application of any mouth rinse to lubricate the mucosal surface, to clean the oral cavity from the debris, and to allow the healing and renewal of mucosal tissue.[25]

Our study has limitations, the most significant being the small number of recruited patients, although this was countered by every patient applying each of the rinse solutions. It is evident that a higher number of recruited patients would have resulted in a more accurate estimate. The

priori expected ratio of the incidence of oral symptoms or mucositis while using Caphosol compared to saline was 1.29; the observed ratio includes this number (1.57, 95% CI 0.93–2.66 for ChIMES Q1–Q4 ≥ 3) and therefore our study does not formally exclude the possibility of benefit from using Caphosol. This being said, the shape of the results and the low incidence of symptoms do not suggest that the main conclusion of the study would have changed, had the number of cases been higher. Another limitation is the use of patient-reported symptoms as a metric as these are subject to individual interpretation, and assessment may vary across patients/caretakers.

In conclusion, Caphosol and saline solutions did not show clinically significant difference in the prevention of oral mucositis or symptoms in pediatric patients undergoing conventional chemotherapy. The relatively low number of significant mucosal findings encourages routine use of saline solution as a preventive measure against mucositis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

The study was approved by The Regional EthicsCommittee of Tampere University Hospital. All patients and/or their parents provided written informed consent prior to participation. Every subject was given a study code number, and analyses were carried out without personal identification data.

DATA SHARING STATEMENT

The authors elect to not share data.

AUTHOR CONTRIBUTIONS

Olli Lohi, Egle Immonen, Liisa Aine, Timo Peltomäki, and Mika Helminen conceived the study. Egle Immonen, Olli Lohi, Mataleena Parikka, Sauli Palmu, Kaisa Vepsäläinen, and Marika Grönroos recruited the patients. Atte Nikkilä, Olli Lohi, and Mika Helminen analyzed the data. Olli Lohi supervised the study. Olli Lohi, Egle Immonen, and Atte Nikkilä drafted the manuscript, and all the authors reviewed and accepted it.

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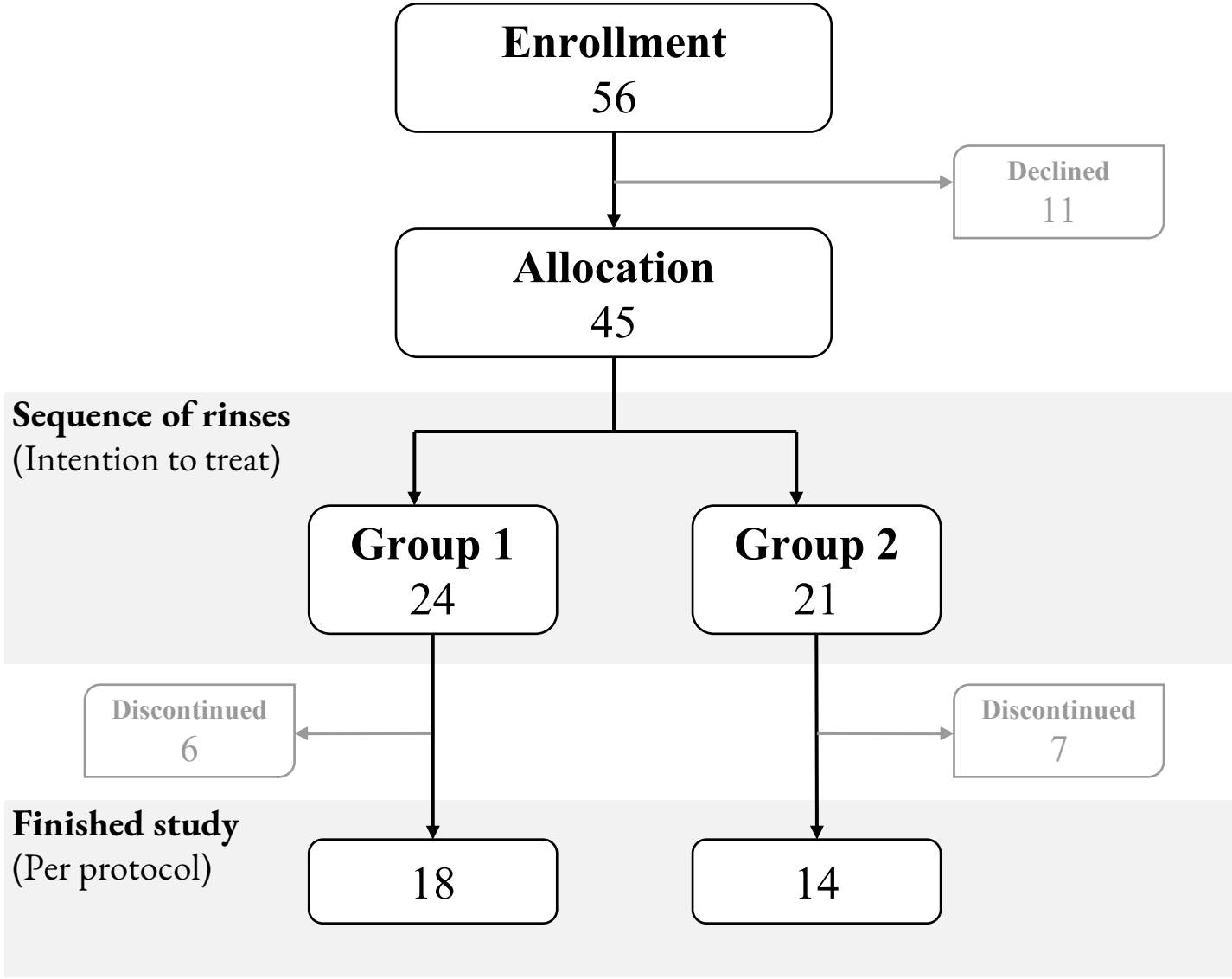
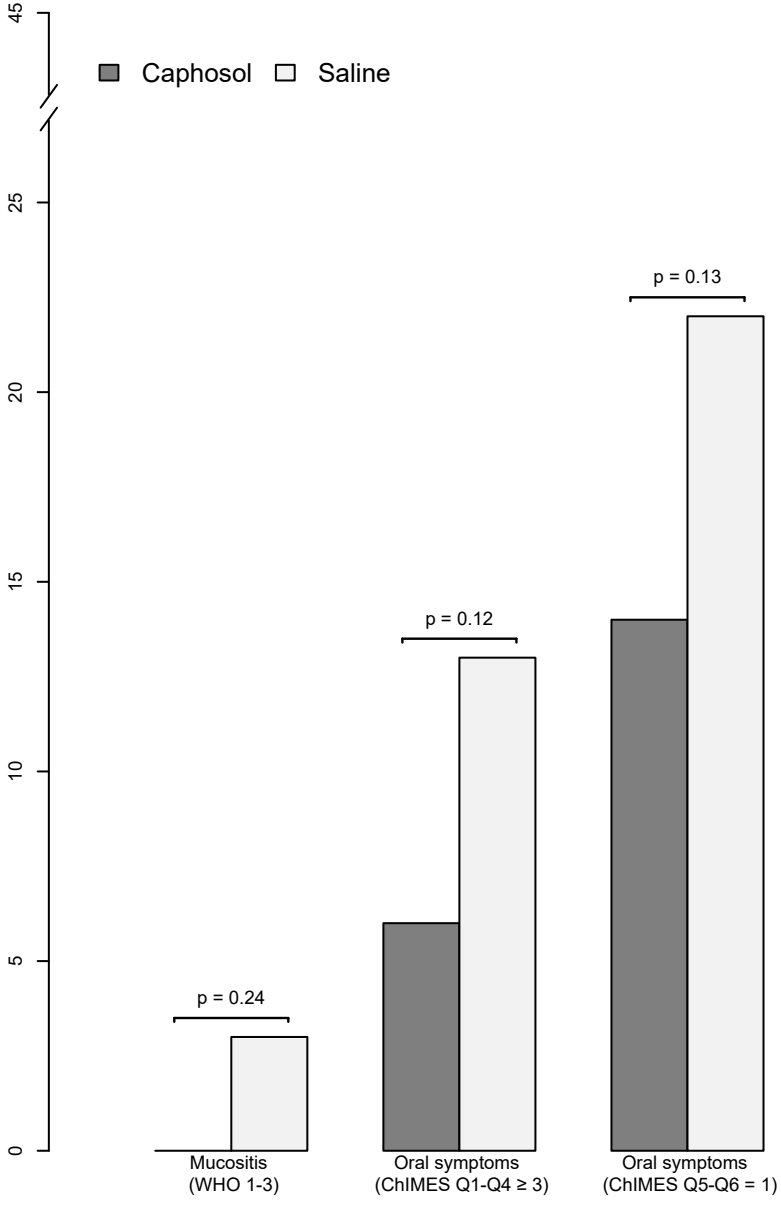
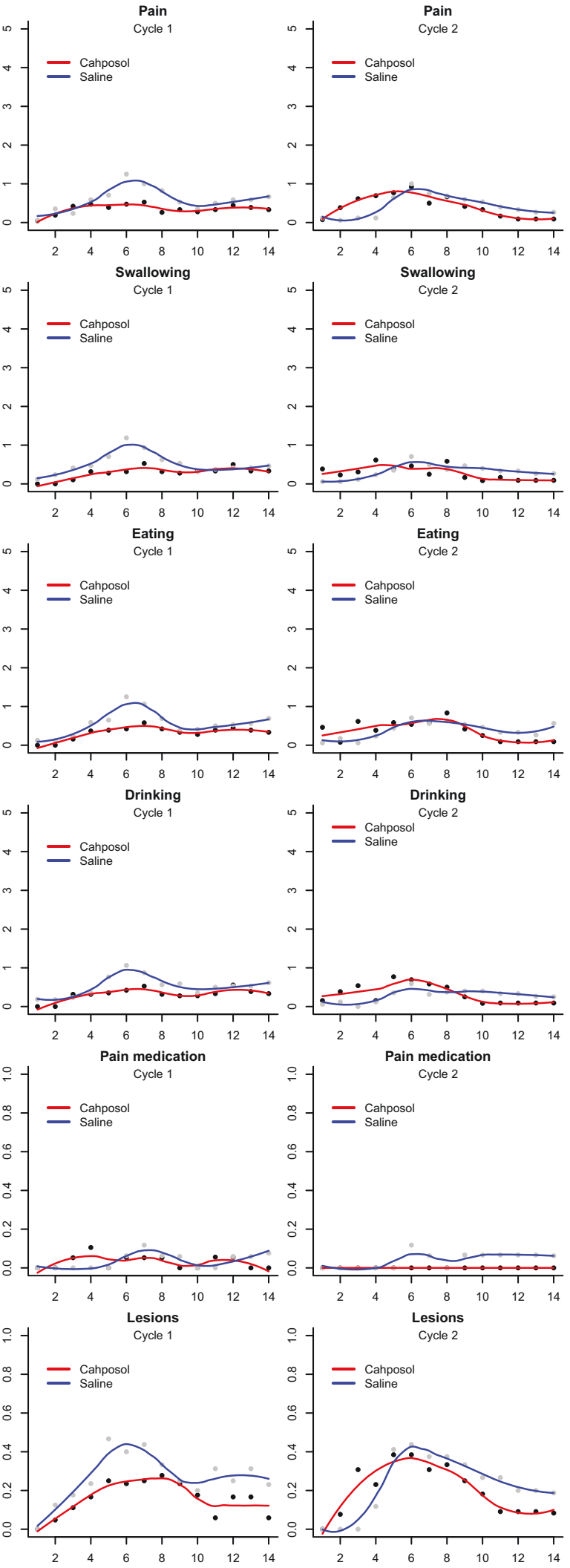

Enrollment
56
Declined
11
Allocation
45
Sequence of rinses
(Intention to treat)
Group 1
24
Group 2
21
Discontinued
6
Discontinued
7
Finished study
(Per protocol)
18
14


Caphosol
Saline
45
25
20
15
10
5
0
p = 0.24
p = 0.12
p = 0.13
Mucositis
(WHO 1-3)
Oral symptoms
(ChIMES Q1-Q4 ≥ 3)
Oral symptoms
(ChIMES Q5-Q6 = 1)


Pain
Cycle 1
Cahposol
Saline
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Cycle 2
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Swallowing
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Eating
Cycle 1
Cahposol
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Eating
Cycle 2
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Saline
Pain medication
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Saline
Lesions
Cycle 1
Cahposol
Saline
Lesions
Cycle 2
Cahposol
Saline

TABLE 1. Baseline characteristics of the study cohort by rinse order allocation

	TOTAL (n=45)	Group 1 (n=24) Caphosol → Saline	Group 2 (n=21) Saline → Caphosol
Age, Median(*range*)	6.5 (*2.1, 17.1*)	6.0 (*2.1, 14.7*)	7.2 (*3.1, 17.1*)
Sex, N(*%*)			
Female	20 (*44%*)	13 *(54%)*	7 *(33%)*
Male	25 (*56%*)	11 *(46%)*	14 *(67%)*
Diagnosis, N*(%)*			
Hematological malignancy	28 (*62%*)	13 *(54%)*	15 (*71%*)
Solid tumor	7 (*16%*)	4 *(17%)*	3 (*14%*)
CNS tumor	10 (*22%*)	7 *(29%)*	3 (*14%*)
Discontinued, N*(%)*	13 (*29%*)	6 (*25%*)	7 (*33%*)
Cycle 1			
Treatment, N(*%*)			
High-dose methotrexate	27 (*60%*)	13 (54%)	14 (*67%*)
Other chemotherapy	18 (*40%*)	11 (46%)	7 (*33%*)
Blood values, median(*IQR*)			
WBC (10^9/l)	3.8 (*2.8, 5.2*)	3.5 (*2.8, 4.6*)	3.9 (*3.3, 5.3*)
ANC (10^9/l)	1.6 (*0.9, 2.3*)	1.6 (*0.9, 2.1*)	1.5 (*0.9, 2.3*)
CRP (mg/l)	0 (*0, 3*)	0 (*0, 1*)	0 (*0, 4.4*)
Cycle 2			
Treatment, N(*%*)			
High-dose methotrexate	27 (*60%*)	14 (*58%*)	13 (*62%*)
Other chemotherapy	17 (*38%*)	10 (*42%*)	7 (*33%*)
Not available [a]	1 (*2%*)	0 (*0%*)	1 (*5%*)
Blood values, median(*IQR*)			
WBC (10^9/l)	3 (*1.9, 4.6*)	2.5 (*1.9, 4.3*)	3.3 (*2.3, 4.6*)
ANC (10^9/l)	1.2 (*0.7, 2.1*)	1.1 (*0.8, 2*)	1.4 (*0.6, 2.1*)
CRP (mg/l)	0 (*0, 1.8*)	0 (*0, 1.4*)	0 (*0, 4.6*)

CRP values coded as <5 or <1 were treated as zeros.

[a] Subject had finished his treatment protocol before the second chemotherapy cycle.

CNS - Central nervous system
IQR - Interquartile range
WBC - White blood cell count
ANC - Absolute neutrophil count
CRP - C-reactive protein

TABLE 2 – AUC (area under curve) values for patient-reported ChIMES scores for saline and Caphosol rinses

	Total	Caphosol	Saline	Adjusted p-value
	Mean *(SE)*	Mean *(SE)*	Mean *(SE)*	
Group 1		*Cycle 1*	*Cycle 2*	
Use of rinse	21.9 *(0.45)*	22.8 *(0.54)*	21.0 *(0.72)*	0.02
Pain	5.2 *(0.58)*	4.7 *(0.62)*	5.7 *(1.04)*	1
Swallowing	4.0 *(0.52)*	3.8 *(0.56)*	4.3 *(0.95)*	1
Eating	4.7 *(0.53)*	4.3 *(0.60)*	5.0 *(0.94)*	1
Drinking	4.0 *(0.53)*	4.3 *(0.66)*	3.8 *(0.89)*	1
Pain medication	0.5 *(0.12)*	0.4 *(0.15)*	0.5 *(0.18)*	1
Lesions	2.6 *(0.25)*	2.2 *(0.32)*	3.1 *(0.38)*	0.06
Group 2		*Cycle 2*	*Cycle 1*	
Use of rinse	22.8 *(0.42)*	22.9 *(0.65)*	22.7 *(0.55)*	1
Pain	7.0 *(0.72)*	5.7 *(1.12)*	7.9 *(0.94)*	1
Swallowing	5.5 *(0.62)*	3.7 *(0.75)*	6.9 *(0.93)*	<0.001
Eating	6.3 *(0.69)*	4.8 *(1.06)*	7.4 *(0.89)*	0.36
Drinking	5.9 *(0.65)*	4.4 *(0.97)*	6.9 *(0.87)*	0.17
Pain medication	0.3 *(0.09)*	0	0.5 *(0.16)*	-
Lesions	3.3 *(0.29)*	2.8 *(0.42)*	3.6 *(0.40)*	0.91
Both Groups		*Cycle 1&2*	*Cycle 1&2*	
Use of rinse	22.3 *(0.31)*	22.8 *(0.41)*	21.8 *(0.45)*	0.40
Pain	6.0 *(0.45)*	5.1 *(0.58)*	6.8 *(0.69)*	0.10
Swallowing	4.7 *(0.40)*	3.8 *(0.45)*	5.6 *(0.65)*	0.001
Eating	5.4 *(0.42)*	4.6 *(0.55)*	6.2 *(0.64)*	0.06
Drinking	4.8 *(0.41)*	4.3 *(0.56)*	5.3 *(0.62)*	1
Pain medication	0.4 *(0.08)*	0.3 *(0.09)*	0.50 *(0.12)*	0.17
Lesions	2.9 *(0.19)*	2.4 *(0.26)*	3.4 *(0.27)*	0.004

For rinsing, the AUC-value's upper limit is 28 (7d) or 56 (14d). Respectively for pain, swallowing, eating and drinking, the upper limit is 70. As for the pain medication and lesions, the limit is 14.

AUC values and their standard deviations were calculated using R-package *PK*'s function *auc()*. The null-hypothesis tests were carried our using the *test()*-function from the same package.

All p-values were adjusted using the Bonferroni method with R's base function *p.adjust()*.

TABLE 3 – Linear mixed-effects regression model for patient-reported ChIMES scores

	β	95% CI	p-value	interaction p-value
Use of rinse	0.18	-0.12, 0.47	0.24	0.99
Pain	-0.03	-0.28, 0.22	0.80	0.08
Swallowing	-0.05	-0.28, 0.18	0.65	0.78
Eating	0.02	-0.19, 0.22	0.88	0.06
Drinking	0.04	-0.25, 0.32	0.75	0.52
Pain medication	0.00	-0.05, 0.05	0.95	0.26
Lesions	0.00	-0.11, 0.1	0.95	0.26

Model was fitted using R-package *nlme*'s *lme*()-function. Autocorrelation structure was defined for time variable by patient. Beta-coefficient represents the change in the respective ChIMES score for a change from saline solution to Caphosol.

As independent variables, the full model included the day (0-14) as a factor, the treatment cycle (1 or 2) as a binary variable, the used rinse (Caphosol or saline) as a binary variable and the interaction term between the time and treatment variables as a factor. For a significant difference in the shape of ChIMES curves, a significant time-rinse interaction term is a requirement, as we defined a common origin for all ChIMES curves.