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Caphosol® versus State-of-the-Art Mouth Care in Patients with Allogeneic Stem Cell Transplantation: A Randomized Controlled Trial

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Abstract

Objective: Oral mucositis (OM) is a common side effect of allogeneic stem cell transplantation and can lead to infections with increased morbidity, mortality, higher costs and an impact on the quality of patients' lives. We conducted a study on the stem cell transplantation ward of a Swiss university hospital which treats oral mucositis with state-of-the-art measures.

Method and participants: In a randomized controlled, non-blinded trial involving 72 patients with allogeneic stem cell transplantation, we investigated the effectiveness of the oral rinse Caphosol® versus filtered water, in terms of duration of OM (primary endpoint), manifestation of OM and occurrence of pain, dry mouth, swallowing problems and changes in perception of taste (secondary endpoints).

Results: Results show Caphosol® had no effect on the duration of OM, with no difference in pain, dryness of mouth, swallowing problems and changes in perception of taste between the two groups. Predictors which seem to be associated with longer duration of OM are myeloablative conditioning and female gender. The number of oral rinses per day and in total show no significant correlation to duration of OM.

Conclusion: Consequently, in the setting of allogeneic stem cell transplantation in a patient group with a high risk for severe OM, oral rinsing with Caphosol® is not more effective than filtered water.

Keywords: Allogeneic stem cell transplantation; Oral mucositis; Oral rinse; Caphosol®; Mouth care; High dose chemotherapy

Background

OM is a common side effect of allogeneic stem cell transplantation (SCT) and can occur in up to 100% of patients with high dose chemotherapy and SCT [1]. Severe OM (grades 3-4) was observed in 60% of patients when total body irradiation (TBI) was applied; without TBI incidence rates approached 30–50% [2]. The clinical complications of OM are pain, bleeding, xerostomia, changes in the perception of taste, fatigue, fever, infections, malnutrition, anorexia and cachexia [3]. OM impacts patients' quality of life to the degree that they have difficulty eating, swallowing or talking. Social interactions and emotional well-being are also affected [4-6]. In adult patients with SCT, 87% require total parenteral nutrition (TPN) and 80% need analgesia with opioids [2]. With severe OM, mortality rates increase significantly in the first 100 days after transplantation [7]. OM increases the number of days with fever, length of hospitalization, use of opioids and TPN and leads to higher costs of $ 42.749 per patient [7].

State-of-the-art recommendations from the literature for assessing OM include the use of an objective, validated and reproducible mucositis scoring system such as the World Health Organization grading system, which combines functional and symptomatic variables [2,8]. One component of the instrument is a gradation of the OM from 0 (no OM) to 4 (life-threatening OM). Before beginning treatment a risk assessment needs to be conducted, followed by daily assessments until complete healing of the OM transpires [9]. All evidence-based guidelines for prevention and treatment of OM recommend a basic oral care regimen [1,10-13]. For patients, basic oral care consists of regularly verbal and written education, daily assessment of the oral cavity, brushing teeth twice a day for 90 s with a soft toothbrush, flossing once a day if platelets are not too low and rinsing the mouth at least four times daily. Alcohol, tobacco and irritating foods should be avoided. For lip care, a water-based moisturizer should be used and adequate hydration should be ensured. All of these measures are part of the prevention and treatment of OM. If OM occurs, analgesia with opioids and TPN are prescribed [10-14]. Infections are treated with antibiotics, antifungal agents and virostatics. For mouth rinsing, saline, water or sodium bicarbonate are recommended [15].

New mouth rinses have been developed in the last few years. One of them is Caphosol®, a supersaturated calcium phosphate mouth rinse designed to moisten, lubricate and clean the oral cavity. Calcium counteracts the process of inflammation and protects against infections while phosphate is accountable for restoration of natural pH-value in the mouth. Caphosol® has no known side-effects [16]. There are three major studies that have examined the issue. In a double-blind, prospective, randomized clinical trial involving 95 patients with autologous and allogeneic stem cell transplantation, Caphosol® and fluoride treatment were tested against fluoride rinse

only. Results showed statistically significant decreases in number of days with OM, duration of pain, dose of morphine, days morphine was administered and days before the onset of engraftment with absolute neutrophil count >200 mm^3 [17]. However, the effectiveness of fluoride mouth rinse as a solution for prevention and treatment of OM was not clear. Another study involving 32 patients with autologous SCT and a retrospective control group of 24 patients showed that treatment with BEAM (lomustine, etoposide, cytarabine, melphalan) with adjunctive Caphosol® produced a significant reduction in the incidence of OM of 3 to 4 degrees, the duration of OM and the use of painkillers. In the treatment with high dose Melphalan there was no difference shown [18]. However, the rinse solution and other measures in the control group were not mentioned. A third study, a randomized, non-blinded clinical trial involving 40 patients with allogeneic SCT showed significantly lower mean degrees of WHO oral toxicity, duration of OM and peak mouth pain. Length of analgesic need was of significantly shorter duration and the need for TPN significantly lower [19]. The solution of the control group contained salvia leaf extract, povidine-iodine and fluconazole. In evidence-based guidelines, mixed mouth rinses are not recommended and none of the three solutions is recommended on its own for prevention and treatment of OM [13].

In order to reach a solid conclusion about the efficacy of the mouth rinse Caphosol® versus filtered water we conducted a randomized controlled trial (RCT) involving patients with allogeneic SCT, a patient group at high risk for developing OM.

Methods

Design and setting

We conducted a randomized controlled study in a Swiss university hospital between January 2013 and August 2014 in which the effectiveness of Caphosol® as an oral rinse was examined in comparison to the state-of-the-art rinsing with filtered water. Blinding of the rinses was not possible because EUSA-Pharma was not able to manufacture ampules with placebo. So after randomization, patients and nurses knew who was in which group. The trial was terminated after completion of participants.

Participants

Patients with allogeneic SCT were included. Inclusion criteria were allogeneic SCT regardless of conditioning, >18 years of age and a signed informed consent. Exclusion criteria were inability to communicate in German and a low salt diet. Participants were not asked about prior use of an oral rinse during induction therapy. We obtained an informed consent from each patient and all patients got a copy of the signed informed consent.

Intervention

The rinse solutions were prepared just before use. Caphosol® was mixed from both ampules, water taken from a tap fitted with a filter (Aquasafe AQ31S1S, Pall Corporation, Port Washington, New York). Patients were instructed to rinse at least four times a day (morning, midday, afternoon and evening), with patients able to increase to as many as ten rinses per day as needed. Both, application of the rinsing with Caphosol® and the filtered water were to last two minutes. An hourglass was employed to control the application time. All rinse activity was recorded in a patient diary, allowing the process to be tracked.

Outcome

The primary endpoint of the study was the duration of OM. The secondary endpoints of the study were the characteristics of the OM according to WHO, as well as the manifestation of pain, dryness of the oral mucosa, difficulty swallowing and perception of taste.

On the day of admission the demographic variables age, gender, height and weight were collected. Clinical variables regarding disease, remission status, the conditioning (myeloablative conditioning=MAC; reduced intensive conditioning=RIC) and type of donors (related or unrelated) were also gathered. Assessment and management of OM was carried out following state-of-the-art recommendations from the literature. From the admission onwards, nurses conducted a daily examination of the patient's oral cavity until the point at which the OM was fully healed. For this purpose, the Prospective Oral Mucositis Audit (POMA, 2004) was used: an assessment instrument developed by the European Group for Blood and Marrow transplantation (EBMT) and adapted to patients with SCT. It is based on the WHO's assessment scale. In addition, the variables bleeding, ulcers, saliva production and fever were collected. Patients were instructed to indicate the manifestation of symptoms such as pain, dryness of the oral mucosa, difficulty swallowing and changes in the perception of taste by using the Numeric Rating Scale (NRS). In the case of the variables pain, dryness of the oral mucosa, and difficulty swallowing, 0 means «no symptoms» and 10 «worst symptoms possible». For the variable perception of taste, 0 signifies «normal perception of taste» and 10 «complete loss of the sense of taste». In addition, every day the number of rinses that occurred were recorded in a rinse diary. The nurses were trained in the use of the assessment instrument before the start of the study and again after recruiting half of the patients in order to improve inter-rater reliability. Training included the use of the assessment instrument and practicing the correct gradation of the scale with the aid of images.

Sample size

Power in the study was 90% with a level of significance of 0.05 based on the data of Blijlevens et al. [20] assuming a difference of 3 days in the more severe OM grades 3 and 4. This resulted in a minimal number of 29 patients per group. Since we chose a per-protocol-model, the number of patients was increased to 36 per group.

Randomisation

On the day of admission, the nurse manager of the SCT ward informed the patients about the study both verbally and in writing. When they agreed to participate, they were randomized to the intervention or control group. Randomization, data input and monitoring were carried out by means of electronic case report forms (eCRF).

Statistical method

All analyses were conducted using SPSS Version 20. The figures were done in Graphpad Prism Version 5. For all quantitative variables, number of observations (n), minimum (min), 1st quartile (Q1), median, mean, 3rd quartile (Q3), maximum (max), standard deviation (sd), and interquartile range (IQR) are given. For nominal variables, the absolute (n) and relative (%) frequency is shown. The mean ranks for all primary and secondary endpoints were compared by means of the Mann-Whitney U test between the treatment groups. For the binary variable peak mucositis, a chi-square test was performed.

For continuous variables with zero-inflation, an additional two-step approach was chosen. First, a chi-square-test was used to establish whether the proportion of zeros was significantly different between the treatment groups. Than a check was made to see whether the values >0 were distributed differently between the treatment groups. A negative binominal regression was run for all count data with zero-inflation.

However, by using the Mann-Whitney U test and Kendall's tau, it was checked whether sex, body mass index (BMI), TBI, MAC, non-related donors and number of oral rinses were associated with duration of mucositis. As only 4 patients were older than 65, the influence of advanced age was not evaluated. As treatment groups did not seem to be evenly distributed with respect to MAC, certain analyses were repeated by holding constant MAC.

Ethical Considerations

This single-center study was approved by the cantonal ethics committee.

Results

Of 72 total participants, 36 patients were randomised to the control group with filtered water and 36 were randomised to the intervention group with Caphosol®. Three patients in the control group and six in the intervention group dropped out of the study. Reasons for dropping out in the control group were delirium (1 patient) and deterioration of condition (2 patients). The reasons for drop-out in the intervention group were nausea (3 patients) and dry mouth (1 patient) due to Caphosol®, deterioration of condition (1 patient), and postponement of transplantation, which made further participation impossible (1 patient). Patients who discontinued the treatment with Caphosol® because of the taste or dry mouth, continued rinsing with filtered water. Analyses were based on available data, i.e., missing data were not replaced. The CONSORT RCT flow-chart of patients is shown in Figure 1.

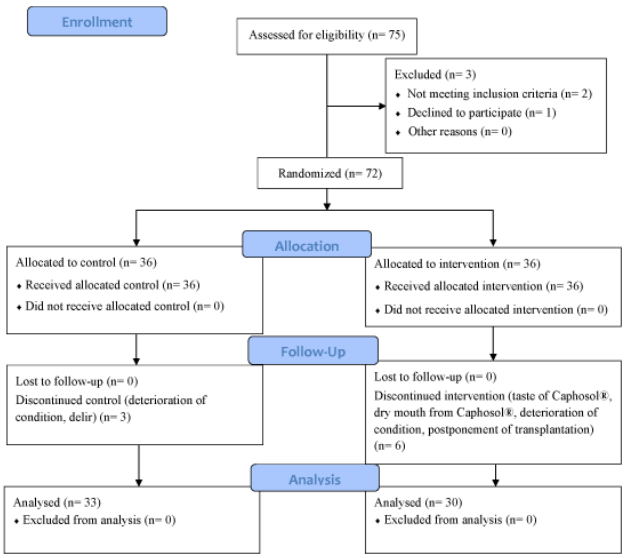

Figure 1: CONSORT RCT participant flow diagram [26].

Table 1 shows demographics and clinical data. Distribution of patients between the two groups was quite similar regarding age, gender and BMI; in total, more men were included in the study (58.3%). The most common reason for allogeneic transplantation was leukemia (65.3%). Overall, 31.9% of the patients had MAC therapy. However, in the intervention group more of those dropping out had MAC therapy so that the percentage of patients with MAC regimen was 20% in the intervention group, as opposed to 40% in the control group.

Variables	Control group N (%)	Intervention group N (%)	Significance
	n=36	n=36	
Gender			0.339[1]
Male	23	19	
Female	13	17	
Age (mean/SD):	47.3 (12.8)	48.2 (12.5)	0.757[2]
Height (m): mean (SD)	1.74 (0.10)	1.72 (0.09)	0.373[2]
Weight (kg): mean (SD)	75.7 (18.6)	67.7 (14.2)	0.076[2]
BMI (kg/m^2): mean (SD)	25.0 (5.2)	22.9 (4.0)	0.180[2]
Mouth washes:			
Mouth washes total: mean (SD)	23.909 (5.96)	23.13 (3.95)	0.138[2]
Mouth washes per day: mean (SD)	4.315 (1.27)	3.803 (0.708)	0.277[2]
Disease			0.858[3]
Leukemia	22 (61.1)	25 (69.4)	
Lymphoma	2 (5.6)	2 (5.6)	
Multiple Myeloma	5 (13.9)	3 (8.3)	
Myelodysplastic Syndrome	1 (2.8)	2 (5.6)	
Other	6 (16.7)	4 (11.1)	
Regimens for Conditioning			0.807[3]
Fludarabine - Busulfan	22 (61.1)	22 (61.1)	
Cyclophosphamide - TBI	10 (27.7)	8 (22.2)	
Cyclophosphamide - Busulfan	3 (8.3)	2 (5.6)	
Cylophosphamide - Fludarabine	1 (2.8)	1 (2.8)	
Cyclophosphamide	0	1 (2.8)	

Fludarabine, Amsacrine, Cytarabine	0	2 (5.6)	
TBI			0.422[1]
Yes	10 (30.6)	8 (22.2)	
No	25 (69.4)	28 (77.8)	
Myeloablative Conditioning			0.448[1]
Yes	13 (36.1)	10 (27.8)	
No	23 (63.9)	26 (72.2)	
Unrelated donor			0.812[1]
Yes	21 (58.3)	20 (55.6)	
No	15 (41.7)	16 (44.4)	
Drop Outs			0.285[1]
Reduced Intensive Conditioning (RIC)	3 (8.3)	2 (5.6)	0.643[1]
Myeloablative Conditioning (MAC)	0	4 (11.1)	0.040[1]
[1] chi-quadrat	[2] Mann-Whitney	[3] Fisher's exact test	

Table 1: Demographics and clinical data.

From the descriptive statistics it is evident that the intervention had no effect on the duration of OM, our primary endpoint. The mean of duration of OM is 9.8 days (SD 7.9) in the control group and 8.7 days (SD 8.0) in the intervention group. The Mann-Whitney U test confirmed that the duration of OM was not significantly different between the treatment groups (p=0.508). Moreover, controlling for gender and MAC had no effect on this result. As the primary endpoint, duration of OM, did not differ significantly between the treatment groups, the planned regression analysis controlling for gender, age, BMI, TBI, non-related donors, and number of oral rinses was not performed.

The only predictors apparently associated with duration of mucositis were TBI (p=0.001), gender (p=0.037), and MAC (p<0.001). Thus, patients with TBI and MAC and female patients experienced a longer duration of mucositis. There were slightly more females in the Caphosol® group, but the difference is not significant (p=0.339; chi-square test). Nonetheless, a linear regression with duration of OM as dependent variable was run, and did not indicate any differences between the treatment groups (p=0.699) when controlling for sex (p=0.473) and MAC (p<0.001). There was no association between non-related donors and duration of mucositis (p=0.366). Kendall's tau for BMI (τ=0.039; p=0.660), total number of oral rinses (τ=0.110; p=0.216), and number of oral rinses per day (τ=-0.085; p=0.338) indicated no significant correlation with duration of mucositis. The minimum rinse activity in the control group was 2.83 per day and in the intervention group it was 2.52. The maximum was 8.45 in the control group and 5.23 in the intervention group. The minimum number of days rinsing was undertaken for the control group was 11, the maximum 44. In the intervention group the minimum number of days rinsed was 16, the maximum 32 days.

Table 2 shows peak mucositis, one of the secondary endpoints, which did not differ significantly between the treatment groups (p=0.238). However, when recoding peak mucositis into a binary variable with low values (grades 0-2) versus high values (grades 3-4), the intervention group had a smaller proportion of high values than the control group (p=0.036). Stratifying by MAC showed that high values for peak mucositis were present mainly for patients with MAC. In a logistic regression analysis, the odds ratio for the intervention group was 0.269 (p=0.043), which dropped to 0.310 (p=0.193) when controlling for MAC.

Peak mucositis	**Control group N (%)**	**Intervention group N (%)**
	n=33	**n=30**
WHO Grade 0	5 (15.2)	5 (16.7)
WHO Grade 1	8 (24.2)	8 (26.7)
WHO Grade 2	8 (24.2)	13 (43.3)
WHO Grade 3	8 (24.2)	3 (10.0)
WHO Grade 4	4 (12.1)	1 (3.3)
	Patients without myeloablative conditioning	
	n=20	n=24
Low (0-2)	19 (95.0)	23 (95.8)
High (3-4)	1 (5.0)	1 (4.2)
	Patients with myeloablative conditioning	
	n=13	n=6
Low (0-2)	2 (15.4)	3 (50.0)
High (3-4)	11 (84.6)	3 (50.0)

Table 2: Peak mucositis.

The mean number of days with pain was 5.7 (SD 5.6) in the control group and 3.0 (SD 4.7) in the intervention group (Figure 2a). The mean ranks for number of days with pain was not significantly different between treatment groups (p=0.092). However, a negative binomial regression indicated that there was a significant impact of treatment group on number of days with pain (p=0.027). By controlling for MAC, this effect vanished (p=0.394). The mean ranks for AUC pain were not significantly different between treatment groups (p=0.108).

Moreover, the proportion of zeros was not significantly different between treatment groups (p=0.572). However, the non-zero values were significantly different between the control group (n=21) and the intervention group (n=17) (p=0.021). The mean ranks for peak pain were not significantly different between the treatment groups (p=0.174). Moreover, the proportion of zeros was not significantly different between the treatment groups (p=0.572), and also the non-zero values were not significantly different between the control group (n=21) and the intervention group (n=17) (p=0.070).

The mean number of days with dryness was 13.9 (SD 9.0) in the control group and 15.1 (SD 7.7) in the intervention group (p=0.767) (Figure 2b). The AUC for dryness was not significantly different between treatment groups (p=0.695) and also the median peak dryness was not significantly different between treatment groups (p=0.528).

The mean number of days with swallowing problems was 8.3 (SD 7.7) in the control group and 5.4 (SD 6.6) in the intervention group (p=0.133) (Figure 2c). Moreover, a negative binomial regression indicated that the intervention group had no significant influence on number of days with swallowing problems (p=0.121). The mean ranks for AUC swallowing problems were not significantly different between treatment groups (p=0.076). Moreover, the proportion of zeros was not significantly different between treatment groups (p=0.099), and also the non-zero values were not significantly different between the control group (n=27) and the intervention group (n=19) (p=0.422). The mean ranks for peak swallowing problems were not significantly different between treatment groups (p=0.071). Moreover, the proportion of zeros was not significantly different between treatment groups (p=0.099), and also the non-zero values were not significantly different between the control group (n=27) and the intervention group (n=19) (p=0.392).

The mean number of days with perception of taste >0 was 14.2 (SD 7.4) in the control group and 11.5 (SD7.6) in the intervention group (p=0.129) (Figure 2d). The AUC for perception of taste was not significantly different between treatment groups (p=0.135) and the peak perception of taste was not significantly different between the treatment groups (p=0.178) (Figure 3).

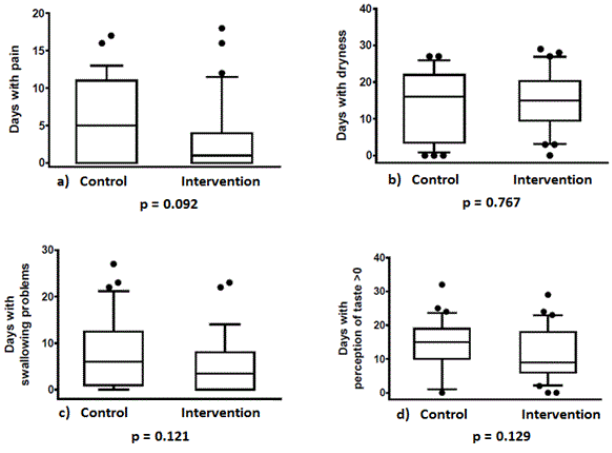

Figure 2: Boxplots of days with symptoms.

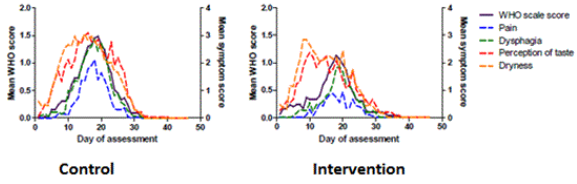

Figure 3: Mean WHO and symptom score.

On the mean WHO symptom score we see an immediate increase of the symptoms dryness of mouth and perception of taste on day 2. These symptoms persist until nearly day 40 after beginning of conditioning. There was a peak of dryness in the intervention group which could be an indication that Caphosol® is responsible. The peak of the WHO scale score occured on day 18 and correlates with pain and dysphagia. AUC for the WHO score did not differ significantly between the treatment groups (p=0.670).

Discussion

In this randomized controlled non-blinded trial involving 72 patients with allogeneic SCT we were able to show that, compared to filtered water, Caphosol® rinse had no effect on the length and manifestation of OM and the presentation of the symptoms pain, dryness of the oral mucosa, difficulty swallowing and perception of taste. Predictors of an extended period of OM were MAC, TBI and female gender. Neither BMI nor an unrelated donor had an impact on the duration of the OM. Neither did the number of oral rinses, whether per day nor in total, shows a correlation to the duration of the OM. These results contrast therefore with previous studies involving Caphosol®. In addition, there were four patients in the intervention group who discontinued the treatment because of the taste of Caphosol® and dryness of mouth that it brought about. The feeling of temporary suspension of salivary secretion was mentioned by one patient in the evaluation by Jarfaut et al. [21], and in a small study from Grenoble University Hospital, two paediatric patients discontinued treatment because of the bad taste of Caphosol® [22].

Previous studies using Caphosol® showed it to be more effective in comparison to other oral rinse solutions in regard to duration and extent of OM, duration of pain, administration of opioids and TPN [17-19]. The Papas et al. [17] study includes patients with allogeneic and autologous transplantation resulting in a higher rate of patients with MAC. It is possible that in a patient population with higher intensity conditioning Caphosol® would have a greater effect, as is shown in Table 2. Unfortunately, the number of patients in our study is too small to confirm this result. In the der Papas et al. [17] study, patients in the Caphosol® group were additionally pre-treated with topical fluoride treatments whereas the control group received a placebo gel. Possibly this fluoride treatment also had an influence on the OM. In all three studies testing Caphosol® [17-19] the distribution of the patients was identical in the intervention group and the control group. As in our study, no significant differences were found between the two groups as regards illness, sex and conditioning. In contrast to our study, patients in the other studies were treated much more frequently with MAC or, in the case of autologous transplantation, with medication that routinely triggered OM [17-19]. This might

indicate Caphosol® being more effective in cases of severe OM. Our patients with RIC indicated having only mild signs of OM, a finding that is not unexpected, but so far not yet described in the literature. One review of the literature on the effectiveness of Caphosol®, which found 30 studies and included 24, showed Caphosol® to have an effect on the occurrence and duration of OM as well as on the extent of pain caused by OM [23]. We were unable to confirm these findings in our study. Various risk factors of OM are described in the literature such as conditioning with TBI [24] or female gender [20]. In our study we are able to show that these factors also lead to a longer duration of OM. Other known risk factors such as unrelated donors [24] or a BMI>25 [25] were not confirmed in our study. However, our study included very few patients with a BMI>25. Surprisingly, the number of oral rinses had no effect on the duration or extent of OM, given that frequent and regular oral rinsing is recommend in all guidelines [10–14].

Limitations

This study was conducted on the SCT ward in a well-controlled setting in which the patients were under careful observation and which allowed for precise data collection. However, because we did not stratify the patients according to MAC or RIC, the sample sizes were relatively small in the sub-groups and MAC was underrepresented (31.9%), which clearly limits these results. We conducted the power analysis with the assumption of a difference of 3 days due to major clinical relevance for the patients. Our results only showed a difference of 2 days between the groups. Therefore, we cannot draw any firm conclusions as the study was not powered to show a statistical significance of 2 days.

Conclusion

The results of our study indicate a possible effect of Caphosol® on patients with MAC. In order to substantiate the tendency shown in the findings of the study, a large, randomized trial made up exclusively of patients with MAC would be of value. Given that neither the number of oral rinses in total nor the number of rinses per day correlated with the duration of the OM, a randomized controlled trial studying the number of oral rinses in more depth is to be recommended. In general, patients are advised to rinse their mouths at least 4 times daily, if not more often. In a future study, rinsing 4 times a day could be compared to rinsing twice a day and the patients re-evaluated and surveyed on a regular basis using the assessment instrument.

In terms of implications for clinical practice, our study shows that continued use of filtered water as a rinse solution is warranted, since the use of a specific rinse did not improve results. Given that patients with aplasia have great difficulty coping with frequent oral rinses, necessitating a great deal of support from nurses, the number of oral rinses could be reduced. More frequent oral rinsing had no effect on the duration of OM.

Our results show that the oral rinse Caphosol® has no effect on duration of OM, dryness of the mouth, difficulty to swallow or on perception of taste. It is possible that Caphosol® has an effect on OM in cases of patients with MAC. However, the sample size is too small to allow a conclusive statement to be made. A statistically significant effect was shown on the number of days with pain experienced by the intervention group. However, this effect disappeared after controlling for MAC. In summary, it can be concluded that rinsing with filtered water is as effective in the prevention and treatment of OM as Caphosol®.

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