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ORIGINAL RESEARCH

Effectiveness, Tolerability, and Safety of Ectoine-Containing Mouthwash Versus Those of a Calcium Phosphate Mouthwash for the Treatment of Chemotherapy-Induced Oral Mucositis: A Prospective, Active-Controlled, Non-interventional Study

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ABSTRACT

Introduction: Oral mucositis is a frequent complication of cancer chemotherapy and radiotherapy. Ectoine is a natural extremolyte that can stabilize biological membranes and counteract inflammatory reactions. This study investigated ectoine-containing mouthwash for the prophylaxis and the treatment of oral mucositis. Its effectiveness, tolerability, and safety were compared to those of the local standard-of-care calcium phosphate mouthwash.

Methods: This prospective, active-controlled, observational study was conducted in two study centers in Hungary from January 2016 to October 2017. Sixty patients undergoing chemotherapy were to be recruited and allocated to one of three treatment arms: prophylactic treatment with ectoine (20 patients), active treatment with ectoine (20 patients), or calcium phosphate (20 patients). The study lasted 21 days, comprising four visits on day 0, day 7, day 14, and day 21.

Results: In all, 45 patients were included in the study (prophylactic ectoine, 10 patients; active ectoine, 20 patients; calcium phosphate, 15 patients). In the prophylactic ectoine group, few mucositis symptoms of mild or moderate severity occurred throughout the study. In the active ectoine and the calcium phosphate groups, symptoms of mild and moderate severity at inclusion were reduced significantly after 14 days of treatment and were mostly resolved at the end of the study. The difference between the active ectoine and the calcium phosphate groups was not significant. According to patients' assessments, ectoine mouthwash was

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more effective and tolerable than calcium phosphate mouthwash.
Conclusions: Ectoine mouthwash is safe, well tolerated, and effective for the active treatment of oral mucositis following chemotherapy. Its effectiveness is comparable to that of calcium phosphate. Patients prefer ectoine mouthwash to calcium phosphate mouthwash.
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PLAIN LANGUAGE SUMMARY

Oral mucositis is the inflammation of the mucosa of the oral cavity. It is a frequent complication of cancer chemotherapy and radiotherapy. Approximately 20–40% of patients undergoing chemotherapy suffer from oral mucositis. It is very painful, impairs eating, drinking, and quality of life. One of the most effective yet simple measures to prevent and treat oral mucositis is oral care with mouthwash. Ectoine is a natural substance that was discovered in halophilic (salt-loving) bacteria. Ectoine can protect these bacteria against dehydration because it can attract water molecules and strengthen biological membranes. Ectoine is used to treat many diseases caused by allergens, UV light, air pollution, heat, and dryness. Ectoine (Ectoin®) mouthwash is produced by bitop AG (Dortmund, Germany) to treat dry mouth and other symptoms of inflamed oral mucosa.

This study investigated ectoine mouthwash for the treatment of oral mucositis following chemotherapy. It was compared to the local standard-of-care calcium phosphate mouthwash. One group of patients was treated with ectoine mouthwash and the other with calcium phosphate mouthwash. After 14 days, mucositis symptoms were substantially reduced in both groups. After 21 days, all patients were almost cured of oral mucositis. Additionally, after the treatment, patients rated how effective and tolerable the treatment was. Here, more patients treated with ectoine rated their treatment as effective and tolerable than those treated with calcium phosphate.

This study shows that ectoine mouthwash is tolerable and effective for the treatment of mucositis. Patients preferred ectoine mouthwash to calcium phosphate mouthwash.

Keywords: Chemotherapy; Ectoine; Mouthwash; Mucositis; Oral care

INTRODUCTION

Oral mucositis, clinically defined as inflammation of the mucosal lining of the oral cavity, is a frequent complication of cancer chemotherapy and radiotherapy. It occurs in 20–40% of patients undergoing standard chemotherapy [1] and in almost every patient receiving bone marrow transplantation [2]. Risk factors for the development of mucositis include age, nutritional status, type of malignancy, and oral care during cancer treatment [3]. Mucositis is very painful, often requires analgesics, and impairs eating, drinking, and quality of life. Severe mucositis can even necessitate reducing or discontinuing cancer therapy. Medical costs for mucositis are considerable because of symptom management, nutrition support, and hospitalization [4, 5].

There are numerous interventions for mucositis, such as basic oral care, anti-inflammatory agents, anti-radical scavengers, antimicrobials, coating agents, laser therapy, and cryotherapy. Basic oral care, despite being the least invasive treatment option, is vital in preventing infections. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines for Mucositis recommend basic oral care for preventing oral mucositis following all cancer treatments in all age groups. However, at present, there is no standard treatment guideline for oral mucositis [4]. A systematic review on currently available oral care protocols, dental care as well as mouthwash containing saline, sodium bicarbonate, chlorhexidine, mixed medication, and calcium phosphate has yielded insufficient and conflicting evidence [6].

The development of mucositis is divided into five phases, each of which is characterized by inflammatory and apoptosis-triggering factors, such as reactive oxygen species (initiation phase), TNF-α, IL-1β, IL-6, the mitogen-activated protein kinase pathway, the ceramide signaling pathway (damage response and signal amplification phase) as well as bacterial and fungal colonization (ulceration phase) [7–10].

Ectoine is a natural extremolyte which has been shown to counteract inflammatory reactions involving IL-6, IL-8, TNF-α, IL-1β [11–13], the ceramide signaling pathway [14], and the mitogen-activated protein kinase signaling pathway [15]. It has also been shown to rescue cells from apoptosis [16, 17]. Furthermore, ectoine can stabilize biological membranes and rehydrate dry, irritated mucosa [18–20], which is essential for the body's defense against oral infections. These membrane-stabilizing and inflammation-reducing effects of ectoine-containing products have been demonstrated in several clinical studies [21–23]. Taken together, ectoine can be expected to thwart the development of oral mucositis.

This study investigated ectoine-containing mouthwash for the prophylaxis and the treatment of oral mucositis. Its effectiveness, tolerability, and safety were compared to those of the local standard-of-care calcium phosphate mouthwash.

MATERIALS AND METHODS

Study Design

This prospective, active-controlled, observational study was conducted in two study centers in Hungary from January 2016 to October 2017. Patients were included in the trial after the decision about the treatment option had been made on the basis of the patients' preference. The study complied with laws and regulations effective in Hungary, namely §17 para (1), point c) of Government Regulation 235/2009. (X.20.). It was carried out in accordance with legal statutes and regulations for the protection of human subjects. This study was approved by the Department of Medical Devices at the Healthcare Registration and Training Center (ENKK), Budapest, Hungary (Reference number: 001654/2016). It is listed at clinicaltrials.gov under the number NCT02816515.

We aimed to recruit 60 male and female adult patients who had an inoperable/metastatic small cell lung cancer (SCLC) tumor, non-small cell lung cancer (NSCLC) tumor, gastrointestinal stromal tumor, renal cell carcinoma, or pancreatic neuroendocrine tumor. Patients receiving targeted tyrosine kinase inhibitor anticancer therapy were treated with sunitinib (Sutent®, Pfizer Pharma GmbH). Patients could be chemotherapy-naïve or have had chemotherapy before the study.

Patients were allocated to one of three treatment arms: prophylactic treatment with ectoine (20 patients), active treatment with ectoine (20 patients), or calcium phosphate (20 patients). In the prophylactic ectoine arm, patients received ectoine mouthwash on the first day of chemotherapy. In the active ectoine arm and the calcium phosphate arm, treatment was initiated when mucositis occurred.

The study lasted 21 days, comprising an initial visit (V1) on day 0, visit 2 (V2) on day 7, visit 3 (V3) on day 14, and visit 4 (V4) on day 21.

Study Medications

Ectoine (Ectoin®) mouthwash is a registered medical device manufactured by bitop AG (Dortmund, Germany). An ampoule (single dose unit) contains 5 ml preservative-free solution of ectoine (2%), hydroxyethyl cellulose (for better viscosity), and xylitol (for sweetness) in phosphate buffer and water. It was administered at least three times daily, each time for 30 s with 1–2 ampoules.

Caphosol® mouthwash (EUSA Pharma, UK) is a supersaturated calcium phosphate solution. It was used at least four times daily according to the manufacturer's instructions.

Clinical Assessments

Effectiveness was assessed on the basis of symptom scores and mucositis grading results

(World Health Organization (WHO) classification) [24]. The symptoms of dry mucosa, coated tongue, mucosal irritation, unpleasant breath, decreased saliva production, pain, swelling, ulcer, difficulties speaking, and difficulties eating/drinking were assessed by the physicians together with the patients at each visit on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The grade of mucositis was determined for each patient at each visit: grade 0 = none, grade I = mild (oral soreness, erythema), grade II = moderate (oral erythema, ulcers, solid diet tolerated), grade III = severe (oral ulcers, liquid diet only), and grade IV = life-threatening (oral alimentation impossible). Changes in symptom scores and mucositis grades from V1 to V2, V3, and V4 were compared between groups.

At the last visit, patients rated the overall effectiveness and tolerability of the treatment as well as its effectiveness against the individual symptoms of redness, burning sensation, swelling, pain, mucosa irritation, and dry mucosa (0 = very poor, 1 = poor, 2 = neither poor nor good, 3 = good, and 4 = very good). Additionally, patients were asked to rate their likelihood of buying or recommending the product after the study (0 = no, 1 = maybe, and 2 = yes).

All adverse events and serious adverse events were to be documented. Their possible relations to the treatment were evaluated by the investigators.

Statistical Analyses

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). As this was an exploratory study, no sample size calculation was performed. There was a 95% probability that side effects occurring at an incidence of 5.9% or higher would have been detected (Clopper–Pearson).

Symptom scores, general effectiveness, and tolerability that had been measured on a standard scale were analyzed descriptively, and the Wilcoxon signed-rank test was used to detect significant differences between the baseline scores and the final scores during and after treatment. Frequencies and percentages of mucositis grades were presented by visit and treatment group. Frequencies and percentages were determined for the variables from the patient questionnaires at the end of the study. Comparisons between treatment groups were performed using the two-sided Fisher's exact test with an α-level of 5%.

Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study

RESULTS

Study Population

In all, 45 patients were recruited: 10 patients were allocated to the prophylactic ectoine arm, 20 to the active ectoine arm, and 15 to the calcium phosphate arm. The distribution of female and male patients in these groups was 1 and 9, 7 and 13, and 6 and 9, respectively. The mean age of patients was similar across all groups (prophylactic ectoine, 61.10 ± 7.11 years; active ectoine, 61.55 ± 7.52 years, and calcium phosphate, 63.87 ± 6.45 years). In total, 29 patients had lung cancer (SCLC/NSCLC) and 16 patients had metastatic renal cell carcinoma (mRCC). These 16 patients were treated with sunitinib.

Prophylactic Treatment with Ectoine

During prophylactic treatment with ectoine, 3 out of 10 (30%) patients were completely free of symptoms (WHO grade 0). Symptoms of mild intensity (WHO grade I) were reported in 2 patients at V2 and V3. In 6 patients (60%), mild symptoms (WHO grade I) occurred at V4 (Tables 1, 2, Fig. 1).

Table 1 Changes in mucositis grades (WHO classification) over time

	Grade 0	Grade I	Grade II	Grade III	Grade IV
Prophylactic ectoine					
V1					
N	10	–	–	–	–
%	100.0				
V2					
N	9	1	–	–	–
%	90.0	10.0			
V3					
N	8	1	1	–	–
%	80.0	10.0	10.0		
V4					
N	3	6	1	–	–
%	30.0	60.0	10.0		
Active ectoine					
V1					
N	–	8	9	3	–
%		40.0	45.0	15.0	
V2					
N	1	6	11	2	–
%	5.0	30.0	55.0	10.0	
V3					
N	2	15	2	1	–
%	10.0	75.0	10.0	5.0	
V4					
N	16	2	1	1	–
%	80.0	10.0	5.0	5.0	
Calcium phosphate					
V1					
N	–	3	11	–	1
%		20.0	73.3		6.7
V2					
N	–	3	11	–	1
%		20.0	73.3		6.7

Table 1 continued

	Grade 0	Grade I	Grade II	Grade III	Grade IV
V3					
N	–	9	5	–	–
%		64.3	35.7		
V4					
N	6	7	1	–	–
%	42.9	50.0	7.1		

Table 2 Symptom scores

Symptom	Treatment	V1 (mean ± SD)	V2 (mean ± SD)	V3 (mean ± SD)	V4 (mean ± SD)
Dry mucosa	Prophylactic ectoine	0.0 ± 0.0	0.2 ± 0.6	0.5 ± 0.8	0.5 ± 0.8
	Active ectoine	1.7 ± 0.6	1.4 ± 0.6	1.0 ± 0.7	0.4 ± 0.9
	Calcium phosphate	1.9 ± 0.5	1.7 ± 0.6	1.3 ± 0.5	0.6 ± 0.5
Mucosa irritation	Prophylactic ectoine	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 0.8	0.5 ± 0.8
	Active ectoine	1.7 ± 1.7	1.4 ± 0.7	1.1 ± 0.9	0.3 ± 0.6
	Calcium phosphate	1.9 ± 0.5	1.6 ± 0.6	1.1 ± 0.4	0.6 ± 0.5
Coated tongue	Prophylactic ectoine	0.0 ± 0.0	0.2 ± 0.6	0.2 ± 0.6	0.0 ± 0.0
	Active ectoine	1.4 ± 0.9	1.1 ± 0.8	0.4 ± 0.9	0.3 ± 0.9
	Calcium phosphate	1.8 ± 0.6	1.6 ± 0.6	0.9 ± 0.5	0.4 ± 0.5
Unpleasant breath	Prophylactic ectoine	0.2 ± 0.4	0.0 ± 0.0	0.3 ± 0.9	0.2 ± 0.6
	Active ectoine	1.3 ± 0.7	0.9 ± 0.8	0.4 ± 0.6	0.1 ± 0.4
	Calcium phosphate	1.7 ± 0.6	1.5 ± 0.6	0.9 ± 0.8	0.4 ± 0.5
Decreased saliva production	Prophylactic ectoine	0.0 ± 0.0	0.2 ± 0.6	0.2 ± 0.6	0.3 ± 0.7
	Active ectoine	1.2 ± 0.7	0.8 ± 0.5	0.4 ± 0.9	0.3 ± 0.9
	Calcium phosphate	1.6 ± 0.6	1.5 ± 0.6	0.9 ± 0.6	0.3 ± 0.5

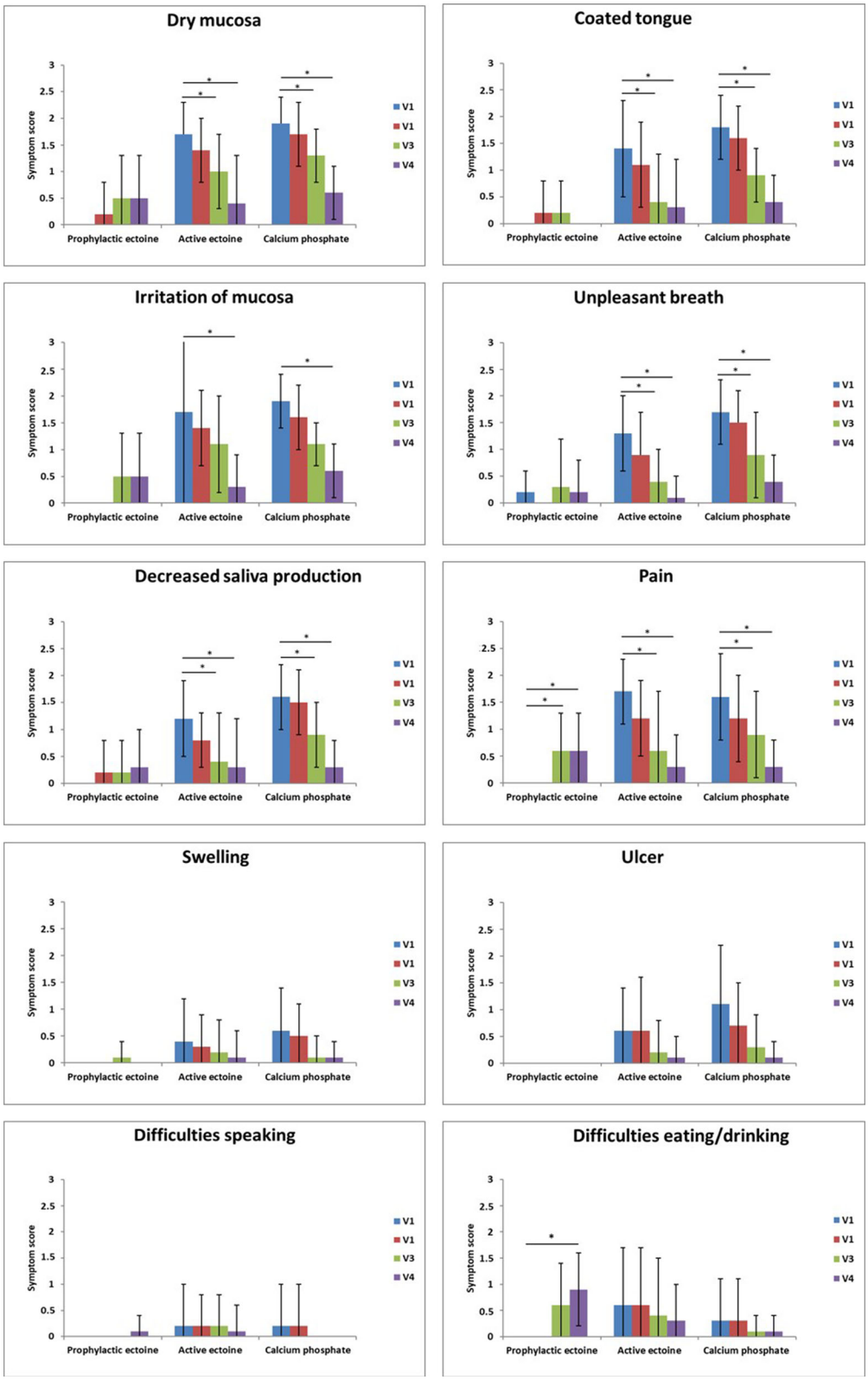
Table 2 continued

Symptom	Treatment	V1 (mean ± SD)	V2 (mean ± SD)	V3 (mean ± SD)	V4 (mean ± SD)
Pain	Prophylactic ectoine	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 0.7	0.6 ± 0.7
	Active ectoine	1.7 ± 0.6	1.2 ± 0.7	0.6 ± 1.1	0.3 ± 0.6
	Calcium phosphate	1.6 ± 0.8	1.2 ± 0.8	0.9 ± 0.8	0.3 ± 0.5
Swelling	Prophylactic ectoine	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0
	Active ectoine	0.4 ± 0.8	0.3 ± 0.6	0.2 ± 0.6	0.1 ± 0.5
	Calcium phosphate	0.6 ± 0.8	0.5 ± 0.6	0.1 ± 0.4	0.1 ± 0.3
Ulcer	Prophylactic ectoine	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Active ectoine	0.6 ± 0.8	0.6 ± 1.0	0.2 ± 0.6	0.1 ± 0.4
	Calcium phosphate	1.1 ± 1.1	0.7 ± 0.8	0.3 ± 0.6	0.1 ± 0.3
Difficulties speaking	Prophylactic ectoine	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.3
	Active ectoine	0.2 ± 0.8	0.2 ± 0.6	0.2 ± 0.6	0.1 ± 0.5
	Calcium phosphate	0.2 ± 0.8	0.2 ± 0.8	0.0 ± 0.0	0.0 ± 0.0
Difficulties eating/drinking	Prophylactic ectoine	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 0.8	0.9 ± 0.7
	Active ectoine	0.6 ± 1.1	0.6 ± 1.1	0.4 ± 1.1	0.3 ± 0.7
	Calcium phosphate	0.3 ± 0.8	0.3 ± 0.8	0.1 ± 0.3	0.1 ± 0.3

Active Treatment with Ectoine vs. Calcium Phosphate

The distribution of mucositis grades in the active ectoine group at inclusion was 8 patients (40%) with grade I, 9 patients (45%) with grade II, and 3 patients (15%) with grade III. After 21 days of treatment, 16 patients (80%) were completely cured, 2 patients (10%) had grade I, 1 patient (5%) had grade II, and 1 patient had grade III. At V1, the calcium phosphate group consisted of 3 patients (20%) with grade I, 11 patients (73.3%) with grade II, and 1 patient (6.7%) with grade IV. At V4, 6 patients (42.9%) were completely cured, 7 patients (50.0%) had grade I, and 1 patient (7.1%) had grade II (Table 1).

Analyses of the symptom scores show that patients in the two groups had comparable symptoms at V1. Symptoms such as dry mucosa, mucosa irritation, coated tongue,


Dry mucosa
Coated tongue
Irritation of mucosa
Unpleasant breath
Decreased saliva production
Pain
Swelling
Ulcer
Difficulties speaking
Difficulties eating/drinking
Symptom score
Prophylactic ectoine
Active ectoine
Calcium phosphate
V1
V1
V3
V4

◀**Fig. 1** Symptom scores assessed by the physicians together with the patients at V1, V2, V3, and V4 (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Values plotted are mean ± standard deviation (SD). Significant differences between visits were determined using the Wilcoxon signed-rank test. *Indicates $P < 0.05$

unpleasant breath, decreased saliva production, and pain were mild or moderate at V1 and reduced to very mild or mild at V4. Significant reductions in all symptoms, except for irritated mucosa, were recorded at V3 in both groups ($P < 0.05$). Symptoms such as swelling, ulcer, difficulties speaking, and difficulties eating/drinking were very mild or mild at V1 and mostly resolved at V4 (Table 2, Fig. 1). The reductions in symptom scores were not significantly different between groups.

Patients' Assessments

The overall effectiveness and tolerability of the treatment as well as its effectiveness against individual symptoms were assessed as "good" and "very good" by patients in both ectoine groups and as "good" by calcium phosphate patients. The superiority of the active ectoine group over the calcium phosphate group was significant ($P < 0.05$). The difference between the two ectoine groups was not significant (Fig. 2).

In the prophylactic ectoine arm, 90% of patients would buy the product (mean score = 1.9 ± 0.3), and 100% would recommend the product (2.0 ± 0.0). In the active ectoine group, 80% of patients would buy the product (1.8 ± 0.6), and 87.6% would recommend the product (1.8 ± 0.6). It should be understood that the term "this product" referred to the product and the specific treatment regimen (i.e., prophylactic or active treatment with ectoine), not only the product itself. In contrast, 40% of calcium phosphate patients would buy the product (1.3 ± 0.6), and 53.3% would recommend the product (1.5 ± 0.5). The difference between the active ectoine group and the calcium phosphate group was significant ($P < 0.05$) (Fig. 3).

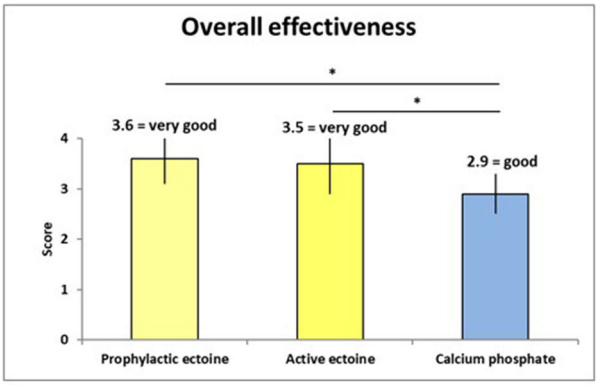
Safety

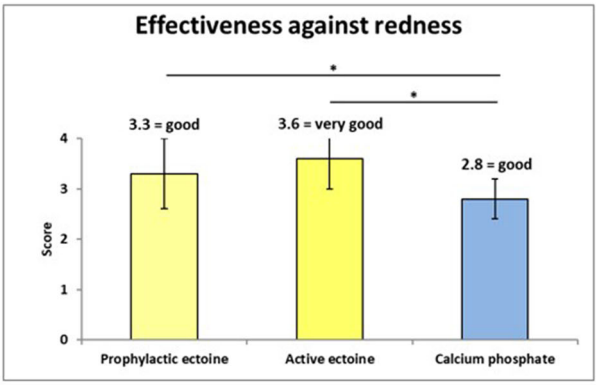
One patient suffered from exsiccosis and fever 2 months after the completion of the study and died shortly after that. These events were classified as unrelated to the study treatment.

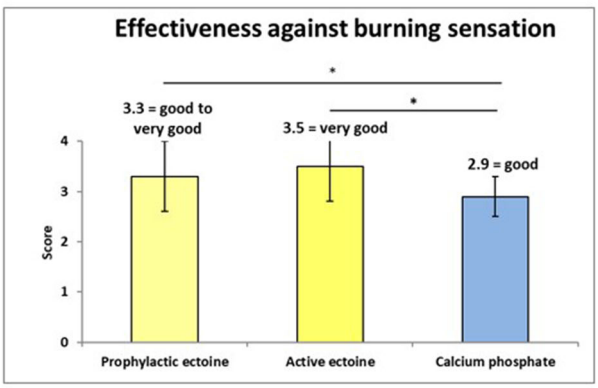
DISCUSSION

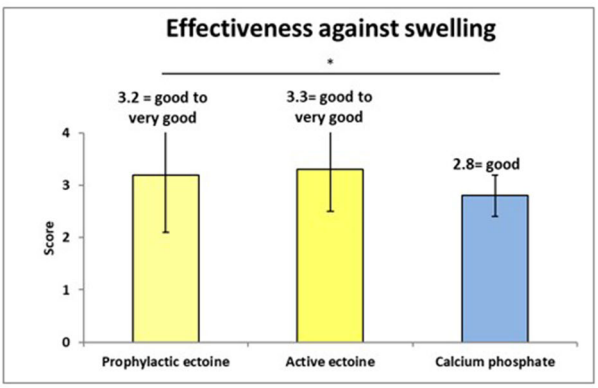
Patients applying ectoine prophylactically show few mild or moderate symptoms throughout the study. As a result of the lack of placebo, it is not possible to extrapolate the actual percentage of patients who would not develop mucositis at all, even without being treated prophylactically. In the literature, the incidence of mucositis following chemotherapy with sunitinib ranges from 12% to 29% [25–27]. In general, 20–40% of patients receiving conventional chemotherapy develop mucositis [4]. Considering that the majority of patients did not necessarily need to be treated, prophylactic treatment with ectoine may nevertheless be beneficial for patients in whom symptoms of dry mucosa, coated tongue, unpleasant breath, and decreased saliva production occur. However, one should not disregard the study design and patients' medical history when making cross-study comparisons. Therefore, we cannot draw robust conclusions about the prophylactic effects of ectoine on the basis of the results of this study.

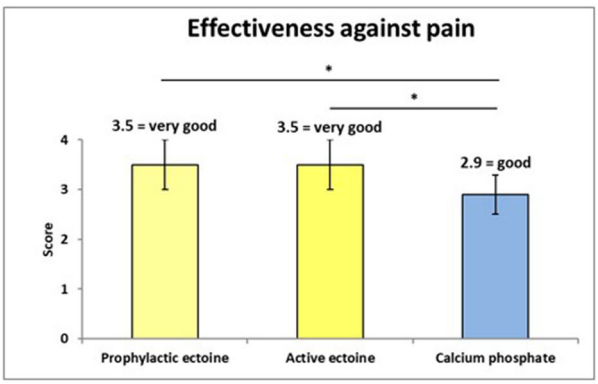
Ectoine mouthwash seemed to be better than calcium phosphate mouthwash for the active treatment of oral mucositis. The reductions in symptom scores were comparable; however, patients rated the effectiveness and tolerability of ectoine more favorably. We found conflicting evidence for the effectiveness and tolerability of calcium phosphate mouthwash in the literature. In a systemic review of 30 studies in patients undergoing chemotherapy and/or radiotherapy, 24 studies reported that calcium phosphate mouthwash reduced symptoms and analgesics needed as well as the incidence and mean days of the disease [28]. However, in many studies the results were not statistically significant. Recent data suggests that calcium phosphate mouthwash is not more beneficial

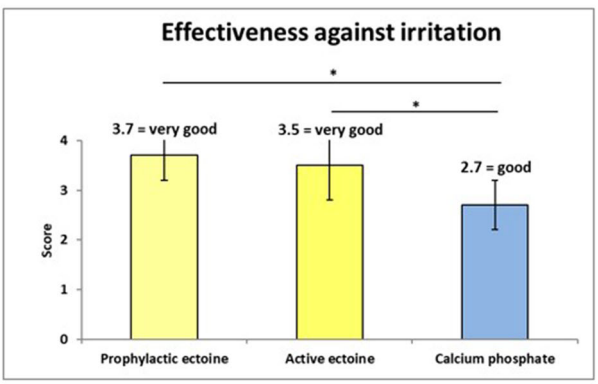

Overall effectiveness
3.6 = very good
3.5 = very good
2.9 = good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate

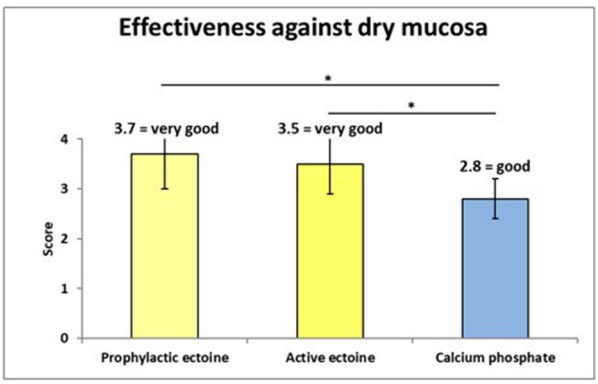

Effectiveness against redness
3.3 = good
3.6 = very good
2.8 = good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate

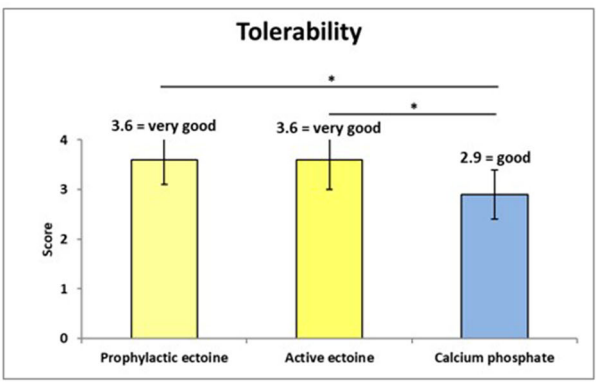

Effectiveness against burning sensation
3.3 = good to very good
3.5 = very good
2.9 = good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate


Effectiveness against swelling
3.2 = good to very good
3.3= good to very good
2.8= good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate


Effectiveness against pain
3.5 = very good
3.5 = very good
2.9 = good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate


Effectiveness against irritation
3.7 = very good
3.5 = very good
2.7 = good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate


Effectiveness against dry mucosa
3.7 = very good
3.5 = very good
2.8 = good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate


Tolerability
3.6 = very good
3.6 = very good
2.9 = good
Score
Prophylactic ectoine
Active ectoine
Calcium phosphate

◀**Fig. 2** Effectiveness and tolerability of investigational products assessed by the patients at V4 (0 = very poor, 1 = poor, 2 = neither poor nor good, 3 = good, and 4 = very good). Data plotted are mean ± SD. Differences between groups were analyzed using the two-sided Fisher's exact test. *Indicates $P < 0.05$

than saline/aspirin mouthwash, cryotherapy, or even placebo [29–31]. Another study showed that calcium phosphate mouthwash did not reduce the incidence of WHO mucositis grade II below historic rates [32]. Taken together, while the evidence-based efficacy of calcium phosphate mouthwash is still disputable, ectoine mouthwash can be a viable treatment option for oral mucositis.

Recently, two studies have shown that ectoine reduced DNA damage caused by ionizing radiation. The authors described ectoine as a hydroxyl radical scavenger and suggested its use as a protective agent in radiotherapy [33, 34]. Hence, one might extrapolate that ectoine mouthwash can be beneficial not only for chemotherapy-related but also for radiotherapy- and radiochemotherapy-related oral mucositis.

This study was conducted as a non-interventional study under routine clinical practice. Though placebo control and randomization were not permitted in this study design according to §17 para (1), point c) of Government Regulation 235/2009 (X.20.) effective in Hungary, this study compared ectoine mouthwash to an active control—calcium phosphate mouthwash. This study design allows for comparison of the effectiveness between these two treatments under real-life conditions. The relatively low number of patients was a limitation in our study. However, the similar baseline characteristics allowed us to compare the effectiveness of the treatment between groups.

Given that ectoine is a natural substance that has remarkably few side effects, we recommend ectoine mouthwash for the active treatment of oral mucositis. Follow-up, placebo-controlled studies are needed to confirm its prophylactic effects.

CONCLUSIONS

Mucositis following chemotherapy can be safely and effectively treated with ectoine-containing mouthwash. Significant reductions of symptoms were detected on day 14. After 21 days of treatment, symptoms were almost completely resolved. Physicians' assessments deduce that ectoine is as effective as calcium phosphate. According to patients' assessments, ectoine is more effective and tolerable than calcium phosphate. Further studies are needed to confirm the effects of ectoine for the prophylaxis of mucositis.

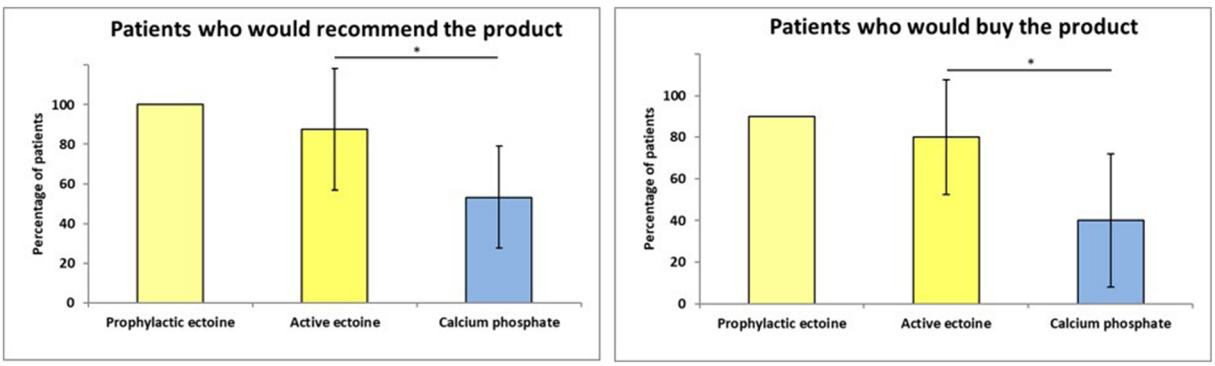


Fig. 3 Patients' likelihood of buying or recommending the product after the study, which confirms their satisfaction with the treatment results. Significant differences between treatment groups were determined using the two-sided Fisher's exact test. *Indicates $P < 0.05$

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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