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ORIGINAL ARTICLE

The plaque and gingivitis inhibiting capacity of a commercially available mouthwash containing essential oils and ethyl lauroyl arginate. A randomized clinical trial

Liv O. Valør[a], Inghild K. R. Norton[a], Odd C. Koldsland[a], Anne Merete Aass[a], Andrej M. Grjibovski[b] and Hans R. Preus[a]

[a]Department of Periodontology, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Oslo, Norway; [b]Northern State Medical University, Arkhangelsk, Russian Federation

ABSTRACT

Objective: A commercially available mouth rinse with ethyl lauroyl arginate and essential oils claims to have better antimicrobial properties than the traditional essential oil products. The aim of this study was to compare the plaque and gingivitis inhibiting effect of the commercial product containing essential oils with ethyl lauroyl arginate with one placebo and one negative control in a modified experimental gingivitis model.

Materials and methods: In three groups of healthy volunteers, experimental gingivitis was induced and monitored over 21 d, simultaneously treated with the commercial test solution, 21.6% hydro-alcohol solution and sterile water, respectively. The maxillary right quadrant of each individual received mouthwash only, whereas the maxillary left quadrant was subject to both rinsing and mechanical oral hygiene. Compliance and side effects were monitored at d 7, 14, and 21. Plaque and gingivitis scores were obtained at baseline and d 21.

Results and conclusion: Although the commercial product containing essential oils with ethyl lauroyl arginate performed statistically significantly better regarding average plaque scores on all surfaces combined than the placebo ($p = .018$) and negative control ($p = .003$) when no mechanical tooth cleaning was performed, the product still left the patient with enough plaque to cause gingivitis and thus seemed of questionable clinical benefit to the patient. ClinicalTrials.gov Identifier is NCT02884817.

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Dental plaque; oral hygiene; preventive dentistry

Introduction

Mouthrinses containing essential oils in 21–26% alcohol (EO) have claimed to be potent inhibitors of plaque formation [1,2]. However, a recent study suggests otherwise [3].

Recently, a new product in this series of mouthrinses was introduced in which an additional antimicrobial agent, Ethyl Lauroyl Arginate (ELA) [4–6] had been added to the essential oil product (EOELA). ELA acts as a cationic surfactant by modifying the permeability of microorganisms' membranes [7], and is used in cosmetic and toiletry products for antimicrobial purposes [8,9]. The Scientific Committee on Consumer Safety consider ELA as safe in oral products in concentrations $<0.15\%$ [10]. The manufacturer of EOELA claims that ELA inhibits the formation of dental biofilms by preventing the bacteria from adhering to the pellicle [11]. The manufacturer announces that this represents 'an entirely new' way to combat 'gum disease' as they claim that it reduces plaque colonization of dental surfaces with up to 42.6% and bleeding with up to 50.9% after 4 weeks of use [11,12].

To our knowledge, only one study has been published on the oral antimicrobial effect of ELA, concluding that a '0.15% LAE (=ELA) containing mouthrinse was well tolerated and significantly reduced plaque, gingivitis and bleeding when used as an adjunct to tooth brushing for 4 weeks' [5].

The aim of the present study was to test the plaque- and gingivitis-inhibiting capacity of commercially available EOELA, with or without mechanical oral hygiene, using a modified experimental gingivitis model with 21.6% hydro-alcohol and sterile water as controls.

Materials and methods

The design of the study was a double masked, parallel group, placebo-controlled, randomized clinical trial (RCT). To induce gingival inflammation, the experimental gingivitis model [13], with modifications by Preus et al. [14] was used. The Norwegian Regional Committee for Medical Research Ethics approved the study (REK 2015/417). http://www.clinicaltrials.gov identifier is NCT02884817.

Seventy-four dental-, medical-, and hygienist students volunteered to participate (Figure 1), and were given a lecture about oral rinsing products in general and EO/EOELA products as well as information on the planned study, in particular. Fifteen individuals withdrew because they had to abstain

CONTACT Hans R. Preus hpreus@odont.uio.no Department of Periodontology, IKO, Faculty of Dentistry, University of Oslo, POB 1109, Blindern, NO-0317 Oslo, Norway

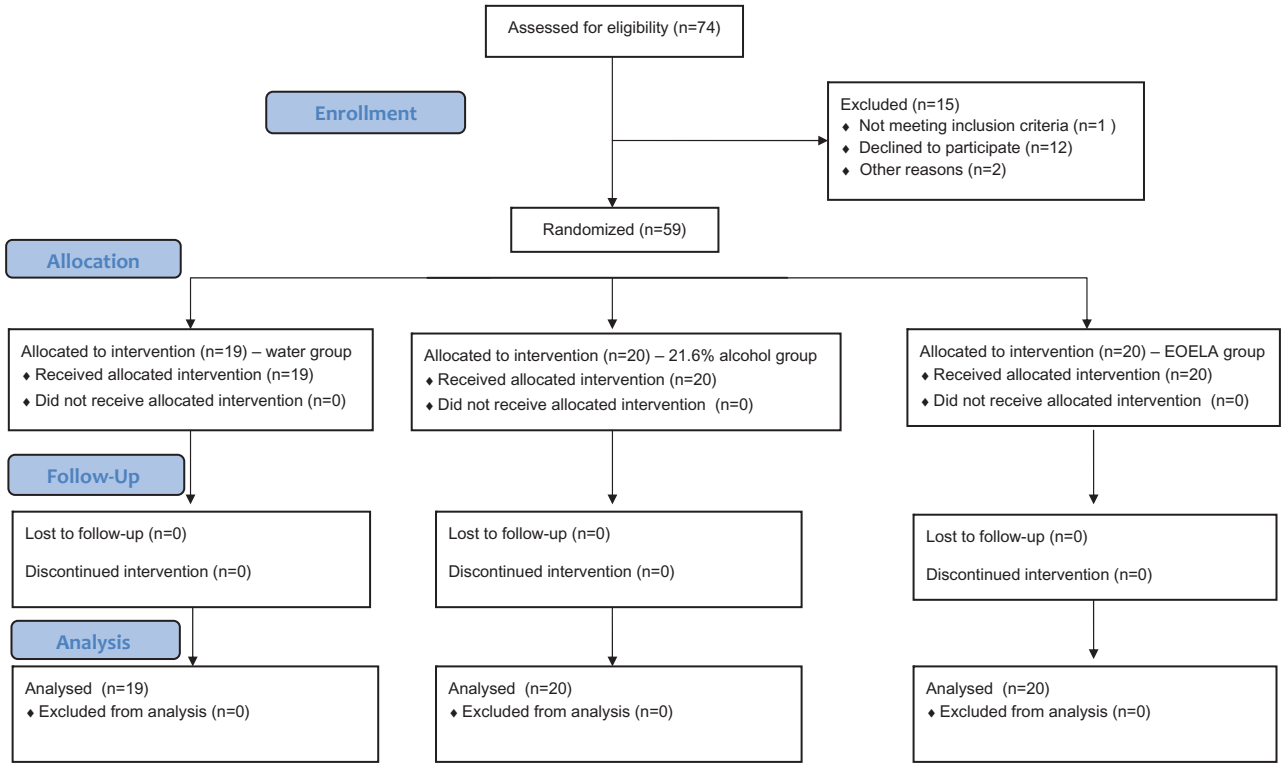

Figure 1. Patient flow diagram.

from brushing their teeth in the first quadrant for three weeks, resulting in fifty-nine participants signing the informed consent form. Mean age was 25 years (sd. 3.2) and 78% was female. Study venue was the Department of Periodontology, Faculty of Dentistry, University of Oslo, Oslo, Norway during November 2015.

Inclusion criteria comprised healthy subjects of both genders having at least three of the following teeth in maxillary right (Q1) and left quadrant (Q2): the canine, 1st bicuspid, 2nd bicuspid, 1st molar, as well as healthy gingiva and periodontium. Exclusion criteria: smoking or use of non-smoking tobacco, pregnancy, lactation, any chronic diseases, clinical signs or symptoms of acute infection in the oral cavity, any prescribed or non-prescription systemic or topical medication except oral contraceptives, use of systemic antibiotics the last 3 months prior to the start of the study, history of alcohol or drug abuse or participation in other clinical studies in the last 4 weeks.

The test solution was the commercially available mouthwash product EOELA[1]. The placebo control was a 21.6% hydro-alcohol solution, and the negative control was plain sterilized water. Both control solutions contained 0.2% NaF in order to prevent the development of early carious lesions during the course of the study. Due to possible interference with the chemistry of the product, the test solution was used without any additives. The test solution (EOELA) was purchased at a local pharmacy, whereas placebo and negative control solutions were produced at the clinical laboratory at the Faculty of Dentistry, Oslo, Norway. The three solutions were filled on to identical bottles labeled 1, 2 or 3.

Simple, restricted randomization was carried out using a computer generated random allocation table [15] assigning the participants to three study groups with 20 test subjects in each of the placebo-, alcohol-, and test (EOLA) groups and 19 in the negative control (water) group. They were all instructed to rinse for 30 s twice a day with 10 ml of their designated mouthrinse as recommended by the manufacturer for the test solution. The statistician performed the randomization whereas the project leader distributed the rinsing solutions and instructions after a list generated as described [15].

At baseline, all participants received professional tooth cleaning with rubber cup, pumice paste and dental floss. Subsequently they were instructed to rinse, individually supervised by the project leader, as described above with the allocated solution. This action was imperative since ELA claims to prevent biofilm formation [9], and should therefore be applied subsequent to its removal. Individual plastic tooth guards had been produced to fit the teeth in the upper right quadrant (Q1) [3,14] (Figure 2) of each participant prior to the study. In addition, they all received identical prophylaxis packs containing a medium texture toothbrush, interdental floss and dentifrice. They were instructed to substitute their daily oral hygiene remedies with the ones given to them, and attach the tooth guard to the toothbrush with a provided rubber string, initially and after use, so that the tooth guard always was remembered when using the brush.

The participants were instructed to insert the tooth guard in Q1 every time they brushed their teeth and to perform mechanical oral hygiene twice a day in the three other quadrants. After brushing properly, the participants rinsed for 30 s with water before and after removing the tooth guard. Subsequently, the participants rinsed with the solution they

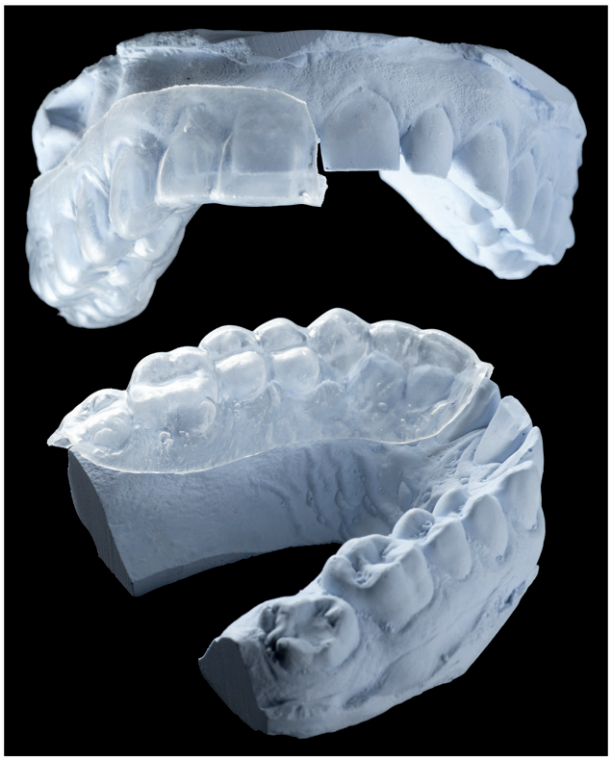

Figure 2. Individual plastic toothguard.

randomly had been assigned, repeating this routine for 21 days. Accordingly, in this experiment the upper right quadrant (Q1) was subject to rinsing solution only (i.e. Group 1: Test solution – EOELA; Group 2: placebo – 21.6% hydro-alcohol solution; and Group 3: negative control – plain sterilized water) whereas the upper left quadrant (Q2) in these respective groups was subject to the same solutions in addition to mechanical oral hygiene as described.

At days 7, 14 and 21, individual participants were interviewed about adverse effects and protocol adherence. Following this interview at day 21, the plaque – (PI) [16] and gingival index (GI) [17] were recorded on the mesial, buccal, distal and palatal aspects of experimental teeth. Adverse events, like discoloration observed during the clinical examination and clinically visible oral mucosal reactions were recorded, and finally the Quigley and Hine plaque index, [18] the Turesky modification [19] was obtained. All clinical recordings were obtained by the same experienced periodontist. Following these scoring procedures, the participants were dismissed after receiving professional tooth cleaning.

Before the examination at day 0 and 21, the project managers advised the participants to refrain from any conversation with the scoring scientists inside the scoring room. The recorders had been instructed likewise. The clinical crew was kept blind to the group allocation at all times, and the only person having access to the codebook was the statistician, who did not participate in the clinical procedures.

Statistical analyses

Mean values of all outcome variables between the three studied groups 21 days after initiation of the study were first compared using one-way analysis of variance (ANOVA). Shapiro–Wilk tests did not detect deviation of the distribution of the outcome variables from normality. Homogeneity of variances was tested using Levene test. Other assumptions for ANOVA were also met. When null hypothesis was rejected using ANOVA, Dunnett's *post hoc* tests was applied with group 3 as the reference.

In a one-way ANOVA study, sample sizes of 16, 16 and 16 are obtained from the 3 groups whose means are to be compared. The total sample of 48 subjects achieves 81% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means is represented by their standard deviation that was assumed to be 0.14. The common standard deviation within a group is assumed to be 0.30.

All analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc, Chicago, IL). Sample size calculation was performed using PASS-2000 software[2].

Results

Q1: Rinsing only quadrant

Rinsing with EOELA resulted in an average Silness & Løe [16] plaque score after 21 days statistically significantly lower than the results in the two control groups (Table 1) with no significant difference between the latter. Despite the differences, the average plaque scores [16] in all 3 groups remained high, and above 1.3.

The gingival index scores of Löe & Silness [17] were not significantly different among the three groups after 21 days, neither as an average of all sites or single sites separately (Table 2).

Comparing the plaque scores of the Turesky modified plaque index [19], the EOELA group did not perform better than the other groups after 21 days neither as an average of all sites or single sites separately (Table 2).

Q2: Rinsing and mechanical oral hygiene quadrant

In Q2, where tooth brushing, flossing and rinsing were performed simultaneously, the plaque scores were close to zero in all three groups [16,19] and gingival scores [17] were close to normal. No statistically significant differences were recorded among any of these scorings (Table 2).

Adverse effects

'Burning sensation' and 'soreness' of the oral mucosa and tip of the tongue were the most frequent complaints, reported by 6, 9 and 1 participants in the EOELA–, alcohol– and water group respectively. The prevalence of participants with more than one adverse effect was significantly higher in the EOELA and alcohol groups than in the water group (65% vs. 22%, $p = .008$). None complained about discoloration.

The clinical research staff registered no objective clinical adverse effects (Table 3).

Table 1. Quadrant 1: Rinsing only quadrant. Mean Silness & Løe plaque Index with 95% confidence intervals (M, 95%CI) among the participants in the 3 experimental groups after 3 weeks.

	Distal, M (95% CI)	Buccal, M (95% CI)	Mesial, M (95% CI)	Palatal, M (95% CI)	All, M (95% CI)
EOELA[a]	1.6 (1.4–1.8)	1.2 (1.0–1.3)	1.6 (1.4–1.8)	0.8 (0.6–1.0)	1.3 (1.1–1.4)
Alcohol	1.9 (1.7–2.0) ($p = .064$)	1.5 (1.3–1.7) ($p = .040$)	1.9 (1.8–2.1) ($p = .015$)	1.2 (1.0–1.4) ($p = .018$)	1.6 (1.5–1.8) ($p = .003$)
Water	1.9 (1.7–2.2) ($p = .018$)	1.6 (1.3–1.8) ($p = .018$)	2.0 (1.8–2.3) ($p = .002$)	1.3 (1.1–1.5) ($p = .003$)	1.7 (1.5–1.9) ($p < .001$)

[a]Reference group for Dunnett's test.

Table 2. Mean values (M) with 95% confidence intervals (CI) for Løe & Silness' Gingival index and Turesky's modified plaque score respectively for 'rinsing only' quadrant (Q1) and 'brushing and rinsing' quadrant (Q2).

	Løe & Silness' Gingival index		Turesky's modified plaque index	
	Q1	Q2	Q1	Q2
EOELA[a]	1.6 (1.5–1.7)	1.3 (1.2–1.4)	1.2 (1.1–1.3)	0.3 (0.2–0.4)
Alcohol	1.5 (1.4–1.6)	1.2 (1.1–1.3)	1.4 (1.2–1.5)	0.5 (0.4–0.6)
Water	1.6 (1.5–1.7)	1.3 (1.2–1.4)	1.3 (1.1–1.5)	0.5 (0.4–0.6)

[a]Reference group for Dunnett's test.

Table 3. Quadrant 2 – Brushing & rinsing: Mean values (M) with 95% confidence intervals (CI) for Silness and Løe Plaque Index among the participants in the 3 experimental groups after 3 weeks.

	Distal M (95% CI)	Buccal M (95% CI)	Mesial M (95% CI)	Palatal M (95% CI)	All M (95% CI)
EOELA[a]	0.9 (0.8–1.1)	0.1 (0.0–0.2)	0.4 (0.2–0.6)	0.2 (0.0–0.3)	0.4 (0.3–0.5)
Alcohol	1.0 (0.9–1.1)	0.1 (0.0–0.2)	0.5 (0.3–0.7)	0.3 (0.1-0.4)	0.5 (0.4–0.6)
Water	1.1 (0.9–1.2)	0.1 (0.0–0.3)	0.5 (0.3–0.8)	0.3 (0.1–0.5)	0.5 (0.4–0.6)

[a]Reference group for Dunnett's test.
No significant differences.

Discussion

The present study showed that the commercial EOELA product left the patients' dental surfaces with enough plaque to cause gingivitis after 21 days when no mechanical oral hygiene was performed. Gingivitis is the result of prolonged tissue-exposure to supragingival plaque [13,20] and a remaining long standing Silness & Løe plaque score [16] of 1 or more has been shown to induce gingivitis in the long run [13,20,21]. No additional effect from the EOELA product was observed in the quadrant (Q2) where also mechanical tooth cleaning was performed.

The present study was a straightforward double masked, parallel group, randomized, placebo-controlled clinical trial. The differentiation between Q1 and Q2, with the help of the mouth guard, was set up separately to test each of the manufacturers claims that the EOELA products 1) 'removes plaque between teeth, getting to the places that a toothbrush can't always reach' (Q1) [22,23] and 2) 'helps the tooth brush removing plaque' (Q2) [23,24].

With regards to masking, the data collection team was blind to the group allocation. The project leader was not involved in clinical data collection procedures. The complaints of discomfort and side effects were not of a nature that could reveal group allocation. In the interview preceding screening, all students had been explicitly instructed not to talk among themselves about their possible group allocation. The study should therefore be regarded as double masked.

The population in the present study consisted of dental hygienist–, dental–, and medical students who had a clear understanding of how to clean their teeth. One may therefore argue that they could uphold a better oral hygiene than a nonprofessional could. However, the use of the Q1 tooth guard eliminated this possible distinction from the general population. They were all non-smokers, thus staining or masked gingival inflammation due to smoking could not influence the results.

It has been suggested that high alcohol content, rather than the active ingredients might account for parts of the antibacterial effect shown in mouthrinsing studies [25]. Since the test product in the present study contained 21.6% alcohol, a true placebo solution (21.6% hydro-alcohol) and a negative control (water) were selected as the comparators. Studies on EO products have notoriously used water, saline, 5% or 10% hydro-alcohol controls, or only reported 'vehicle control' or 'placebo' without detailing the information [3,26]. This design flaw has followed RCTs into systematic reviews [26–28] and suggestively added to the positive EO reviews. Van Leeuwen et al. [26] compared EO products with their true vehicle controls in a systematic review of 5 RCTs. Obviously, none of these studies [25–28] had included EOELA, and direct comparison cannot be done. Only 3 of the RCTs in Van Leeuwen et al. [26] were found in MEDLINE (Ovid) or PubMed [3,30,31] whereas 2 were personal communication from the manufacturers of EO/EOELA products [32,33], all of which reported a statistically significant better effect of the EO product. However, in all of these studies the remaining plaque scores in the test groups (EO) was high enough to cause gingivitis [13,20,21], which might explain the lack of differences in gingival inflammation [26–29].

The period for a mouthrinsing study should be debated. The present study was conducted in 3 weeks. It is easier to trust a participant adhering to protocol for 3 weeks as compared to a study that goes on for 6 or 9 months [30–34].

Also, there is no scientific evidence that a plaque-inhibiting mouthrinse will perform clinically better after several months than after 3 weeks. On the contrary, the plaque scores of the present study, as well as those from a previous study of identical design [3] are comparable to the ones reported from studies that had been going on for a considerably longer time [30–34]. The experimental gingivitis model [13] has shown repeatedly that the plaque accumulation increases against a limit after three weeks, and therefore this model should suffice in detecting differences in plaque scores among the test and control groups.

The present study applied both Silness & Löe [16] and the Turesky's modified [19] plaque indices simultaneously. A majority of plaque registration studies has applied the Turesky modification [19] only, and a comparison of indices is warranted. When studying the effect on gingivitis and periodontal diseases it should suffice to score the plaque deposits along the gingival margin, and the coronal spread on the tooth surface [18,19] does not seem relevant. This may also be a reason that no statistically significant difference regarding the presence of gingival inflammation was observed [26–34], A possible explanation for these results may be that this plaque index [19] also register some of the protein coating that retains the plaque disclosing solution, making it difficult to distinguish and set a correct score due to different brushing techniques, as well as differences in mechanical wear by the cheeks, tongue and lips. The Silness & Løe Plaque Index [16] detects the plaque accumulation along the gingival margin only.

The pellicle and biofilm starts to form within minutes after tooth brushing. Therefore, in order to perform the preventive effect on biofilm formation, the manufacturer recommends EOELA rinsing directly following tooth brushing. In the present experiment, the first rinsing was performed directly following professional cleaning at baseline (only pumice paste and mechanical plaque and calculus removal), and care was taken to rinse properly with water after tooth brushing at home and before using the experimental mouthrinse. However, as ELA is a cation, and most dentifrices contain sodium lauryl sulphate (SLS), which is an anion, the effect of such a procedure may hypothetically reduce or negate the suggested effect of ELA. To the best of our knowledge, this possible chemical interaction has not been discussed previously.

The introduction of ELA into the mouthrinse and claiming prevention of dental biofilm formation warrants a discussion. Gallob et al. [5] reported 'a 0.15% LAE (ELA) containing mouthrinse was well tolerated and significantly reduced plaque, gingivitis and bleeding when used as an adjunct to tooth brushing for 4 weeks'. However, observing the numbers from this publication, one can observe that the remaining plaque scores were high enough to produce gingivitis [13,20,21] in the long run. The article [5] does not reveal if the tested mouthrinse was a commercially available–, a laboratory produced mouthrinse or the solvent for LAE (ELA), leaving readers uncertain about the nature of the tested mouthrinse and if the 5% hydroalcohol control was an inappropriate–, negative–, positive– or placebo comparator.

The findings of the present study, that EOELA performed significantly better than controls, are in concert with most clinical studies as well as reviews on any type of EO product [2,5,26–34]. However, focusing on the end plaque scores after 21 days, they remained high enough to cause gingivitis in the long run [13,20,21]. This has not been the focus in any of the above mentioned studies [2,5,26–34].

In Q2, the plaque index remained close to zero in all groups, indicating that mechanical cleaning of teeth is sufficient to keep plaque and gingivitis scores at a minimum, which is in agreement with other studies [3,35,36].

Among the self-reported side effects, soreness of the gingiva and mucous membranes (burning sensation) were most commonly communicated, being significantly more often reported by those in the EOELA and alcohol group. Both EOELA and the alcohol rinse contained high enough alcohol concentrations (21.6%) to cause such side effects [37,38], although malignancy has not been reported [39].

Conclusion

The commercial product containing EO with ELA left the patients' dental surfaces with enough plaque to cause gingivitis after 21 days of use.

Notes

1. Listerine Professional Gum Therapy®, Johnson & Johnson, USA
2. Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

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Ranheid Johansen produced the mouth guards and Grazyna Jonski prepared the control solutions.

Disclosure statement

The authors have stated explicitly that there are no conflicts of interest in connection with this study/article.

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