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Efficacy on supragingival plaque control of cetylpyridinium chloride in a slow-release dosage form

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Abstract. To evaluate the relative efficacy of a non-degradable osmotic slow-release dosage form containing 6.6 mg cetylpyridinium chloride (MOTS [Mucosal Oral Therapeutic System] CPC) to inhibit new plaque formation and gingivitis, a single-blind, randomised, parallel group pilot study was set up. 52 healthy volunteers were assigned to receive one of the following treatments for 18 days of non-brushing: holding 1 MOTS CPC 2× daily for 2 h intra-orally, or rinsing 30 s with 15 ml Peridex® 2× daily, or dissolve Cepacol® (each 1.6 mg CPC) lozenges 2× daily unsupervised. Before the test period, the subejcts received a thorough tooth cleaning followed by tooth polishing 1× a week for 3 weeks to achieve clinical gingival health. After the start of therapy, the subjects were examined at day 4, 7 (±2), 14 (±2) and 18 (2±). Relative efficacy was assessed by the modified Navy plaque index, the Quigley and Hein index, the planimetric plaque index, as well as the papillary marginal gingival index. There was an increase in both plaque formation and gingivitis over the 18±2 day period of non-brushing for all subjects in the study. Peridex® was the most effective in inhibiting plaque and gingivitis formation over that period of time. There was no difference between MOTS CPC and Cepacol® at any time point in plaque accumulation and gingivitis intensity. Peridex® was considered more convenient than MOTS CPC. Cepacol® resulted in more staining at 18 days than MOTS CPC and Peridex®.

Key words: cetylpyridinium chloride; chlorhexidine rinse; controlled release system; plaque index; gingival index

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The most common oral diseases, gingivitis and periodontitis, are caused by bacterial plaque accumulation (Lindhe et al. 1973, Löe et al. 1965).

The classical treatment of periodontitis consists of plaque removal by mechanical debridement of the periodontal pockets as such, or in combination with, antimicrobial therapy. Effective preventive care can be obtained by oral hygiene measures (Axelsson & Lindhe 1974). Besides mechanical plaque removal methods, the use of toothpastes and rinses incorporating therapeutic agents has been shown very useful (Axelsson & Lindhe 1987, Ciancio 1988).

The therapeutic effect of a mouthrinse is dependent on numerous factors: the effect of its active ingredients in vivo, the permeability and solubility of the agents, and the substantivity (Goodson 1989).

Penetration of mouthrinses into gingival pockets does not occur. Furthermore, in order to give a long-lasting rinse effect, the minimal inhibitory concentration (MIC) of any antimicrobial mouthrinse should be maintained in the oral cavity as long as possible (Goodson 1989). Adsorption of active components to and subsequent slow release from oral tissues, must ensure such an effect. It is thus not surprising that clinically, the most effective antimicrobial rinse is chlorhexidine (Hull 1980, Addy 1986). Indeed some 30% of the total amount of chlorhexidine adheres to oral tissues after rinsing for 1 minute (Bonesvoll 1977).

Cetylpyridinium chloride (CPC) is a quaternary ammonium compound that also easily binds to mucosal surfaces in the oral cavity. The potential of CPC as an anti-plaque agent is limited by the rapidity by which it is desorbed from the oral tissue sites (Bonesvoll & Gjermo 1978). In other words, CPC does not have the required substantivity to be as effective as chlorhexidine. Quaternary ammonium compounds are sur-

face active agents. According to some studies it results in a significant reduction of plaque accumulation, such as 30% after 10 days (Holbeche et al. 1975, Llewelyn 1980), and even up to 35%–50% in other studies (Ciancio 1986, Bral & Brownstein 1988). Reductions in gingivitis of 24% and 30–58% were also reported (Lobene et al. 1977, De la Rosa & Sturzenberger 1976).

The in vitro antimicrobial activity of cetylpyridinium chloride is better than that of chlorhexidine (Gjermo et al. 1970, Roberts & Addy 1981), whereas its in vivo tested plaque inhibiting effect is much lower (Holbeche et al. 1975, Llewelyn 1980).

The present study investigated whether CPC might be clinically more effective when compensating the lack of substantivity by the use of an intra-oral slow-release dosage form. Since the everyday use of chlorhexidine is restricted, primarily due to taste disturbance and more importantly staining (Flotra et al. 1971), such an alternative treatment would be useful. Other side-effects are desquamation of epithelial cells and soreness of the oral mucosa. Therefore the relative tolerability of the CPC system in staining potential and mucosal tolerability compared with chlorhexidine was also evaluated.

Material and Methods

The study was designed as a single blind, randomised, parallel pilot study. To evaluate the relative tolerability and efficacy of a mucosal oral therapeutic system (MOTS) delivering 6.6 mg of CPC to inhibit new plaque formation and gingivitis, we compared the MOTS to a positive and a negative control. The active product was the MOTS cetylpyridinium chloride (CPC) 6.6 mg (Alza Corporation, Palo Alto, USA), the positive control was Peridex® (Procter & Gamble, Cincinnati, Ohio) containing 0.12% chlorhexidine digluconate, while the control was a Cepacol® lozenge (Merrell Dow Consumer Products Division, Cincinnati, Ohio), containing 1.6 mg CPC.

The MOTS is an osmotic dosage form utilising osmotic energy as a means of delivering precise amounts of a drug over long durations. It comprises a rigid, semipermeable membrane and osmotically active drug core. 2 holes, one on each side, allow this oval tablet to deliver a substantial fraction of it contents at a zero-order rate. In addition, drug delivery rates are substantially independent of agitation and fluctuations in pH or pressure, allowing the system to deliver in vivo as designed. MOTS CPC is designed to provide sustained local delivery of CPC (6.6 mg) to the oral cavity. The tablet draws water across the membrane, causing the drug (6.6 mg) in the core to dissolve. Movement of water through the semipermeable membrane causes the drug to be pushed out through the two delivery orifices. The delivery rate is 3.7 mg CPC over 2 h. Because of its shape and design, a residual of about 10% of the CPC remains inside the MOTS at the end of its effective life. After the dose has been delivered, the membrane shell remains, which the user removes from the mouth and discards. MOTS is targeted to the oral cavity in size and shape for comfort. It has an egg-shaped morphology with dimensions of 13 by 7 mm. MOTS contains a flavouring agent, mint+sodium saccharin, to mask the taste of the CPC and improve the acceptability of the system.

A total of 52 (27 females) healthy volunteers between 17–30 years old enrolled in this study (Table 1). All except one were Caucasian and the majority were non-smokers (71%). None of them had used any antibiotics, corticosteroid or immunosuppressive drugs within the previous month. Nor did they use any antimicrobial product within 2 weeks before or during the study. All these volunteers had 20 or more teeth, including at least five of the following 6 teeth: 15, 21, 24, 35, 41, 44. The probing depth of the pockets around these teeth did not exceed 5 mm.

Prior to the study, each subject received a thorough professional tooth cleaning and polishing of all teeth once a week for 3 weeks. Clinical plaque removal was carefully checked by use of 0.5% erythrosin dye. The plaque level index was required to be zero before the actual trial. At the beginning of the experiment the participants were given a diary, wherein they had to record dates and time of use of the product, plus the acceptability. At the end of the trial, all subjects received a professional prophylaxis again.

The subjects were randomly divided into 3 groups. The 1st group was assigned to keep 1 MOTS CPC in the mouth for 2 h 2× daily, moving it around between cheek and dental arches. The 2nd group had to use the Peridex® mouthwash for 30 s 2× daily and the 3rd group let 2 Cepacol® lozenges simultaneously dissolve on the tongue dorsum. This was repeated within the day, unsupervised. During the test period, all subjects were forbidden to use any oral hygiene method.

Clinical measurements were taken at baseline, and at 4, 7 (±2), 14 (±2), and 18 (±2) days. All measurements were made by one person, an evaluator who was unaware of the treatment assigned to each subject.

It has been demonstrated in a pilot study on 15 patients that there is no statistical difference in gingivitis index and plaque index of the entire dentition and the Ramfjord elements. Thus it was decided to limit our measurements to the Ramfjord elements (16, 21, 24, 36, 41, 44). However, teeth numbers 16 and 36 were replaced by 15 and 35, due to technical difficulties in photographing

Table 1 (a). Baseline characteristics of subjects completing study (n=48)

Measure	MOTS CPC	Peridex®	Cepacol®
	mean (SD)	mean (SD)	mean (SD)
age (years)	20.0 (1.4)	19.4 (1.6)	20.9 (3.2)
height (cm)	176.7 (11.2)	173.3 (9.5)	173.3 (9.0)
weight (kg)	66.3 (14.8)	62.9 (9.6)	66.1 (10.7)
body mass index (kg/m^2)	20.5 (2.4)	20.4 (1.9)	21.4 (2.7)
cigarettes per day	16.2 (9.1)	11.8 (9.6)	6.2 (2.6)

Table 1 (b).

	n (%)	(%)	n (%)
sex			
male	8 (50)	5 (31)	8 (50)
female	8 (50)	11 (69)	8 (50)
ethnic origin			
asian	1 (6)	0 (0)	0 (0)
caucasian	15 (94)	16 (100)	16 (100)
smokers	6 (38)	4 (25)	4 (25)

the buccal sides of the first molars in a standardised way (perpendicularly), which is essential in determining a reproducible planimetric plaque index (Quirynen et al. 1985).

Relative efficacy was assessed by 3 plaque indexes: the modified Navy plaque index (Hancock & Wirthlin 1977), the planimetric plaque index (Quirynen et al. 1985), and the Quigley & Hein (1962) plaque index.

For the planimetric plaque index, color slides at magnification ×2 were made of the buccal side of the 6 investigational teeth in a standardised fashion. This was done at each visit, including the baseline visit. After enlargement of these slides (to×25), the outline of the photographed tooth and the area covered with plaque were drawn on a paper. All slides were traced by the same examiner. These 2 areas were then digitised using an electronic pen. This method consisted of a computerised program with the aid of the geo-Lat I (Geo Instruments, Paperclips BVBA, Kalmthout, Belgium). The amount of plaque was calculated and expressed as a % of the total buccal tooth surface. The intra-examiner reproducibility of the measurements, which were all performed by a single investigator, was extremely high with maximum deviations of 2%.

The modified Navy plaque index (Hancock & Wirthlin 1977) was recorded at each visit, while the Quigley & Hein plaque index (Quigley & Hein 1962) was measured only on day 7 (±2) and 14 (±2).

The gingivitis was expressed by the papillary marginal gingival index (PMGI) (De la Rosa & Sturzenberger 1976), measured at each visit.

Relative tolerability was assessed by extrinsic tooth staining (Lobene index 1968) and mucosal alteration. In addition to the Lobene index taken at all visits, slides of the 12 anterior teeth without erythrosin were taken at baseline and at day 18 (±2) to document tooth staining.

Subjects rated overall acceptability by scoring taste and convenience on a digital scale of 1 (unacceptable) to 10 (good).

Phase-contrast microscopy of vital supragingival plaque diluted in a physiological water solution was performed on day 4 and day 18 (±2) to assess microbial changes over time and between treatments. Plaque samples were taken from other teeth than 15, 21, 24, 35, 41, 44, in order not to disturb the plaque growth on the monitored teeth.

Statistical analysis

An analysis of variance model was used to compare the effects of each regimen on each of the outcome measures. This analysis was performed at each of the 4 time points at which measurements were taken.

Results

48 subjects of the 52, which were enrolled, completed the study. 4 patients dropped out prior to receiving study medications: one (Cepacol®) dropped out due to an unrelated illness, and three (one in each group) were lost to follow-up.

Efficacy results

Peridex® rinses resulted in a lower plaque index than Cepacol® lozenges and MOTS CPC at all timepoints for the 3 different plaque indexes ($p<0.05$ for the modified Navy, $p<0.03$ for the planimetric method and $p<0.01$ for the Quigley & Hein index). There was no significant difference in plaque scores between the MOTS CPC and Cepacol® at any timepoint (Fig. 1).

For gingivitis, there were no statistically significant differences between any of the treatments, although there was a tendency for a slightly lower gingivitis index with Peridex® treatment than with MOTS CPC or Cepacol® (Fig. 2).

Tolerability and acceptability results

All treatments resulted in staining over the 18 day period of non-brushing.

Cepacol® resulted in significantly higher staining area than both MOTS CPC and Peridex® at day 14 ($p<0.05$) and than Peridex® at day 18. There were no significant differences between treatments in stain intensity and Lobene index.

There were no premature terminations due to adverse effects related to the study medications. The most frequently reported adverse effects were three cases of burning sensation (1 for

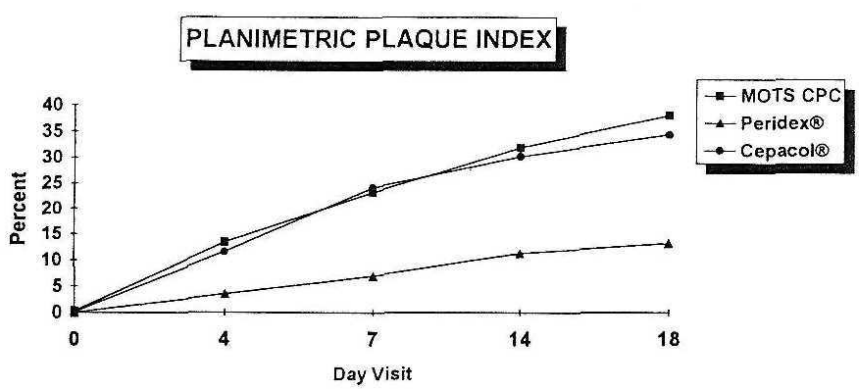

Fig. 1. Mean planimetric plaque index scores.

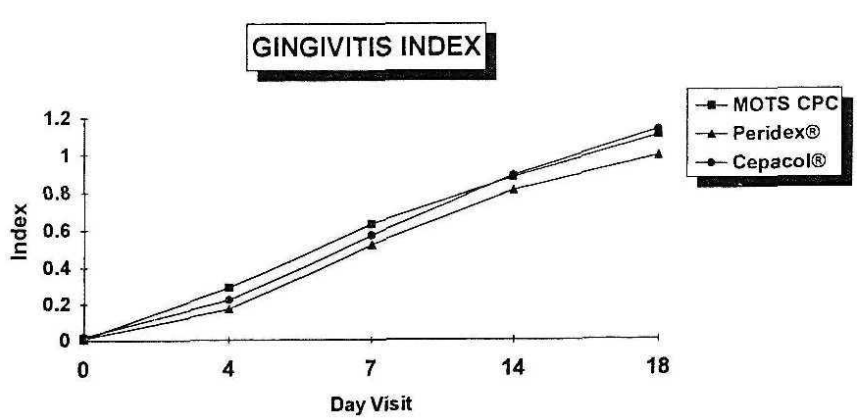

Fig. 2. Mean gingivitis index scores.

each of the 3 treatments), and 4 cases of oral ulceration (2 Cepacol® and 2 MOTS CPC). MOTS CPC and Cepacol® resulted in a similar frequency of adverse effects.

Concerning the overall acceptability (taste and convenience), Peridex® was more convenient than MOTS CPC at all timepoints ($p<0.05$). Cepacol® was better than MOTS CPC, and Peridex® was directionally better than Cepacol®, although this did not reach statistical significance at all timepoints. There was no statistically significant difference in taste scores between any of the treatments at any timepoints.

Microbial results

There was a shift over time in the supragingival flora. The % of cocci went down over the 18-day period of time in the 3 groups. The % of filaments remained lower for subjects rinsing with Peridex® than for subjects using Cepacol®. The % of motile rods tended to be lower for subjects rinsing with Peridex® than for subjects using MOTS CPC. The % of non-motile rods increased with all 3 treatments, while spirochetes were maintained at a low level. The only statistically significant difference was seen between Cepacol® and Peridex® for filaments at day 18 (±2). The results are summarised in Table 2.

Discussion

There exist several slow-release devices for subgingival application to control the subgingival plaque. Among the slow-release forms available are the polymer systems which release drug primarily by diffusion (i.e., Actisite® tetracycline fibre) and ointments (i.e., Elyzol®, Dentocin®).

The present study is one of the few studies to use a slow-release device to control supra-gingival plaque. Ainamo & Etemadzadeh (1987) found good clinical results when a total daily dose of 50 mg chlorhexidine was used as a chewing gum in a four-day non-brushing study. Friedman et al. (1988) applied a cast film comprising ethyl cellulose and 2% CPC to removable appliances in 8 patients. All oral hygiene procedures were withheld during the study. A single application of the film decreased plaque accumulation for 3 days.

In a recent study of Kozlovsky et al. (1994) used a degradable controlled release system. A film-forming preparation containing 9 mg cetylpyridinium (approximately 80 mg of 11% CPC) was compared with the same system without active agent. With the application of the active film-forming solution on the buccal surface of the maxillary and mandibular incisors, they obtained a 58% inhibition of plaque accumulation at the site of application in comparison with the placebo. This impressive result may be related to improved substantivity of the agent.

In the present study, we used a non-degradable controlled delivery dosage form (MOTS), containing 6.6 mg CPC. The active drug is osmotically pushed out of a core when water is drawn across the semipermeable membrane around this core. Volunteers had no periodontitis. The self-applied systems were used with the aim to control the supragingival plaque.

Several studies (Sturzenberger & Leonard 1969, Carter & Barnes 1975, Ciancio et al. 1975, Barnes et al. 1976, Lobene et al. 1977, Ashley et al. 1984, Moran & Addy 1991) emphasize that the CPC containing products should be used as an adjunct to normal oral hygiene procedures. Sturzenberger & Leonard (1969) showed a 17% reduction in scored plaque with a mouthrinse containing 0.025% CPC. Ciancio et al. (1975) and Barnes et al. (1976) obtained a difference of 13–14% plaquereduction for a mouthrinse containing 0.05% CPC compared with a placebo. In the only 6-month study reported (Lobene et al. 1977) there was also a 14% reduction in plaque. Ashley et al. (1984) however did not see significant differences in the clinical plaque scores, but the plaque weight was 25% lower. CPC used as prebrushing rinse (Moran & Addy 1991) or when used in a detergent foam (Addy & Moran 1989) as an adjunct to mechanical plaque control, did not have a beneficial effect on plaque accumulation. In a very recent crossover study, Jenkins et al. (1994) compared the plaque-inhibitory potential of 0.05% and 0.1% CPC-mouthrinse and a 0.05% chlorhexidine-rinse, during a 4-day period of non-brushing. The 0.1% CPC-rinse had the lowest plaque scores, being approximately 26% lower than the control rinse, and 7% lower compared to the 0.05% chlorhexidine. The 0.05% CPC- and 0.05% chlorhexidine-rinse were very similar in their effects. In conclusion, one can say that although not as efficient as 0.2% or 0.12% chlorhexidine, CPC does achieve a limited but statistically significant reduction of plaque. The clinical relevance can however be questioned. Therefore this study associated the CPC with a slow-release device.

A most interesting finding is that although the plaque reduction capacity of the CPC in MOTS is more limited than for Peridex®; it does achieve for the period considered the same inhibitory effect on gingivitis. Plaque indices and even planimetry do indeed not reveal the pathogenicity of the flora present.

The diminished effect of the MOTS CPC in the present study could be related to the differences in oral hygiene and reference product between the above mentioned studies and the present study. Whereas in the study of Kozlovsky et al. (1994), the patients kept their habitual oral hygiene procedures, the students in the present study stopped all oral hygiene measures during the experimental 18-day period. The references used here were two Cepacol lozenges, containing 1.6 mg CPC each. Barnes and colleagues (1975) performed a study with 91 subjects receiving 0 or 1 or 3 lozenges (0.07% CPC), while they continued with their regular oral hygiene routine. CPC appeared to be ineffective in reducing any further plaque accumulations. However, the efficacy of a CPC-lozenge without any

Table 2. Mean (SD) phase contrast microscopy scores ($n=48$)

Outcome measure	Visit day	MOTS CPC	Peridex®	Cepacol®
cocci (%)	4	76.27 (14.99)	74.50 (14.80)	74.87 (12.13)
	18	63.63 (9.67)	63.88 (16.36)	65.44 (12.84)
filaments (%)	4	2.00 (1.97)	0.75 (1.44)	1.50 (1.59)
	18	0.75 (0.93)	0.38 (0.81)	1.33 (1.11)
motile rods (%)	4	2.19 (4.92)	0.06 (0.25)	0.69 (1.78)
	18	1.44 (3.05)	0.56 (1.63)	0.75 (1.24)
non-motile rods (%)	4	20.12 (10.47)	24.62 (14.26)	22.94 (11.35)
	18	34.06 (8.62)	35.13 (16.41)	32.50 (12.12
spirochetes (%)	4	0.00 (0.00)	0.06 (0.25)	0.00 (0.00)
	18	0.13 (0.34)	0.06 (0.25)	0.06 (0.25)

oral hygiene measure is not known. Other studies showed the positive effects for CPC in the absence of tooth cleaning (Llewelyn 1980, Ciancio et al. 1975, Bonesvoll & Gjermo 1978).

In the present study, we observed that CPC in lozenges caused as much staining as Peridex®. Brownish discoloration of the teeth caused by CPC has been also seen in several other studies (Lobene et al. 1977, Lobene et al. 1978, Ciancio et al. 1975). The delivery of CPC by MOTS resulted in a more limited staining.

Concerning the taste and convenience, Peridex® scored the best, probably because of the short time needed to use the product, followed by Cepacol®. The inconvenience of the MOTS CPC was probably related to the need of keeping the vehicle 2 h in the mouth in this group of healthy volunteers.

It is known that the difference in antiplaque efficacy between CPC and chlorhexidine is probably related to the retention time of the agents in the mouth. CPC is cleared from the oral cavity more rapidly than chlorhexidine (Bonesvoll & Gjermo 1978). Quaternary ammonium compounds lose also a part of their activity upon adsorption to surfaces (Moran & Addy 1984).

We used CPC 6.6 mg contained in the MOTS, to obtain a higher substantivity.

Considering that the results with the CPC delivered by MOTS or by lozenges did not differ significantly, it seems that the increased substantivity of the former did not sufficiently compensate for the more limited activity. Increasing the concentration would most probably lead to mucosal alterations as has been observed in animal studies (Encarnacion 1994, personal communication). The association of a more effective antiplaque agent with the MOTS slow release system should be considered.

Acknowledgement

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Zusammenfassung

Die Wirkung des Cetylpyridiumchlorid in einer, die wirksame Substanz langsam freisetzenden, Hülle auf die Kontrolle des supragingivalen Plaque

Um die relative Wirkung einer, 6.6 mg Cetylpridiniumchlorid enthaltenden und langsam osmotisch freisetzenden, nicht-degradierbaren Hülle (*M*ucosal *O*ral *T*herapeutic *Sy*stem, *C*etyl*p*yridium *c*hloride; MOTS CPC) auf die Hemmung neugebildeter Plaqueanlagerung und Gingivitis zu beurteilen, wurde eine einfach blind und nach dem Zufallsprinzip angelegte Parallelgruppen-Pilotstudie konzipiert. Während 18 Tage lang eingestellter Zahnreinigung wurden 52 freiwillige Probanden beauftragt, eine der folgenden Behandlungsformen als Selbstversuch durchzuführen: Zweimal täglich war eine MOTS CPC 2 Stunden lang im Munde zu halten oder den Mund war zweimal täglich, 30 Sekunden lang mit 15 ml Peridex® zu spülen, oder es wurde verlangt, zweimal täglich 2 Cepacol® Tabletten (jede mit 1.6 mg CPC versehen) unbeaufsichtigt im Munde zergehen zu lassen. Zum Erhalt einer klinisch gesunden Gingiva, wurden die Zähne der Probanden 3 Wochen lang vor dem Beginn der Testperiode durch einmal wöchentlich vorgenommenes, sorgfältiges Polieren der Zähne gereinigt. Nach dem Therapiebeginn wurden die Probanden an den Versuchstagen 4, 7 (±2), 14 (±2) und 18 (±2) untersucht. Die relative Wirkung wurde mit dem modifizierten Plaque Index der Navy, dem Quigley & Hein Index, dem planimetrischen Plaque Index, wie auch mit dem Papillen Index der marginalen Gingiva beurteilt. Während der 18 Tage (±2) langen Zeitspanne mit eingestellter Zahnreinigung kam es bei allen, an der Studie teilnehmenden Probanden sowohl zu erhöhter Plaquebildung als auch zu verschlimmerter Gingivitis. Während dieser Zeitspanne erzielte Peridex® hinsichtlich Plaquehemmung und Ausbreitung der Gingivitis die beste Wirkung. Zwischen MOTS CPC und Cepacol® war niemals ein Unterschied vorhanden, weder bezüglich der Plaquebildung noch hinsichtlich der Intensität der Gingivitis. Peridex® wurde angenehmer als MOTS CPC empfunden. Bei Cepacol® kam es nach den 18 Tagen zu intensiverer Verfärbung als bei MOTS CPC und Peridex®.

Résumé

Efficacité du contrôle de la plaque sus-gingivale par un moyen de libération lente de chlorure de cétylpyridinium

Pour évaluer l'efficacité relative d'un système de libération lente non-dégradable contenant 6.6 mg de chlorure de cétylpyridinium (MOTS CPC) à inhiber la formation de la nouvelle plaque dentaire et de la gingivite, une étude pilote en simple aveugle, au hasard et par groupes parallèles a été mise sur pied. 52 volontaires sains ont été répartis pour recevoir un des traitements suivants durant 18 jours sans brossage et sans supervision: tenir un MOTS CPC 2× par jour durant 2 h en bouche, rinçer durant 30 s avec 15 ml de Peridex® 2× par jour ou dissoudre 2 Cepacol® (contenant chacun 1.6 mg de CPC) 2× par jour. Avant la période test les sujets ont reçu un nettoyage dentaire approfondi avec polissage dentaire 1× par semaine durant 3 semaines pour arriver à obtenir une gencive cliniquement saine. Après le début du traitement, les sujets ont été examinés au jour 4, 7 (±2), 14 (±2) et 18 (±2). L'efficacité relative a été enregistrée en utilisant l'indice de plaque modifié de la Navy, l'indice de Quigley & Hein, l'indice de plaque planimétrique et l'indice gingival papillaire. Il y avait une augmentation tant de la formation de la plaque dentaire que de la gingivite durant les 18±2 jours sans nettoyage mécanique chez tous les sujets. Le Peridex® était le plus efficace à inhiber la formation de la plaque et de la gingivite. Il n'y avait aucune différence entre MOTS CPC et Cepacol® à aucun moment. Le Peridex® s'est avéré plus efficace que le MOTS CPC. Le Cepacol® entraînait davantage de coloration après 18 jours que les deux autres produits.

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