Prevention of gingivitis and treatment of periodontitis: Chlorhexidine gels and dental lasers

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PREVENTION OF GINGIVITIS AND TREATMENT OF PERIODONTITIS

- DENTAL LASERS -

PERIODONTOLOGY

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- CHLORHEXIDINE GELS -

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There is a time for work, and a time for love. That leaves no other time!
Coco Chanel

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1.

As a result of research, dental care professionals can apply current knowledge to aid the patient in the selection of an appropriate dentifrice.

Esther Wilkins

INTRODUCTION AND OUTLINE OF PART I OF THE THESIS

General Introduction, part I

People brush their teeth for a number of reasons, such as to sense oral freshness, to feel confidence from having a nice smile, to avoid bad breath and to prevent disease. Oral cleanliness is important for the preservation of oral health and the maintenance of a functional dentition throughout life (Ohrn & Sanz 2009). Oral hygiene procedures remove plaque and prevent plaque from accumulating on teeth (Choo et al. 2001). There is substantial evidence showing that toothbrushing and other mechanical procedures can remove plaque to a reasonable extent, provided that cleaning is performed thoroughly. Evidence from large-cohort studies has demonstrated that high standards of oral hygiene will ensure the longevity of periodontal tissue health (Axelsson 2004, Hujoel et al. 2006, Van der Weijden & Slot 2012).

Dental plaque

It is universally accepted that microorganisms and their products in dental plaque are the primary local environmental factors that initiate inflammatory periodontal disease (Pihlstrom 2014). In the 1960s, Löe and coworkers designed a clinical experiment that changed the basic paradigms of the etiology of gingivitis. The paper "Experimental Gingivitis in Man" was published in 1965 in the Journal of Periodontology (Löe et al. 1965). This study discussed a hypothesis-driven clinical experiment and asked the question, Does plaque mass buildup on the teeth result in gingivitis? During a 3-week period of no oral hygiene, all volunteers developed gingivitis, and upon the reinstitution of oral hygiene practices, they returned to pre-experimental low levels of plaque and gingivitis. The study included the use of healthy young human volunteers with no systemic diseases. This experimental gingivitis study reinforced the critical importance of bacteria in the etiology of periodontal disease and led to advances in disease prevention and guided principles for predictable treatment (Lang 2014). It is also universally recognized that plaque control is fundamental in achieving and maintaining periodontal health (Pihlstrom 2014). Since the publication of Löe et al.'s (1965) landmark study, the paramount role of supragingival plaque control in the prevention of disease and preservation of periodontal health has been well documented (Van der Weijden & Hioe 2005).

Toothbrushing and instruction

In modern societies, toothbrushing is seen as the most efficient oral hygiene method of cleaning one's teeth. As established in a systematic review (Slot et al. 2012), the efficacy of plaque removal following a brushing exercise using a manual toothbrush is represented by a 42% weighted mean reduction from baseline plaque

scores. Depending on the plaque index used, a variation of 30–53% was observed. This process of systematically locating, appraising and synthesizing evidence from individual trials provided a reliable overview based on data from over 10,000 subjects. The available evidence indicates that bristle tuft arrangement (flat trim, multilevel, angled) and brushing duration are factors that contribute to the variation in observed efficacy (Slot et al. 2012). Irrespective of these factors, it appears that there is room for improvement in the efficacy of toothbrushing.

Twice-daily brushing with fluoride toothpaste is now an integral part of most people's daily oral hygiene routine in Western societies. However, it appears that most patients are unable to achieve sufficient plaque removal at each cleaning (Van der Weijden & Slot 2011). A systematic review (Van der Weijden & Hioe 2005) assessed the effectiveness of a single oral hygiene instruction. Studies reviewed included those with a duration of ≥6 months evaluating adults with gingivitis and assessing the level of plaque removal and gingivitis reduction. The results showed that there is a significant, albeit small, positive effect of a single oral hygiene instruction on the reduction of gingival inflammation in adults with gingivitis.

Dentifrice

Because adequate plaque control is difficult to attain by most people, an adjunct to mechanical plaque control would be valuable. The use of chemical agents that can be incorporated in dentifrice or mouthwash formulations has been advocated (Paraskevas 2005, Hioe & Van der Weijden 2005). Research efforts have been directed toward the development of safe and efficacious chemical anti-plaque agents (Gjermo & Saxton 1991). Dentifrices are the ideal vehicles for any active ingredient employed as an oral health preventive measure because they are used with toothbrushing. Among the active agents, the following have been included in toothpastes: enzymes, amine alcohols, herbal or natural products, triclosan, bisbiguanides (chlorhexidine), quaternary ammonium compounds (cetylpyridinium chloride) and different metal salts (zinc salts, stannous fluoride, stannous fluoride with amine fluoride) (Sanz et al. 2013). Fluoride toothpastes have been widely used for over three decades and remain a benchmark intervention for the prevention of dental caries (Marinho et al. 2003, Walsh et al. 2010).

The indications for dentifrices with active ingredients intended for patients with gingivitis are associated with long-term use to prevent bacterial biofilm formation. Only a few ingredients have been systematically evaluated in relation to gingival health. The use of stannous fluoride dentifrices results in gingivitis and plaque reduction when compared to use of a conventional dentifrice (Paraskevas & Van der Weijden 2006). Studies on triclosan toothpastes have concluded that they reduce

plaque and gingival inflammation to a greater extent than do regular fluoride toothpastes (Riley & Lamont 2013, Trombelli & Farina 2013, Hioe & Van der Weijden 2005, Davies et al. 2004). Recently, a systematic review compared the efficacy of triclosan to stannous fluoride dentifrices. Although 11 studies met the eligibility criteria, the meta-analysis provided inconclusive results regarding the outcome variables of gingival health and plaque scores (Sälzer et al. 2015).

Chlorhexidine

In conjunction with mechanical plaque removal, chemotherapeutic agents have the potential to improve oral health beyond tooth brushing alone (Addy & Moran 1997). Although many products have been developed to control plaque and gingivitis, chlorhexidine (CHX) is one of the most widely used. CHX is the best studied and most effective anti-microbial agent in oral care (Paraskevas 2005). Years of research have established that CHX digluconate is safe and stable. This compound contributes to prevention and controls plaque formation by breaking up existing plaque and inhibiting and reducing gingivitis.

Recently, a systematic review of the existing scientific literature on CHX mouthwashes as an adjunct to mechanical oral hygiene was performed (Van Strydonck at al. 2012). The body of evidence was summarized concerning the efficacy of CHX mouthwash regarding plaque growth, gingival inflammation and stain formation in patients with gingivitis. All included studies evaluated the use of CHX in combination with mechanical oral hygiene and provided strong evidence for the anti-plaque and anti-gingivitis effects of a CHX mouth rinse in patients with gingivitis. As could be deduced from studies with a low estimated risk of bias, rinsing with CHX in addition to oral hygiene procedures results in approximately 33% less plaque and 26% less gingivitis compared to controls. The side effect was a significant increase in tooth surface discoloration (Van Strydonck et al. 2012).

The universal advice from dental care professionals is to brush twice daily (for 2 minutes) with a fluoride dentifrice (ADA2015). It would therefore be ideal to incorporate CHX in a dentifrice formulation (Sanz et al. 1994). The potential of this formulation has been demonstrated in a non-brushing study by the use of a tooth shield to protect selected teeth from toothbrushing. The use of CHX dentifrice resulted in significantly reduced plaque accumulation and gingivitis levels compared to the placebo (Putt at al. 1993). Yet, the inclusion of cationic antiseptics, such as CHX, in a dentifrice formulation can pose problems because CHX can be inactivated by flavors and anionic detergents in dentifrice formulations (Addy et al. 1989).

Aims of the Thesis, part I

The purpose of the study, as presented in chapter 2, was to evaluate the use of a 0.12% CHX dentifrice gel compared to a regular dentifrice gel in preventing plaque accumulation. Both dentifrices were applied in a disposable gel application tray in a 'de novo' plaque formation model. In the subsequent clinical trial, the same model and products were used and 1% CHX gel group and a 0.2% CHX mouthwash group were added as optimal positive control (chapter 3). Both non-brushing studies served as a proof of principle for the efficacy of the CHX products used to chemically prevent 'de novo' plaque development.

Following the above clinical non-brushing studies, a systematic evaluation of the current available literature concerning the effect of toothbrushing with a CHX dentifrice or gel was initiated. The clinical parameters of plaque and gingivitis and the presence of side effects such as tooth surface discoloration were considered as parameters of interest (chapter 4). In chapter 5 a systematic review is presented that evaluated the available evidence regarding the effectiveness of CHX dentifrice or gel compared to CHX mouthwash on plaque and gingivitis inhibition and the reduction of tooth surface discoloration.

All chapters in this thesis have already been published in scientific dental journals. The study designs are comparable in various respects, and therefore, some duplication of the text in each chapter is inevitable.

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2.

Most entertainment is trying to get you.
It's tested, like toothpaste.

Albert Brooks

THE EFFECT OF 0.12% CHLORHEXIDINE DENTIFRICE GEL ON PLAQUE ACCUMULATION: A 3-DAY NON-BRUSHING MODEL

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Introduction

The most common method to prevent caries and periodontal diseases is mechanical supragingival plaque control by toothbrush, and interdental aids, such as dental floss, toothpicks and interdental brushes. For most people, however, total plaque removal seems not a realistic goal. Most people remove less than half of the plaque with brushing once a day, leaving approximately 60% after brushing responsible for rapid regrowth (De la Rosa et al. 1979). Therefore, an adjunct to mechanical plaque control would be valuable. Several products for chemical plaque inhibition are available on the market. The bisbiguanide compounds, which include chlorhexidine (CHX) gluconate and alexidine, are the most effective agents currently in use (Baker et al. 1987). CHX is a cationic chlorophenyl biguanide with outstanding bacteriostatic properties. The drug was synthesized and first reported by ICI in 1954 following extensive investigations of its biological properties of polydiguanide compounds (Davies et al. 1954). CHX was initially used in dentistry for presurgical oral disinfection and endodontics (Clarke & Blacklock 1965). The application of CHX as an anti-plaque and calculus agent was suggested by Schroeder & Hirzel (1969). CHX has been proved as an effective plaque inhibitor when used as an adjunct to mechanical cleaning procedures as well as when used alone (Hull 1980).

Chlorhexidine can be applied in a number of ways: as a mouthwash (Keijser et al. 2003, Löe & Schiøtt 1970, Löe et al. 1976, Van Strydonck et al. 2005; Van der Weijden et al. 2005), as a gel (Cutress et al. 1977, Francis et al. 1987, Francis et al. 1987, Kohler & Andreen 1994; Kohler et al. 1983; Pienihakkinen et al. 1995, Porras et al. 2002) and as a spray (Francis et al. 1987, Francis et al. 1987, Burtner et al. 1992, Kalaga et al. 1989). Its efficacy has been extensively investigated. CHX is most commonly used in a mouthwash form. In the Netherlands, CHX gel has traditionally been available in a 1% concentration (Corsodyl®-gel, Glaxo Smith Kline, Zeist, the Netherlands). More recently, a dentifrice gel containing a 0.12% concentration CHX was brought on the market(Perio·Aid®, Dent-Aid, Houten, the Netherlands). The 1% CHX gel was meant for temporary use with a maximum of 15 days, while the 0.12% concentration dentifrice gel has been advocated for long-term twice daily brushing use. So far, no efficacy data on the latter product are available. The purpose of the present study was to evaluate, when compared with a regular dentifrice, whether 0.12% CHX dentifrice gel is effective in preventing 'de novo' plaque formation in a 3-day non-brushing model. As a positive control, the effect of rinsing with 0.12% CHX mouthwash was assessed. In addition, the individual attitude towards the used products was evaluated.

Materials and methods

Ethical aspects/approval

This study protocol was approved by the Medical Ethics Committee of the Academic Medical Centre (AMC) of Amsterdam under registration number 05/189. The study has also been registered by the Dutch Trial Register, international standard randomized controlled trial ISRCT 57974544. Participation as a subject in this study was voluntary.

Subjects

A total of 127 subjects were recruited from a database of the Department of Periodontology Academic Centre for Dentistry Amsterdam (ACTA) and from students of Inholland University responding to an email advertisement. Before enrollment, all subjects were given oral and written instructions and information about the products and purpose, aim, reason, duration demand of benefits and possible harm of study participation. All subjects willing to take part signed an informed consent prior to the study procedures. Inclusion criteria were ≥18 years of age, systemically healthy and a dentition with at least 20 teeth (minimum of five evaluable teeth per quadrant). Exclusion criteria were open caries, pockets ≥5mm, orthodontic appliances or removable (partial) dentures, history of allergic reaction to erythrosine and/or CHX, use of antibiotics in the last 3 months or medication that might interfere with the conduct of the study or possibly influencing normal gingival health.

Design and (clinical) procedures

The study was designed as a single-blind, randomized three-arm parallel clinical trial. At baseline, teeth of all subjects were stained for plaque with an erythrosine disclosing solution applied with a cotton swab subsequently received a professional oral prophylaxis for a maximum of 30 min performed by experienced dental hygienists. Teeth were scaled and polished with the purpose of making them 100% free of plaque, stain and calculus. An ultrasonic scaler (Sonosoft® KaVo Nederland BV Vianen, the Netherlands) and hand instruments (H6/7, SD204, 1/2, 12/13 11/14 American Eagle® American Eagle Instruments Inc., Missoula, MT, USA, and/or Hu-friedy® Hu-Friedy Inc., Leimen, Germany) followed by rotating polishing cups, points and brushes (Hawe-Prophy® #1802, #1805 and #0220), Hawe-Neos Dental Dr H.v.Weissenfluh AG, Bioggio, Switzerland) with polishing paste (cleanpolish® #360, Hawe- Neos Dental Dr H.v.Weissenfluh AG, Bioggio, Switzerland) were used. After debridement, teeth were stained for a second time. Performed to make sure all plaque had been removed. Subsequently, unwaxed floss (Johnson & Johnson, distributor, GABA B.V., Almere, the Netherlands) was used for a professional

interdental cleaning. Distal of the last molars bandage tape (Cotton Tamponning Bandage 1 cm × 5 m sterile Hartmann®, Heidenheim, Germany) was used to make sure that all remnants were removed.

Every subject received a unique trial number and was randomly assigned to one of the three regimens (Table 1) consisting of 0.12% CHX dentifrice gel, regular dentifrice and 0.12% CHX mouthwash. No brushing was allowed in any of the three regimens. Randomization was performed using true random numbers obtained via http://www.random.org. The primary investigator and study coordinator (DES) was responsible for the allocation concealment, subjects were instructed not to reveal their group assignment in any way to the clinical examiner (NAMR). Each subject received a demonstration and verbal instruction from the study coordinator (DES) immediately following the professional dental prophylaxis. In addition, a written instruction form was provided explaining the use of the intervention products. The subjects were given a stopwatch with alarm to keep track of the assigned rinsing or application time. Drinking, eating or rinsing was not allowed for 30 min after the experimental procedures. During a 3-day experimental non-brushing period, subjects abstained from all other forms of mechanical oral hygiene. To check for compliance, subjects were asked to register the time of use of intervention products onto a calendar record chart.

At the second visit (3 days later), all plaque on the teeth was disclosed using cotton swabs with an 1% erythrosine disclosing solution from the same batch of disclosing solution for all subjects. All measurements were carried out under the same conditions and were performed by the same experienced examiner (NAMR) who was blinded to the regimen. This examiner had been trained and calibrated in the plaque scoring system and had applied it in other studies (Van der Weijden et al. 2005, Rosema et al. 2005). Plaque was recorded at six sites per tooth on a five-point scale using the Quigley & Hein (1962) plaque index (PI) as modified by Turesky et al. (1970) and further modified by Lobene et al. (1982). Each subsequent full-mouth plaque assessment lasted approximately 10 min. After the experimental period, habitual oral hygiene procedures were resumed. Finally, all subjects received a questionnaire to evaluate their attitude towards the used product. They were questioned about their opinion of appreciation of taste, alteration of taste, comfort of use, duration of taste and perception of plaque control. Subjects marked a point on a 10-cm-long uncalibrated line with the negative extreme response (0) on the left and the positive extreme (10) at the right end (Visual Analogue Scale, VAS).

Table 1. Following regimens groups who were designed

Regimen CHX-DGel	0.12% Chlorhexidine dentifrice gel* twice a day application in fluoride application tray† for 2 min. No brushing was allowed
Regimen RegD	Regular dentifrice‡ twice a day application in fluoride application tray† for 2 min. No brushing was allowed
Regimen CHX-MW	0.12% Chlorhexidine mouthwash* twice a day mouthwash rinsing with 15 ml for 1 min. No brushing was allowed

* Perio-Aid®, Dentaid, Houten, the Netherlands
† Fluoride application tray large 10EL630 Elmex®, Johnson & Johnson distributor, GABA BV, Almere, the Netherlands
‡ Everclean®, HEMA, Amsterdam, the Netherlands

Statistical analyses

The Quigley & Hein index as assessed after 3 days of 'de novo' plaque accumulation was used as the primary outcome variable. Full-mouth mean PI scores were calculated for each individual. Data considering the VAS scores from the questionnaire to evaluate the subjects' attitude, appreciation and perception towards the used products were secondary outcomes. All analyses comparing differences (PI, VAS scores) between the three regimens were performed using non-parametric tests (Kruskal–Wallis H-tests) with post-testing corrected for multiple comparisons. All data are presented as mean ±SD per regimen. For the difference in PI scores between regimens 95% confidence intervals were calculated. Values of $P \leq 0.05$ were considered as statistically significant.

Sample size

The American Dental Association (ADA) (1998) states in its Acceptance Program Guidelines Toothbrushes (1998) that under unsupervised conditions, a 15% statistically significant reduction in plaque is needed to provide evidence of greater effectiveness in cleaning teeth. Sample size calculations with PS Power and Sample Size Program® showed that given a lower limit for superiority of 15%, a mean PI of 2.7, an SD of 0.3, a difference of 0.4. and an $\alpha=0.05$ to obtain 80% power, 21 subjects would be sufficient for this study (seven subjects in each group). The ADA (1998) also requires that adequate evidence must be provided by entering at least 30 subjects for each into the study at baseline. At least 25 subjects for each product should be available for examination at the end of the study. Considering possible loss to follow-up for the present study 35 extra subjects were included per regimen.

Results

Figure 1 shows a flow chart of the participants that were enrolled for this study. A total of 127 systemically healthy recruited subjects (≥18 years of age) were screened; 22 were excluded for open caries or pockets ≥5mm. Of the 105 subjects, who were enrolled into the study, 98 completed the protocol. Seven subjects (one in the CHX-Dgel group, five in the RegD group and one in the CHX-MW group) were lost to follow- up because they did not attend the second appointment. Being absent was unrelated to the study products. In the end, 96 completed the study protocol without any protocol violation. Two male volunteers, both from the RegD group were excluded from the analysis because each had one protocol violation. One had brushed once and the other had forgotten to use his product once. Subjects' demographics of those included in the analysis are presented in Table 2. Groups were comparable in age. However, due to chance, the randomization procedure resulted in an unequal distribution of the sexes over the groups. There were significantly fewer women in the RegD group.

Table 2. Subjects' demographics presented by regimen

	CHX-DGel	RegD	CHX-MW	P-value
N	34	29	33	
♀ (female)	25	16	28	0.033†
♂ (male)	9	13	5	0.033†
Age in years Mean (SD)	21.9 (4.50)	23.5 (4.15)	21.5 (3.20)	0.440†
Age range in years	18–39 year	18–39 year	18–32 year	

† Chi2 test

Table 3 provides the results for the primary endpoints, the mean PI scores for each regimen after 3 days of plaque accumulation. Mean whole mouth PI for the CHX-DGel was 1.87 compared with 1.93 for the RegD regimen and 1.55 for the CHX-MW regimen. A statistically significant difference between the three regimens was found (P=0.0006). Post-testing between the regimens revealed that PI scores when using dentifrices (CHX-DGel and RegD) were significantly higher when compared with using CHX-MW (P≤0.05). No statistically significant difference between PI scores of the two dentifrices (CHX-DGel and RegD) was found (Table 4).

Fig 1. Flow chart subject enrolments

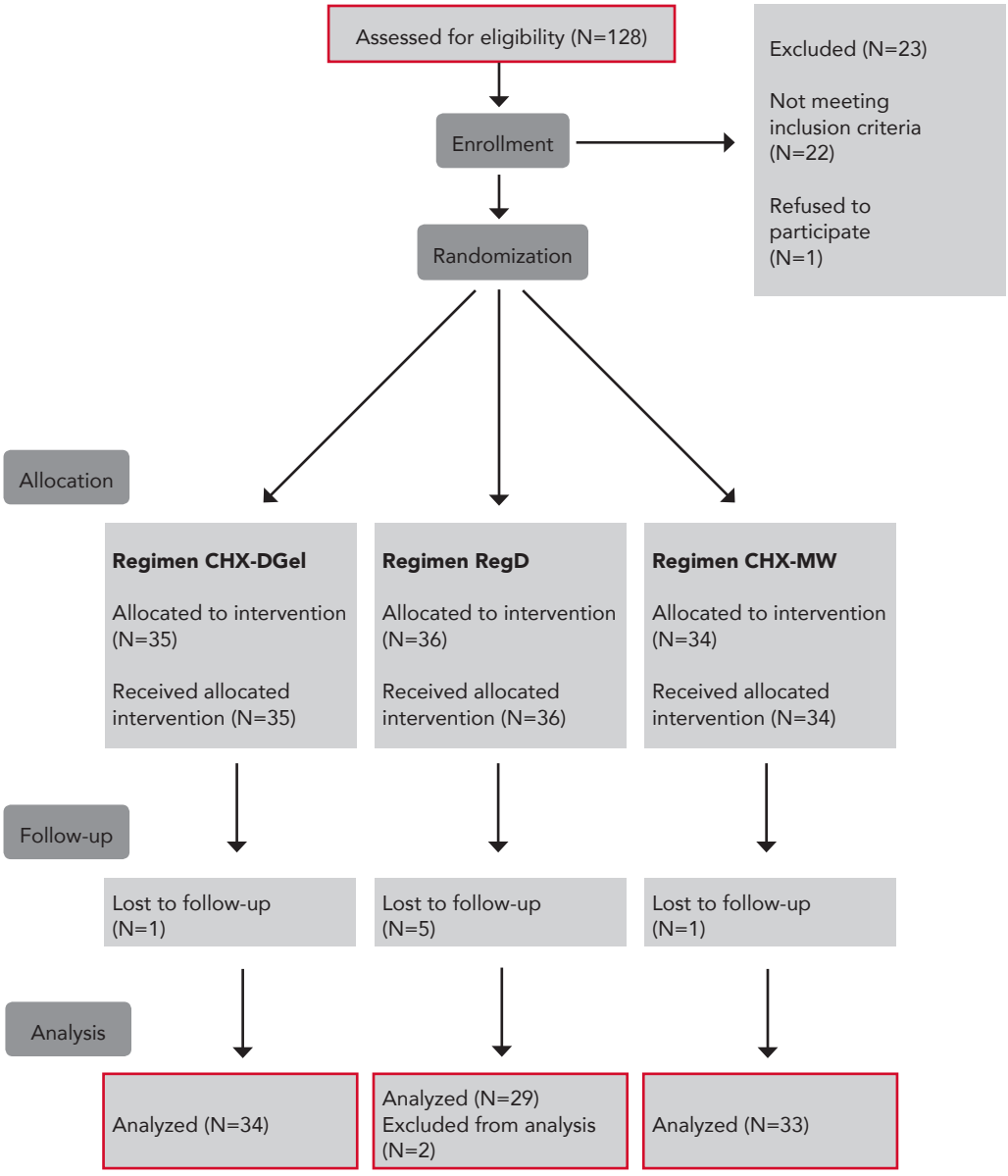

Table 3. Mean overall plaque index (PI) scores (standard deviation in parentheses) for each regimen after 3 days of plaque accumulated and minimum and maximum scores

	CHX-DGel	RegD	CHX-MW	P-value
Mean overall PI	1.87 (0.37)	1.93 (0.46)	1.55 (0.37)	0.0006*
Minimum	1.07	0.77	0.74	
Maximum	2.86	2.73	2.24	

* Kruskal–Wallis H-test with post-testing corrected for multiple comparison

Table 4. Results from the statistical analysis Kruskal–Wallis H-test with post-testing corrected for multiple comparisons and 95% confidence intervals for differences for mean plaque scores between the regimens

	Kruskal–Wallis H-test	Confidence Interval
CHX-DGel – RegD	NS	-0.27 ; 0.15
CHX-DGel – CHX-MW	≤0.05	0.13 ; 0.50
RegD – CHX-MW	≤0.05	-0.59 ; -0.17

Table 5 shows the complete question and the two extremes of the answering possibilities. Table 6 shows the results of the questionnaire. A statistically significant difference between the three groups was found with respect to perception of taste, alteration of taste, comfort of use and duration of taste. No statistically significant differences were found by the application/ rinsing time and subjects' perception of plaque control.

Post-testing showed a significant difference between the perception of taste, alteration of taste and use of comfort for the CHX-MW when compared with the two dentifrices (CHXDGel and RegD). For the duration of the taste of the study products, it appeared that taste of the CHX-DGel product remained shorter when compared with CHX-MW and RegD.

Table 5. Complete questions from Visual Analogue Scale score (0.0–10.0)

Paraphrase	Complete question	With extremes	
		From	To
Taste perception	How was the taste of the product?	Very bad	Very good
Alteration of taste	How was your taste of food and drinks affected?	Negative change	Positive change
Use comfort	What is your opinion about the ease in use of the product?	Not easy	Very easy
Duration of taste	How long did the taste remain?	Very short	Very long
Plaque control	What is your perception of plaque control during this 3 days?	Insufficient	Very efficient

Table 6. Visual Analogue Scale scores questionnaire response (0.0–10.0) of the mean response to the questionnaire (standard deviation in parentheses) presented by regimen

Paraphrase	CHX-DGel	RegD	CHX-MW	P-value
Taste perception	6.68 (1.86)*	6.95 (1.17)*	5.18 (2.21)	0.0008
Alteration of taste	4.79 (0.99)*	4.73 (0.91)*	3.74 (1.52)	0.0052
Use comfort	5.67 (2.27)*	5.38 (2.69)*	7.62 (2.13)	0.0003
Duration of taste	4.41 (2.21)	6.01 (1.95)**	6.38 (2.02)**	0.0014
Plaque control	4.69 (2.37)	4.67 (2.77)	5.77 (2.55)	NS

* Significant differences when compared with CHX-MW
** Significant differences when compared with CHX-DGel

Discussion

This study aimed at evaluating whether CHX-DGel had a potential to inhibit 'de novo' plaque formation. It used a 3-day non-brushing model which allows for plaque accumulation. This design has been used previously to assess the effect of various mouthwashes (Addy & Bates 1977, Binney et al. 1993, Daly & Highfield 1996, Dills et al. 1988, Dona et al. 1998, Zee et al. 1997, Simonsson 1989). Zee et al. (1997) and Simonsson (1989) also used this 3-day model to discern between 'rapid' and 'slow' plaque formers.

The application of the dentifrice in trays was based on a suggestion by Saxton & van der Ouderaa (1989) to apply undiluted dentifrice directly to the test teeth. The method of applying undiluted dentifrice via a tooth shield was reported in an earlier 4-day plaque study by Saxton et al. (1988), which was a modification of a full-mouth technique used by Gjermo & Rølla (1970) and Strålfors (1961). This technique eliminates the variability introduced by the mechanical action of tooth brushing, thus permitting the assessment of chemotherapeutic activity only. Putt et al. (1993) confirmed that this was an effective short-term model to investigate the chemotherapeutic effects of CHX dentifrice on plaque.

The CHX-DGel was positioned against a RegD as benchmark control. This was a commercially available fluoride dentifrice not claiming anti-plaque efficacy. As positive control, a CHX-MW was used which at present is considered the standard and most effective anti-plaque agent (Jones 1997). A positive control compares and positions the efficacy of CHX-DGel and RegD and is frequently used in early no oral hygiene study protocols (Addy 2003).

The results from the present study show that 0.12% CHXDGel is not significantly different from using RegD. Both dentifrices were less effective than the CHX-MW with respect to the plaque inhibition. Considering the small differences between 0.12% CHX-DGel and RegD, one could suggest that the present study suffers from inadequate power. If the observed difference between the 0.12% CHX-DGel and RegD regimen would have been powered with at least 80% and an α=0.05, a sample size of approximately 275 subjects per regimen would have been necessary. Clearly, one could then discuss the clinical relevance of this study design. In this perspective, using the model as chosen with inclusion of both a benchmark RegD as well as positive control (CHX-MW) was an elegant and powerful (power >99%) way to position the CHX-DGel regimen with only approximately 10% of such a large sample size.

The fact that application of a dentifrice use does not contribute to plaque growth inhibition does not necessarily mean an abolishment of its use. Dentifrices are also most effective fluoride carriers and their contribution to caries prevention is well established (Davies et al. 2003). The CHXDGel, however, neither has an effect on plaque growth nor does contain fluoride.

The CHX-DGel has a manufacturer's instruction for use, that states brushing twice daily allows long-term usage in analogy to a regular dentifrice. This might explain the absence of an anti-plaque effect because CHX can be inactivated by flavour and detergent in dentifrice formulations (Addy et al. 1989, Barkvoll et al. 1989, Jenkins et al. 1990). One of the most widely used synthetic detergents in dentifrice is sodium lauryl sulphate (SLS). Unfortunately, CHX and SLS may counteract. Previous studies (Barkvoll et al. 1989, Owens et al. 1997) have shown that CHX and SLS are not compatible even when they are introduced separately in the oral cavity. Earlier Barkvoll et al. (1988) showed that CHX and sodium monofluorophosphate are also not compatible in clinically relevant concentrations.

Another explanation for the absence of an anti-plaque effect could be the amount of CHX digluconate per application. Both CHX-DGel and CHX-MW in this present study contained 0.12% CHX. Each CHX-MW application with 15 ml had delivered 18 mg of CHX digluconate. With a specific gravity of 1.080 g ml-1 for CHX digluconate, each CHX-DGel application with a fluoride tray of approximately 10 g had 12 mg of CHX digluconaat available. Based on studies by Cumming and Loë (1973) and Lang and Ramseier-Grossmann (1981), this amount of CHX should be sufficient to results in plaque growth inhibition. However, diffusion of CHX from the dentifrice formulation might have been prevented, by dentifrice components or may have been decreased (Putt et al. 1991).

In this respect, the manufacturers should be careful when reformulating the CHX-DGel. Children usually apply ±0.25 g of dentifrice (Cochran et al. 2004) on their brush, while adults 0.5 g for electric and 0.9 g for manual tooth brushing (Buijs et al. 2005). So using CHX-DGel on a toothbrush would result in 0.6–1.1 mg of CHX digluconate application. This is not enough to have a sufficient antiplaque effect (Cumming & Löe 1973, Lang & Ramseier-Grossmann 1981). To have sufficient amounts of CHX available, the concentration should be raised to a level of 2.0% to have an applicated dose comparable with the 0.12% CHXMW.

A suggestion for further research would be to raise the CHX concentration in the CHX dentifrice gel to at least 1% level similar to a competitive product already available on the market. However, before another clinical research trail is started, with the involvement of a large group volunteers, it is obligatory to test the efficacy of the new formulation(s) in a laboratory setting first.

Summary and conclusion

Within the limitations of the present 3-day non-brushing study design, it can be concluded that the effect of application of 0.12% CHX dentifrice gel is not significantly different from that of regular dentifrice on plaque accumulation. Using 0.12% CHX mouthwash is significantly more effective. CHX-DGel appears a poor alternative for a dentifrice. It is not an effective inhibitor of plaque growth and does not possess fluoride.

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3.

Efficiency is doing things right;
effectiveness is doing the right things.

Peter Drucker

THE EFFECT OF 1% CHLORHEXIDINE GEL AND 0.12% DENTIFRICE GEL ON PLAQUE ACCUMULATION: A 3-DAY NON-BRUSHING MODEL

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Introduction

Dental plaque is a multispecies biofilm of microorganisms that grows as an ecosystem on hard tissues in the oral cavity. Epidemiological studies revealed a high correlation between supragingival plaque levels and chronic gingivitis (Ash et al. 1964). Clinical research (Löe et al. 1965) showed that plaque was the primary etiologic factor in gingival inflammation. The formation of plaque on a tooth surface is a dynamic and ordered process commencing with the attachment of primary plaque-forming bacteria. Efficient removal of dental plaque is essential for maintaining oral health. The mainstay and most reliable method currently used for supragingival plaque control is mechanical cleaning using a toothbrush (Hancock 1996).This can be manual or powered (Heanue et al. 2003, Robinson et al. 2005). Mechanical tooth cleaning through toothbrushing with toothpaste is the most common and potentially most effective form of oral hygiene practiced in developed countries (Frandsen 1986, Jepsen 1998).

However, for many individuals it is difficult to achieve a level of plaque control comparable with oral health by toothbrushing (with dentifrice) only. In general, individuals remove only around half of the plaque from their teeth even when brushing for 2 min (De la Rosa et al. 1979). Patients' efforts are often compromised by the presence of hard-to-reach areas as well as inadequate skills, poor motivation, and lack of compliance. A significant proportion of all individuals appears to fail to practice a critical standard of plaque removal, and gingivitis is highly prevalent even at an early age (Lavstedt et al. 1982, Addy et al. 1986). The adjunctive use of an antiseptic and/or chemical agent may therefore be justified. After three decades of use in dentistry, chlorhexidine digluconate (CHX) is still considered to be the leading antiseptic for combating biofilms in supragingival and oral musosal sites (Addy 1986, Moran et al. 1997). Despite the ideal nature of toothpaste as a vehicle, most chemical plaque-control agents have been evaluated and later formulated as mouthrinses. Mouthrinses vary in their constituents and are usually considerably less complex than toothpastes. Chlorhexidine is used in various vehicles and concentrations in commercially available products and may be purchased by consumers as mouthwash, spray, or gel.

In the Netherlands, two over-the-counter gels containing CHX are available: a 1% CHX-gel (Corsodyl®-gel; Glaxo- SmithKline, Zeist, the Netherlands) and a dentifrice gel containing 0.12% CHX (Perio-aid®; Dentaid, Houten, the Netherlands). The 1% gel is meant for temporary use for a maximum of 15 days, whilst the 0.12% CHX dentifrice gel has been recommended for long-term use. A previous study showed that application of 0.12% CHX dentifrice gel does not significantly reduce

plaque accumulation, compared to a regular dentifrice (RDF) (Slot et al. 2007). However, a head to head comparison between the 1% and 0.12% gel has not been reported. The purpose of the present study, therefore, was to evaluate whether 1% chlorhexidine gel (CHX-gel) is effective in preventing 'de novo' plaque accumulation when compared to a RDF or 0.12% CHX gel-toothpaste using a 3-day non-brushing model. A 0.2% CHX mouthwash was used as a positive control.

Materials and methods

Ethics approval

The study followed instructions based on the Helsinki principles. The protocol was approved by the Medical Ethics Committee of the Academic Medical Centre (AMC) of Amsterdam under registration number MEC 07/152 # 07.17.1074. The study has also been registered at the Dutch Trial Register (NTR 1429). Subject participation in this study was voluntary. Before enrolment, all subjects were given oral and written instructions, information about the products, and a description of the purpose, aim, reason, duration, possible benefits and possible harms of study participation. All subjects willing to take part signed an informed consent form prior to the study procedures.

Subjects

A total of 115 non-dentally related subjects were recruited by e-mail and a flyer advertising the study. Inclusion criteria required that the subjects were ≥18 years of age, systemically healthy and possessed a dentition with at least 20 teeth (minimum of five evaluable teeth per quadrant). Exclusion criteria were open caries, pockets ≥5mm, orthodontic appliances or removable (partial) dentures, a history of allergic reaction to erythrosine and/or CHX, use of antibiotics in the preceding 3 months, and pregnancy or medication that might interfere with the conduct of the study or possibly influence normal gingival health.

Design and (clinical) procedures

The study was designed as a prospective single-blind, randomized four-arm parallel clinical trial. At baseline, the teeth of all subjects were stained for plaque with an erythrosine disclosing solution applied with a cotton swab. Subjects subsequently received professional oral prophylaxis for a maximum of 30 min, performed by experienced dental hygienists. Teeth were scaled and polished so that they were plaque-, stain-, and calculus-free. An ultrasonic scaler (Sonosoft® KaVo, the Netherlands BV, Vianen, the Netherlands and EMS Electro Medical Systems SA, Nyon, Switzerland) and hand instruments (H6/7,SD204, 1/2, 12/13 11/14 American

Eagle® American Eagle Instruments Inc., Missoula, MT, USA, and/or Hu-Friedy® Hu-Friedy Inc., Leimen, Germany) were used, followed by rotating polishing cups, points and brushes (Hawe-Prophy® #1802, #1805 and #0220), Hawe-Neos Dental Dr H.v.Weissenfluh AG, Bioggio, Switzerland) with polishing paste (Cleanpolish® #360, Hawe-Neos Dental Dr H.v.Weissenfluh AG, Bioggio, Switzerland).

After debridement, teeth were stained for plaque for a second time in order to make sure that all visible and stainable plaque had been removed. Subsequently, unwaxed floss (Johnson & Johnson, distributor, GABA B.V., Almere, the Netherlands) was used for a professional interdental cleaning. Distal to the last molars, bandage tape (Cotton Tamponing Bandage 1 cm 5 m sterile Hartmann®, Heidenheim, Germany) was used to make sure that all remnants of plaque were removed. Next, every subject received a unique trial number and was randomly assigned to one of the four regimens (Table 1) consisting of 1% CHX gel, 0.12% CHX dentifrice gel, RDF and 0.2% CHX mouthwash. Allocation concealment to treatment assignment was performed by keeping the registration form in an opaque sealed envelope which was stored by the study coordinator. Case record forms only include subject numbers and made no refer whatsoever to any treatment assignment.

Randomization was performed using true random numbers obtained via http://www.random.org. Each subject received a demonstration and verbal instructions immediately following the professional dental prophylaxis. In addition, a written instruction form was provided to explain the use of the intervention products. The dentifrice/gel groups received a large 10EL630 Elmex® fluoride application tray (Johnson & Johnson distributor, GABA BV, Almere, the Netherlands) for the twice daily application. All subjects were given a stopwatch with an alarm to keep track of the assigned rinsing or application time (Table 1). Drinking, eating and rinsing were not allowed for 30 min after the experimental procedures. During a 3-day experimental non-brushing period, subjects abstained from all other forms of oral hygiene. To check for compliance, subjects were asked to register the time of use of intervention products on a calendar record chart.

At the second visit (3 days later), all plaque on the teeth was detected using cotton swabs with an 1% erythrosine disclosing solution; the same batch was used for all subjects. All measurements were carried out under the same conditions and were performed by the same experienced examiner (NAMR). Plaque was assessed at six sites per tooth on a six-point scale using the Quigley & Hein's (1962) plaque index (PI) as modified by Turesky et al. (1970) and further modified by Lobene et al. (1982), in which the absence or presence of plaque was recorded on a 0–5 scale (0=no plaque, 5=plaque covering more than two-thirds of the tooth surface). The

level of gingival inflammation was then assessed by another examiner (DES) using the Bleeding on Marginal Probing (BOMP) score (Van der Weijden et al. 1994, Van der Weijden et al. 1994, Lie et al. 1998). Bleeding was elicited with a WHO-approved ball-ended probe (Ash Probe EN15, Dentsply International, York, PA, USA). The gingival margin was briefly probed at an angle of approximately 60° to the longitudinal axis of the tooth. The absence or presence of bleeding was scored within 30s of probing on a scale of 0–2 (0=non-bleeding, 1=pinprick bleeding, 2=excess bleeding). Both examiners (NAMR, DES) were calibrated and blinded to the regimens. Subjects were instructed not to reveal their group assignment in any way to the clinical examiners.

Finally, all subjects received a questionnaire to evaluate their attitude towards the product they had used. They gave their opinions of the product taste, alteration of taste, comfort of use, duration of taste, and perception of plaque control. Subjects marked a point on a 10-cm-long uncalibrated line with the negative extreme response (0) on the left and the positive extreme (10) on the right end [Visual Analogue Scale (VAS)]. After the experimental period, the subjects resumed their normal oral hygiene procedures.

Table 1. Regimens

Regimen	Product	Use of intervention
CHX-DFG	0.12% Chlorhexidine dentifrice gel Dentaid®	Twice daily application in fluoride application tray for 2 min. No brushing was allowed
CHX-Gel	1% Chlorhexidine gel Corsodyl®	Twice daily application in fluoride application tray for 2 min. No brushing was allowed
RDF	Regular dentifrice HEMA	Twice daily application in fluoride application tray for 2 min. No brushing was allowed
CHX-MW	0.2% Chlorhexidine mouthwash Corsodyl®	Twice daily mouthwash rinsing with 10 ml for 1 min. No brushing was allowed

Sample size

The American Dental Association (ADA) (2009) Toothbrush Acceptance Program Guidelines state that adequate evidence from at least one clinical investigation of at least 25 subjects per group at baseline must show that the product can provide a 15% statistically significant reduction in plaque versus baseline when employed under unsupervised conditions by the average layman. Therefore, 15% is generally accepted as a clinically relevant difference in PI. Sample size calculations were performed with PS Power and Sample Size Program®. These analyses provided a lower limit for 15% superiority, with a mean PI of 1.87 based on an earlier study

(Slot et al. 2007). With a group standard deviation (σ) of 0.4, a difference (δ) of 0.28 and α=0.05 to obtain 80% power, 88 subjects would be sufficient for this study (22 subjects in each group). A sufficient number of additional subjects were included to compensate for possible loss to follow-up.

Statistical analyses

Subject demographics (gender, mean age) are presented by regimen; the statistical differences amongst groups were calculated. The Quigley & Hein PI (Quigley & Hein, 1962) as assessed after 3 days of 'de novo' plaque accumulation was the primary outcome variable. Full-mouth mean PI scores were calculated for each individual. Secondary outcome variables were BOMP after 3 days as well as the VAS scores from the questionnaire. All analyses comparing differences (PI, BOMP, VAS scores) amongst the four regimens were performed using a one-way anova test. All data are presented as mean and SD per regimen and analysed by 'Intention to Treat'. Normality was tested by Kolmogorov–Smirnov (with Lilliefors Significance Correction) and by Shapiro–Wilk analyses. For post-testing between the regimens the T-test was used to test for differences between regimens. The 95% confidence intervals were calculated for differences in plaque and BOMP scores between groups. P-values ≤ 0.05 were considered statistically significant. The statistical analyses were performed before breaking the allocation code.

Results

Figure 1 is a flow chart of the participants who were enrolled in this study. A total of 115 systemically healthy recruited subjects (±22 years of age) were screened. Three were excluded for not meeting the inclusion criteria and 112 subjects were enrolled in the study. Groups were comparable in age and sex ratio (Table 2). All but one subject (in the CHX-DFG group) completed the protocol without any protocol violation; she was lost to follow-up because she did not attend the second appointment. Her absence was determined to be unrelated to the study products.

Table 2. Subject demographics, presented by regimen

	CHX-DFG	CHX-Gel	RDF	CHX-MW	P-value
N	27	29	29	26	
♀ female	21	23	22	20	0.991*
♂ male	6	6	7	6	
Age in years Mean (SD)	22.1 (2.55)	22.3 (3.05)	23.5 (3.64)	22.2 (2.23)	0.838*
Age range	19-29	19-31	19-32	18-26	

* Chi-square comparison amongst the four groups

Table 3 provides the results for the primary response variable, i.e., the mean PI scores for each regimen after 3 days of plaque accumulation. Mean whole-mouth PI was 1.16 (0.46) for the chlorhexidine dentifrice-gel (CHX-DFG) group and 0.88 (0.39) for the CHX-Gel group, compared to 1.31 (0.40) for the RDF group and 0.79 (0.36) for the chlorhexidine mouthwash (CHX-MW) group. A statistically significant difference was found amongst the four regimens (P=0.000).

Table 3. Mean (standard deviation), minimum, and maximum overall plaque (PI) scores for each regimen after 3 days of plaque accumulation

	CHX-DFG	CHX-Gel	RDF	CHX-MW	P-value
Mean overall PI	1.16 (0.46)	0.88 (0.39)	1.31 (0.40)	0.79 (0.36)	<0.001*
Minimum	0.38	0.27	0.51	0.27	
Maximum	2.21	1.99	2.21	1.68	

* One-way ANOVA test

Post-testing between the regimens revealed that the PI scores of both CHX-MW and CHX-Gel groups were significantly lower than those of the CHX-DFG and RDF groups. No statistically significant differences were found between the PI scores of CHX-DFG and RDF or between CHX-MW and CHX-Gel (Table 4). The mean bleeding index (BOMP) for each regimen is presented in Table 5. No significant differences in the BOMP score were found amongst the four different regimens.

Table 4. Post hoc statistical analysis: t-tests and 95% confidence intervals for differences in mean plaque scores between the regimens

Regimens	T-test	Confidence Interval	P<0.05
CHX- Gel : RDF	<0.001	[-0.63 ; -0.21]	Yes
CHX- Gel : CHX-MW	0.343	[-0.11 ; 0.30]	No
CHX- Gel : CHX- DFG	0.018	[-0.50 ; -0.05]	Yes
RDF : CHX-MW	<0.001	[0.31 ; 0.73]	Yes
RDF : CHX-DFG	0.210	[-0.08 ; 0.37]	No
CHX- MW : CHX-DFG	0.002	[-0.60 ; -0.15]	Yes

Figure 1. Flowchart of subject's enrollment

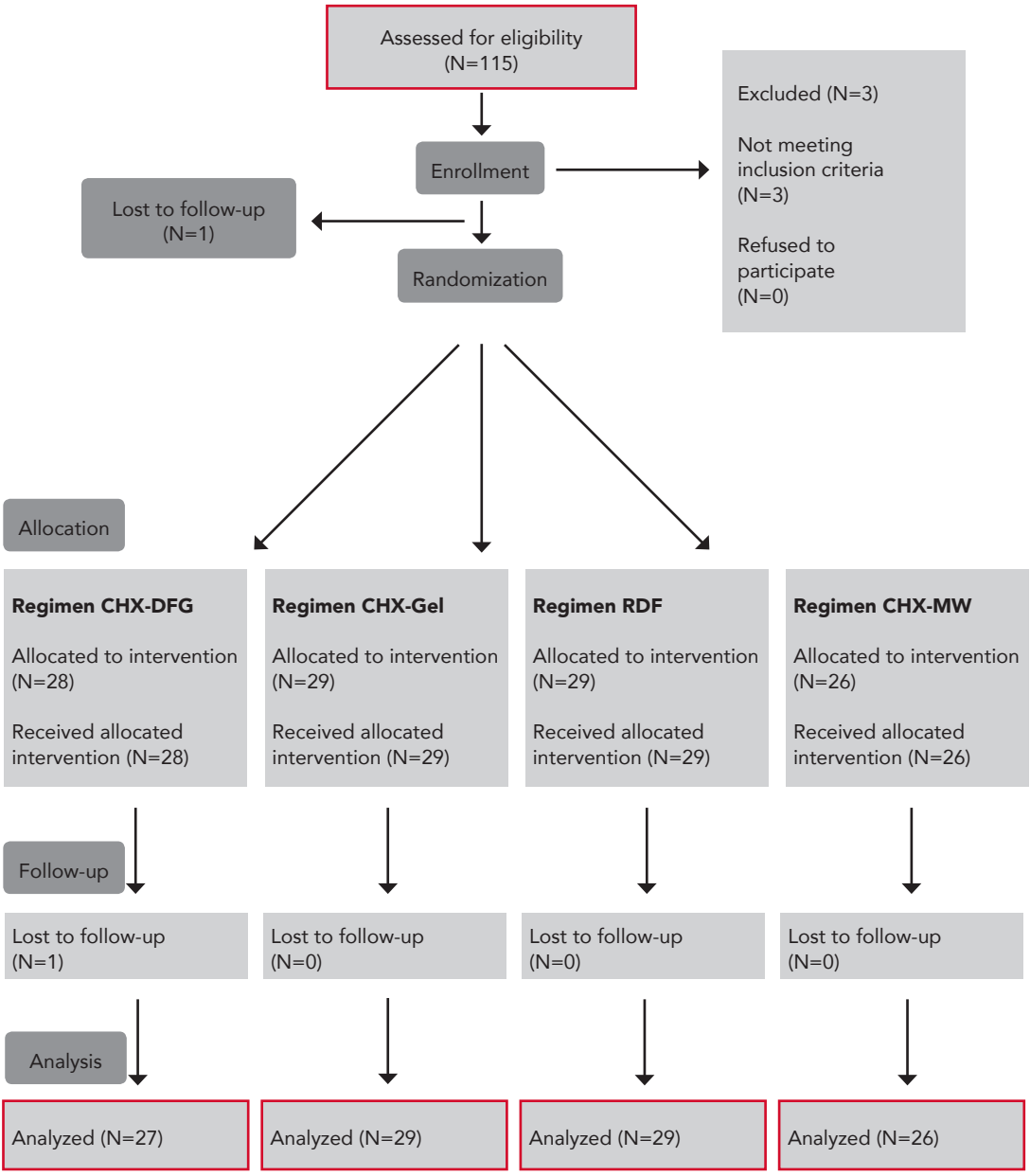

Table 5. Mean (standard deviation), minimum, and maximum overall Bleeding on Marginal Probing (BOMP) scores for each regimen after 3 days of plaque accumulation

	CHX-DFG	CHX-Gel	RDF	CHX-MW	P-value
Mean overall BOMP	0.36 (0.19)	0.28 (0.16)	0.33 (0.13)	0.30 (0.17)	0.325*
Minimum	0.11	0.03	0.08	0.07	
Maximum	0.85	0.68	0.60	0.74	

* One-way ANOVA test

Table 6 shows the complete questionnaire and the two extremes of the response options. Table 7 shows the results of the questionnaire. A statistically significant difference amongst the four groups was found with respect to perception of taste, comfort of use and subjects' perception of plaque control. No statistically significant differences were found for alteration of taste, duration of taste, or the application/rinsing time. Both data from plaque and bleeding scores were normal distributed. With respect to perception of taste, CHX-MW and CHX-Gel were not as well appreciated as the CHX-DFG and RDF. The comfort of use of the mouthwash was perceived as significantly higher than that of the application tray. Subjects using RDF considered plaque control to be less effective when compared to CHX-Gel and CHX-MW.

Table 6. Complete set of questions from Visual Analogue Scale questionnaire (scored from 0 to 10)

		With extremes	
Paraphrase	Complete question	From	To
Taste perception	How was the taste of the product?	Very bad	Very good
Duration of taste	How long did the taste remain?	Very short	Very long
Alteration of taste	How was your taste of food and drinks affected?	Negative change	Positive change
Time of application	What is your opinion about the application time of the product?	Very short	Very long
Use of comfort	What is your opinion about the ease in use of the product?	Not easy	Very easy
Plaque control	What is your perception of plaque control during this 3 days?	Insufficient	Very efficient

Table 7. Results of the questionnaire response on the Visual Analogue Scale Mean scores (standard deviation) are presented by regimen

Question	CHX-DFG	CHX-Gel	RDF	CHX-MW	P-value*
Taste perception	6.26 (2.42) †/‡	2.47 (1.93) †	6.14 (1.99) †/‡	4.68 (2.30)	<0.001
Alteration of taste	4.54 (0.39)	4.24 (1.74)	4.34 (0.92)	3.93 (1.40)	0.351
Duration of taste	5.28 (2.06)	5.20 (2.72)	5.91 (2.09)	6.08 (2.53)	0.413
Time of Application	5.49 (1.79)	4.57 (2.02)	5.18 (1.68)	4.27 (1.79)	0.061
Comfort of us	4.55 (2.17) †/‡	5.84 (2.47) †	5.83 (2.70) †	8.08 (1.55)	<0.001
Plaque control	4.65 (2.77)	6.02 (2.95)	3.66 (2.73) †/‡	5.72 (2.76)	0.007

* One-way ANOVA test
† Post-tested with t-test, significant differences ≤0.05 compared with CHX-MW
‡ Post-tested with t-test, significant differences ≤0.05 compared with CHX-Gel

Discussion

Model

Short-term plaque regrowth studies are perhaps the most commonly used clinical experiments for screening chemical oral hygiene products. They have the advantage of assessing the chemical action of the formulation separate from the indeterminate variable of toothbrushing. Typically, plaque regrowth from a zero baseline is recorded to determine the influence of the test agent. This method was originally used for mouthrinses and has been modified for toothpaste by delivering the formulation in a tray applied to the teeth (Etemadzadeh et al. 1985). Study periods range from 24 h to several days. A negative (benchmark) control and a positive control such as chlorhexidine may be used. These help to determine the activity of the test formulations in relation to known formulations. The present study evaluated the plaque-inhibiting effect of CHX products in a 3 day non-brushing model during which plaque was allowed to accumulate freely. This design has been used previously to assess the effect of 0.12% DFG (Slot et al. 2007). The results of the present study confirm the observations of a previous study, which showed no significant difference between CHX-DFG and RDF. In addition the present study showed that the inhibition of plaque formation with a 1% CHX gel was not significantly different from a 0.2% CHX mouthwash.

1% CHX-gel

The 1% CHX-Gel product is commercially available over the counter and can be delivered via a toothbrush or in trays. The distribution of a gel throughout the mouth over the tooth surfaces by toothbrush appears to be poor, and preparations must

be delivered to all surfaces to be effective (Saxén et al. 1976). CHX-Gel delivered via a tray was found to be particularly effective against plaque and gingivitis in handicapped individuals (Francis et al. 1987a). However, the acceptability of the tray delivery system to the recipients and the care-takers was found to be poor (Francis et al. 1987b). The 1% CHX gel has also been used in subgingival applications after scaling and root planing. This results in a statistically lower gingival index than scaling and root planning alone (Vinholis et al. 2001). Bleeding on probing was also significantly reduced compared to a placebo gel (Perinetti et al. 2004). Other studies have shown a reduction in the frequency and detection of several peridontopathic microorganisms (Vinholis et al. 2001, Perinetti et al. 2004).

Dose response

The anti-plaque effect of the 0.12% CHX dentifrice gel may be similar to that of a RDF due to the amount of CHX digluconate per application. The CHX-MW, CHX-Gel and the CHX-DFG all contained various percentages of CHX. Given a specific gravity of 1.080 g ml-1 for CHX digluconate, each CHX-DFG application with a fluoride tray of approximately 10 g contained 12 mg of available CHX digluconate. For the 1% CHX gel, the application of approximately 10 g provided around 100 mg of CHX digiclonate. Although no direct comparison can be made between a gel and a mouthwash, it is clear that the 12 mg provided by CHX-DFG is insufficient to exceed the effect of RDF. The reason for this may be 2-fold.CHX in CHX-DFG could be inactivated by dentifrice components (Addy et al. 1989, Barkvoll et al. 1989, Jenkins et al. 1990), and diffusion of CHX from the dentifrice formulation might be inhibited or decreased by dentifrice components (Putt et al. 1991). Alternatively, for a gel dosing should be higher. The effect of the dosis has been shown to be the case with application of CHX via an oral irrigator; in this situation 80 mg was found to be the optimal dosage (Lang & Ramseier-Grossman, 1981).

Bleeding scores

Several studies have shown that the development of plaque may be dependent on a number of factors such as diet (Rateitschak-Plüss & Guggenheim 1982), tooth surface roughness (Quirynen et al. 1990), periodontal condition (Rowshani et al. 2004) and bacterial salivary load (Dahan et al. 2004). An experimental gingivitis study by Hillam & Hull (1977) showed that the amount of plaque developing in 24 h in patients with good gingival health at baseline was considerably less than the amount of plaque developed in 24 h at the end of the experimental gingivitis period. More extensive studies were performed earlier (Lang et al. 1973; Brecx et al. 1980, Goh et al. 1986, Quirynen et al. 1991, Ramberg et al. 1994a,Ramberg et al. 1994b, Ramberg et al. 1995, Daly & Highfield 1996, Rüdiger et al. 2002) all confirmed that periodontal condition is of foremost importance in the rate of 'de novo' plaque formation. The

use of four separate groups in the present parallel design could have introduced an unwanted effect as a result of varying levels of gingival health. Therefore, in this study, the level of gingival health was assessed in conjunction with the to plaque levels to evaluate whether this factor potentially could have impacted the outcome of the study. In other words whether differences in plaque scores after 3 days could be explained by differences in the level of gingival inflammation this appeared not to be the case (Table 5). In terms of BOMP, bleeding scores were found to be comparable amongst groups and therefore not considered to be a confounding factor for the plaque scores.

Conclusion

Within the limitations of the present 3-day non-brushing study design, it can be concluded that the tray application of 1% CHX gel is significantly more effective than 0.12% CHX dentifrice gel or RDF in the inhibition of plaque accumulation. When applied via a tray, the 1% CHX gel was not significantly different from rinsing with 0.2% CHX-MW.

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Conflict of interest and source of funding statement

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4.

Were there none who were discontented with what they have, the world would never reach anything better.

Florence Nightingale

THE EFFICACY OF CHLORHEXIDINE DENTIFRICE OR GEL ON PLAQUE, CLINICAL PARAMETERS OF GINGIVAL INFLAMMATION AND TOOTH DISCOLORATION: A SYSTEMATIC REVIEW

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Introduction

Removal of plaque by the individual continues to be considered as the foremost effective tool to control and prevent gingivitis (Sheiham 1991, Sanz et al. 1994). The most reliable methods currently used for plaque removal are toothbrushing and other mechanical cleaning procedures (for review, see van der Weijden & Slot 2011). As adequate plaque control is difficult to attain by most people, research efforts have been directed towards the development of safe and efficacious chemical antiplaque agents (Sanz et al. 1994, Gjermo & Saxton 1991).

Löe and Schiott (1970) reported on the inhibition of plaque formation and gingival inflammation in students rinsing twice daily with a 0.2% solution of chlorhexidine (CHX). Ever since, the effect of CHX digluconate has been of interest in dental research and various modes of administration have been studied. CHX mouthrinse as adjunct to mechanical oral hygiene versus placebo or control mouthrinse provides significant reductions in plaque and gingivitis scores. This has recently been established by Van Strydonck and co-workers (2012) established in a systematic review of the existing scientific literature that in gingivitis patients, the corollary is a significant increase in tooth surface discoloration score. Discoloration of tooth surfaces, restorations and the dorsum of the tongue, desquamation and soreness of the oral mucosa (Flötra et al. 1971, Hansen et al 1975) are all well-known side effects of CHX. Another systematic review has recently been published on medicated chewing gum (Keukenmeester et al. 2014). The meta-analysis showed that CHX provides a beneficial effect on plaque inhibition.

It would be ideal to incorporate CHX in a dentifrice formulation (Sanz et al. 1994) as most patients daily use a dentifrice. The potential of this has been shown in a non-brushing study where the use of CHX dentifrice resulted in significant less plaque and gingivitis as compared to the placebo (Putt et al. 1993). At present, a systematic evaluation has not yet been performed on the effect of toothbrushing with a CHX dentifrice or gel on clinical parameters of plaque and gingivitis, evaluating the side effects and tooth surface discoloration. Therefore, this paper systematically evaluated the current scientific literature on brushing with CHX dentifrice or gel to add 'evidence-based' knowledge.

Materials and methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA statement, Moher et al. 2009).

Focused question

What is the effect of brushing with chlorhexidine (CHX) dentifrice or gel versus a placebo/control dentifrice or gel on parameters of plaque, gingival inflammation and tooth surface discoloration in adult patients with gingivitis?

Search strategy

Three Internet sources of evidence were used to search for appropriate papers that satisfied the study purpose. These included the National Library of Medicine, Washington, DC. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). All databases were searched starting from their earliest records until 01 July 2013. The structured search strategy was designed to include any published paper that evaluated the effect of CHX dentifrice and/or gel on plaque and the parameters of gingival health. The search strategy was customized according to each database that was searched (for details on the used search terms, see Box 1).

Screening and selection

Two reviewers (DES & GAW) independently screened the titles and abstracts for eligible papers. If the eligibility aspects were present in the title, the paper was selected. If none of the eligibility aspects were mentioned in the title, the abstract was read in detail to screen for suitability. When the abstract was not clear or no abstract was available but the title seemed to be relevant, the paper was selected for full-text reading. After selection, the full-text papers were read in detail by two reviewers (CEB & DES). Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, the judgement of a third reviewer (GAW) was decisive. Papers that fulfilled all selection criteria were processed for data extraction. All reference lists of the selected studies were hand searched by two reviewers (CEB & DES) for additional published work that could possibly meet the eligibility criteria of the study. Unpublished work was not sought.

Box 1. Search terms used for PubMed–MEDLINE, Cochrane–CENTRAL and EMBASE

The search strategy [<{Agent} AND {vehicle}> AND {outcome/disease}] was customized appropriately for each of the additional databases being used taking into account differences in controlled vocabulary and syntax rules.
The following terms were used in the search strategy:

[<{Agent: [MeSH terms /all subheadings] chlorhexidine OR [textwords] chlorhexidine OR chlorhexidine phosphanilate OR chlorhexidine di-gluconate OR chlorhexidine gluconate OR chlorhexidine di-acetate OR zinc-chlorhexidine OR chlorhexidine gluconate lidocaine hydrochloride OR CHX OR CHX formulations}
AND
{Vehicle: [MeSH terms /all subheadings] Toothpaste OR Dentifrices OR [text words] toothpaste OR toothpastes OR dentifrices OR dentifrice OR gel}>
AND
{Outcome/disease: [MeSH terms /all subheadings] gingivitis OR gingival hemorrhage [text words] gingivitis OR gingivit* OR gingival bleeding OR gingival hemorrhage OR gingival diseas* OR gingival index OR gingival inflammation OR bleeding on probing OR papillary bleeding OR bleeding index OR sulcus bleeding index OR plaque index OR dental plaque OR plaque OR interdental plaque OR interproximal plaque OR dental deposit* OR stain OR discoloration OR calculus OR tartar}]

The asterisk (*) was used as a truncation symbol.

The eligibility criteria were as follows:

- Randomized controlled clinical trials (RCTs) or controlled clinical trials (CCTs).
- Conducted in humans:
    - ≥16 years of age.
    - Good general health.
    - Participants with gingivitis/no periodontitis patients.
- Intervention: toothbrushing with CHX dentifrice and/or gel.
- Control group: toothbrushing with placebo dentifrice and/or gel.
- Supragingival use of CHX dentifrice and/or gel.
- Clinical outcome parameters: plaque, gingivitis, bleedingupon probing and tooth surface discoloration.
- No dental implants, orthodontic treatment or (partial)dentures.
- Duration of ≥4 weeks [for rationale, see Adjunctive Dental, Therapies for the Reduction of Plaque and Gingivitis (ADA 2008)].
- Manuscripts written in the English language.

Assessment of heterogeneity

Factors that were recorded to evaluate the heterogeneity of the primary outcome across studies were as follows:

- Characteristics of the participants.
- Characteristics of the interventions.
- Characteristics of the trial settings and investigators.

Quality assessment

Two reviewers (CEB & DES) scored the methodological qualities of the included studies. This was assessed according to the method that has been described in detail by Keukenmeester et al. (2013). For the criteria listed, see online Appendix S2. In short, when random allocation, defined eligibility criteria, blinding of examiners, blinding of patients, balanced experimental groups, identical treatment between groups (except for the intervention) and reporting of follow-up were present, the study was classified as having a low risk of bias. When one of these seven criteria was missing, the study was considered to have a moderate risk of bias. When two or more of these criteria were missing, the study was considered to have a high risk of bias, as proposed by Van der Weijden et al. (2009).

Statistical analyses

DATA EXTRACTION

From the papers that met the eligibility criteria, data were extracted with regard to the effectiveness of CHX gel and/or dentifrice by two reviewers (CEB & DES). Mean values and standard deviations (SDs) of baseline, end and incremental scores on the parameters of interest were extracted from the text. For studies that presented intermediate assessments, the baseline and final evaluations were used for this review. Some of the studies provided standard errors of the mean. Where possible, the authors calculated standard deviation based on the sample size ($SE=SD/\sqrt{N}$). For those articles that provided insufficient data to be included in the analysis, the first or corresponding authors were contacted whether they could provide additional data. This warrants a precise estimate because any data approximation in figures was avoided.

DATA ANALYSIS

Studies were analysed for similarities and suitability for meta-analysis. After a preliminary evaluation of the selected papers, it was found that considerable heterogeneity was present in the study designs, characteristics, outcome variables and results. It was therefore not possible to perform a quantitative analysis of the data and subsequent meta- analysis. The pooled data were analysed in a descriptive format by vote counting.

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as proposed by the GRADE working group was used to rank the evidence emerging from this review (GRADE working group, Guyatt et al. 2008) regarding CHX dentifrice and CHX gel. Two reviewers (DES & GAW) rated the quality of the evidence as well as the strength of the recommendations according to the following aspects: risk of bias of the individual studies, consistency and precision among the study outcomes, directness of the study results and detection of publication bias. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Summary of included studies

The searches of the three databases resulted in 389 unique papers (for details, see Figure 1). In total, 363 papers were excluded based on title and/or abstract. Of the 26 remaining papers selected for full-text evaluation, 15 papers were not suitable in relation to the focused question. Reasons for exclusion are detailed in the online Appendix S1. In total, 11 publications were considered eligible and were processed for assessment of heterogeneity. These provided 12 experiments and 16 comparisons, of which nine evaluated CHX dentifrice and seven CHX gel.

Assessment of study quality and heterogeneity

Table 1 provides a brief overview of the design details of the 11 included studies. Evaluation of the selected papers showed considerable heterogeneity, which is described below.

Characteristics of the participants

Information about the number, gender and age of participants is given in Table 1 (study number in Roman numerals). Selection criteria of the included studies for the level of gingivitis were clinical evidence of gingivitis (GI>0.7) (IV), a mean GI of ≥0.5 (VI), a GI of ≥2 in a minimum number of teeth in each quadrant (II) and a bleeding index ≥30% (I). The other studies provided no specific information of the participants' gingival status (II, V, VII, VIII, IX, XI). Claydon (2006) (II) and Yates et al. (1993) (VI) were the only authors who mentioned the number of smokers in their groups. Claydon (II) mentioned that a randomization schedule was used which stratified for smokers, and Soukoulos et al. (2004) (III) and Pereira et al. (2013 (I) selected only non-smokers.

Figure 1. Search, selection and analysis process

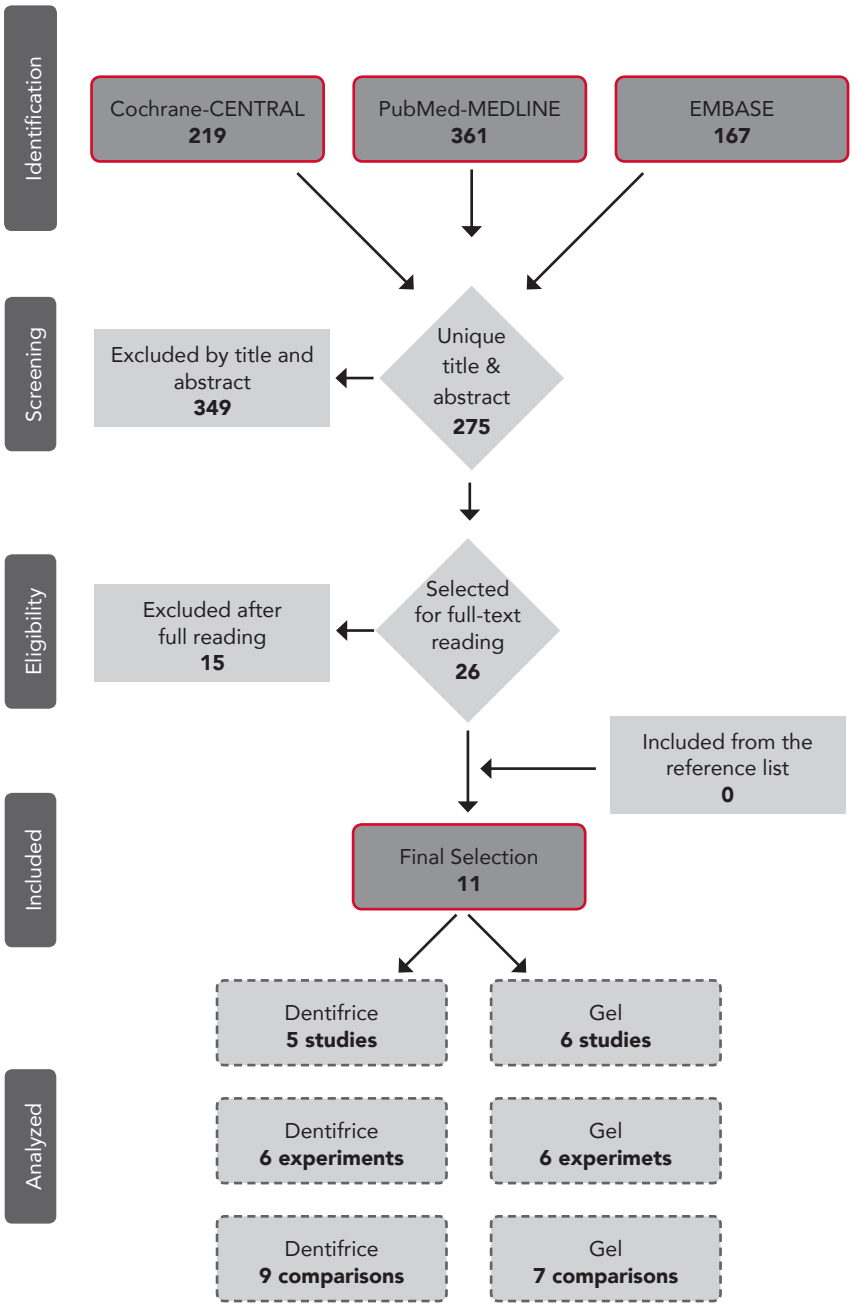

Table 1. Overview of the studies processed for data extraction

# Authors (year)	Study design, duration	# Participants baseline (end), Gender, age, Oral prophylaxis (OP)	Groups	Regimen: Use & instruction	Conclusions of the authors of the orginal papers
I Pereira et al. (2013)	RCT Parallel Double blind 3 months	20 (20) ♀: ? ♂: ? Mean age: ? Age range: ? No OP	CHX gel 2% Placebo gel	Brush 3x daily for 1 minute CHX gel: A full toothbrush head Placebo gel: A full toothbrush head No special brushing technique	At day 90, there was a statistically significant difference in PI and BI scores between the control and test group.
II Claydon et al. (2006)	RCT Parallel Single blind 6 weeks	164 (157) ♀: ? ♂: ? Mean age: ? Age range: ? OP	CHX gel 1% CHX gel 1% reduced Fluoride dentifrice	Brush 2x daily for 1 minute Reduced: 2x brushing of which 1 time with CHX gel CHX gel: A full toothbrush head Fluoride dentifrice: A full toothbrush head No special brushing technique No interdental cleaning was allowed	A low dose of CHX gel at night and a whitening paste in the morning produced a significant amount of stain that 30% of participants considered unacceptable.
III Soukoulis & Hirsch (2004)	RCT Parallel Double blind 8 weeks	33 (?) ♀: 17 ♂: 16 Mean age: 45.6 Age range: 23-63 No OP	CHX gel 0.2% (Periogard, Colgate, NSW, Australia) Placebo gel	The gel was to be used as a dentifrice for a minimum of two minutes daily One toothbrush-length of the gel OHI: pamphlet, making sure that it made contact with gingival tissues adjacent to the teeth No other dentifrice or interdental cleaning were allowed No rinsing, eating or drinking was allowed for 30 minutes after gel application	No statistical difference in plaque scores and gingivitis scores between the groups.
IV Sanz et al. (1994)	RCT Parallel Double blind 6 months	137◊ (125◊) ♀: 81 ♂: 56 Mean age: 32.3◊ Age range: 18-65 OP	CHX dentifrice 0.4%+ Placebo mouthrinse Placebo dentifrice+ Placebo mouthrinse	Brushing 2x daily Rinsing 2x daily with placebo rinse No additional OHI	CHX containing dentifrice was effective in reducing plaque accumulation and gingival inflammation over a six month period.

V Smith et al. (1994)	RCT Parallel Single blind 6 weeks	120 (114) ♀: ? ♂: ? Mean age: ? Age range: ? OP	CHX gel 0.2% Regular dentifrice	Brush 2x daily for 1 minute OHI: ? No other dentifrice or interdental cleaning were allowed	0.2% CHX gel significantly reduced the amount of plaque formed compared to regular dentifrice over a period of 6 weeks.
VI Yates et al. (1993)	RCT Parallel Double blind 6 months	296 (269) ♀: 197 ♂: 99 Mean age: ? Age range: 18-61 OP	CHX dentifrice 1% CHX dentifrice 1%+ NaF Placebo dentifrice	Brushing 2x daily for 1 minute Using sufficient paste to cover the head of the brush No OHI No use of other oral hygiene products allowed	Plaque, gingival and bleeding scores improved significantly in the active groups.
VII Emilson & Fornell (1976)	RCT Parallel Double blind 12 months	37 (36) ♀: 13 ♂: 24 Mean age: 23 Age range: 21-28 No OP	CHX gel 0.5% Placebo gel	Brush once a day for two minutes One toothbrush-length strip of the gel ±0.5g No OHI No use of any other dentifrice besides the gel	The active gel did not markedly influence plaque formation, gingival conditions as compared with placebo gel treatment.
VIII Saxton et al. (1976)	CCT Parallel Double blind 4 weeks	40 (29) ♀: ? ♂: ? Mean age: ? Age range: 18-30 OP?	CHX dentifrice 0.8% Placebo dentifrice	?	0.8% CHX dentifrice significantly reduced the bleeding and the plaque after 4 weeks.

IX Hansen et al. (1975)	RCT Cross-over Double blind 4 weeks	36 (36) ♀: ? ♂: ? Mean age: 18 Age range: 16-21 No OP	1% CHX gel Placebo gel	Brush in the evening One toothbrush-length of the gel No OHI Addiional toothbrushing to the test brushing was performed with a standard commercial dentifrice without abrasives or fluoride	CHX containing gel seemed to have no effect on gingivitis and only a slight inhibitory effect on plaque formation. Furthermore, an increase in the degree and frequency of tooth discoloration of the tooth surfaces related to the use of active gel were observed.
X Johansen et al. (1975)	RCT Parallel Double blind 2 years	73 (60) ♀: ? ♂: ? Mean age: ? Age range: 19-23 OP	CHX dentifrice Abr 1%‡ CHX dentifrice Abr 0.4%‡ Placebo dentifrice Abr‡ CHX dentifrice 0.4%‡ Placebo dentifrice‡	Brushing 2x daily 1 g dentifrice No OHI	No differences were found in the PI and the GI indices between the active and the placebo dentifrices. Discolorations of anterior teeth and fillings were the only side effects observed.
XI Gjermo & Rölla (1971)	RCT Parallel Double blind 2 months	53 (52) ♀: ? ♂: ? Mean age: 23 Age range: ? OP	CHX Dentifrice 0.8%‡ CHX Dentifrice 0.6%‡ Dentifrice‡	Brush 2x daily for two minutes 1g dentifrice No particular instructions concerning toothbrushing methods were given No interdental cleaning was allowed	Dentifrice as a vehicle for CHX might be of value in the general preventive application of the agent.

OP, at initial appointment, all teeth were thoroughly scaled and polished; ◊, calculated by the authors of this review based on the presented data in the selected paper; ?, unknown/not given; ‡, Agents known to interfere with antibacterial activity of CHX (sulphates, phosphates) were excluded from the dentifrices.

Characteristics of the trial

Six studies performed oral prophylaxis at baseline consisting of scaling and polishing (II, IV, V, VI, X, XI). Five studies did not perform a dental prophylaxis or did not specifically mention whether an oral prophylaxis was performed (I, III, VII, VIII, IX). One of these mentioned that no dental prophylaxis, that is, scaling and polishing the teeth, was carried out before and during the trial, except for treatment of some carious lesions (VII). Another study mentioned that when tooth surface discoloration became unacceptable, participants could attend the study dental hygienist involved in the study to have tooth surface discoloration removed by polishing (VII). Teeth were polished on the last day of the experiment after the indices were recorded in one study (I).

Side effects

All included studies reported on observed side effects, both local and systemic. Apart from the taste (bitter or alteration) (II, VII, VIII) and tooth surface discoloration, no other side effects were reported.

Industry funding source and publication bias

Five of 11 papers mentioned involvement of a third party. This was described as 'supported by' (II, VI, VII, IX, XI) or as co-authors being related to industry (II, IV). The studies I and V share co-authors, and the studies IX, X and XI all are from the same research group in Oslo Norway.

Study quality and risk of bias assessment

Quality assessment values, including the internal, external and statistical validity, are presented in online Appendix S2. Based on a summary of these criteria, the estimated potential risk of bias is low for five studies (I, III, IV, VI, IX), moderate for three studies (V, VII, XI) and high for three studies (II, VIII, X).

Comparison between groups upon completion of the study

Mean (SD) scores for the different intervention groups with various indices and their modifications and within-group analysis are presented in online Appendix S2. Table 2 presents a summary of the descriptive data concerning significant differences with respect to scores of plaque, gingival index, bleeding on probing and tooth surface discoloration as presented separately for CHX dentifrice and gel.

Table 2. A descriptive summary of statistical significance of CHX dentifrice/gel to a comparison

Study #	Intervention	CHX %	PS	GI	BS	SI	Comparison
X	CHX dentifrice	0.4	0	0	□	-	Placebo dentifrice
	CHX dentifrice	0.4	0	0	□	0	Placebo dentifrice
IV	CHX dentifrice	0.4	+	+	+	-	Placebo dentifrice
XI	CHX dentifrice	0.6	+	□	□	?	Placebo dentifrice
	CHX dentifrice	0.8	+	□	□	?	
VIII	CHX dentifrice	0.8	+	□	+	□	Placebo dentifrice
X	CHX dentifrice	1.0	0	0	□	-	Placebo dentifrice
VI	CHX dentifrice	1.0	+	+	+	-	Placebo dentifrice
	CHX NaF dentifrice	1.0	+	+	+	-	
V	CHX gel	0.2	+	□	□	□	Placebo dentifrice
III	CHX gel	0.2	0	0	?	□	Placebo gel
VII	CHX gel	0.5	0	0	□	?	Placebo gel
II	CHX gel	1.0	□	□	□	-	Placebo dentifrice
	CHX gel reduced	1.0	□	□	□	-	
IX	CHX gel	1.0	0	□	0	0	Placebo gel
I	CHX gel	1.0	+	□	+	□	Placebo gel

PS, plaque scores; GI, gingival index; BS, bleeding scores; SI, staining index; +, significant difference in favour of test group; -, significant difference in favour of control group; 0, no significant difference; □, no data available; ?, inconclusive data that do not allow to draw conclusions concerning statistical significance; NaF, natrium fluoride.

Six of the nine comparisons using CHX dentifrice evaluated the effect on plaque scores. The CHX dentifrices with concentration of 0.4%, 0.6%, 0.8% and 1% all had a significant positive effect on plaque inhibition compared with the placebo (IV, VI, VIII, XI). In addition, three of six comparisons with the CHX dentifrice found a significant improvement in the gingival index in favour of the CHX dentifrice (IV, VI). Moreover, all four CHX dentifrice comparisons that assessed gingival bleeding found a significant effect in favour of the CHX dentifrice (III, VI, VIII). Tooth surface discoloration following the use of CHX dentifrice was reported as a corollary effect (II, VI, X). One comparison (III) did not show increased tooth surface discoloration.

Two of the seven comparisons using CHX gel did not find a significant effect as compared to a placebo. In the five comparisons evaluating CHX gel, two studies (I, V) found a significant effect in favour of the CHX gel on plaque score reduction. Only one of three studies assessing the bleeding scores showed a significant effect (I). Two

comparisons (II) showed significantly more tooth surface discoloration, whereas one (IX) showed no increased staining.

Grading the 'body of evidence'

Table 3 shows a summary of the various aspects, which were used to rate the quality of evidence and strength of recommendations according to GRADE (GRADE working group, Guyatt et al. 2008). Because the data are rather inconsistent for CHX gel, with on average a 'moderate estimated risk of bias', and the studies' results are not generalizable as daily oral care products, the strength of the recommendation to use CHX gel is 'weak' to 'very weak'. For CHX dentifrice, being a product that one could use for daily oral care, the strength is considered to be 'moderate'.

Table 3. GRADE body of evidence profile for impact of CHX gel and dentifrice compared with the placebo on plaque, clinical parameters of gingival inflammation and tooth discoloration from the presented systematic review

	CHX dentifrice	CHX gel	
GRADE	PS, GI, BS, stain	PS, GI	BS, stain
Risk of bias	Low to moderate	Low to moderate	Low to moderate
Consistency	Consistent	Consistent	Inconsistent
Directness	Indirect	Indirect	Indirect
Precision	Moderate	Low	Low
Publication bias	Not detected	Not detected	Not detected
Body of evidence	**Moderate**	**Weak**	**Very weak**

For abbreviations, see Table 2.

Discussion

By virtue of common usage, the ideal vehicle for the carriage of plaque control agents is a dentifrice (Forward et al. 1997). A number of ingredients are added to dentifrices to influence the consistency and stability of the product or its function (Forward et al. 1997). The inclusion of cationic antiseptics, such as CHX, in a dentifrice formulation poses problems (Addy et al. 1989). Notably, antiseptics can be inactivated by other ingredients, including detergents, for example sodium lauryl sulphate (SLS) (Kolahi & Soolari 2006). The Addy et al. (1989) study showed that a CHX toothpaste can be formulated, albeit at the expense of available CHX. Nevertheless, CHX has been formulated, successfully, into dentifrices, although few products have reached or lasted in the market- place. A reason for this might be the observed side effects (Sanz et al. 1994, Yates et al. 1993).

The aim of this systematic review was to establish the differential effects of CHX dentifrice or gel versus placebo dentifrice/gel. The selected papers were derived from three databases and provided information that was relevant to the focused question. Evaluating the studies by vote counting showed that a CHX-containing dentifrice can be effective with regard to the control of plaque and gingivitis. For CHX gel, such an effect could not be established. Consequently, brushing with CHX gel was not found to provide a benefit. Tooth surface discoloration was observed as a side effect with both gels and dentifrices that potentially can have a negative impact on patients' compliance (Van Strydonck et al. 2012).

One study (X) does not support the clinical benefit of CHX dentifrice. The explanation brought forward by the authors is that the experimental participants in this study were highly selected being young dental students with good oral hygiene, healthy gingiva and low caries activity. Moreover, influenced by the environment of a dental school, and possibly by experiment itself, their oral hygiene improved during the first 6 months of the study, then stayed relatively constant for the next 12 months. When the students at this time started their clinical training, a further drop in the plaque index values was observed in all groups. Thus, it seems conceivable that a plaque-inhibiting effect of CHX dentifrice in this study design may have been masked by the excellent mechanical tooth cleaning performed by the test participants (Johansen et al. 1975).

Risk of bias assessment

Today, practitioners are under increasing pressure to make sound decisions based on scientific evidence. Partly as a consequence of this daunting challenge, a growing number of organizations have developed ways to arrange our thinking about information and its quality in recent years. These organizations have created evidence, grading schemes to generate dependable systematic reviews of evidence. These schemes or systems continue efforts to reduce the bias that can enter reviews (Boruch & Rui 2008). The risk of bias assessment as performed in the present review included all relevant aspects and was a compilations of items as found in various available checklists. The presented high and moderate risk of bias can be a result of poor reporting instead of introducing risk factors during the trial itself. For instance, only three papers (I, II, III) were published during the last decade, while the other papers have been published up to 40 years ago. Therefore, using a modern assessment tool based on the current reporting methodological quality items may lead to on overestimation of the risk of bias. For example, if as suggested to the Cochrane collaboration, 'allocation concealment' (Higgins & Green 2011) was used as a discriminating criterion, this would have had a major impact on the estimated risk of bias and would subsequently reduce the level of all included studies by one step.

Side effects

CHXs' most clinically undesirable effect is its propensity to stain teeth on prolonged use. It has been reported that CHX may also interfere with the taste function. Another objectionable feature of the antimicrobial is a very bitter taste and CHX can enhance calculus formation (Overholser et al. 1990). Although tooth surface discoloration with CHX products may be an unwelcome side effect, lack of tooth surface discoloration with CHX products would suggest lack of clinical activity as is commonly stated 'If it does not stain it does not work' (Addy et al. 2005). Former research evaluating CHX mouthrinses which claimed not to produce tooth surface discoloration was subsequently shown to lack clinical activity (Jenkins et al. 1989). Also, results from this systematic review point in the same direction where the two studies (IX, X) providing experiments without a significant increase in tooth surface discoloration also were ineffective for any of the parameters. Based on a recent systematic review, there is moderate evidence that alternately using CHX and oxygenating mouth rinses reduces tooth surface discoloration without interfering with plaque growth inhibition (Van Maanen-Schakel et al. 2012). The explanation being that the oxidizing agent probably does not interfere with the CHX but removes food dyes and chromogens which bind to surfaces (for review, see Eriksen et al. 1985), leaving a greyish tooth surface discoloration (Gründemann et al. 2000).

Limitations

One limitation is examiner/patient blinding. Because the CHX experimental groups with a long observational period will reveal themselves by tooth surface discoloration, this may have affected the examiner and patient blinding to a certain extent. This is a particular limitation related to CHX that cannot be overcome.

The ADA requirements for a seal of acceptance Chemotherapeutic Products for Control of Gingivitis (2008) are a study period of 4 weeks to evaluate both the efficacy and safety of chemical agents as well as patients' compliance. According to Gunsolley (2006), intermediate length trials (2 weeks to 2 months), which allow for the assessment of gingivitis, have limitations in that they may not reflect the patients' actual long-term use of the product. However, two studies on CHX dentifrice extended up to 6 months (IV, VI) and both showed a significant effect in favour of the CHX product. Two included CHX dentifrice studies provided data up to 1–2 years (VII, X), both failed to show a positive effect. But, as discussed before, this may find its origin in other factors such as a highly dentally motivated group of participants.

With respect to the gels and dentifrices in the included studies, no exact information on the formulation of each of these products was provided. This is a major factor when considering the physical–chemical properties and the vehiculation of the active

ingredients with detergents, given that CHX is a very reactive cation, components from which pastes and gels are usually formulated are sometimes anionic and thus interfere with the action (bioavailability) of the CHX.

Effectiveness of CHX in non-brushing studies

Previous work using a non-brushing model showed that application of CHX with a tray for 3 weeks allowing for experimental gingivitis to develop resulted in a significant reduction in plaque and gingivitis when comparing the specially formulated CHX dentifrice to a placebo (Putt et al. 1994). More recent work using a 3-day non-brushing model shows that 0.12% CHX dentifrice/gel applied in a tray did not differ on plaque accumulation as compared to a regular dentifrice (Slot et al. 2007). Using this same model results showed that a 1% CHX gel significantly inhibits plaque formation as compared to a 0.12% CHX dentifrice/gel or a regular dentifrice. In addition, the 1% CHX gel also was comparably effective as a 0.2% CHX mouthwash (Slot et al. 2010). This is in agreement with Francis et al. (1987) who showed that CHX gel, applied in trays to physically handicapped children, resulted in comparable reductions in buccal and lingual, plaque and gingivitis similarly to a 0.2% CHX mouthrinse.

Various other studies have allowed subjects to apply a pea-sized amount of CHX gel on the teeth gums with the index finger and leaving it undisturbed for approximately 5 min before rinsing. This resulted in significant improvement (as evaluated in studies 6–24 weeks) over the placebo gel group on plaque scores and the gingival index (Pai et al. 2004, Pradeep et al. 2010, Pradeep et al.2012a, Pradeep et al. 2012b). The outcome of these studies taken together with the result of this review indicates that CHX gel is not effective in combination with toothbrushing but is effective when applied with a finger to teeth and gums. The studies did not provide an explanation for this observation, but hypothetically the local dose/ concentration appears to be a factor in efficacy. This is sup- ported by the study with a positive effect for the 2% CHX gel (I) as compared to three studies using a lower concentration not finding an effect. Also, the plaque inhibitory effect of CHX is derived from the antiseptic adsorbed onto tooth surfaces (for review, see Addy & Moran 2008). An earlier study indicated that the CHX gel did not readily break up and dissolve in saliva and then adsorb onto other tooth surfaces. This investigation, often described as the 'buccal brushing study', also has (Saxen et al. 1976) revealed that brushing a 1% CHX gel on the buccal surfaces of teeth had no effect on plaque growth on lingual and palatal tooth surfaces. Therefore, local (finger) application may be the best method for obtaining a benefit from CHX gels.

Conclusion

Within the limitations of this analysis, it may be concluded that toothbrushing with a CHX gel does not provide conclusive evidence. Brushing with a CHX-containing dentifrice is effective with regard to the control of plaque and gingivitis. Tooth surface discoloration was observed as a negative side effect, which potentially may have a negative impact on patients' compliance.

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Conflict of interest and source of funding

The authors declare that they have no conflict of interest. This study was self-funded by the authors and their institutions.

Implications for future research

CHX-containing dentifrices with an antidiscoloration system are available on the market. This could improve patients' compliance. However, their clinical beneficial effect and side effects need to be properly evaluated.

Clinical Relevance

SCIENTIFIC RATIONALE FOR THE STUDY

Plaque control is essential in the control of gingivitis. CHX may be useful when individuals are unable to maintain adequate levels of plaque using mechanical methods alone.

PRINCIPLE FINDINGS

When a CHX-containing dentifrice is used during mechanical oral hygiene procedures, reductions in plaque, gingivitis and bleeding are obtained when compared to a placebo/control. For CHX gel, this could not be established. However, the effect could not be quantified via a meta-analysis and tooth surface discoloration as a side effect is an obstacle to the generalized use of CHX dentifrice or gel.

PRACTICAL IMPLICATIONS

CHX dentifrice may contribute to a plaque reduction and improvement in gingival health. Tooth surface discoloration is observed as a negative side effect, which potentially can have an impact on patients' compliance limiting the usefulness in daily practice. CHX gel should not be used in combination with toothbrushing.

PRACTICAL LIMITATION

CHX dentifrice usually does not contain fluoride and may therefore be a poor alternative for daily oral home care.

Supporting information

Additional supporting information may be found after the references of this article.

- Appendix S1. Overview of the studies and reason for rejection that were excluded after full-text reading.
- Appendix S2. Methodological quality and risk of bias scores of the included studies.
- Appendix S3. Mean (SD) scores for the different intervention groups with various indices and their modifications. Within groups analysis are presented.

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♦ Studies included from the search and selection process for this review.

Supporting information

Appendix S2. Methodological quality and risk of bias scores of the included studies

Study		CHX gel						CHX dentifrice				
Quality criteria		I	II	V	VII	IX	IV	V	VI	VIII	X	XI
Internal validity	Random allocation*	+	+	+	+	+	+	+	+	-	-	+
	Allocation concealment	?	?	?	?	?	?	?	?	NA	NA	?
	Blinded to patient*	+	-	+	+	+	+	+	+	+	+	+
	Blinded to examiner*	+	+	+	+	+	+	+	+	+	+	+
	Blinding during statistical analysis	?	?	?	?	?	?	?	?	?	?	?
	Balanced experimental groups*	+	+	+	+	+	+	+	+	+	+	+
	Reported loss to follow up*	+	+	+	+	+	-	+	+	+	+	+
	# (%) of drop-outs	0 (0%)	?	?	?	1 (2.7%)	?	12 (8.8%)	27 (9.1%◊)	11 (27.5%)	13 (17.8%◊)	5 (9.4%)
	Treatment identical, except for intervention*	+	-	+	+	+	+	+	+	+	+	+
External validity	Representative population group	+	+	+	+	+	+	+	+	+	+	+
	Eligibility criteria defined*	+	+	+	NR	-	-	+	+	-	-	-

Statistical validity	Sample size calculation and power	?	+	?	+	?	?	?	?	?	?	?
	Point estimates presented for the primary outcome	+	+	-	+	+	-	+	-	+	-	+
	Measures of variability presented for the primary outcome	+	+	-	+	+	-	-	-	-	-	+
	Intergroup statistical significance mentioned	+	+	+	-	+	-	+	+	+	+	-
	Intragroup statistical significance mentioned	+	-	+	+	+	+	+	+	+	-	+
	Include an intention- to-treat analysis	?	?	?	?	?	?	?	?	?	?	?
Authors estimated risk of bias		Low	High	Low	Mod	Mod	Low	Low	Low	High	High	Mod

Each aspect of the score list was given a rating of '+' for informative description of the item at issue and a study design meeting the quality standard, '-' for an informative description without a study design that met the quality standard and '?' for lacking or insufficient information. When random allocation, defined eligibility criteria, blinding of examiners, balanced experimental groups, identical treatment between groups (except for intervention) and report of follow-up were present, the study was classified as having a low risk of bias. When one of these six criteria was missing, the study was considered to have a moderate potential risk of bias. When two or more of these criteria were missing, the study was considered to have a high potential risk of bias, as proposed by Van der Weijden et al.

For abbreviations, see Table 2
? = not specified/unclear, + = yes, - = no, * = reporting criteria for estimation the potential risk of bias, ◊: calculated by the authors of this review based on the presented data in the selected paper
NA = not applicable, NR = not reported, Mod = moderate

Appendix S3. Mean (SD) scores for the different intervention groups with various indices and their modifications. Within groups analysis are presented.

S3a. Plaque Scores

#	Index	Intervention groups		Mean (SD)			Significant within groups
		Product	% CHX	Baseline	End	Difference	
VII	Plaque Index (Silness & Löe, 1964)	CHX gel placebo gel	0.5%	0.99 (0.36◊) 0.89 (0.29◊)	0.90 (0.31◊) 0.76 (0.29◊)	0.09◊ 0.13◊	No No
XI	Plaque Index (Silness & Löe, 1964)	CHX dentifrice CHX dentifrice placebo dentifrice	0.8% 0.6%	0◊ 0◊ 0◊	0.39 (0.27) 0.52 (0.19) 0.76 (0.36)	0.39◊ 0.52◊ 0.76◊	? ? ?
IV	Plaque Index (Silness & Löe, 1964)	CHX NaF dentifrice placebo dentifrice	0.4%	0.91 0.86	0.66◊ ₪	-0.25◊ ?	? ?
IX	Plaque Index (Löe, 1967)	CHX gel placebo gel	1%	₪ ₪	₪ ₪	? ?	? ?
X	Plaque Index (Löe, 1967)	CHX abr dentifrice CHX abr dentifrice placebo abr dentifrice	1% 0.4%	₪ ₪ ₪	₪ ₪ ₪	₪ ₪ ₪	? ? ?
		CHX dentifrice placebo dentifrice	0.4%	₪ ₪	₪ ₪	₪ ₪	? ?
I	Turesky et al. (1970) modification of the Quigley & Hein plaque index (1962)	CHX gel placebo gel	2.0%	2.94 (0.53) 2.87 (1.0)	1.43 (0.79) 2.10 (0.56)	-1.51◊ -0.77◊	Yes No
V	Turesky et al. (1970) modification of the Quigley & Hein plaque index (1962)	CHX gel Crest regular dentifrice	0.2%	2.20 (0.36) 2.23 (0.38)	1.18 (0.54) 1.55 (0.36)	-1.02◊ -0.68◊	? ?

VI	Turesky et al. (1970) modification of the Quigley & Hein plaque index (1962)	CHX dentifrice CHX+NaF placebo	1% 1%	₪ ₪ ₪	₪ ₪ ₪	? ? ?	? ? ?
VIII	Modification of the method proposed by Quigley & Hein (1962) (Cowell et al, 1975)	CHX dentifrice placebo	0.8%	2.15 2.10	1.71 2.16	-0.44◊ +0.06◊	Yes No
III	Plaque Surface Score (modification by Turesky of the plaque index (Fischman et al, 1986)	CHX gel placebo	0.2%	? ?	? ?	? ?	No No

For abbreviation see table 1 and 2

◊ = calculated by the authors of this review based on the presented data in the selected paper

? = unknown/not given

₪ = insufficient data presentation

S3b. Bleeding Scores

#	Index	Intervention groups		Mean (SD)			Significant within groups
		Products	% CHX	Baseline	End	Difference	
I	Ainamo & Bay 1975	CHX gel placebo gel	2.0%	0.52 (0.13) 0.48 (0.08)	0.25 (0.16) 0.38 (0.12)	0.27◊ 0.10◊	Yes No
IX	Per cent of bleeding gingival areas after probing (Lenox & Kopczyk 1973, Ainamo & Bay 1974)	CHX gel placebo gel	1%	₪ ₪	₪ ₪	? ?	? ?
IV	Number of bleeding sites	CHX dentifrice placebo dentifrice	0.4%	82.1 74.7	63.4◊ ₪	-18.7◊ ?	? ?
VIII	Number of bleeding sites	CHX dentifrice placebo	0.8%	6.40 5.10	6.00 5.80	-0.40◊ +0.70◊	? ?
III	Papillary Bleeding Index (PBI)	CHX gel placebo	0.2%	₪ ₪	₪ ₪	? ?	No No
VI	Probing for bleeding (GI=2)	CHX dentifrice CHX+NaF placebo	1% 1%	₪ ₪ ₪	₪ ₪ ₪	? ? ?	? ? ?

For abbreviation see table 1 and 2
◊ = calculated by the authors of this review based on the presented data in the selected paper
? = unknown/not given
₪ = insufficient data presentation

S3c. Gingival Index

#	Index	Intervention groups		Significant within groups			Significant within groups
		Products	% CHX	Baseline	End	Difference	
VI	Gingival Index (Löe, 1963)	CHX dentifrice CHX+NaF dentifrice placebo	1% 1%	₪ ₪ ₪	₪ ₪ ₪	? ? ?	? ? ?
IV	Gingivitis index (GI) using a modification of the gingival index (GI) of Löe (1967)	CHX dentifrice placebo dentifrice	0.4%	1.57 1.53	? ?	? ?	? ?
X		CHX abr dentifrice CHX abr dentifrice placebo abr dentifrice	1% 0.4%	₪ ₪ ₪	₪ ₪ ₪	₪ ₪ ₪	? ? ?
		CHX dentifrice placebo dentifrice	0.4%	₪ ₪	₪ ₪	₪ ₪	? ?
VII	Gingival Index (Löe, 1963)	CHX gel placebo gel	0.5%	0.92 (0.40◊) 0.76 (0.37◊)	0.74 (0.40◊) 0.59 (0.33◊)	0.18◊ 0.17◊	Yes Yes
III	Gingival Index (Löe, 1963)	CHX gel placebo	0.2%	₪ ₪	₪ ₪	? ?	Yes Yes

For abbreviation see table 1 and 2
◊= calculated by the authors of this review based on the presented data in the selected paper
? = unknown/not given
₪ = insufficient data presentation

S3d. Tooth Discoloration Index

#	Index	Intervention groups		Mean (SD)			Significant within groups
		Product	% CHX	Baseline	End	Difference	
II	Lobene Index (Lobene, 1968)	CHX gel	1%	?	2.82 (1.70)	?	?
		Dentifrice+reduced CHX gel	1%	?	1.92 (1.28)	?	?
		placebo dentifrice		?	0.82 (0.54)	?	?
VII	Standardized color photographs				*Percentage of subjects*		
		CHX gel	0.5%	?	73.7%◊	?	?
		placebo gel		?	17.6%◊	?	?
IX	Standardized color photographs				*Percentage of subjects*		
		CHX gel	1%	₪	66.7%	?	?
		placebo gel		₪	19.%	?	?
IV	Standardized color photographs	CHX dentifrice	0.4%	₪	₪	?	?
		placebo dentifrice		₪	₪	?	?
XI	Standardized color photographs were taken of the front teeth				*Percentage of Vestibulair surfaces*		
		CHX dentifrice	0.8%	₪	15.3%◊	?	?
		CHX dentifrice	0.6%	₪	14%◊	?	?
		placebo dentifrice			6.9%◊	?	?
					Percentage of Interproximal surfaces		
		CHX dentifrice	0.8%	₪	34.6%◊	?	?
		CHX dentifrice	0.6%	₪	38.6%◊	?	?
		placebo dentifrice			10.3%◊	?	?
X	Discolorations were evaluated microphotometrically (Eriksen & Gjermo, 1973)				*Percentage of toothsurfaces*		
		CHX abr dentifrice	1%	0?	7.1% (10.19)	?	?
		CHX abr dentifrice	0.4%	0?	4.8% (6.88)	?	?
		CHX dentifrice	0.4%	0?	4.8% (3.57)	?	?
		placebo abr dentifrice		0?	0.06% (2.87)	?	?
		placebo dentifrice		0?	2.0% (3.50)	?	?

VI	Extrinsic stain by area (SA), using the modification (Addy et al. 1983) of the Stain Index (Shaw & Murray 1977)	CHX dentifrice CHX+NaF dentifrice placebo	1% 1%	₪ ₪ ₪	₪ ₪ ₪		₪ ₪ ₪	? ? ?
	Tooth discoloration intensity (Yates et al, 1993)	CHX dentifrice CHX+NaF dentifrice placebo	1% 1%	₪ ₪ ₪	₪ ₪ ₪		₪ ₪ ₪	? ? ?

For abbreviation see table 1 and 2

◊ = calculated by the authors of this review based on the presented data in the selected paper

? = unknown/not given

₪ = insufficient data presentation

Appendix S1. Overview of the studies and reason for rejection that after full-text reading

Author(s) (year)	Reason for rejection
Bonesvoll et al. (1978), Watts et al. (1979), Rölla et al. (1971), Sturzenberger et al. (1988)	CHX rinsing
Pai et al. (2004), Pradeep et al. (2010) Pradeep et al. (2012, Pradeep et al. (2012)	Non brushing
Lennon et al. (1975)	3 weeks
Serfaty et al. (1988)	CHX irrigation
Bain et al. (1978), Lie & Enersen (1986)	Periodontitis patients
Bassiouny & Grant (1975)	Participants with partial dentures
Gjermo & Eriksen (1972)	IADR abstract
Chlorhexidine gel (Corsodyl) for gingivitis? Author unknown	Non retrievable

5.

Research is creating new knowledge.

Neil Amstrong

THE EFFECT OF CHLORHEXIDINE DENTIFRICE OR GEL VERSUS CHLORHEXIDINE MOUTHWASH ON PLAQUE, GINGIVITIS, BLEEDING AND TOOTH DISCOLORATION: A SYSTEMATIC REVIEW

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INTERNATIONAL JOURNAL OF DENTAL HYGIENE
2014 EARLY VIEW

Introduction

Dental plaque is a multispecies biofilm of microorganisms that grows on hard and adjacent soft tissues in the oral cavity. It has a well-established role as an aetiological factor in chronic gingivitis and periodontitis (Löe et al. 1965, Theilade et al. 1966, Timmerman & Van der Weijden 2006). As such, plaque control through daily oral hygiene is key to the prevention of these conditions (Axelsson 2006). The most reliable methods currently used for plaque removal are tooth brushing and, when indicated, interdental cleaning (Van der Weijden & Slot 2011). In conjunction with mechanical plaque control, chemotherapeutic agents have the potential to inhibit plaque growth, reduce gingivitis and improve oral health beyond tooth brushing alone (Addy & Moran 1997). Of the chemical plaque control agents, chlorhexidine (CHX) is the most studied and effective antimicrobial agent in oral care (Paraskevas 2005).

Recently, a systematic review of the existing scientific literature established that, in patients with gingivitis, CHX mouthwash (MW), as an adjunct to mechanical oral hygiene, provided significant reductions in plaque and gingivitis scores (Van Strydonck et al. 2012). The corollary was a significant increase in tooth discoloration. In another systematic review, it was concluded that tooth brushing with a CHX-containing dentifrice (DF) was effective in the control of plaque and gingivitis but again that tooth surface discoloration was an apparent side effect (Slot et al. 2014). To our knowledge, no head-to-head comparison of CHX-DF or gel with CHX-MW has been made in a systematic manner. Therefore, the aim of this systematic review was to summarize and evaluate the available evidence on the effectiveness of CHX-DF or gel (CHX-DF/gel) compared with CHX-MW when used as intervention products in one and the same investigation on plaque, gingivitis and tooth discoloration scores.

Materials and methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic reviews and Meta-Analyses (PRISMA statement, Moher et al. 2009).

Focused question

What is the effect of CHX-DF/gel compared to CHX-MW in patients with gingivitis on plaque, bleeding, gingival inflammation and tooth discoloration scores?

Search strategy

Three Internet sources were used to search for appropriate papers satisfying the study purpose: the National Library of Medicine, Washington, D.C. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). All databases were searched for studies conducted up to September 2013. The search was designed to include any published study that evaluated the effect of CHX-DF/gel and CHX-MW within the same experiment for details see Box 1. All reference lists of the selected studies were hand-searched for additional papers that could meet the eligibility criteria of this study. Case reports, letters and narrative/historical reviews were not included in the search. Papers without abstracts but with titles suggesting that they were related to the objectives of this review were also selected so that the full text could be screened for eligibility.

Screening and selection

The papers were screened independently by two reviewers (SCS & GAW), first by title and abstract. If the eligibility aspects were present in the title, the paper was selected. If none of the eligibility aspects were mentioned in the title, the abstract was read in detail to screen for suitability. After selection, full-text papers were read in detail by two reviewers (DES & SCS). Those papers that fulfilled all selection criteria were processed for data extraction. Disagreements were resolved by discussion. If disagreement persisted, the judgment of a third reviewer (GAW) was decisive. Two reviewers (DES & SCS) hand-searched the reference lists of all included studies for additional articles.

The eligibility criteria were:

- Randomized controlled trials (RCTs) or controlled clinical trials (CCTs).
- Studies conducted in human adults ≥18 years old in good general health without dental implants or (partial) dentures.
- Intervention: chlorhexidine dentifrice or gel (CHX-DF/gel).
- Comparison: chlorhexidine mouthwash (CHX-MW).
- CHX-DF/gel and CHX mouthwash compared in the same experiment.
- Topical supragingival use of the CHX-DF or gel.
- Evaluation parameters: plaque, gingivitis, bleeding and tooth discoloration scores.
- Manuscripts written in the English or Dutch language.

Box 1. Search terms used for PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE. The search strategy {<[Agent] AND [vehicle]> AND <[outcome/disease]>} was customized appropriately for each of the additional databases used taking into account differences in controlled vocabulary and syntax rules.

The following terms were used in the search strategy:

Active ingredients: {<(chlorhexidine [MeSH] OR chlorhexidine OR chlorhexidine phosphanilate OR chlorhexidine di-gluconate OR chlorhexidine gluconate OR zinc-chlorhexidine OR chlorhexidine gluconate lidocaine hydrochloride OR CHX OR CHX formulations [textwords])
AND
Vehicle: (Mouthwashes OR Toothpaste OR Dentifrices [MeSH] OR Mouthwashes OR Mouthwash OR mouthwash* OR mouthrinses OR mouthrinse OR gel OR Toothpaste OR Toothpastes OR Dentifrices OR Dentifrice [textwords])>
AND
Outcome: <Search gingivitis [MeSH] OR gingivitis OR gingivit* OR gingival pocket OR gingival bleeding OR gingival inflammation OR gingival diseas* OR gingival index OR gingival hemorrhage OR bleeding on probing OR bleeding-on-probing OR papillary bleeding index OR bleeding index OR sulcus bleeding index OR plaque removal OR plaque index OR dental plaque OR plaque OR removal OR interdental plaque OR interproximal plaque OR dental deposit* OR stain OR discoloration OR pseudo pocket OR pseudopocket OR periodontal index OR oral tissue OR calculus OR tartar [textwords]>}

The asterisk (*) was used as a truncation symbol.

Assessment of heterogeneity

The heterogeneity across studies was detailed according to the following factors:

- Study design, evaluation period, oral prophylaxis and industry funding.
- Participant characteristics.
- Chlorhexidine: brand, dosage and regimen.

Quality assessment

Two reviewers (DES & SCS) scored the methodological qualities of the included studies. This was assessed according to the method which has been described in detail by Keukenmeester et al. (20013) and Van der Weijden et al. (2009). For the criteria listed, see Appendix S1.

Statistical analyses

DATA EXTRACTION

From the collection of papers that met the inclusion criteria, data were extracted with regard to the effectiveness of CHX-DF/gel versus CHX-MW by two reviewers (DES & SCS). Mean values and standard deviations (SDs) of baseline, end and

incremental scores on the parameters of interest were extracted from the text (DES & SCS). For studies that presented intermediate assessments, the baseline and final evaluations were used for this review. Also, the within-group statistical analyses and between-study groups were obtained if presented.

DATA ANALYSIS

Only baseline data and end-trial assessments were available. Where possible, a meta-analysis was performed and the difference in means (DiffM) was calculated using the Review Manager 5.1 software (RevMan version 5.1 for Windows, Kopenhagen, Denmark; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Difference in means values between test and control at both baseline and end was calculated using a fixed-effects model. Heterogeneity was tested by chi-square test and the I^2 statistic. When a study had multiple CHX-DF/gel treatment arms, data from the CHX-MW group were used in more than one comparison, the number of subjects (n) in this group was divided by the number of comparisons. Only two studies could be included for this quantitative analysis of the total body of evidence. Therefore additionally, data were also summarized using vote counting in a descriptive manner.

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, as proposed by the GRADE Working Group (2000), was used to grade the evidence emerging from this review with respect to the outcome parameters, i.e. PPD and CAL (GRADE, Guyatt et al. 2008). Two reviewers (DES & GAW) rated the quality of the evidence as well as the strength of the recommendations according to the following aspects: risk of bias of the individual studies; consistency and precision among the study outcomes; directness of the study results; and detection of publication bias. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Summary of included studies

The search resulted after removing the duplicates in 2256 papers (for details, see Figure 1). The screening of titles and abstracts initially resulted in 12 full-text articles. Seven papers were excluded because of insufficient data presentation on the clinical parameters. The reasons for exclusion are specified in Appendix S2. No additional papers emerged from hand-searching of the reference lists. Consequently, five studies were identified as eligible for inclusion in this review according to defined

criteria for study design, participants, intervention and outcome. These five trials, all experimental clinical studies, were processed for data extraction.

Assessment of quality and heterogeneity

Considerable heterogeneity was observed in the five included clinical trials regarding study design, participants, evaluation period, oral prophylaxis, intervention regimen, outcome variables and results. Information regarding the study characteristics including study population (number, gender and age of participants) interventions and regimens is displayed in Table 1. In this review, different indices and their modifications are used. Three studies (III, IV and V) used a non-brushing design. Two studies used a brushing design (I and II); in study I, the CHX-DF was used as a dentifrice during brushing, while in study II the participants performed brushing with their normal toothpaste and applied additionally the CHX gel with a finger thoroughly in the oral cavity.

Study design, evaluation period, oral prophylaxis and industry funding

All studies excluded patients with systemic disorders that might interfere with the outcome of the study, such as diabetes mellitus, known allergies or haematological disorders (II) or the use of antibiotics during the trial or 3 months prior to commencing (III). None of the studies considered smoking as an exclusion. Study duration differed among studies: 3 days (IV, V), 6 weeks (II), 6 months (I) and 5 days per leg of each regimen within the cross-over design done by Addy 1989 (III). In most studies, oral prophylaxis was performed at the start of each experiment (I, III, IV, V), except for one (II). Not one of the studies presented information regarding industrial funding. Only III acknowledges Colgate-Palmolive for help and (financial) support for the study.

Study quality and risk of bias assessment

Quality assessment values, including external, internal and statistical validity, are presented in Appendix S1. Based on a summary of these criteria, the estimated potential risk of bias is low in four of the five studies (I, III, IV and V) and moderate for one study (II). Study outcomes Comparison baseline – end (results within groups) Appendix S3 A–D shows the results from the data extraction. Statistically significant improvements between baseline and end data were not part of the report in any of the selected studies.

Figure 1. Search and selection results and analysis process

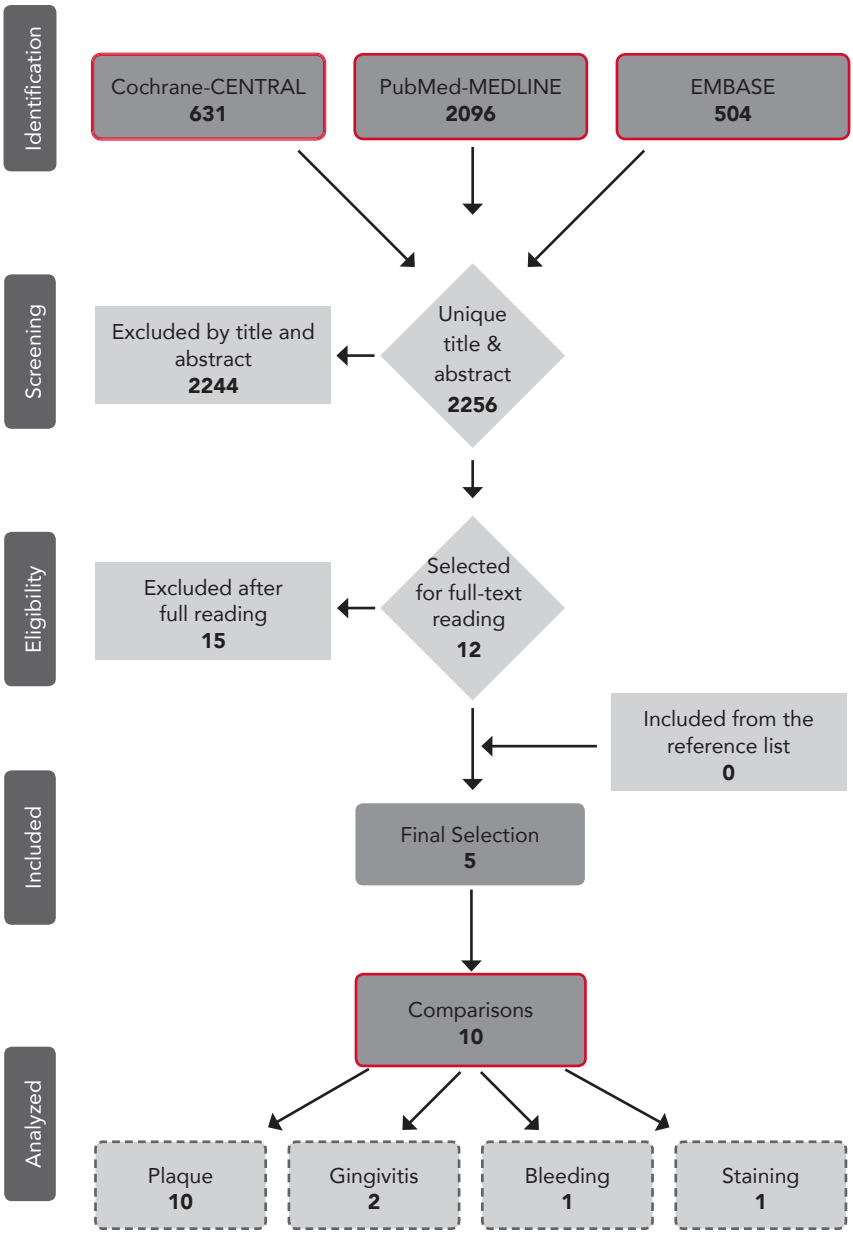

Table 1. Overview of the brushing/non-brushing studies processed for data extraction

	Authors (year)	Design, Blinding, Testperiod	Subjects (follow up), Gender, Age	Groups, Brand	Regimen	Conclusion
Used with a toothbrush	(I) Sanz et al. (1994)	RCT Parallel Double blind 6 months	*Participants with gingivitis (GI>0.7)* 140◊ (127◊) ♀ 84◊ ♂ 56◊ Mean Age: 32.3◊ Range: 18-61 years	Experimental-DF (CHX 0.4%) + placebo-MW DF + CHX-MW (0.12%) PeridexTM Procter & Gamble, USA	Brushing Rinsing / twice daily Brushing Rinsing / twice daily	No significant difference between CHX 0.4% DF and 0.12% CHX-MW. CHX 0.4% DF will contribute less staining compared with using a 0.12% CHX-MW.
Brushing + Finger application	(II) Pai et al. (2004)	RCT Parallel ? 6 weeks	? 24◊ (24◊) ♀ ? ♂? Mean Age: ? Range: 25-39	CHX gel (0.2%) CHX-MW (0.2%) Rexidine Centaur Labs, India	Applying 1 gram with index finger throughout the oral cavity / twice daily Rinsing / 10 ml / twice daily / 1 min	Better therapeutic efficacy can be achieved using CHX gel for treating oral infections than conventional treatment using a CHX-MW.
Non-Brushing	(III) Addy et al. (1989)	RCT Cross-over Single blind 5 days per regimen	*Participants with a high standard oral hygiene and gingival health* 15 (15) ♀ 10 ♂ 5 Mean Age: 23◊ Range: 19-28 years	DF Colgate® Palmolive, USA (0.5% CHX+0.525% Betaine) DF Colgate® Palmolive, USA (0.5% CHX+0.76% miranol C2M) DF Colgate® Palmolive, USA (0.5% CHX + 2% Tween 20) DF Colgate® Palmolive, USA (0.5% CHX+0.5% Emphos) DF Colgate® Palmolive, USA (0.5% CHX Emphos + monofluorophosphate) CHX-MW (0.2%) Corsodyl® GlaxoSmithKline, UK	Rinsing with slurry (3 gram + 10ml water) / twice daily / 1 min Rinsing / 10 ml / twice daily / 1 min	All CHX 0.5% DF's were less effective than a 0.2% CHX-MW.

Non-Brushing	(IV) Slot et.al. (2007)	RCT Parallel Single blind 3 days	*Non periodontitis patients* 69◊ (67◊) ♀ 53◊ ♂ 14◊ Mean Age: 21.7◊ Range: 18-39	CHX-DFgel (0.12%) Perio-Aid® Dentaid, Spain CHX-MW (0.12%) Perio-Aid® Dentaid, Spain	Applying gel in fluoride tray / twice daily / 2 min Rinsing / 15 ml / twice daily / 1 min	0.12% CHX-MW is significantly more effective, than the application of 0.12% CHX-DFG via a tray.
	(V) Slot et al. (2010)	RCT Parallel Single blind 3 days	*Non periodontitis patients* 83◊ (82◊) ♀ 64◊ ♂ 18◊ Mean Age: 22.2◊ Range: 18-31	CHX-DFgel (0.12%) Perio-Aid® Dentaid, Spain CHX gel (1%) Corsodyl® GlaxoSmithKline, UK CHX-MW (0.2%) Corsodyl® GlaxoSmithKline, UK	Applying gel in fluoride tray / twice a day / 2 min Applying gel in fluoride tray / twice daily / 2 min Rinsing / 10 ml / twice daily / 1 min	The effect of a 1% CHX gel application is significantly greater than that of 0.12% CHX-DFgel. The 1% CHX gel applied via a tray and 0.2% CHX-MW rinse were comparably effective.

RCT = Randomised Clinical Trial
CHX-MW = Chlorhexidine mouthwash
CHX gel = Chlorhexidine gel
Placebo-MW = Placebo mouthwash
? = Not specified/unknown

CHX = Chlorhexidine
CHX-DFG = Chlorhexidine Dentifrice gel
CHX-DF = Chlorhexidine dentifrice
DF = Dentifrice

Comparison between groups

Table 2 shows the individual outcomes of the studies with respect to differences between the CHX-DF/gel and the CHX-MW. The non-brushing studies all showed a significant difference in plaque scores in the favour of the CHX-MW over the various CHX-DF/gel formulations (III, IV, V). With the exception of the 1% CHX-DF/gel product there was no statistical significant difference with the 0.2% CHX-MW product used in V. The only study assessing bleeding scores (I) showed no significant difference between the CHX-DF/gel and CHX-MW. Only study II with a 6-week duration showed a significant difference in favour of the CHX-DF/gel on both plaque and gingivitis scores. The 6-month brushing study (I) did not reveal a significant difference in plaque and gingivitis scores; moreover, this was the only study that showed data on tooth discoloration where significantly more staining was found for the use of the CHX-MW compared to the CHX-DF/gel.

Meta-analysis

From the collective data of the studies, a meta-analysis only appeared possible on 'the novo' plaque accumulation studies after 3 days of non-brushing (IV, V). Figure 2 shows a significant effect in favour of the CHX-MW (DiffM 0.27, (P<0.0001), 95% CI: [0.14;0.39]) as compared to the CHX-DF/gel. Test for heterogeneity was not significant (P=0.21).

Figure 2. Meta-analysis on plaque scores for non-brushing studies

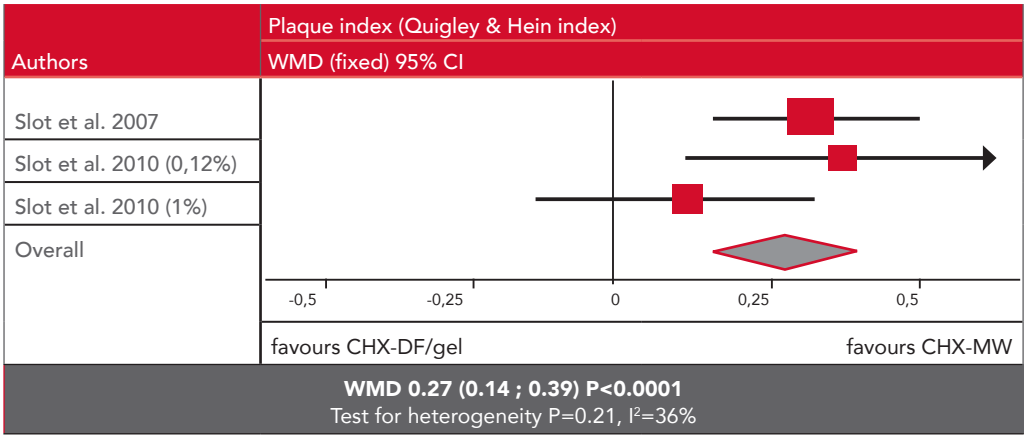

Table 2. A descriptive summary of statistical significance between the intervention and the comparison

Method	# Author(s)	Intervention	Concentration (%)	Plaque scores	Gingival index	Bleeding scores	Tooth dis-coloration scores	Comparison	Concentration (%)
Used with a toothbrush	(I)	CHX-DF + placebo-MW	0.4	0	0	0	+	CHX-MW + DF	0.12
Brushing + Finger application	(II)	CHX gel	0.2	+	+	□	□	CHX-MW	0.2
Non-Brushing	(III)	CHX-DF/ Betaine	0.5	-	□	□	□	CHX-MW	0.2
		CHX-DF/ Miranol	0.5	-	□	□	□	CHX-MW	0.2
		CHX-DF/ Tween	0.5	-	□	□	□	CHX-MW	0.2
		CHX-DF/ Emphos	0.5	-	□	□	□	CHX-MW	0.2
		CHX-DF/ Emphos+MFP	0.5	-	□	□	□	CHX-MW	0.2
	(IV)	CHX-DFgel	0.12	-	□	□	□	CHX-MW	0.12
	(V)	CHX-DFgel	0.12	-	□	□	□	CHX-MW	0.2
		CHX gel	1	0	□	□	□	CHX-MW	0.2

Grading the 'body of evidence'

Table 3 shows a summary of the various aspects which were used to rate the quality of evidence and strength of recommendations according to GRADE (GRADE working group, Guyatt et al. 2008). Tooth discoloration and bleeding scores were not weighted because there was only one publication providing information on both these aspects. Because the data are on average fairly consistent, including studies that had a 'low-to-moderate estimated risk of bias', overall results are generalizable as daily oral care products, but the data are imprecise with the possibility of a publication bias. Taken as a whole, the strength of the recommendation emerging from this systematic review is therefore considered to be 'moderate' for plaque scores and low for the gingival index outcome.

Table 3. GRADE evidence profile, for the impact of CHX-MW compared to CHX-DF/gel on plaque, clinical parameters of gingival inflammation and tooth discoloration from the presented systematic review

	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of recommendation
Plaque scores	Low to moderate	Moderate	Partly generalizable	Imprecise	Possible	Moderate
Gingival Index	Low to moderate	Inconsistent	Indirect	Imprecise	Possible	Low

Discussion

The bisbiguanide antiseptic CHX is the most thoroughly investigated antiplaque substance. It has been clinically tested and successfully used in dentistry for various clinical applications for more than 40 years (Lang & Brecx 1986). It has excellent plaque inhibitory properties with an immediate antibacterial effect as well as a prolonged bacteriostatic effect on the oral flora (Grossmann et al. 1989). Clinical studies ranging from 3-month up to 2-year duration with CHX- containing mouth rinses have demonstrated significant reductions in plaque and gingivitis (Van Strydonck et al. 2012). Long-term clinical studies have also confirmed the excellent safety profile of CHX formulations (Gjermo 1989). The observed plaque inhibitory action of CHX has yet to be superseded (Hull 1980, Addy 1986). Encouraging results from experimental CHX-containing dentifrices have been obtained (Gjermo & Rolla 1971, Gjermo & Eriksen 1974). It has also been apparent, however, that the activity of a CHX-MW is difficult to equal (Addy et al. 1989). The antimicrobial and antiplaque properties of CHX may be compromised by components contained in any formulation including anionic detergents, some dentifrice abrasives, calcium ions

and sodium monofluorophosphate, all of which may reduce the availability of CHX in a DF. This is why most of the earlier studies showed no efficacy for CHX-DFs mainly because the CHX had been inactivated in the formulation. It is therefore not possible to extrapolate results from the use of active ingredients in a simple mouthwash formulation to effects achievable with complex vehicles such as toothpastes (Addy et al. 1989).

CHX dose, delivery and activity

Discussing the findings of this systematic review and the results of the individual studies revealed that it is necessary to consider factors relevant to the plaque inhibitory action of CHX. In an extensive narrative review of the literature pertaining to CHX, it was established that when delivered as a rinse, plaque inhibition is dose dependent (Addy & Moran 2007). Moreover, it was concluded that the plaque inhibitory effect of CHX is derived from the antiseptic adsorbed to the tooth surface and not from the originally hypothesized slow release from an oral reservoir. This explains why small doses of CHX applied directly to the teeth, for example from a spray, provide a similar plaque inhibitory effect as compared to much larger doses from mouth rinses (Stoeken et al. 2007). Extrapolating this further, it becomes apparent that the mode of CHX delivery is important to ensure contact of the antiseptic with all tooth surfaces as is the activity of CHX within any formulation.

Considering the delivery method, a previous systematic review found that brushing with a CHX gel compared to a regular dentifrice was not effective against plaque and gingivitis, but when the CHX is incorporated in a DF, it can be effective (Slot et al. 2014). Brushing produced evidence showing poor distribution of CHX from the gel over tooth surfaces and much better results have been reported when the CHX gel was delivered in trays (for review, see Addy & Moran 2007). This is consistent with the comparable findings for the 1% CHX gel in trays and 0.2% CHX-MW used in the study of Slot et al. (26). The lack of similar findings for the 0.12% CHX-DF/gel delivered in trays compared to the 1% CHX gel in trays and 0.2% CHX-MW in this study (Slot et al. 2010) could be the CHX dosage. A similar conclusion, concerning dosage, could be drawn for the related study (Slot et al. 2007), where the same 0.12% CHX-DF/gel was less effective than a 0.12% CHX-MW.

Two hypotheses go against dose as the only explanation for the results of these two studies. When estimating the dose of CHX from the DF/gel at 7–9 mg, which was approximately half that of the 0.12% MW (Slot et al. 2007) and one-eighth that of the 1% CHX gel (Slot et al. 2010), such a dose applied directly to the teeth is still high on the CHX dose–response curve for plaque inhibition and certainly higher than employed in studies using 0.2% CHX sprays (for review, see Addy & Moran 2007). However, the 0.12% CHX-DF/gel in both studies (Slot et al. 2007, Slot et al. 2010) did

not provide a significant difference compared to a conventional fluoride toothpaste. Taking both study results into account, the data suggest that the CHX-DF/gel was partially or totally inactive in respect of CHX. A similar argument can be employed in respect of the findings of the Addy et al. (1989) study to explain the findings of the reduced plaque inhibitory effects of the CHX-DF/gel formulations compared to CHX-MW. A similar argument can be found in the discussion section of the published paper. Essentially, the authors pointed out that the various CHX-DF/ gel formulations were used at a dose of 15 mg twice per day, which was well within the effective range for CHX delivered as a MW. This together with the finding of greater plaque inhibition than the placebo DF but no difference from the triclosan zinc citrate DF suggests a significant inactivation of CHX in the various CHX-DF/gel formulations used in this study III (Addy et al. 1989).

The two brushing studies on plaque and gingivitis (I, II) are more difficult to discuss in respect of the action of the experimental CHX-DF/gel formulations used.

Both studies used test formulations in a 'normal tooth brushing' model in which additionally the Hawthorne effect of improved mechanical cleaning can be expected (for review, see Addy & Moran 2007). The improved mechanical oral hygiene narrows the margin to demonstrate benefits derived from chemical adjuncts such as CHX. In study I, a Hawthorne effect was apparent as plaque and gingivitis scores decreased in both the CHX groups and the control group. To further interpret the results however, one has to make two assumptions as to the use of the various formulations because exact details were not specified. Firstly, the amount of DF used on the brush was similar to that reported for 'usual' tooth brushers, namely 1–1.2 g. Secondly, the CHX-MW product in the positive control group was used as recommended by the manufacturer, namely 15 ml rinsed for 30 s. If these assumptions are correct, the CHX-DF/gel would deliver a dose of 4–5 mg of CHX and the MW 18 mg of CHX. While this is a large difference in dose, one has to remember that the CHX-DF/gel was delivered directly to the teeth but the MW was used throughout the mouth. Combined with an expected Hawthorne effect, this could explain the findings for the CHX-DF/gel similar to the CHX-MW on plaque and gingivitis, particularly because both were significantly more effective than the control group of DF with a placebo rinse. Unfortunately, it does not explain the increased tooth staining in favour of the CHX-MW over the CHX-DF/gel; CHX activity in the latter does not appear in question as staining was greater than in the control group.

Study II is perhaps more difficult to interpret. Nevertheless, as with study I, a Hawthorne effect was apparent with improvements in plaque and gingivitis in all groups including the control group. Surprisingly however, the 0.2% CHX-DF/ gel was significantly more adjunctive to tooth brushing with toothpaste than 0.2% CHX-MW despite the fact that the gel delivered 2 mg CHX throughout the mouth

on a finger compared to 20 mg CHX from the rinse product. Possible inactivity of the CHX-MW is not out of the question and has been reported for a well-known European mouth rinse (for review, see Addy & Moran 2007), although this is unlikely to have been the complete explanation as the CHX-MW group was significantly better than control. The observed efficacy of the CHX gel was suggested to be the result of the mucoadhesive property of the carbopol, which was used as a gelling agent. Carbopol has the property to stay in the oral cavity for an extended period, thereby permitting drug release for a prolonged duration (Bremecker et al. 1984, Peh & Wong 1999). This is unlikely to explain the findings because the substantivity of CHX from MW is in itself more than 12 h, and as stated, the mechanism of action is from CHX adsorbed to teeth and not derived from a slow-release mechanism (for review, see Addy & Moran 2007). The tray application used in study IV and study V is a research model to test the potential of CHX gel or dentifrice without the mechanical interference of a toothbrush. Finger application as performed by study II is not a representative oral hygiene intervention. This item is addressed in the methodological quality and risk of bias scores (Appendix S1). However, it is not taken into account for estimating the authors' estimated risk of bias.

Series of papers

The present review is the last one out of a series of four studies addressing the efficacy of CHX dentifrice or gel. The first investigation evaluated a 0.12% CHX-DF/gel product (Slot et al. 2007) marketed for long term, according to the manufacturer's instruction to be used twice daily, on a toothbrush. The study showed that within the limitations of the 3-day non-brushing design, application of 0.12% CHX dentifrice gel in a prefab fluoride tray was not significantly different from a similar application of a regular fluoride DF on plaque accumulation. Use of a 0.12% CHX-MW, however, proved to be significantly more effective than that of the 0.12% CHX-DF/gel (Slot et al. 2007). In the Netherlands, a 1% CHX gel is available, intended according to the manufacturer's instruction for short-term use up to a maximum of 15 days.

A second study (Slot et al. 2010) using a fluoride tray for application comparing the previous 0.12% CHX-DF/gel, a 1% CHX gel, a 0.2% CHX-MW and a regular fluoride toothpaste also in a 3-day non-brushing design showed a significantly greater plaque inhibition by the 1% gel and the 0.2% CHX-MW than by the 0.12% CHX-DF/gel and no significant difference between the 1% gel and 0.2% CHX-MW products. Again, the 0.12% CHX-DF/gel was not significantly different from the fluoride toothpaste against plaque. Slot et al. (2014) recently performed a systematic review to evaluate the effect of tooth brushing with a CHX-DF or gel on clinical parameters of plaque, gingivitis and tooth staining. From the collective evidence, it was concluded that

tooth brushing with a CHX gel did not provide a significant effect on plaque scores and gingival inflammation. The evidence for brushing with a CHX-DF, however, indicated that a DF formulation can be effective with regard to the control of plaque and gingivitis. As expected, the known side effect of tooth staining with these CHX products was observed, and the authors of the review repeated concerns over the negative impact that this may have in patient compliance with their use (Slot et al. 2014).

The present review has shown that compared to CHX-MW, the CHX-DF/gel or CHX-DF is less effective with regard to plaque scores and no difference in bleeding scores or the gingival index data was observed. Recently with respect to CHX-MW, a systematic review was performed. It was concluded that in patients with gingivitis, CHX-MW together with oral hygiene versus placebo or control MW provides significant reductions in plaque and gingivitis scores, but also as a corollary significant increase in staining scores (van Strydonck et al. 2012). The present systematic review comparing CHX-DF/gel to CHX-MW also found an increased tooth surface discoloration with the CHX-MW in the reports of the selected papers.

Side effects

Reversible local side effects such as staining of teeth, fillings, the tongue, impaired taste sensation (Pader 1989), increased formation of supragingival calculus and occasionally mucous embrane irritation and desquamation (Mandel 1988) are associated with the prolonged use of CHX mouth rinse. To a varying degree, all these factors may adversely affect patient compliance. Therefore, it would be ideal to incorporate CHX in a dentifrice formulation, thus combining mechanical cleaning (and hence reducing its side effects), fluoride delivery, antiplaque benefit and resulting antigingivitis benefit with no added discomfort for patients (Addy et al. 1989). Irrespective of which type of vehicle is used, the extrinsic staining effect remains problematic. To reduce this tendency, a number of strategies could be suggested: reduce the overall oral dosage of the gel, use the product just before retiring to bed and use a whitening dentifrice (Claydon et al. 2006). The use of the whitening paste has been shown to reduce CHX induced staining and may be expected to have a beneficial effect (Claydon et al. 2004). The findings of a study by Claydon et al. (2006) highlighted the significant problem of staining seen with the use of CHX products. But even when used at reduced dosage as the last effort before bedtime and when used in conjunction with the whitening dentifrice, 30% of the participants still found the staining unacceptable (Claydon et al. 2006).

Limitations

- One limitation is patient blinding, because both CHX experimental groups used different products with their own application method. And whether a brushing or a non-brushing model is used blinding is not feasible.
- The ADA requirements for a seal of acceptance Chemotherapeutic Products for Control of Gingivitis require a study period of 6 months to evaluate both the efficacy and safety of chemical agents as well as patients' compliance (ADA 2008). Only one study on CHX dentifrice extended up to 6 months (study I) and did not show a significant effect in favour of any product.
- This summary of the evidence is primarily established by vote counting, which does not take into account the variation in scoring indices used. Vote counting procedures probably constitute the most common quantitative technique used in the reviewing of research. Such a technique is appealing because it is easy to use, requires a minimal amount of statistical data from each study to be integrated and permits the merging of analyses from different studies. However, vote counting does not include differences between methods applied within the studies and does not account for differences in the sample size or the actual strengths of the values (Keukenmeester et al. 2013).
- Because there were fewer than four studies, fixed-effects analysis was used, as the estimate of between-study variance is poor for analyses with low numbers of studies (Higgens & Green 2011).

Conclusion

This review has shown that CHX gel can be successfully formulated and will inhibit plaque growth to some degree, but not to the same extent, as a CHX-MW. When CHX-DF/gel is used in a non-brushing model, it is significantly less effective in plaque inhibition compared to CHX-MW. Based on one study when CHX gel was applied with a finger after brushing, it was significantly more effective on plaque scores and the gingival index. The only other long-term brushing study also with a long follow- up showed that there is no significant difference between CHX-DF and CHX-MW. However, as a corollary, significantly more tooth discoloration was observed with the CHX-MW. Altogether, the data show that when daily oral hygiene cannot be performed, CHX-MW is the first product of choice.

Declaration of interest and source of funding statement

The authors declare that they have no conflict of interest. This study was self-funded by the authors and supported by their institution Academic Centre for Dentistry (ACTA).

Supporting information

Additional supporting information may be found after the references of this article.

- Appendix S1. Methodological quality and risk of bias scores of the included studies.
- Appendix S2. Overview of the excluded studies and reasons for rejection after full-text reading.
- Appendix S3. Mean (SD) scores for the different intervention groups with various indices and their modifications. Within groups analysis are presented.
- Appendix S4. Meta-analysis on the 'the novo' plaque accumulation after 3 days non-brushing.

Clinical Relevance

SCIENTIFIC RATIONALE FOR THE STUDY

Plaque control is essential for the prevention of gingivitis. Chlorhexidine (CHX) may be a useful adjunct to oral hygiene when individuals are unable to achieve satisfactory plaque control by mechanical methods alone.

PRINCIPLE FINDINGS

Chlorhexidine MW was significantly more effective on plaque scores than CHX-DF/gel. Use of the CHX-MW resulted in significantly more tooth discoloration than that of the CHX-DF/gel.

PRACTICAL IMPLICATIONS

Chlorhexidine contributes to plaque reduction and improvement of gingival health. CHX-MW is a valuable preventive intervention in dentistry for short- to medium-term use in cases where mechanical plaque control is difficult or impossible. There is limited evidence to support the use of CHX-DF with tooth brushing. Finger application with CHX gel seems promising. However, the side effect and tooth discoloration is an obstacle to the generalized use of CHX products and potentially can have a negative impact on patients' compliance limiting the usefulness in daily practice.

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♦ Studies included from the search and selection process for this review.

Supporting information

Appendix S2. Overview of the excluded studies and reason for rejection that after full-treading

Author(s), (year)	Reason for rejection
Claydon et al (2006)	No CHX-MW was used
Heitz et al. (2004)	CHX-MW was used in both test and control group
Addy & Moran (1997)	Narrative review
Vandekerckhove et al (1996)	CHX-DF and CHX-MW was used in one group, no comparison
Claydon and Addy (1995)	No CHX-MW was used
Brown et al. (1996)	Narrative review
Löe and Schiott (1970)	Participants did use a CHX containing product which was not a DF or gel

- Addy M. & Moran JM. (1997) Clinical indications for the use of chemical adjuncts to plaque control: chlorhexidine formulations. Periodontology 2000, 15: 52–54.
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- Claydon N. & Addy M. (1995) The use of plaque area and plaque index to measure the effect of fluoride and chlorhexidine toothpastes on 24-h plaque regrowth. Journal of clinical periodontology; 22: 540–542.
- Heitz F, Heitz-Mayfield LJ, Lang NP. (2004) Effects of post-surgical cleansing protocols on early plaque control in periodontal and/or periimplant wound healing. Journal of clinical periodontology; 31: 1012–1018.
- Löe H, Schiøtt CR. (1970) The effect of mouthrinses and topical application of chlorhexidine on the development of dental plaque and gingivitis in man. Journal of periodontal research, 5: 79–83.
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Appendix S1. Methodological quality and risk of bias scores of the included studies

Brushing/Non-brushing		Brushing		Non-Brushing		
		Used with a toothbrush	Finger application			
Study / Quality criteria		I	II	III	IV	V
Internal validity	Random allocation*	+	+	+	+	+
	Allocation concealment	?	?	?	+	+
	Blinded to patient*	+	?	-	-	-
	Blinded to examiner*	+	?	+	+	+
	Blinding during statistical analysis	?	?	?	?	+
	Balanced experimental groups*	+	+	+	+	+
	Reported loss to follow up*	+	-	+	+	+
	# of drop-outs(all groups)	13◊	0◊	0	2◊	1◊
	% of drop-outs(all groups)	9◊	0◊	0◊	3◊	1◊
	Treatment identical, except for intervention	+	+	+	+	+
External validity	Representative population group	+	+	+	+	+
	Representative interventions	+	-	-	-	-
	Eligibility criteria defined*	+	+	+	+	+

Statistical validity	Sample size calculation and power	?	?	?	+	+
	Outcome point estimates presented outcome	+	+	+	+	+
	Outcome measures of variability presented	-	+	+	+	+
	Include a per protocol analysis	+	+	+	+	+
	Include an intention- to-treat analysis	-	-	-	-	-
	Authors estimated risk of bias	Low	Moderate	Low	Low	Low

Each aspect of the score list was given a rating of '+' for informative description of the item at issue and a study design meeting the quality standard, '-' for an informative description without a study design that met the quality standard and '?' for lacking or insufficient information. When random allocation, defined eligibility criteria, blinding of examiners, balanced experimental groups, identical treatment between groups (except for intervention) and report of follow-up were present, the study was classified as having a low risk of bias. When one of these six criteria was missing, the study was considered to have a moderate potential risk of bias. When two or more of these criteria were missing, the study was considered to have a high potential risk of bias, as proposed by Van der Weijden et al. 2009.

Abbreviations

*	reporting criteria for estimation the potential risk of bias
?	Not specified/unclear
+	Yes
-	No
◊	Calculated by the authors
NA	Not Applicable

Appendix S3. Mean (SD) scores for the different intervention groups with various indices and their modifications within group analysis are presented

A. Plaque score

B/NB		#	Index	Groups	Mean (SD)			Significant Base-End
					Baseline	End	Difference	
Brushing	Finger application	II	Plaque Index (Silness & Löe, 1964)	CHX gel (0.2%) CHX-MW (0.2%)	1.63 (0.30) 1.62 (0.28)	0.62 (0.29) 0.98 (0.20)	-1.01◊ -0.64◊	? ?
	Used with a toothbrush	I	Plaque Index (Silness & Löe, 1964)	CHX-DF (0.4%) + placebo-MW DF Blend-a-med + CHX-MW (0.12%)	0.91 0.89	? ?	? ?	? ?
Non-brushing		IV	Plaque Index (Quigley & Hein, 1962 modified by Turesky et al. 1970)	CHX-DFgel (0.12%) CHX-MW (0.12%)	0◊ 0◊	1.87 (0.37) 1.55 (0.37)	1.87◊ 1.55◊	? ?
		V	Plaque Index (Quigley & Hein, 1962 modified by Turesky et al. 1970)	CHX-DFgel (0.12%) CHX gel (1%) CHX-MW (0.2%)	0◊ 0◊ 0◊	1.16 (0.46) 0.88 (0.39) 0.79 (0.36)	1.16 (0.46)◊ 0.88 (0.39)◊ 0.79 (0.36)◊	? ? ?
		III	Plaque/Debris Index (Greene & Vermillion, 1960)	DF (0.5% CHX + 0.525% Betaine) DF (0.5% CHX + 0.76% miranol C2M) DF (0.5% CHX + 2% Tween 20) DF (0.5% CHX + 0.5% Emphos) DF (0.5% CHX Emphos+MFP CHX-MW (0.2%)	0◊ 0◊ 0◊ 0◊ 0◊ 0◊	2.24 (0.30) 2.45 (0.42) 2.36 (0.45) 2.42 (0.29) 2.47 (0.34) 1.92 (0.27)	2.24◊ 2.45◊ 2.36◊ 2.42◊ 2.47◊ 1.92◊	No No No No No No

Non-brushing		Plaque by area using Stain Index (Shaw & Murray, 1977)	DF (0.5% CHX + 0.525% Betaine)	0◊	0.16 (0.12)	0.16◊	?
			DF (0.5% CHX + 0.76% miranol C2M)	0◊	0.23 (0.12)	0.23◊	?
			DF (0.5% CHX + 2% Tween 20)	0◊	0.18 (0.10)	0.18◊	?
			DF (0.5% CHX + 0.5% Emphos)	0◊	0.18 (0.07)	0.18◊	?
			DF (0.5% CHX Emphos+MFP	0◊	0.21 (0.09)	0.21◊	?
			CHX-MW (0.2%)	0◊	0.10 (0.05)	0.10◊	?

- Silness J, Löe H. (1964) Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontologica Scandinavica, 22, 121–135.
- Quigley GA, Hein JW. (1962) Comparative cleansing efficiency of manual and power brushing. The Journal of the American Dental Association, 65: 26–29.
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- Greene JC, Vermillion JP. (1960) Oral hygiene index: a method for classifying oral hygiene status. The Journal of the American Dental Association, 61: 172–179.
- Shaw L, Murray JJ. (1977) A new index for measuring extrinsic stain in clinical trials. Community dentistry and oral epidemiology, 5: 116–120.

B. Gingival Index

B/NB		#	Index	Groups	Mean (SD)			Significant Base-End
					Baseline	End	Difference	
Brushing	Finger application	II	Gingival Index (Löe & Silness, 1966)	CHX gel (0.2%)	1.21 (0.22)	0.52 (0.25)	-0.69◊	?
				CHX-MW (0.2%)	1.24 (0.19)	0.92 (0.21)	-0.32◊	?
	Used with a toothbrush	I	Gingivitis Index (Löe, 1967)	CHX-DF (0.4%) + placebo MW	1.57	?	?	?
				DF Blend-a-med + CHX-MW (0.12%)	1.57	?	?	?

- Silness J, Löe H. Periodontal disease in pregnancy III. Response to local treatment. Acta Odontol Scand 1966; 24: 747–759. Löe H. The gingival index, the plaque index and the retention index systems. J Periodontol 1967; 38: 610–616.

C. Bleeding scores

B/NB	#	Index	Groups	Mean (SD)			Significant Base-End
				Baseline	End	Difference	
Brushing CHX used with a toothbrush	I	Number of bleeding sites	CHX-DF (0.4%) + placebo MW	82.1	?	?	?
			DF Blend-a-med + CHX-MW (0.12%)	79.6	?	?	?

D. Tooth discoloration scores

B/NB	#	Index	Groups	Mean (SD)			Significant Base-End
				Baseline	End	Difference	
Brushing CHX used with a toothbrush	I	Tooth staining	CHX with NaF dentifrice (0.4%) + placebo MW	0◊	₪	?	?
			DF Blend-a-med + CHX-MW (0.12%)	0◊	₪	?	?

For abbreviations see table 1 ◊ = calculated by the authors of this systematic review ₪ = Inappropriate data presentation

Appendix S4. Meta-analysis on the "novo-plaque" accumulation after 3 days non brushing

Index	Studies	DiffM	Test for overall effect 95% CI P-value		Test for heterogeneity I^2 (%) P-value	
PI Quigley & Hein (1962)	(IV) 0.12% CHX-DF/gel vs. 0.12% CHX-MW	0.27	[0.14;0.39]	<0.0001	36	0.21
	(V)* 0.12% CHX-DF/gel vs. 0.12% CHX-MW 1% CHX-DF/gel vs. 0.2% CHX-MW					

PI = Plaque index DiffM = Difference in means CI = Confidence Interval * = Providing two experiments

- Quigley GA, Hein JW. (1962) Comparative cleansing efficiency of manual and power brushing. The Journal of the American Dental Association, 65: 26–29.

Do what you can with what you have, where you are.

Theodore Roosevelt

SUMMARY, DISCUSSION AND CONCLUSIONS OF PART I OF THE THESIS

Although various chemical products have been used for plaque inhibition and gingivitis reduction, chlorhexidine (CHX) is one of the most widely used and thoroughly investigated antiseptics. Years of documented research have established that CHX digluconate in a mouthwash is safe, stable and effective in preventing and controlling plaque formation, breaking up existing plaque, and inhibiting and reducing the development of gingivitis (Löe et al. 1976, Lang & Brecx 2006, Gunsolley 2006, Gunsolley 2010). Based on a systematic review of 30 publications, strong evidence emerged for the anti-plaque and anti-gingivitis effect of a CHX mouthwash used as an adjunct to regular oral hygiene in patients with gingivitis (Van Strydonck et al. 2012). However, in addition to the positive clinical effects, tooth surface staining, bitter taste and enhanced formation of calculus have been reported (Ovenholser et al. 1990).

The 0.2% CHX solution was the first to become commercially available and became the standard concentration in Europe. A lower concentration of 0.12% CHX came onto the international market later. The relative effectiveness of the two different concentrations was systematically reviewed by Berchier et al. (2010). A meta-analysis of seven studies using the same plaque index showed a significant mean difference between 0.2% and 0.12% CHX in favor of the original concentration. The data on gingivitis were sparse, therefore preventing the ability to draw a firm conclusion. Although the results showed a small but significant difference in plaque scores in favor of the 0.2% CHX concentration, the clinical relevance of this difference was considered by the authors likely to be negligible. The 0.12% concentration of CHX was found to be similarly effective as 0.2% if the volume of the rinse was increased from 10 to 15 ml, yielding an 18 mg CHX dose on each occasion. In addition to the widely used CHX mouthwash, in the last decade, a dentifrice gel containing a 0.12% concentration CHX was introduced to the Dutch market. Even though its popularity and wide spread use no efficacy data were available. Therefore, the purpose of the first study (chapter 2) presented in this part of the thesis was to assess the effect of a twice daily application of 0.12% CHX dentifrice gel on 'de novo' plaque accumulation. Participants without periodontitis as established by a screening for pockets ≤5mm, received a professional oral prophylaxis to remove all visual plaque and abstained from all forms of mechanical oral hygiene during a 3-day period. The participants were randomly assigned to one of three regimens: The test group used 0.12% CHX dentifrice gel, whereas the benchmark control group used a regular dentifrice. In both groups, the dentifrices were applied by means of a disposable gel application tray. The positive control group rinsed with a 0.12% CHX mouthwash. After 3 days, the amount of 'de novo' plaque accumulation was assessed. The full-mouth plaque scores showed that both dentifrices were significantly less effective in preventing de novo plaque formation compared to the CHX mouthwash. No

significant difference between plaque scores of the dentifrices was found. Within the limitations of the 3-day non-brushing study design, it was concluded that the application of 0.12% CHX dentifrice gel is not significantly different from the application of a regular dentifrice on plaque accumulation. The use of a 0.12% CHX mouthwash was significantly more effective than the use of a 0.12% CHX dentifrice gel or a regular dentifrice. CHX dentifrice gel appears to be a poor alternative for a dentifrice because it is not an effective inhibitor of plaque growth and does not contain fluoride.

The purpose of a follow-up study (chapter 3) was to compare the effects of treatments, including 1% CHX dentifrice gel, 0.12% CHX dentifrice-gel, a regular dentifrice, and 0.2% CHX mouthwash. A similar 3-day non-brushing model as in chapter 2 was used in a young adult population with pockets ≤5mm. Again in this experiment, no significant difference was found in plaque accumulation between the 0.12% CHX dentifrice gel and a regular dentifrice. The regular dentifrice and 0.12% CHX dentifrice gel were both significantly less effective than the 1% CHX-gel and the 0.2% CHX mouthwash in preventing 'de novo' plaque formation. The level of gingival health was assessed in conjunction with the plaque levels because gingival inflammation could potentially have impacted the outcome of the study. In other words, could differences in plaque scores after 3 days be explained by differences in the level of gingival inflammation? This appeared not to be the case. Bleeding on marginal probing scores were found to be comparable among groups and therefore not considered to be a confounding factor for the observed differences in plaque scores.

Both studies were performed used a short-term non-brushing model in which only the plaque accumulation could be evaluated. Experimental Traditionally experimental gingivitis studies have been carried out for evaluation of the anti-plaque effect of various antimicrobial compounds in oral care products. The test period for this type of study can vary between 14 and 21 days (Wennström 1988). The original experimental gingivitis study model (Löe et al. 1965) included a 3-week period of no oral hygiene wherein all participants predictably developed gingivitis. Upon reinstitution of oral hygiene practices, participants returned to low pre-experimental levels of plaque and gingivitis (Löe et al. 1965). Based on the time required for this model and the temporary although reversible development of gingivitis, it can also be seen as onerous for participants and unnecessarily expensive for researchers. Therefore, short-term plaque regrowth studies are perhaps the most commonly used clinical experiments for screening chemical oral hygiene products. Such studies have the advantage of assessing the chemical action of the formulation separate from the indeterminate variable of toothbrushing.

Typically, plaque regrowth from a zero baseline is recorded to determine the influence of the test agent. This method was originally used for mouthwashes and has been modified for toothpaste by delivering the formulation in a disposable gel application tray applied to the teeth (Etemadzadeh et al. 1985). Chapters 2 and 3 evaluated the plaque-inhibiting effect of CHX products in a 3-day non-brushing model during which plaque was allowed to accumulate freely. This protocol is a relatively quick and inexpensive model for a proof of principle to demonstrate the feasibility of the product in reducing plaque accumulation. Based on the negligible effect of 0.12% CHX dentifrice gel there appears to be no need for further extensive research to support the process of evidence-based decision making.

A critical remark on the use of the non-brushing model has been that products were not used according to the recommendations of the manufacturer. Therefore, following these non-brushing studies, an evaluation of CHX dentifrice gel in combination with toothbrushing was indicated because gels and pastes may have different properties under static conditions as compared to situations in which they are shaken, agitated, or otherwise stressed, for example due to toothbrushing. Subsequently, the existing scientific literature was evaluated concerning the effect of toothbrushing with CHX dentifrice/gel compared to a regular or placebo dentifrice/gel on plaque and gingivitis scores (chapter 4). As a secondary parameter, tooth surface discoloration was evaluated as a side effect. Three online databases were searched to identify eligible studies. Included were controlled clinical trials of self-performed brushing by adults without periodontitis with a minimum duration of 4 weeks.

Due to the lack of available appropriate data upon which to perform a meta-analysis, a descriptive analysis was carried out. Regarding plaque score reduction, the majority of experiments using a CHX dentifrice showed that such a dentifrice had a significant positive effect compared to a regular or placebo dentifrice/gel. All studies assessing gingival bleeding as a parameter for gingivitis observed a significant reduction in favor of CHX dentifrice over placebo dentifrice. Tooth surface discoloration was more pronounced with CHX dentifrice than regular or placebo dentifrice/gel. The combined data concerning parameters of interest for CHX gel compared to a placebo did not show a trend toward a beneficial effect on plaque and bleeding scores. Within the limitations of this descriptive analysis, there was inconclusive evidence that toothbrushing with a CHX dentifrice inhibits plaque or reduces gingivitis. For both gels and dentifrices, tooth surface discoloration was observed as a side effect, which might potentially have a negative impact on patients' compliance. The systematic review was restricted to patients with gingivitis. This criterion is in line with the various indications of the manufacturers

for the use of a CHX dentifrice or gel, which includes its use between dental visits as part of a professional program for the treatment of gingivitis. This is particularly relevant because long-term gingivitis increases the risk of loss of attachment, and the prevention of gingival inflammation might reduce the prevalence of mild to moderate periodontitis (Lang et al. 2009).

Dentifrice is a general term used to describe preparations that are used together with a toothbrush to clean and/or polish the teeth. Dentifrices can be prepared as powders, gels or toothpastes, depending on the water content (Sanz et al. 2013). The most essential dentifrice recommended by dental care professionals is fluoride toothpaste (ADA 2015). Toothpastes usually, but not necessarily, have a high water content, whereas powders have almost none. In gels, most of the water content is replaced by humectants (Sanz et al. 2013). The constitution of a gel is a solid, jelly-like material that can have properties ranging from soft and weak to hard and tough, whereas a paste serves as an abrasive because mild abrasives help to remove debris and residual surface stains (ADA 2015). A gel does not contain mild abrasives, and the main purpose of gels is not to be used in conjunction with a toothbrush. In the systematic review (chapter 4), the gels were used during brushing and might therefore not have been effective. Dentifrice gels, which have the appearance of a gel, do contain abrasives and are often called toothpastes.

The constitution of the dentifrices used in the included studies of the systematic review were often not clear due to insufficient reporting. The manner of reporting in the time period during which the majority of the selected studies were published did not follow current standards. The Consolidated Standards of Reporting Trials (CONSORT 2010) group created a statement and a checklist that provides an evidence-based, minimum set of recommendations for reporting randomized trials. This checklist offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, reducing the influence of bias in their results, and aiding in their critical appraisal and interpretation (CONSORT 2010). Although the first set of Standardized Reporting criteria was published in the early 1990s, but in contrast to the medical literature it was not commonly followed in the dental literature until the first year of the new millennium. Although the original authors were contacted for additional data, most of the authors were unable to respond or provide further information on the products used. Therefore, the original terminology of the paper was used.

The last review in this section of the thesis systematically evaluated the available scientific evidence on the effectiveness of CHX dentifrice or gel compared to CHX mouthwash on plaque, bleeding, gingival inflammation and tooth surface

discoloration scores (chapter 5). This last review supplemented the review of chapter 4 and the systematic review on CHX mouthwash by Van Strydonck et al. (2012). In addition it used the outcome of the previous two clinical trials (chapters 2 & 3). The comprehensive search was designed to include any published study that evaluated the effect of CHX dentifrice or gel and CHX mouthwash. Independent screening of the 2256 unique titles and abstracts resulted in five publications. The included studies provided 10 comparisons, and considerable heterogeneity was found between them. Descriptive analysis showed that three of the five studies showed lower plaque scores in favor of the CHX mouthwash. With respect to gingival index and bleeding scores, no significant differences were found. CHX mouthwash, however, showed significantly more tooth surface discoloration than CHX dentifrice or gel. A meta-analysis of the effect on 'de novo' plaque formation of CHX dentifrice or gel versus CHX mouthwash resulted in a 0.27 difference in means of Quigley & Hein (1962) plaque scores (95% CI: 0.14; 0.39). It was concluded that CHX gel can be successfully formulated and will inhibit plaque growth to some degree but not to the same extent as a CHX mouthwash. Altogether, the data show that when daily oral hygiene cannot be performed, CHX mouthwash is the first product of choice.

For daily oral hygiene, the general advice from dental care professionals is to brush teeth twice a day using a fluoride toothpaste (ADA 2015). The most commonly used foaming agent in dentifrices is the anionic surfactant sodium lauryl sulfate (SLS). SLS assists in the solubilization of flavoring agents and active dentifrice ingredients and might counteract the effects of CHX (Kolahi & Soolari 2006). Based on the in vitro findings, currently, the general recommendation from dental care professionals and manufacturers is to rinse with a CHX mouthwash 30 minutes after brushing or to use an SLS-free dentifrice. A recent systematic review demonstrated that when CHX mouthwash is recommended, it can be used in combination with an SLS dentifrice without any interference regarding its inhibiting effect on dental plaque, regardless of the order of use. Only when a CHX mouthwash was used in combination with an SLS dentifrice slurry rinse was a significant reduction in CHX activity observed. The relevance of these SLS dentifrice slurry data is questionable, because they are most likely not representative of normal, daily personal oral care. Consequently, the collective evidence indicates that the combined use of dentifrice and CHX mouthwash is not contra-indicated (Elkerbout et al. 2015).

Although still the gold standard in chemical plaque control, an unwelcome side effect of CHX products is tooth surface discoloration. Addy et al. (2005) suggested that a lack of tooth surface discoloration suggests a lack of clinical activity of CHX products. The authors summarized this finding as follows: "If it does not stain it does not work." Tooth surface staining is generally recognized as an esthetic problem and

may interfere with patient compliance in long-term treatment regimens. Therefore, it has been suggested that in order to improve patients' compliance, the development of CHX-containing products with an anti-discoloration system could be explored. In 2004, Bernardi et al. (2004) published the first study that compared a commercially available 0.2% CHX mouthwash to a 0.2% CHX mouthwash with Anti Discoloration System (ADS). ADS is a patented system that interferes with the Maillard reaction. Due to sodium metabisulfite, dischetosamines are transformed into Bertagnini compounds, interrupting the sequence of these reactions. The authors concluded that that there was no statistically significant difference in the ability of the two mouthwashes to prevent bacterial plaque, but the CHX-induced tooth staining was much less prevalent in the ADS group. Nevertheless, a recent double-blind RCT with a 35-day follow up period showed that a CHX mouthwash with ADS was less effective in plaque reduction compared to 2 traditional CHX mouthwashes but more effective in reducing gingival inflammation. CHX with ADS was also associated with significantly less staining (Graziani et al. 2014). This outcome is not in line with research by Li and co-workers (2014), who evaluated the anti-gingivitis effect of an ADS-CHX mouthwash during experimental gingivitis. The authors concluded that CHX with ADS did not prevent the development of plaque or gingivitis and was not significantly different from the placebo. Thus, there is a need to systematically review the available literature on this topic and maybe even further studies which are sufficiently powered in order to establish the relative effectiveness of CHX mouthwash with ADS to 0.12% or 0.2% CHX.

Another approach to reduce staining as unwanted side effect is to use an oxygenating agent (OA), which has a potential inhibiting effect on CHX-induced tooth staining. Van Maanen–Schakel and co-workers (2012) systematically evaluated the literature that compared the effects of CHX mouthwash combined with an OA to the effects of CHX alone. Based on 4 publications, the extracted data allowed for meta-analyses of intermediate-length studies. The results showed that combining an OA with CHX mouthwashes led to a significant reduction in tooth staining and plaque scores compared to the use of CHX alone. The results of the meta-analysis also showed that the ability of CHX to inhibit supragingival plaque does not seem to be disturbed when CHX is used in combination with an OA. The review was limited by the availability of data, and the included studies were methodologically and clinically heterogeneous. Three of the four included studies had an evaluated period of 14 days in a non-brushing model. Only one study, in which the participants rinsed as an adjunct to toothbrushing, had a follow-up of 90 days. Consequently, the reviewing authors concluded that there is moderate evidence that a combination of CHX and an OA reduces tooth staining without interfering with plaque growth inhibition (Van Maanen–Schakel et al. 2012).

Despite its positive effects, CHX mouthwash use might remain limited due to its side effects when used long term. Tooth surface and tongue discoloration is the main limitation to routine usage. In addition, bad taste, altered taste perception, desquamations and oral mucosa soreness have been reported. Because of the side effects, there are objections to the use of CHX mouthwashes in preventive dentistry. Therefore until new formulations are obtained, the use of CHX mouthwashes is recommended for short periods only (Flötra et al. 1971). Mouthwashes containing essential oils (EOs) are indicated for daily long-term use. These are possibly the oldest commercially available mouthwashes that use a fixed and controlled formula. Staining is currently not a recognized side effect of EO mouthwash. In a systematic review, Van Leeuwen et al. (2011) evaluated the efficacy of a CHX mouthwash compared to an EO mouthwash with respect to plaque and parameters of gingival inflammation. In total, 19 publications met the eligibility criteria. A meta-analysis of long-term studies (duration ≥4 weeks) showed that the CHX mouthwash provided significantly superior plaque inhibition versus EO mouthwash. No significant difference in the reduction of gingival inflammation was found between EO and CHX mouthwash. The conclusion was that the standardized formulation of EO mouthwash appeared to be a reliable alternative to CHX mouthwash with respect to gingival inflammation. From a costs perspective, there is also no difference between using a CHX or an EO mouthwash. However, for indications where plaque control is the main focus, such as in post-surgery wound healing, a CHX mouthwash remains the first product of choice.

In conclusion, the overall data show that when daily oral hygiene cannot be performed, 0.2% CHX mouthwash is the first product of choice. This mouthwash can be used in conjunction with any regular fluoride toothpaste. The 0.12% CHX dentifrice gel appears to be a poor alternative to a dentifrice because it is not an effective inhibitor of plaque growth and does not contain fluoride.

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Wat is de vraag?

Youp van ’t Hek

Nederlandse samenvatting voor leken

Deel 1

Zoals te lezen valt in de patiëntenvoorlichtingsfolder van de Nederlandse Vereniging van Parodontologie heeft het gebit een aantal belangrijke functies. Primair dient het voor afbijten en kauwen van voedsel, daarbij bepaalt het gebit een deel van het uiterlijk wat sociaal gezien van belang is. Rondom de tanden en kiezen bevindt zich het parodontium. Dit steunweefsel bestaat uit het tandvlees, de vezels en het kaakbot. De vezels verbinden de wortel van de tanden en kiezen met het kaakbot en het tandvlees. Bij het tandvlees zit er boven de vezels een smalle ruimte tussen het tandvlees en het tandoppervlak, deze wordt een pocket genoemd. Gezond tandvlees is roze van kleur, niet pijnlijk en bloedt niet bij poetsen, eten of het gebruik van mondhygiënehulpmiddelen tussen de tanden en kiezen. Het tandvlees ligt strak om de tanden en kiezen heen. Als het wordt onderzocht door de mondhygiënist of tandarts bloedt het niet en is het pijnloos.

Bij een mooi en gezond gebit hoort gezond tandvlees. Tandvleesontsteking is echter een veel voorkomend fenomeen (50% van de Nederlandse volwassenen) waarvan de mate kan verschillen per persoon. Omdat een tandvleesontsteking meestal geen pijn doet, wordt het helaas vaak laat herkend en behandeld. Een tandvleesontsteking ontstaat primair door bacteriën, deze zijn van nature in de mond aanwezig. Het laagje bacteriën dat zich gemakkelijk in de mond hecht aan het tandoppervlak wordt tandplak genoemd. Indien de tandplak zich langs de rand van het tandvlees bevindt, veroorzaakt het een ontsteking aan het tandvlees. Dit eerste stadium heet "gingivitis". Het tandvlees is veelal rood, gezwollen en slap. Daarmee sluit het niet meer strak om de tanden en kiezen. Alhoewel het vaak pijnvrij verloopt, kan het wel gemakkelijk bloeden bij het poetsen of het gebruik van mondhygiënehulpmiddelen tussen de tanden en kiezen. Dit stadium is reversibel zonder blijvende schade indien het op tijd wordt behandeld. Om de mond gezond te houden is het daarom raadzaam om tandplak secuur te verwijderen. Dit is niet altijd even gemakkelijk omdat de tandplak voornamelijk langs de tandvleesrand gaat zitten, rondom de tanden en kiezen.

Het algemene tandheelkundige advies is om tweemaal per dag tanden te poetsen met een fluoride tandpasta. Met alleen gebruik van een tandenborstel is het lastig om alle plak tussen de tanden en kiezen te verwijderen. Daarom is het raadzaam om ook de tussenruimten te reinigen met bijvoorbeeld floss, stokers, ragers of de monddouche. Naast fluoride tandpasta's zijn er diverse speciale tandpasta's met toevoegingen. Bijvoorbeeld tegen gevoelige tandhalzen, tegen tandsteen en om tanden witter te maken. Diverse ingrediënten worden toegevoegd waarvan geclaimed wordt dat ze werken tegen oppervlakkige tandvleesontstekingen. Ook

mondspoelmiddelen kunnen een extra bescherming geven tegen het ontstaan van tandplak en het ontstaan van gaatjes in de tanden en kiezen. Een meerwaarde is dat deze een fris gevoel in de mond geven. Het idee is dat tandpasta's en spoelmiddelen ook op de plaatsen komt die niet worden bereikt met een tandenborstel, zo zou het effect van het poetsen worden versterkt.

In de loop der tijd zijn vele verschillende chemische producten toegevoegd aan tandpasta en spoelmiddelen zoals bijvoorbeeld tin fluoride en triclosan. Chloorhexidine (CHX) is het meest toegevoegde en onderzochte product. Er is sterk bewijs dat wanneer het aan een spoelmiddel wordt toegevoegd, CHX effectief is in het voorkomen van plakgroei en het ontstaan en reduceren van tandvleesontsteking. CHX spoelmiddel en zijn voornamelijk verkrijgbaar in een 0.12% en 0.2% concentratie wat vergelijkbare resultaten oplevert. Op de Nederlandse markt is er ook een 0.12% CHX gel tandpasta verkrijgbaar. Hoofdstuk 2 van het proefschrift presenteert een klinisch onderzoek waarin het effect van dit product wordt geëvalueerd. Proefpersonen zonder ernstige tandvleesontsteking werden door een mondhygiënist plakvrij gemaakt door het polijsten van het gebit. In de onderzoeksperiode van 3 dagen mochten zij vervolgens niet poetsen en geen mondhygiënemiddelen gebruiken. Het lot bepaalde in welke van de drie groepen ze kwamen en welke producten ze tweemaal daags moesten gebruiken. De testgroep gebruikte de 0.12% CHX gel tandpasta en een controlegroep gebruikte een gewone fluoride tandpasta. Beide groepen gebruikten een applicatielepel voor de toepassing in de mond. De andere controlegroep gebruikte een 0.12% CHX mondspoeling. Na de drie dagen werd er met behulp van een plakscoringsindex bepaald hoeveel tandplak er aanwezig was op het gebit. Beide tandpastagroepen hadden significant meer plaque dan de CHX spoelgroep. Er werd geen verschil gevonden tussen de twee tandpasta's. Realiserend dat het driedaagse model niet direct vertaald kan worden naar dagelijkse toepassing, werd er geconcludeerd dat de 0.12% CHX gel tandpasta een matig alternatief is voor een fluoride tandpasta omdat het geen fluoride bevat.

Het onderzoek in hoofdstuk 3 is opgezet om 1% CHX gel, 0.12% CHX gel tandpasta en gewone fluoride tandpasta te vergelijken met een 0.2% CHX mondspoeling. Dit laatste wordt gezien als de "gouden standaard" onder chemische plakremming. Een vergelijkbare groep proefpersonen en soortgelijk onderzoeksmodel werd gebruikt als in het voorgaande hoofdstuk. Wederom werd er geen verschil gevonden tussen de 0.12% CHX gel tandpasta en gewone fluoride tandpasta. Beide tandpasta's waren ook significant minder effectief in het voorkomen van plakgroei dan de 1% CHX gel en de 0.2% CHX mondspoeling. Omdat tandvleesontsteking een rol kan spelen bij de mate van plakgroei werd ook de ontstekingsgraad van het tandvlees gemeten door de bloedingsneining te scoren. Er was echter geen verschil tussen de

vier groepen. De ontstekingsgraad van het tandvlees bleek dan ook geen invloed te hebben als verstorende factor op de gevonden plakscores.

Beide studies werden uitgevoerd als korte termijn studies die louter de hoeveelheid van het ontstaan van nieuwe tandplak konden evalueren. Een kritisch punt is wel dat de producten niet conform de gebruiksaanwijzing van de fabrikant zijn gebruikt. Het poetsen met de producten zou wellicht andere resultaten hebben gegeven. Daarom werd er vervolgens in hoofdstuk 4 een systematisch literatuuronderzoek gedaan naar het effect van tandenpoetsen en het gebruik van een CHX gel/tandpasta vergeleken met een placebo of een reguliere fluoride tandpasta. Plakscores, de mate van tandvleesontsteking en het ontstaan van aanslag waren de uitkomstmaten waarnaar gezocht werd. In drie databases werd gezocht naar geschikte artikelen die een klinisch onderzoek beschreven waarin de proefpersonen geen ernstige tandvleesontsteking hebben en zelf poetsten voor een periode van minimaal 4 weken. Ten aanzien van de plakscores presenteerde het merendeel van de studies die CHX tandpasta gebruikten een positief significant effect. Alle studies die de tandvleesbloeding evalueerden, rapporteerden een significant matig positief effect voor de CHX tandpasta. De vorming van aanslag kwam wel vaker voor bij de groepen met CHX tandpasta. De gegevens over CHX gel lieten geen positieve trend zien bij gebruik op de plak- en bloedingsscores. De conclusie heeft betrekking op mensen met een lichte tot matige tandvleesontsteking. Dit sluit aan bij de indicatie van de fabrikant.

Het laatste systematische literatuuronderzoek van dit eerste gedeelte van het proefschrift in hoofdstuk 5, evalueert het effect van CHX gel of tandpasta met CHX mondspoeling op plak, bloedingsneiging, tandvleesontsteking en aanslag. Dit is de ontbrekende verbinding tussen het voorgaande hoofdstuk en het reeds bestaande sterke bewijs in effectiviteit van CHX mondspoelmiddel. De beperkte gegevens die in de wetenschappelijke literatuur beschikbaar waren over het effect op tandvleesontsteking lieten geen verschil zien tussen CHX tandpasta of CHX spoelmiddel. Van de 5 vergelijkingen die het effect op de hoeveelheid tandplak evalueerden lieten er 3 een significant beter effect zien bij het gebruik van CHX mondspoelmiddel. Er werd echter ook meer aanslag op de tanden en kiezen waargenomen. Geconcludeerd werd dat CHX met succes kan worden verwerkt in een gel of tandpasta maar niet met dezelfde effectiviteit als een CHX mondspoelmiddel. Indien het niet mogelijk is om de dagelijkse mondhygiëne uit te voeren, is CHX mondspoelmiddel daarom de beste keuze.

Additionele bronnen

- Folder: Parodontitis. Tandvleesontsteking: oorzaak, gevolg en behandeling. (2014) BV diensten NVvP. ISBN 978-90-818530-1-9.
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ETC = End of Thinking Capacity

List of frequently used abbreviations

AAP	American Academy of Periodontology
ACTA	Academic Centre for Dentistry Amsterdam
ADA	American Dental Association
AMC	Academic Medical Centre
BOMP	Bleeding on Marginal Probing
BOP	Bleeding On Probing
BOPP	Bleeding On Pocket Probing
BS	Bleeding Scores
CAL	Clinical Attachment Loss
CCT	Controlled Clinical Trial
CHX	Chlorhexidine
CONSORT	Consolidated Standards Of Reporting Trials
DiffM	Difference in Means
DL	Diode Laser
EMBASE	Excerpta Medical dataBASE
EO	Essential Oil
Er:YAG	Erbium-Doped:Yttrium-Aluminum-Garnet
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GI	Gingival Index
MA	Meta-Analysis
MEDLINE	Medical Literature Analysis and Retrieval System Online
NA	Not Applicable
Nd:YAG	Neodymium:Yttrium-Aluminium Garnet
NR	Not Reported
NVvP	Nederlandse Vereninging voor Parodontologie (Dutch Society of Periodontology)
OA	Oxynating Agent
PD	Probing Depth
PDT	Photo Dynamic Therapy
PI	Plaque Index
PISA	Periodontal Inflamed Surface Area
PMC	Periodontal Maintenance Care (programme)
PPD	Probing Pocket Depth
PS	Plaque Scores
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PubMed	Public Medline database
REC	Recession (distance from the marginal gingiva to the cemento–enamel junction)
RCT	Randomized Controlled Trial
RTF	Reduced Transport Fluid
SA	Stain Area
SD	Standard Deviation
SE	Standard Error
SLS	Sodium Lauryl Sulphate
SNOSE	Sequentially Numbered Opaque Sealed Envelopes
SRP	Scaling and Root Planing (non-surgical periodontal debridement)
(T)CFUs	(Total) Colony-Forming Units
TSBV	Trypticase -Serum–Bacitracin–Vancomycin
US	Ultrasonic Scaling
VAS	Visual Analogue Scale

CV

Rustig aan, in je eigen tempo.

Jan Slot

Curriculum Vitae

Dagmar Else Slot (1975) started her career in dentistry in 1994 when she graduated as a dental assistant from the "Damland College". While she continued studying dental hygiene at the "Hogeschool Midden Nederland" in Utrecht, she started working 'ad hoc' as a dental assistant in a private practice in Amsterdam which focuses on preventive and cosmetic dentistry (ACCT) and is owned by the dentist Bart Beekmans. In 1997 she received her dental hygienist diploma and continued her job at ACCT with a change in position to dental hygienist and has been working there ever since. Still continuing with studying she earned a pedagogical Bachelor of Education degree for primary school teaching from the "Educatieve Faculteit Amsterdam" in 1999. For teaching students at applied science level she received an education/didactical degree in 2001 from the "Hogeschool Utrecht". Continuing with Master of Science program in Evidence Based Practice from the faculty of medicine of University of Amsterdam, Dagmar received her degree in 2005. She also followed the necessary courses to receive a Bachelor of Health degree for dental hygienist, when in 2006 this qualification in the Netherlands was established.

During the years 1999-2007 she was a faculty member at the school of dental hygiene, first at the "Hogeschool" in Utrecht and later at "Inholland" in Amsterdam". Since 2007 Dagmar changed this position to become a researcher at the Department of Periodontology of the Academic Center for Dentistry Amsterdam (ACTA). She is team member of the research group guided by Professor dr. Fridus van der Weijden focusing on preventive and therapeutic procedures in dentistry and more specific in oral health and periodontology. She has been involved in various clinical research projects some of which have been conducted in conjunction with Industry. Furthermore she has participated in a series of systematic reviews which aim to establish the scientific evidence supporting prevention and therapy of periodontal diseases. She has supervised Bachelor and Master students with their research projects and publications. Dagmar is an associate editor of the "International Journal of Dental Hygiene" and ad hoc reviewer of many other peer reviewed journals. She is frequently invited for lectures both for national and international congresses.

She has been author/co-author of over 70 peer reviewed international papers, 4 book chapters and almost 40 articles in Dutch. In 2013 she received the World Dental Hygienist Award in the category "research". She was a board member of de Dutch Dental Hygiene Association (NVM) and also has been and still is an active member of various committees for several professional associations being involved with i.e. organizing annual scientific meetings and in the preparing clinical guidelines for dental care professionals.

With her true love Dirk she lives in the World Heritage "Beemster Polder" where they run a dairy farm. This is also where she makes her renowned blackberry jam.

...promoveer niet voor je 40 bent...

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Pubs

You will do it because you know that knowledge is beautiful, and because if only a hundred people share your passion, that is enough.

Ben Goldarce

Other publications from the author

PubMed indexed

- Hennequin-Hoenderdos NL, Slot DE, Van der Weijden GA. (2015) The incidence of complications associated with lip and/or tongue piercings: a systematic review. International Journal of Dental Hygiene, (early view).
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Notes

Prevention of gingivitis and Treatment of periodontitis

- chlorhexidine gels and dental lasers -

Dagmar Else Slot

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Coldplay

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7.

When you possess light within, you see it externally.

Anaïs Nin

INTRODUCTION AND OUTLINE OF PART II OF THE THESIS

General Introduction, part II

To achieve oral health, comfort, esthetics, and function, the goals of periodontal therapy are to preserve, improve, and maintain the natural dentition. A healthy periodontium is characterized by the absence of inflammation, in terms of redness, swelling, suppuration, and bleeding on probing (AAP 2011a). Gingivitis ("inflammation of the gum tissue") is a non-destructive periodontal disease (AAP 1989) in response to bacterial biofilms (also called dental plaque) on tooth surfaces. In the absence of treatment, gingivitis can progress to periodontitis. Periodontitis is an inflammatory disease involving the supporting tissues of the teeth, that results in a progressive destruction of the periodontal ligament and alveolar bone with pathological pocket formation, recession, or both. The latter is the most destructive form of periodontal disease (AAP 2000). As a result of advances in knowledge and therapy, the majority of patients can retain their dentition over their lifetime with appropriate treatment, reasonable dental plaque control, and continuing maintenance care (AAP 2011a).

Periodontal therapy

Egyptian hieroglyphics dating as far back as 3000-4000 years revealed that non-surgical periodontal treatment was already in practice. Control of the root surface environment has been considered an essential component of periodontal therapy for at least 1000 years, when a Middle Eastern healer named El Zahwari (Albucassis) wrote in his treatise that "*ye shall remove the encrustations on the teeth lest they be lost.*" We have come a long way since then, but the basic requirements for periodontal health have not changed (Bader 2009). Even today, scaling and root planing (subgingival debridement) remain an essential component of successful periodontal therapy. The collective evidence from numerous clinical trials reveals a consistency of clinical response in the initial treatment of chronic periodontitis by subgingival debridement. This therapy includes manual, sonic and/or ultrasonic instrumentation in conjunction with supragingival plaque control (Cobb 2002). A systematic review of the literature evaluated the effect of subgingival debridement in terms of bleeding on probing, pocket depth and probing attachment level in patients with chronic periodontitis. Subgingival debridement was found to be an effective treatment in reducing probing pocket depth and improving the clinical attachment level (Van der Weijden & Timmerman 2002).

Lasers

In addition to traditional subgingival debridement, innovations in dentistry have produced many new technologies and methods for the treatment of periodontitis.

Educational and marketing efforts have resulted in the adoption of new treatment modalities by an increasing number of providers (Flemmig & Beikler 2013). Since their introduction in the early 1990s, the clinical application of lasers for the treatment of periodontal disease has continued to expand (AAP 2011b). The history of the laser in dentistry was recently reviewed by Polhaus (2012). The word "laser" is an acronym for Light Amplification by Stimulated Emission of Radiation. In 1916, Albert Einstein wrote to a friend, "A splendid light has dawned on me about the absorption and emission of radiation." Einstein never created a laser, but at that time, he theorized the concept of stimulated emission, which is the scientific basis for the creation of laser light. A laser beam is created from a substance known as an active medium, which when stimulated by light or electricity, produces photons of a specific wavelength. The first ruby laser was developed in 1960, and many other lasers were created rapidly thereafter. Dental researchers began investigating lasers' potential, and Stern and Sognnaes reported in 1965 that a ruby laser could vaporize enamel. Wavelengths were studied over the ensuing decades for both hard and soft tissue applications. Practitioners and researchers began to discover clinical oral soft tissue uses of medical lasers until 1990, when the first pulsed Neodymium:Yttrium-Aluminium Garnet (Nd:YAG) lasers designed specifically for the dental market were released. Semiconductor-based diode lasers emerged in the late 1990s (Polhaus 2012).

Manufacturers note lasers' ease of use and effectiveness in the short and long term, reduced association with pain/discomfort or swelling, and reduced treatment time. Dental laser systems are cleared for marketing in the United States via the Food and Drug Administration (FDA). The Nd:YAG lasers are considered safe and have been FDA approved for soft tissue treatment in the oral cavity. Despite FDA approval, no laser system has received the American Dental Association's (ADA) Seal of Acceptance. Many questions remain regarding the use of lasers as a monotherapy or as an adjunct to the conventional treatment modalities for periodontitis. The latter is less controversial, although well-designed, randomized, blinded, controlled longitudinal studies are necessary to provide clear and meaningful evidence to validate the use of this technology in periodontal therapy (Cobb et al. 2010).

Literature reviews

The search strategy of a systematic review (Schwarz et al. 2008) on lasers in non-surgical periodontal therapy used eligibility criteria that eventually resulted in only one included paper on diode lasers and one paper on the Nd:YAG laser. The major reason for excluding studies in this review was lack of a definition of inclusion and exclusion criteria for participants. Another review by Karlsson et al. (2008) evaluated the effect of laser therapy as an adjunct to non-surgical periodontal treatment, but

this review lacked a reproducible search strategy and used studies with a duration of ≥ 12 weeks of follow-up as part of the inclusion criteria. This review also retrieved only one paper on Nd:YAG lasers, but not the same paper as that in review by Schwarz and co-workers (2008). No paper using a diode laser was found to be eligible. Cobb and co-workers (2010) performed a thorough narrative review on lasers in the treatment of chronic periodontitis. Ten studies were identified that used the Nd:YAG lasers, resulting in an average increased mean probing pocket depth (PPD) reduction of 0.09mm and a 0.33mm gain in clinical attachment loss (CAL) compared to the control groups. Based on the five included studies, the use of the diode laser as an adjunct to subgingival debridement yielded an average mean difference of a 0.56mm reduction in PPD and a 0.18mm gain in CAL. The outcome of these reviews was insufficient to draw a clear conclusion regarding the benefit of diode and Nd:YAG lasers.

Aims of the Thesis, part II

SYSTEMATIC REVIEWS

Practicing evidence-based dentistry, every dental professional must make a well-considered decision concerning the treatment provided to a patient. To make a well-informed decision, the clinical expertise, patient values, available instruments and best evidence must be integrated. The best evidence is usually found in clinically relevant research that has been conducted using sound methodology (Sacket et al. 2000). The premise of systematic reviews is to consider the totality of the evidence. There appeared to be more eligible studies when using different eligibility criteria regarding the use of the diode and Nd:YAG laser. Therefore, there was room for new, more comprehensive and focused systematic reviews. The aim of the systematic review as presented in chapter 8 was to assess the adjunctive effect of a diode laser following non-surgical subgingival debridement during the initial phase of periodontal therapy on the clinical parameters of periodontal inflammation. The aim of the systematic review presented in chapter 9 was to evaluate in a systematic manner the (additional) therapeutic effects of using a pulsed Nd:YAG laser in the initial treatment of patients with periodontitis.

CLINICAL STUDIES

New technological features of laser equipment such as a water-coolant laser might provide improved treatment outcomes. The use of an air–water spray for irrigation during laser irradiation might provide a thermal gradient for the removal of heat from tissue surfaces (Spencer et al. 1996) and reduce the clogging of the probe with debris (Qadri et al. 2010). The purpose of the clinical study presented in chapter 10 was to test whether the use of a Nd:YAG laser with water and air coolant as

an adjunct to hand- and ultrasonic subgingival debridement resulted in greater clinical improvements compared to subgingival ultrasonic debridement alone. Additional purposes were to investigate the reduction in the number of subgingival microorganisms immediately following subgingival debridement with or without adjunctive Nd:YAG laser application and to evaluate post-operative experiences and patient comfort with regard to the treatments provided. A second clinical study, presented in chapter 11, evaluated the adjunctive clinical effect of this water-cooled Nd:YAG laser in patients attending a periodontal maintenance care program.

Given that most chapters are based on separate scientific publications and often concern the same topic, there are inevitably considerable overlaps between chapters. Different journal requirements have also created some variations in terminology from one chapter to the next. For expository reasons, the chapters in this thesis are not arranged chronologically.

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The Wrong Direction

Passenger

THE EFFECT OF THE THERMAL DIODE LASER (WAVELENGTH 808-980 NM) IN NON-SURGICAL PERIODONTAL THERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS

SLOT DE
JORRITSMA KH
COBB CM
VAN DER WEIJDEN FA

JOURNAL OF CLINICAL PERIODONTOLOGY
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Introduction

Periodontitis is one of the major causes of tooth loss in adults (Jenkins et al. 1988) and, therefore, deserves timely and adequate treatment. Eliminating the source of this complex disease is a difficult challenge. It is essential during the initial phase of periodontal therapy to remove microbial biofilms that exist on the tooth and/or subgingival epithelial surfaces. Conventional treatment, using manual and ultrasonic scalers, has proven to be effective for removal of subgingival biofilms (Van der Weijden & Timmerman 2002).

However, non-surgical periodontal therapy has limitations (Cobb1996), and so, many clinicians have proposed the use of several kinds oflasers, adjunctive to SRP, as a more effective method of non-surgical therapy. Over the last decade, various laser wavelengths have been used byclinicians in the treatment of periodontitis; most commonly the diodelasers (DL) (809–980 nm), Nd:YAG(1064 nm), Er:YAG and Er,Cr:YSGG (2940 and 2780 nm respectively) and the CO_2 (10,600 nm)(Cobb et al. 2010). Lasers are used as a mono therapy and as adjunct toSRP. The DL has been used in dentistry since the early 1980s (Pirnat 2007, Aoki et al. 2008). Overtime, the DL has become more popular with clinicians, primarily because of its relatively small size and low cost.

DLs have promising attributes for periodontal therapy (Schwarz et al. 2003) and are effective for soft-tissue applications, such as incision, haemostasis, and coagulation (Romanos & Nentwig 1999). Diode wavelengths when combined with the appropriate choice of parameters can result in penetration of soft tissues ranging from about 0.5 to 3mm (Aoki et al. 2008) and exhibits poor energy absorption in mineralized tissues. Thus, the DL is contraindicated for calculus removal. Given the current recommended parameters, the possibility of inducing collateral damage with the DL, such as root surface alterations, is not likely to occur (Cobb et al. 2010).

The purported benefits of the DL in periodontal therapy are based on the premise that subgingival curettage is an effective treatment and that significant reduction in subgingival microbial populations is predictably achieved (Cobb et al. 2010). Romanos et al. (2004) in an in vitro histological study on pigs reported the ability of the DL at 2.0 W to completely remove the pocket epithelium. In addition, the application of a DL supposedly has benefits such as promotion of haemostasis, decreased requirement of anaesthesia during treatment, and less post-operative pain. Last, the ability to detect subgingival calculus, due to specific diode wavelengths, is a useful quality when performing periodontal treatment (Folwaczny et al. 2004).

There are several narrative reviews, and one recent systematic review concerning the DL (Sgolastra et al. 2013). The latter, however, mixed results of both initial and maintenance therapy in their meta-analysis (MA). Furthermore, they included a study in which the laser delivery tip was not introduced into the pocket but was limited to the buccal gingiva during irradiation.

The premise of systematic reviews is to consider the totality of the evidence. There appear to be more eligible studies which, when viewed collectively, justified a new, more comprehensive and focused systematic review. Thus, the aim of this article was to assess the adjunctive effect of a DL following non-surgical periodontal debridement (SRP) during the initial phase of periodontal therapy on the clinical parameters of periodontal inflammation.

Material and Methods

This systematic review was conducted in accordance with the Cochrane handbook (Higgins & Green 2009) for systematic reviews of interventions that provides guidance for the preparations and the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement, available at: http://www.prisma-statement.org/) (Moher et al. 2009).

Focused PICOS question (Copanitsanou & Valkeapää 2013)

Based on randomized controlled clinical trials (RCTs) what is the effect of the adjunctive use of a DL following non-surgical periodontal debridement (SRP) during the initial phase of periodontal therapy on the clinical parameters of periodontal inflammation, i.e. probing pocket depth (PPD), clinical attachment level (CAL) measurements, plaque score (PS), bleeding score (BS) and Gingival Index (GI), compared to SRP alone.

Search strategy

Three Internet sources were used to search for appropriate papers that satisfied the study purpose. These sources included the National Library of Medicine, Washington, DC (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). For this comprehensive search, all three databases were searched for eligible studies up to September 2013. The structured search strategy was designed to include any relevant published paper that evaluated the adjunctive effect of the DL following non-surgical periodontal treatment. For details regarding the search terms used, see Box 1.

Screening and selection

Two reviewers (GAW & KHJ) independently screened the titles and abstracts for eligible papers. If eligibility aspects were present in the title, the paper was selected for further reading. If none of the eligibility aspects was mentioned in the title, the abstract was read in detail to screen for suitability. After selection, the full-text papers were read in detail by two reviewers (DES & KHJ). Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, the judgment of a third reviewer (GAW) was decisive. The papers that fulfilled all of the selection criteria were processed for data extraction.

All of the reference lists of the selected studies were hand searched by two reviewers (DES & KHJ) for additional published work that could possibly meet the eligibility criteria of the study. Unpublished work was not sought.

Box 1

Search terms used for PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE. The search strategy was customized according to the database being searched
The following strategy was used in the search:

{(Intervention) AND (outcome)}
{(Intervention: <[MeSH terms] lasers OR laser therapy OR [text words] laser> AND <diode laser OR diode OR low level>)
AND
(Outcome: [MeSH terms] Periodontal Diseases OR dental deposits OR [text words] papillary bleeding index OR sulcus bleeding OR bleeding on probing OR gingival bleeding OR Gingival Index OR gingival inflammation OR gingival disease* OR gingivitis OR periodontitis OR periodontal disease* OR periodontal pocket OR gingival pocket OR pocket depth OR plaque removal OR plaque index OR dental plaque OR plaque OR dental deposit OR calculus OR clinical attachment loss)}

The asterisk (*) was used as a truncation symbol.

The eligibility criteria were as follows:

- RCTs.
- Papers written in the English or Dutch language.
- Studies conducted in humans:
    - ≥18 years old.
    - In good general health.
    - Diagnosed with periodontitis.
- Intervention: use of a thermal DL as adjunct to non-surgical conventional periodontal initial therapy with fibre insertion into the pocket during the same visit.
- Comparison: non-surgical conventional initial periodontal therapy using ultrasonic

scalers and/ or hand instrumentation with/ without sham laser use.
- Evaluation with one or more of the following clinical evaluation parameters: PPD, CAL, PS, GI and BS.
- Minimum evaluation period of ≥4 weeks (Slot et al. 2009).

Exclusion criteria included use of DLs in combination with an additional photo sensitizer, e.g. photodynamic therapy.

Assessment of heterogeneity

The heterogeneity of the outcome parameters across studies was detailed according to the following factors:

- Study design, study population, evaluation period.
- Subjects characteristics and smoking habits.
- Intervention: type of DL, settings and procedures.
- Lost to follow-up, side effects and industry (commercial) funding.

Quality assessment

Two reviewers (DES & KHJ) scored the methodological qualities of the included studies according to the method described in detail by Keukenmeester et al. 2013. In short, when random allocation, defined eligibility criteria, masking of examiners, masking of patients, balanced experimental groups, identical treatment between groups (except for the intervention) and reporting of follow-up were present, the study was classified as having a low risk of bias. In addition to these criteria, for this review in particular, the unit of analysis was considered as an item where analysis was performed at a subject level. When, one of these eight criteria was missing, the study was considered to have a moderate risk of bias. When two or more of these criteria were missing, the study was considered to have a high risk of bias, as previously proposed by Van der Weijden et al. (2009).

Statistical analyses

DATA EXTRACTION

The data from those papers that met selection criteria were extracted and processed for further analysis. For studies that presented an intermediate outcome assessment, only the baseline and final evaluations were used. Two reviewers (DES & KHJ) evaluated the selected papers for baseline, end and incremental mean values and standard deviation (SD). Disagreements were resolved by discussion, and if the disagreement persisted, the judgment of a third reviewer (GAW) was decisive. For those papers that provided insufficient data to be included in the analysis the first or corresponding authors were contacted to determine if additional data could be provided. To warrant a precise estimate any data approximation in figures was avoided.

DATA ANALYSIS

The variables of interest were PPD and CAL but the variables, PS, GI and BS were also taken into account. When appropriate, a MA was performed, and the difference in means (DiffM) was calculated using the Review Manager 5.1 software (RevMan version 5.1 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The "random effects" model was used to calculate a weighted average of the treatment effects across the studies under review. As the estimate of between study variance is poor for analyses due to the low number of studies, a "fixedeffect" analysis was used if there were fewer than four studies (Higgins & Green 2009). Heterogeneity was tested by chi-square test and the I^2 statistic. A chi-square test resulting in a $p < 0.1$ was considered an indication of significant statistical heterogeneity. As a rough guide for assessing the possible magnitude of inconsistency across studies, I^2 statistic of 0–40% was interpreted as not to be imperative, and above 40% moderate to considerable heterogeneity was supposed to be present. The formal testing for publication bias that was proposed by Egger et al. (1997) could not be used owing to insufficient statistical power because less than 10 studies were included in the MA (Higgins & Green 2009).

Subgroup level analysis was performed on the basis of the unit of analysis being either the subject, the site or one site within a subject. For those studies that used the site as the unit of analysis, the number of subjects in a group was used in the MA instead of the number of sites. Furthermore, subanalysis was performed differentiating between a parallel or split-mouth research model. In addition, the collective data of all individual included studies are summarized and presented in a descriptive manner.

Grading the "body of evidence"

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, as proposed by the GRADE Working Group (2000), was used to grade the evidence emerging from this review with respect to the outcome parameters, i.e. PPD and CAL (GRADE, Guyatt et al. 2008). Two reviewers (DES & GAW) rated the quality of the evidence as well as the strength of the recommendations according to the following aspects: risk of bias of the individual studies; consistency and precision among the study outcomes; directness of the study results; and detection of publication bias. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Search and selection results

The searches resulted in 416 unique papers (for details, see Figure 1). The screening of titles and abstracts initially resulted in 23 papers. Based on detailed reading of full-texts, 14 papers were excluded, the reasons for exclusion are explained in the Appendix S1. Hand searching of the reference lists did not reveal any additional suitable papers. Consequently, nine studies were identified as eligible for inclusion in this systematic review according to defined criteria for study design, participants, intervention and outcome.

Assessment of heterogeneity

Considerable heterogeneity was observed in the nine clinical trials with respect to study design, evaluation period, study population, number, gender and age of participants. Information regarding the study characteristics is displayed in detail in Table 1. Various clinical indices and their modifications are used.

Study design, research groups, evaluation period

All included studies were RCTs, the majority used a split-mouth design (II, III, IV, V, VI, VII, VIII) and two a parallel design (I, IX). The evaluation period varied from 6 weeks (V, IX) up to 6 months (I, III, IV,VI, VII). Procedures for allocation concealment were not described in any of the selected studies with the exception of II. Masking (blinding) of the examiner was described in all but one (VII). Two studies (III, V) performed a true double-blind tail by introducing a control treatment with sham laser instrumentation.

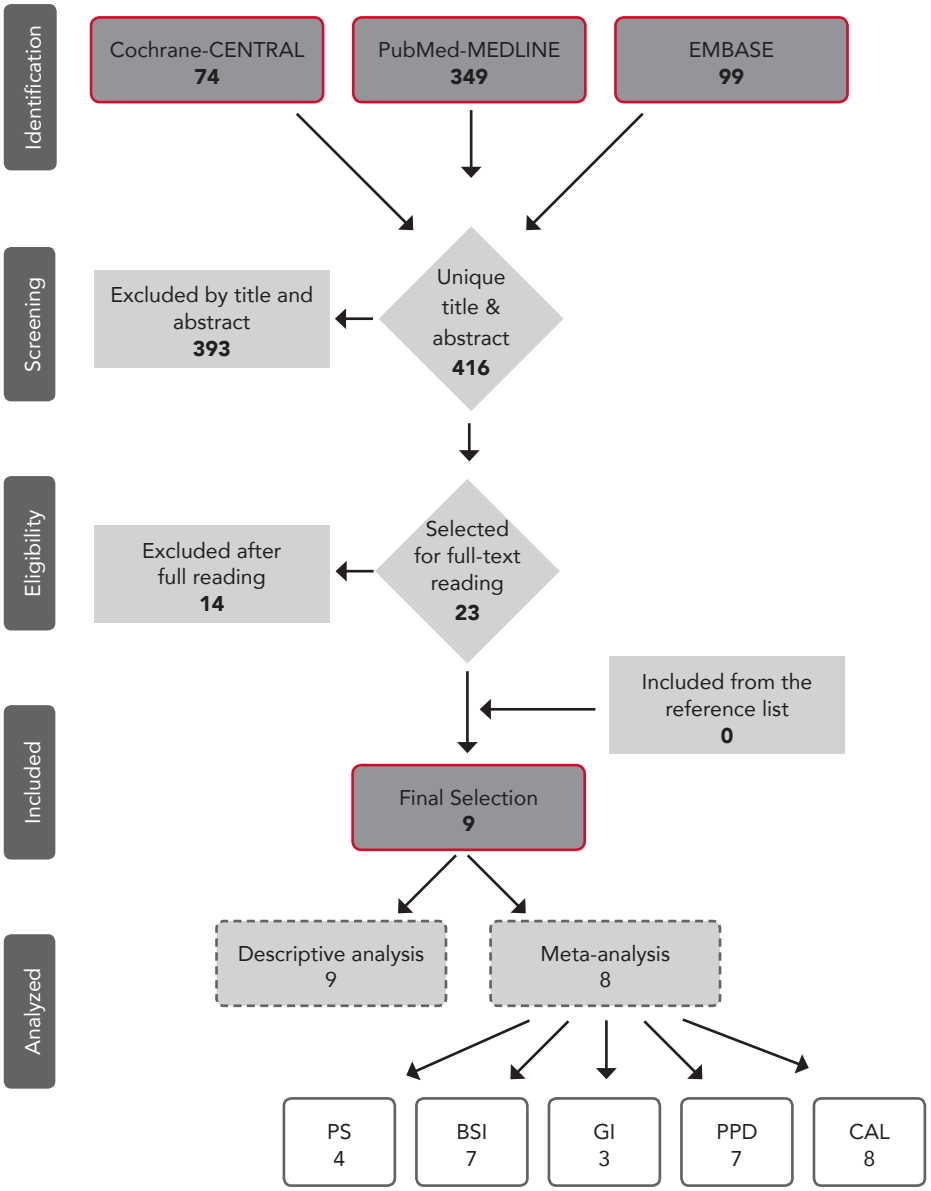
Table 1. Overview of the included studies and characteristics processed for data extraction

ID Author (year)	Study design, blinding, evaluation period	Subjects # baseline (end) Gender Age (years)	Groups	Original authors' conclusion
I Saglam et al. (2012)	RCT Parallel Single blind ‡ 6 months	Chronic periodontitis 30 (30) ♀:12 ♂:18 Mean age: 41.5◊	SRP + DL SRP	Diode laser provided significant improvements in clinical parameters.
II Dukic et al. (2012)	RCT Split-mouth Single blind ‡ 18 weeks	Chronic periodontitis 35 (35) ♀:14 ♂:21 Mean age: 37	SRP + DL SRP	Compared to SRP alone, multiple adjunctive applications of a 980-nm diode laser with SRP showed PD improvements only in moderate periodontal pockets (4 to 6mm).
III Euzebio Alves et al. (2013)	RCT Split-mouth Double blind †,‡ 6 months	Chronic periodontitis PPD ≥5mm 37 (36) ♀:23 ♂:13 Mean age: 46.8	SRP + DL SRP + sham DL	The high-intensity diode laser has not shown any additional benefits to the conventional periodontal treatment.
IV Zingale et al. (2012)	RCT Partially Split-mouth / Partially Parallel Single blind † 6 months	Chronic periodontitis PPD 5-9mm 25 (25) ♀:9 ♂:16 Mean age: 55.8	DL + SRP + DL DL + SRP SRP	The adjunctive use of the diode laser did not significantly differ from SRP alone in decreasing PDD/BOP.
V De Micheli et al. (2010)	RCT Split-mouth Double blind †,‡ 6 weeks	Chronic periodontitis PPD ≥5mm 28 (27) ♀:19 ♂:8 Mean age: 48.5 Age range: ?	SRP + DL SRP + sham DL	The high power diode laser adjunct to the non- surgical periodontal treatment did not promote additional effects to the conventional periodontal treatment

VI Kamma et al. (2009)	RCT Split-mouth Single blind ‡ 6 months	Aggressive severe periodontitis CAL ≥5mm (2-3 sites >14 teeth) 30 (30) ♀:16 ♂:14 Mean age: 41.8 Age range: ?	SRP + DL SRP	Diode laser-assisted treatment with SRP showed a superior effect over SRP for certain clinical parameters in patients with aggressive periodontitis.
VII Caruso et al. (2008)	RCT Split-mouth Single blind ‡ 6 months	Periodontal lesions PPD ≥5mm 13 (13) ♀:? ♂:? Mean age: ? Age range:?	SRP + DL SRP	The diode laser may lead to a slight improvement of clinical parameters.
VIII Kreisler et al. (2005)	RCT Split-mouth Single blind ‡ 12 weeks	Periodontal treatment needs PPD ≥3mm 25 (22) ♀:15 ♂:7 Mean age: 45 Age range: ?	SRP + DL SRP	The diode laser in the treatment of inflammatory periodontitis at the irradiation parameters is a safe clinical procedure and can be recommended as an adjunct to conventional scaling and root planing.
IX Borrajo et al. (2004)	RCT Parallel Double blind †,‡ 6 weeks	Moderate periodontal disease 30 (29) ♀:? ♂:? Mean age ? Age range?	US+SRP+DL+SRP+DL US+SRP	Scaling and root planing in combination with laser produced moderate clinical improvement over traditional treatment.

†	blinded to patient	‡	blinded to examiner
RCT	Randomized Controlled Trial	SRP	Scaling and rootplaning
DL	Diode laser	US	Ultrasonic Scaling
PPD	Probing Pocket Depth	?	unknown

Figure 1. Search and selection results



Subject characteristics and smoking habits

All of the study subjects in the selected studies were in good general health. The following criteria and periodontal diagnoses were considered when selecting subjects; chronic periodontitis (I, II, III, IV, V), aggressive or severe periodontitis (VI), moderate periodontal disease (IX), periodontal lesions (VII) or a need of periodontal treatment (VIII). Two studies noted that some study subjects were smokers (IV, VI). Smoking more than 10 cigarettes per day was an exclusion criterion for one study (VIII). In three studies (I, II, V), non-smokers were included in the studies and three studies (III, VII, IX) did not report the smoking status of the included participants. The effect of smoking status on the clinical outcome parameters was not further analysed in any of the included studies.

Intervention: type of DL, settings and procedures

Study II provided supragingival cleaning using a sonic device 2 weeks prior to starting the treatment protocol. Mechanical debridement using scalers and curettes was mentioned in most studies (III, IV, V, VII, VIII). Study IX performed supragingival calculus removal first with ultrasonic instruments followed by hand instrumentation. The full-mouth subgingival SRP in studies I and II was performed using hand instruments and sonic devices. In study VIII, subsequent to mechanical instrumentation, all the sites were rinsed with 3% H2O2. The endpoint of SRP was classified in three studies as: treatment was continued until the root surfaces were adequately debrided and cleaned (VIII); the operator achieved a hard, smooth and calculus-free root surface (VII); or root smoothness was determined with the use of a pigtail explorer (IV). In study IX, the treatment protocol dictated a repeated scaling in the DL group but not in the control group. In the identified nine papers, different brands of DLs were used as test products with different energy settings, tips, contact times and fibre insertion. For details see Table 2. Two studies (III, V) were truly double- blind in that they performed a sham DL treatment (laser was applied without activation). The laser in study IX was provided with a refrigeration pump that worked with sterile saline coupled to the handpiece to avoid undesired increases in tissue temperature. While in other studies, the periodontal pockets were irrigated with saline solution after each irradiation session (I, V). And, only in case of bleeding during laser irradiation, was a thorough rinsing with saline solution performed to prevent thermal damage to the root surface (VI). Study VIII rinsed only the control quadrants with saline and study I rinsed both the intervention and the control group. Two studies used a protocol that provided multiple DL applications, i.e. study II on days 1, 3, 7 after SRP and study III only on days 1 and 7.

Table 2. Overview of the selected studies and diode laser parameters of interest

Diode laser / Nanometer Brand	Energy settings Pulsed/ Continues wave Power density Cooling	Tip Ø	Procedure and Contact tim	Fiber insertion	Local Anesthesia
I 940 nm Ezlase, Biolase, USA	1.5 W Pulsed wave 15 J/ cm² ?	Fiberoptic delivery system Ø=300 µm	SRP + DL 20 s per tooth	Fiber inserted into the periodontal pocket base in parallel alignment with the root surface, the device was activated, and the fiber was slowly moved from apical to coronal in a sweeping motion during the laser light emission.	Yes
II 980 nm GENTLEray, KaVo Dental,Germany	2 W Pulsed wave ? W/ cm² ?	Fiberoptic delivery system Ø=300 µm	SRP + DL 20 s per tooth DL on day one, three and zeven.	Fiber placed parallel to the cement surface with apical-cervical scanning movements.	Yes
III 808 ±5 nm Zap Lasers, CA, USA.	1.5 W Continues wave 1,193.7 W/ cm² ?	Fiberoptic delivery system Ø=400 µm	SRP + DL 20 s per tooth DL on day one and after one week	Fiber, introduced in the periodontal pocket parallel to the long axis of the tooth, one millimeter coronal to the base of the pocket, and it was moved coronally with sweeping movements	?
IV 810 nm Odyssey Diode Laser, Ivoclar Vivadent, Inc	0.8 W Continues wave ? W/ cm² ?	Fiber tip Ø=? µm	SRP + DL 30-45 s per site	Fiber inserted to the full depth of the pocket and the sulcus epithelium was removed using a continuous curetting motion against the soft-tissue wall.	Yes
V 808 ±5 nm Zap Lasers, CA, USA.	1.5 W Continues wave 1,193.7 W/ cm² ?	Fiberoptic delivery system Ø=400 µm	SRP + DL 20 s per pocket	Fiber introduced by 1mm less than the value obtained to the probing procedure. Parallel to the cement surface, with apical- cervical scanning movements.	Yes

VI 980 nm Smilepro 980 tm Biolitec, Jena, Germany.	2.0 W Continues wave 94.3 J/cm² ?	Flexible fiber Ø=300 µm	SRP + DL 30 s per pocket DL on day one and after one week	Fiber moved towards the top of the pocket with overlapping horizontal and vertical strokes, maintaining contact with the soft tissue at all times. Repeated until the full circumference of the tooth was irradiated. Lasing was complete when signs of a new wound site (fresh bleeding) appeared.	Yes
VII 980 nm Valure S9-lasering medical laser, Modena, Italy.	2.5 W Pulsed ? ?	Optic fiber Ø=400 µm	SRP + DL 30 s each pocket twice with 60 s interval	Fiber moved from the coronal to the apical side of the pocket in parallel paths with inclination of approximately 20°.	?
VIII 809 nm GaAlAs semiconductor laser ?	1.0 W Continues wave ? ?	Optical fibre Ø=600 µm	SRP + DL 10 s/pocket? - every 10 s 30 s interruptions - mesially, distally, buccally and ligually Average=?	Fiber inserted into the periodontal pocket, the laser activated, and the fiber slowly moved from apical to coronal in a sweeping motion. This was done mesially, distally, buccally and lingually	Yes
IX 980 nm InGalAsP Intermedic. Barcelona, Spain.	2.0 W Pulsed ? Yes with saline serum	Optic fibre Ø=2000 µm	SRP + DL SRP DL 10 s by tooth face	Fiber introduced for slow ascending and descendant movements. Direction of the optical fiber is parallel to the tooth root main axis.	Yes

W	Watt	SRP	Scaling and rootplaning
s	Second	DL	Diode laser
J	Joules	US	Ultrasonic Scaling
µm	Micrometer	Ø	diameter
nm	Nanometer	?	unknown

Side effects and industry funding

The majority of papers did not report on adverse events during the follow-up period. However, studies I, VIII and IX did note a lack of adverse clinical side effects caused by use of the DL. Two studies mentioned funding from a grant by a state research fund (III, V) and Saglam et al. (2014) was supported by the University scientific office. None of the studies mention industry funding, but IV acknowledged Ivoclar Vivadent for their support. Studies I, II, III, IV and VI included a disclosure statement that there was no conflict (financial) of interest.

Quality assessment

Quality assessment values, including external, internal and statistical validity, are presented in Appendix S2. Based on a summary of these criteria, the estimated potential risk of bias is low in three studies (I, III, V), moderate for study II and high for five other studies (IV, VI, VII, VIII IX). Three studies (I, IV, IX) claimed to be double-blind but did not perform a sham laser treatment, which does not allow masking of the patient regarding the type of intervention. Therefore, the low risk of bias in study I is over-estimated and it should be considered instead as having a moderate risk of bias.

Study outcomes results

The Appendix S3 shows the results from the data extraction. In this review, different indices and their modifications are used. Indeed, it should be noted that study IX used two different bleeding indices. Information regarding the changes within each intervention group for the various indices is also presented in Appendix S3. Within group analyses was not commonly reported in the included studies considered in this review.

Between groups

Table 3 is a descriptive analysis of the individual studies, which summarizes the significant differences as reported between the use of the DL and the comparison treatment. Regarding PS, GI and BS the effect pattern is clear. In the majority of the selected papers, no significant benefit was observed as a result of the adjunctive use of the DL. For PPD and CAL, there was an inconsistent pattern. In general, the majority of studies provided no significant differences favouring the adjunctive use of the DL with SRP.

Table 3. A descriptive summary of the comparison and intervention indicating whether there is a significant difference between the intervention and comparison (0=no difference, +=significant difference in favor of intervention, -=significant difference in favor of comparison, □ = no data available)

Author(s) #	Intervention	PS	BS	GI	PPD	CAL	Comparison
III	SRP + DL	O	O	□	O	O	SRP + sham DL
V	SRP + DL	O	O	□	-	?	SRP + sham DL
I	SRP + DL	+	O	+	+	+	SRP
II	SRP + DL	O	O	□	+	O	SRP
IV	DL + SRP	□	O	□	O	□	SRP
VI	SRP + DL	O	O	□	+	-	SRP
VII	SRP + DL	O	+	O	O	O	SRP
VIII	SRP + DL	O	O	O	+	-	SRP
IX	SRP+ US + DL + SRP + DL	□	+	□	□	O	SRP + US

?, unknown/not reported; BS, bleeding scores; GI, Gingival Index; CAL, clinical attachment level; DL, diode laser; PPD, probing pocket depth; PS, plaque scores; SRP, scaling and root planing; US, ultrasonic scaling.

Meta-analysis

The available data for PS (Silness & Löe 1964), BS, PPD and CAL were amenable to MA. Some studies could not be included in the MA because they used incompatible indices or lacked a SD. None of the MA using baseline scores showed a significant difference between the groups for any of the parameters of interest (Appendix S4–23). Table 4 shows the MA for outcome measures as end scores and reveals no significant effect favouring the adjunctive use of the DL for PPD [DiffM=-0.11; P=0.68; 95% CI (-0.65; 0.43)] and for CAL [DiffM=0.04; P=0.80; 95% CI (-0.26; 0.34)]. Explorative subgroup analysis using the basis of level of analysis (subject, site, one site within a subject), and the research model (parallel or split mouth) also did not provide a significant difference. Only PPD end scores analysed on subject level provided a significant difference. Neither was there a significant DiffM found for PS (Appendix S12– 15). The only significant differences favouring the adjunctive use of the DL was observed for the outcome parameters, i.e. GI (Löe & Silness (1963), Löe (1965)) DiffM=0.09 [P=0.008; 95% CI (-0.16; -0.02)] and BS with a DiffM=5.34 [P=0.03; 95% CI -10.14; -0.54)] (Appendix S16–19). For details of the MA see Appendix S4–23.

Table 4. Meta-analysis for the end scores of the outcome parameters of interest (PPD and CAL) comparing the adjunctive use of the diode laser by scaling and rootplaning including the studies with a subject level analysis. Explorative sub-group analysis for subject, site or one site with one subject (1S1S) level analysis used in the original study, and in addition for the research model being used (parallel or split mouth)

Index		Studies	Model	DiffM	Test for overall		Test for heterogeneity	
					95% CI	P-value	I^2 value (%)	P-value
PPD	Subject	I, II, VI	fixed	-0.88	[-1.01 ; -0.75]	<0.00001	90	<0.0001
	1S1S	III, V	fixed	0.70	[0.19 ; 1.21]	0.007	0	1.00
	Site	VII, VIII	fixed	-0.30	[-0.68 ; 0.07]	0.11	0	0.97
	Parallel	I	fixed	-1.00	[-1.14 ; -0.86]	<0.00001	NA	NA
	Split mouth	II, III V,VI VII,VIII	random	0.03	[-0.32 ; 0.39]	0.85	54	0.05
	Overall	**I, II, III V,VI VII,VIII**	**random**	**-0.11**	**[-0.65 ; 0.43]**	**0.68**	**90**	**<0.00001**
CAL	Subject	I, II, VI, IX	random	-0.16	[-0.36 ; 0.04]	0.13	0	70
	1S1S	III, V	fixed	1.10	[0.34 ; 1.85]	0.004	0	0.83
	Site	VII, VIII	fixed	-0.17	[0.62 ; 0.27]	0.45	0	0.55
	Parallel	I, IX	fixed	-0.17	[-0.39 ; 0.05]	0.13	1	0.31
	Split mouth	II,III V,VI, VII, VIII	random	0.14	[-0.29 ; 0.58]	0.80	41	0.10
	Overall	**I, II,III V,VI, VII, VIII, IX**	**random**	**0.04**	**[-0.26 ; 0.34]**	**0.80**	**41**	**0.10**

NA Not applicable

Evidence profile

Table 5 shows a summary of the various factors used to rate the quality of evidence and strength of recommendations, according to GRADE (Guyatt et al. 2008). Since the data are fairly consistent, indirect and moderately precise, the body of evidence considering for the adjunctive use of the DL is judged to be "moderate" for changes in PPD and CAL.

Table 5. GRADE evidence profile for impact of the use of a diode laser as adjunct to non-surgical periodontal treatment during the initial phase of periodontal therapy as compared to conventional therapy (ultrasonic and/or hand instrumentation) on the primary outcome measurement probing pocket depth (PPD) and clinical attachment level (CAL) from the presented systematic review

GRADE	PPD	CAL
Risk of bias	Low to high	Low to high
Consistency	Fairly consistent	Fairly consistent
Directness	Indirect	Indirect
Precision	Moderate	Moderate
Publication bias	Possible	Possible
Body of evidence	**Moderate**	**Moderate**

Discussion

Based on the presented evidence regarding the adjunctive use of the DL with SRP indicates that, during the initial phase of periodontal therapy, the combined treatment provides an effect comparable to that of SRP alone. The most commonly used lasers in the diode family are the gallium-aluminium-arsenide laser (810 nm) and the indium-gallium-arsenide laser (980 nm). Low initial investment costs and ease of use by the dental care professional are undoubtedly major factors for this popularity (Cobb et al. 2010). Lasers are used as a monotherapy or as an adjunct in the treatment of periodontitis. The adjunctive use of lasers with traditional treatment modalities is, at best, controversial (Cobb et al. 2010). So far no systematic quantitative evaluation with a MA approach, specifically focusing on the adjunctive "in the periodontal pocket use" of the DL during initial periodontal treatment has been performed. Thus, in an attempt to consider the adjunctive use of DLs in the treatment of periodontitis from an "evidence-based" perspective, this study aimed to evaluate systematically and perform a MA on selected and relevant published clinical trials.

Other (systematic) reviews

With a high divergence in energy settings, irradiation times or application modes, the impact of the present MA has to be discussed very carefully. Cobb et al. (2010) published a review on various laser types in the treatment of chronic periodontitis. In the present systematic review, three (VI, VIII, IX) out of the nine papers were also included in the Cobb et al. (2010) review. More recently, Sgolastra et al. (2013) published a systematic review regarding the use of the DL but with wider inclusion criteria (e.g. also including periodontal maintenance) but more stringent requirements on the quality of reporting. Their analysis included five studies of which, only two were considered eligible for the present review (III, VII). Critical use of search terms, variation in defined inclusion criteria and availability of newly published studies all have influence on the number of selected studies in various reviews.

In the study by Cobb et al. (2010), an average of the means was calculated. When comparing the laser treatment groups with the controls, the laser groups showed greater reductions in PPD (1.70mm versus 1.14mm), but a nearly equivalent gain in CAL (1.52mm versus 1.34mm) and reduction in bleeding on pocket probing (BOP)% (68 versus 53). Sgolastra et al. (2013) also performed a MA on the DiffM PPD of 0.10mm [P=0.35, 95% CI (-0.11; 0.31)] and a DiffM in CAL of 0.02mm [P=0.91, 95% CI (-0.39; 0.44)]. A similar pattern was seen in the present MA, although this was not performed on incremental data. Sgolastra et al. (2013) concluded that use of the DL adjunctive to conventional non-surgical periodontal therapy did not provide an additional clinical benefit. Cobb et al. (2010) did not assess GI. Sgolastra et al. (2013) did assess GI and reported no significant difference. This review noted a significant difference in GI but this likely is the result of impact weight of over 90% in the MA of one study (I) of the three included in the analysis that reported significant differences.

Bleeding scores as an outcome parameter were not analysed by Sgolastra et al. (2013). The BOP reduction in Cobb et al. (2010) for the laser groups was 68% and for the control treatment 53%, a difference of 15%. In this systematic review, based on MA of baseline and endpoint data from the included studies, it is clear that no significant DiffM is obtained for the parameters PPD and CAL between the treatment modalities. As parameter, BS reductions showed a small but statistically significant DiffM that favours the adjunctive use of the DL. Considering the magnitude of the difference (DiffM=-5.34%) one may question the clinical relevance. Thus, the clinically detectable difference in product performance is probably negligible.

Furthermore, the results of this review support the American Academy of Periodontology Statement on the Efficacy of Lasers in the Non-Surgical Treatment of Inflammatory Periodontal Disease that there is minimal evidence to support use of a laser for the purpose of subgingival debridement, either as a monotherapy or adjunctive to SRP (American Academy of Periodontology, (AAP) 2011).

Wave lengths

The reviewed papers used a diverse combination of parameters and in theory each combination will have subtle or not so subtle impact on outcome measures. Due to wavelength (805–980 nm) absorption characteristics the DL exhibits an affinity for pigmented tissues, haemoglobin and oxyhaemoglobin. Consequently, the DL is often cited as providing clinical benefit due to the reduction in subgingival pigment- producing microbes such as Porphyromonas gingivalis or Prevotella intermedia (Cobb et al. 2010). Of course this ignores the fact that the vast majority of subgingival microbes are not pigment producers (Socransky et al. 1999). Another interesting consideration is that the combination of blood adherence to root surfaces and prolonged duration or an excessive number of irradiation exposures may result in heat absorption leading to heat-induced damage to root surfaces (Cobb et al. 2012).

One caveat must be addressed and that is when evaluating published research regarding use of any laser in the treatment of periodontal disease or during periodontal maintenance, one must distinguish between use of the laser as a "monotherapy", i.e. application of the laser as the only therapeutic modality and the adjunctive application of the laser, such as application of the laser following scaling and root planing. Obviously, given the definitions above, laser monotherapy and the adjunctive application of a laser when combined with another therapeutic modality have the potential to produce different clinical responses to treatment.

Study designs

The study protocols used were both parallel and split-mouth designs. The split-mouth model was most frequently used and is a popular design in oral health research. The attractiveness of the split-mouth design is that it removes much of the interindividual variability from estimates of treatment effect, allowing for a smaller sample size that, in turn, offers efficiency (Lesaffre et al. 2009). A potential problem of the split-mouth design is that a biased estimate of treatment efficacy due to carry-across effects will cause a downward based impact on the differences in treatment (Lesaffre et al. 2009). Presumably this will not play a major role with the mechanical effect of the DL. No "leaking" effect from one site to another is likely to occur. Another problem with the split-mouth design involves the difficult recruitment of

patients, because of necessity for symmetrical disease patterns among all segments of the dentition that are randomized. This selection pressure may introduce bias (Hujoel 1998). In view of the differences between estimates from splitmouth and parallel group studies addressing the same research question, we performed a MA at a subgroup level with split-mouth and parallel group trial designs (separately) to investigate for systematic differences. No systematic differences were found regardless of how it was analysed, i.e. overall or based on the research model used.

Site or subject level analyses

Clinical data are usually collected with the tooth surface as the unit, but may subsequently be analysed by aggregating the data at the level of the individual subject (Scheutz et al. 2003). Site versus subject level analysis is an ongoing issue within dentistry research but hopefully any clustering is taken into account in the analysis (Hannigan 2004). However, the precision of the estimate increases considerably when the site is the unit of analysis as compared to subject. With site-based analysis, the mean estimate is not as much of a concern as increasing the number of sites provides a better estimate for the mean – assuming sites show some uniformity in distribution among subjects, as was the case in the selected studies for this review. As the number of sites was evenly distributed the precision of the mean estimate is representative of the mean of each study group in this review.
The bigger problem is the estimate of the SD. This is a necessary element for combining studies in a MA as a measure of the variability in the data. The estimate may be lower if there is a substantial number of sites, since between-subject variability could be diminished in the estimate. To determine if this was a problem, those studies reporting sitebased analysis were compared to those reporting on a subject-basis to see if the SDs were similar. In this regard, the original SD could be used in the MA. Furthermore, as sample size for each included study reported on a site-level analysis, the number of subjects was entered in the MA. To elucidate possible systematic differences, a subgroup analysis was performed by separating those studies that performed subject level analysis and those using site-level analysis. Results of this subanalysis showed that only the PPD end scores, analysed on a subject level using a fixed model, provided a significant difference DiffM -0.88 [P<0.00001, 95% CI:(-1.01; -0.75)]. It is worthy of note that one (study I) of the three studies included in this subanalysis, reported a much larger treatment effect than the other two studies for the DL treatment group, with a weight of 85%, which probably explains the statistical difference. When a random model was used, this effect could not be repeated, DiffM -0.47 [P=0.18, 95% CI:(-1.15; 0.21)]. The majority of the subanalyses support the overall analysis in that no systematic effect was demonstrated.

Microbiological data

Data on subgingival microbial reductions were not the focus of this systematic review. However, five studies did provide a microbiological assessment adjunctive to the clinical assessment (III, V, VI, VII, VIII). A purported benefit of the DL is the favourable reduction in subgingival bacterial load (Cobb et al. 2010). Three of the studies (III, V, VII) included in this review reported no significant difference in reduction of the subgingival microbial load when comparing SRP+ DL versus SRP alone. Study VI stated that for all treatment modalities, there was a beneficial improvement in reduction in mean counts of bacterial species. Interestingly, only study VI reported that DL treated sites showed a statistically significantly lower total bacterial load, including reductions in P. gingivalis and Treponema denticola at 6 months post treatment compared to SRP alone.

Limitations

- This systematic review reports only on the use of the DL as an adjunctive treatment to SRP during initial therapy and not as a monotherapy nor of its use during the maintenance phase of periodontal therapy.
- A major concern for this review is the definition and classification of periodontitis. What signs and symptoms must be present in any specific individual to justify categorizing this specific individual as a "patient with periodontitis" (Van der Weijden et al. 2005). The original papers did not differentiate between aggressive or chronic periodontitis according to a suitable classification.
- Following non-surgical periodontal therapy smokers will experience less reduction in PPD (Labriola et al. 2005). Due to heterogeneity and poor reporting of the included studies, this could not be analysed.
- Only those papers that used the DL with insertion of the energy beam delivery fibre into the pocket were evaluated. The laser when applied to the buccal gingival surface was not part of this review. In the selected papers there is a large variation in the different settings and energy parameters. This makes a summary even more difficult because divergence in results could be due, in part, to variations in energy parameters used in different studies.
- To pool the studies, the weighted mean difference was used. The problem with many clinical studies is that values are analysed with parametric statistical tests. Presumably, means are normally distributed, if they are based on a considerable number of data points. Most of the studies included in the present MA are based on a low number of patients. None of the included studies provided data regarding normality.
- Due to heterogeneity in the included studies smoking, different wavelengths and laser settings could not be considered further for subgroup analysis.
- A cost-effectiveness analysis could not be performed because the costs (in relative

to effectiveness) of the laser equipments were not reported by any of the included studies.
- Although no formal test could be performed, in view of the relatively recent development of this therapy and the industry interest, the risk of publication bias must be considered high.

Conclusion

The collective evidence regarding adjunctive use of the DL with SRP indicates that the combined treatment provides an effect comparable to that of SRP alone. That is for PPD and CAL. The body of evidence considering the adjunctive use of the DL is judged to be "moderate" for changes in PPD and CAL. With respect to BS, the results showed a small but significant effect favouring the DL, however, the clinical relevance of this difference remains a question. This systematic review questions the adjunctive use of DL with traditional mechanical modalities of periodontal therapy in patients with periodontitis.

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Conflict of interest and source of funding statement

The authors declare that they have no conflict of interest. This study was self-funded by the authors and their institutions.

Clinical Relevance

SCIENTIFIC RATIONALE FOR THE STUDY

Conventional periodontal therapy with hand instruments and ultrasonic scalers has proven to be effective during the initial phase of non-surgical periodontal therapy (SRP). The diode laser can remove pocket epithelium, which purportedly provides an adjunctive effect. Therefore, various investigators have proposed use of the diode laser as an adjunct to SRP to improve initial treatment outcomes.

PRINCIPAL FINDINGS

This systematic review did not show a clinical improvement of periodontal parameters and PS favouring the adjunctive use of a diode laser with subgingival mechanical SRP. For bleeding scores and the Gingival Index was a significant DiffM observed. The clinical significance of this statistically detectable difference remains a question.

PRACTICAL IMPLICATIONS

The results of this study are applicable for periodontitis patients during the initial phase of periodontal treatment. Clinical results of conventional "non surgical" periodontal therapy are not enhanced with the additional use of the diode laser. The adjunctive use of the diode laser, therefore, provides no therapeutic benefits with respect to the primary outcome parameters of pocket depth and clinical attachment level. The possibility of substituting conventional non-surgical periodontal treatments for laser therapy, however, was not investigated.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

- Appendix S1. Overview of reason for rejection of the studies that wereexcluded after full-text reading.
- Appendix S2. Methodological, validity and quality scores and estimated risk of bias of the included studies.
- Appendix S3. Overview of clinical outcomes of the selected studies and parameters of interest with various indices and their modifications. Baseline, end measurements, differences are presented by mean and standard deviations (SD) in parentheses. Statistical significant changes within groups are presented.
- Appendix S4–23. Forrest Plots of the performed meta-analysis.
- Appendix S4–7 PPD.
- Appendix S4 PPD baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S5 PPD baseline scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S6 PPD end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S7 PPD end scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S8–11 CAL
- Appendix S8 CAL baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S9 CAL baseline scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S10 CAL end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S11 CAL end scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S12–15 Plaque Scores (Löe & Silness 1963).
- Appendix S12 PS baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S13 PS baseline scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S14 PS end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S15 PS end scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S16–19 Gingival Index (Löe and Silness 1963, Löe et al. 1965).
- Appendix S16 GI baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S17 GI baseline scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S18 GI end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S19 GI end scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S20–23 Bleeding upon Probing.
- Appendix S20 BOP baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S21 BOP baseline scores and subgroup analysis on the research model used (parallel or split mouth).
- Appendix S22 BOP end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).
- Appendix S23 BOP end scores and subgroup analysis on the research model used (parallel or split mouth).

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♦ Studies selected for this review.

Supporting information

Appendix S1.

Overview of reason for rejection of the studies that were excluded after full-text reading

Reason for rejection	Author(s), (year)
Gingivitis patients	Assaf et al. 2007 Pejcic et al. 2010
< 4 weeks evaluation period	Ribeiro et al. 2008 Angelov et al. 2009
No adjunctive use with SRP	Lin et al. 2010 Moritz et al. 1997 Moritz et al. 1998
Maintenance patients	Giannopoulou et al. 2011 Cappuyns et al. 2012
No fiber use into the periodontal pocket	Aykol et al. 2011 Makhlouf et al. 2012 Qadri et al. 2005 Yilmaz et al. 2002
In combination with photo sensitizer	Lui et al. 2011

Appendix S2.

Methodological, validity and quality scores and estimated risk of bias of the included studies

Study / Quality criteria		IV	I	II	II	IX	V	VI	VII	VIII	IX
Interne validity	Random allocation*	+	+	+	+	+	+	+	+	+	+
	Allocation concealment	?	?	+	?	?	?	?	?	?	?
	Blinded to patient*	+	+	-	+	+	+	-	-	-	-
	Blinded to examiner*	?	+	+	?	+	+	+	+	+	?
	Blinding during statistical analysis	?	+	?	?	?	?	?	?	?	?
	Balanced experimental groups*	+	+	+	+	+	+	+	+	+	+
	Reported loss to follow up*	+	+	+	+	+	+	-	+	-	-
	#(%) of drop-outs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%◊)	1 (4%◊)	0 (0%)	3 (12%◊)	?	0 (0%)
	Treatment identical, except for intervention*	+	+	+	+	+	+	+	+	-	+
External validity	Representative population group	+	+	+	+	+	+	+	+	+	+
	Eligibility criteria defined*	+	+	+	+	+	+	+	+	-	+

Statistical validity	Research model used	SM/ Paralell	Parallel	SM	SM/ Paralell	SM	SM	SM	SM	Parallel	SM
	Sample size calculation and power	?	+	+	?	+	+	+	?	?	?
	Point estimates	+	+	+	+	+	+	+	+	+	+
	Measures of variability presented for the primary outcome	-	+	+	-	+	+	+	+	+	+
	Unit of analysis*	Site	Subj	Subj	Site	Subj/ 1site	Subj/ 1site	Subj/ quadrant	Site	Subj	Site
	Include an per protocol analysis	?	?	?	?	?	?	?	?	?	?
	Include an intention- to-treat analysis	?	?	?	?	?	?	?	?	?	?
	Correction for multiple comparisons	?	+	+	?	?	?	+	?	?	?
Authors estimated risk of bias		High	Low	Mod	Low	High	Low	High	High	High	High

Criteria were designated for each domain of internal validity, external validity, and statistical methods. Each aspect of the score list was given a rating of '+' for an informative description of the item at issue and a study design meeting the quality standard, '-' for an informative description without a study design that met the quality standard, and '?' for insufficient information.

+ = Yes
- = No
? = Not specified/unclear
◊ = Calculated by the review authors
NA = Not Applicable
SM = Split Mouth
Mod = Moderate

ONLINE Appendix S3.

Overview of clinical outcomes of the selected studies and parameters of interest with various indices and their modifications. Baseline, end and incremental data are presented as means and standard deviations (SD) in parentheses. Statistical significant changes within groups are presented.

A. Probing Pocket Depth (PPD)

#	Groups	Mean (SD)			Statistical significant
		Baseline	End	Difference	
I	SRP + DL SRP	3.6 (0.3) 3.5 (0.5)	1.7 (0.2) 2.7 (0.2)	1.9◊ 0.8◊	? ?
II	SRP + DL SRP	5.25♦ (1.41♦) 4.94♦ (1.25♦)	3.20♦ (1.01♦) 3.24♦ (1.1♦)	2.05♦ (1.46♦) 1.7♦ (1.25♦)	YES YES
III	SRP + DL SRP + sham DL	6.13 (1.35) 5.69 (0.95)	3.63 (1.49) 2.93 (1.33)	-2.56 (1.79) -2.76 (1.13)	YES YES
IV	DL + SRP + DL DL + SRP SRP	6.00 5.82 5.72	4.37 4.19 4.15	-1.62◊ -1.72◊ -1.57◊	YES YES YES
V	SRP + DL SRP + sham DL	6.2 (1.4) 5.8 (1.0)	4.1 (1.6) 3.4 (1.4)	-2.1 -2.4	YES YES
VI	SRP + DL SRP	6.67 (1.291) 6.47 (1.356)	3.87 (0.915) 4.13 (1.060)	-2.8◊ -2.34◊	YES YES
VII	SRP + DL SRP	6.05 (0.70) 6.05 (0.91)	4.63 (1.06) 4.95 (1.26)	-1.42◊ -1.10◊	? ?
VIII	SRP + DL SRP	4.2 (1.15) 4.3 (1.26)	2.4 (0.67) 2.7 (0.73)	-1.8 -1.6	YES YES

SRP Scaling and rootplaning
DL Diode laser
◊ = Calculated by the review authors
♦ = Additional data provided by the original authors
? = Unknown / Not Reported

B. Clinical Attachment Loss (CAL) and change

#	Groups	Mean (SD)			Statistical significant
		Baseline	End	Increment‡	
I	SRP + DL SRP	2.7 (0.4) 2.8 (0.6)	1.7 (0.2) 1.9 (0.4)	1.0◊ 0.9◊	? ?
II	SRP + DL SRP	3.15♦ (2.06♦) 3.15♦ (2.11♦)	2.53♦ (1.4♦) 2.49♦ (1.38♦)	0.61♦ (1.34♦) 0.66♦ (1.4♦)	YES♦ YES
III	SRP + DL SRP + sham DL	6.91 (1.94) 6.50 (1.74)	5.33 (2.13) 4.30 (2.08)	+1.70 (1.72) +2.10 (1.64)	YES YES
V	SRP + DL SRP + sham DL	6.9 (1.9) 6.4 (1.5)	5.7 (2.6) 4.5 (1.8)	+1.2 +1.9	YES YES
VI	SRP + DL SRP	7.07 (1.710) 7.07 (1.580)	4.93 (1.624) 5.20 (1.656)	+2.14◊ -1.87◊	? ?
VII	SRP + DL SRP	7.12 (0.9) 6.91 (1.0)	5.09 (0.8) 5.12 (0.9)	+2.03◊ +1.79◊	? ?
VIII	SRP + DL SRP	5.5 (1.42) 5.5 (1.57)	3.9 (1.03) 4.2 (1.04)	+1.6 +1.3	YES YES
IX	SRP + DL SRP	5.12 (1.14) 4.78 (1.25)	4.17 (1.17) 3.93 (1.14)	+0.95◊ +0.85◊	YES YES

SRP Scaling and rootplaning
DL Diode laser
◊ = Calculated by the review authors
♦ = Additional data provided by the original authors
? = Unknown / Not Reported
‡ = Positive representing clinical attachment gain

C. Plaque Scores (PS)

#	Plaque Index	Groups	Mean (SD)			Statistical significant
			Baseline	End	Difference	
I	Silness & Löe (1964)	SRP + DL SRP	1.9 (0.1) 2.0 (0.2)	1.3 (0.2) 1.4 (0.2)	-0.6◊ -0.6◊	? ?
III	Silness & Löe (1964)	SRP + DL SRP + sham DL	(0.99) 1.47(0.9)	0.66(0.88) 0.60 (0.77)	-0.76 (1.30) -1.03 (1.27)	YES YES
V	Silness & Löe (1964)	SRP + DL SRP + sham DL	1.6 (0.9) 1.8 (0.7)	(0.3) (0.3)	-1.4◊ -1.6◊	YES YES
VII	Silness & Löe (?)	SRP + DL SRP	1.26 (0.45) 1.26 (0.45)	1.105 (0.56) 1.315 (0.58)	-0.158◊ -0.052◊	NO NO
II	Lange (1986)	SRP + DL SRP	0.53 (0.29) 0.54 (0.23)	0.39 (0.27) 0.28 (0.24)	0.14◊ 0.26◊	YES YES
VI	O'Leary et al. (1972)♦	SRP + DL SRP	52.7 (8♦) 54.1 (8♦)	29.2 (7♦) 32.6 (8♦)	-23.5 (11♦) -21.5 (11♦)	YES YES
VIII	Quigley & Hein (1962)	SRP + DL SRP	1.3 (0.9) 1.4 (0.9)	0.9 (0.6) 0.9 (0.7)	-0.40 -0.5	YES YES

SRP Scaling and rootplaning
DL Diode laser
◊ = Calculated by the review authors
♦ = Additional data provided by the original authors
? = Unknown / Not Reported

D. Gingival Index (GI)

#	Gingival Index	Groups	Mean (SD)			Statistical significant
			Baseline	End	Difference	
VIII	Löe & Silness (1964)	SRP + DL SRP	1.8 (0.8) (0.8)	1.0 (0.6) 1.0 (0.6)	-0.8 -0.7	YES YES
VII	Löe & Silness ?	SRP + DL SRP	2 (0) 1.95 (0.2)	1.79 (0.53) 1.79 (0.53)	-0.21◊ -0.16◊	NO NO
I	Löe (1967)	SRP + DL SRP	1.8 (0.1) 1.9 (0.2)	1.2 (0.1) 1.3 (0.1)	0.6◊ 0.6◊	? ?

SRP Scaling and rootplaning
DL Diode laser
◊ = Calculated by the review authors
? = Unknown / Not Reported

E. Bleeding Scores (BS)

#	Bleeding Index	Groups	Mean (SD)			Statistical significant
			Baseline	End	Difference	
I	Bleeding on probing	SRP + DL SRP	81 (7) 83 (10)	19 (9) 31 (13)	62◊ 52◊	? ?
II	Bleeding on probing Ainamo & Bay (1975)	SRP + DL SRP	35 (23) 31 (18)	6 (4) 8 (6)	29◊ 23◊	YES YES
III	Bleeding on probing	SRP + DL SRP + sham DL	97.2 (16.6) 94.4 (23.2)	40.1 (49.3) 33.6 (47.2)	-0.60 (0.49) -0.63 (0.49)	YES YES
IV	Bleeding on probing	DL + SRP SRP	1 1	0.35 0.32	0.65◊ 0.68◊	? ?
V	Bleeding on probing	SRP + DL SRP + sham DL	100 (0.0) 96.2 (19.5)	51.8 (50.9) 40.7 (50.0)	-48.2◊ -55.5◊	YES YES
VI	Bleeding on probing Ainamo & Bay (1975)♦	SRP + DL SRP	82.4(0.06♦) 81.6(0.06♦)	24.3(0.07♦) 25.8(0.07♦)	-58.1 (0.09♦) -55.8 (0.09♦)	YES YES
VII	Bleeding on probing	SRP + DL SRP	100 94.7	84.2 84.2	-15.8◊ -10.5◊	NO NO
VIII	Bleeding on probing	SRP + DL SRP	70.7 (46♦) 71.9 (45♦)	32.8 (47♦) 38.4 (49♦)	-38.2♦ (53♦) -33.1♦ (53♦)	YES YES
IX	Bleeding on probing	SRP + DL SRP	39.37 (19.90) 58.97 (17.71)	11.02 (7.36) 27.71 (14.41)	-28.35◊ -31.26◊	YES YES
IX	Papilla bleeding index (Greenstein et al. 1981)	SRP + DL SRP	0.95 (0.57) 1.38 (0.61)	0.24 (0.13) 0.43 (0.22)	-0.71◊ -0.95◊	YES YES

SRP Scaling and rootplaning
DL Diode laser
◊ = Calculated by the review authors
♦ = Additional data provided by the original authors
? = Unknown / Not Reported

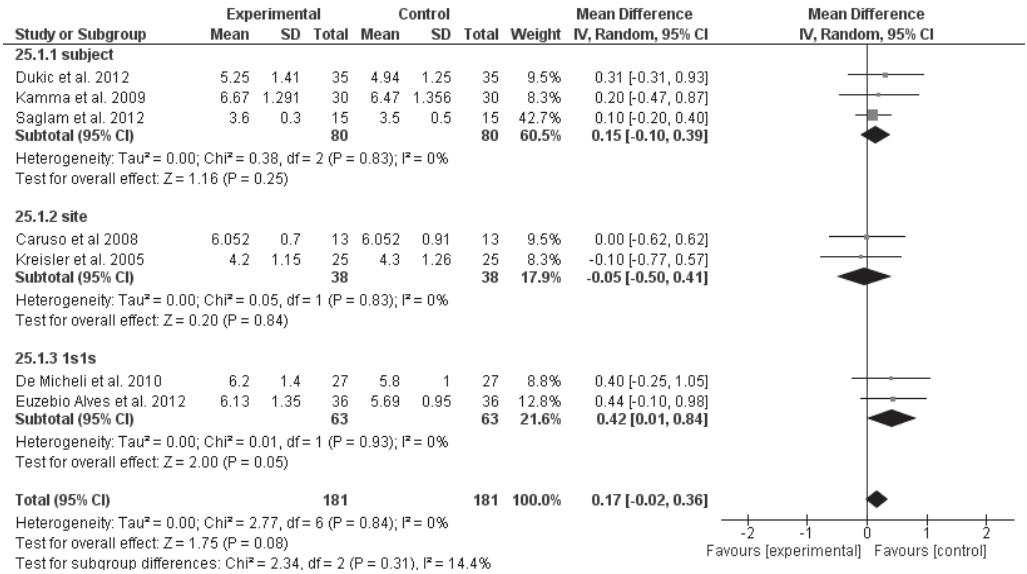
Appendix S4-23

Forrest Plots of the performed meta-analysis.

Appendix S4-7 PPD

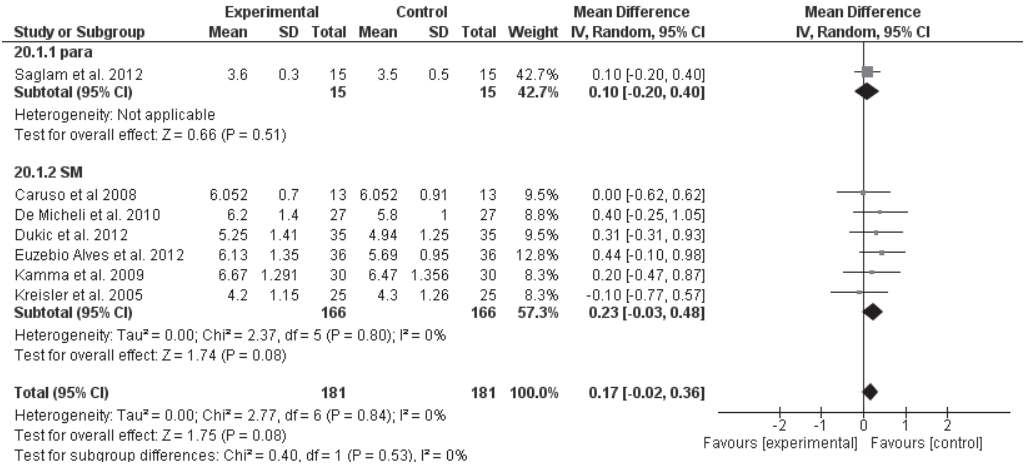
Appendix S4

PPD baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



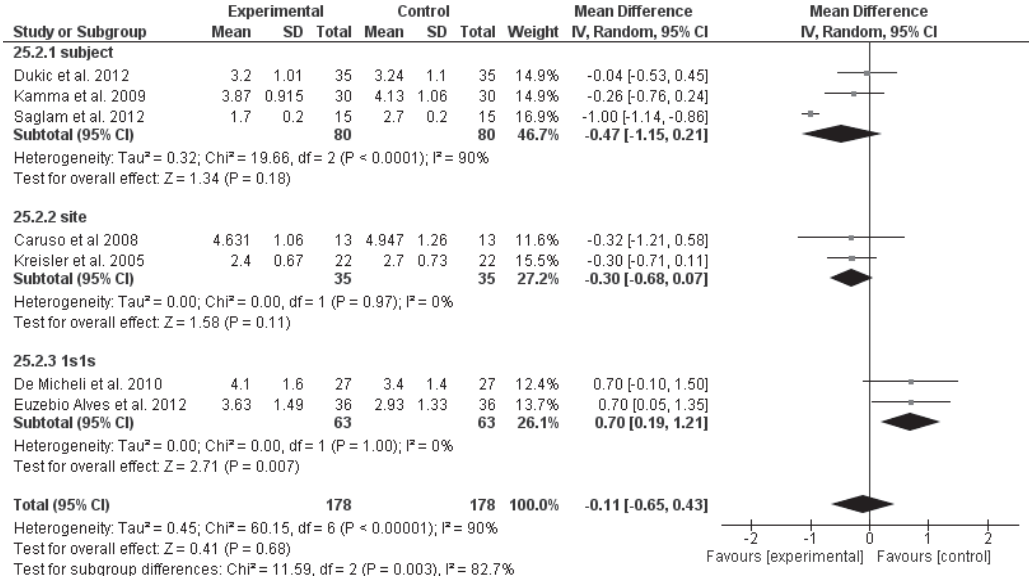
Appendix S5

PPD baseline scores and subgroup analysis on the research model used (parallel or split mouth).



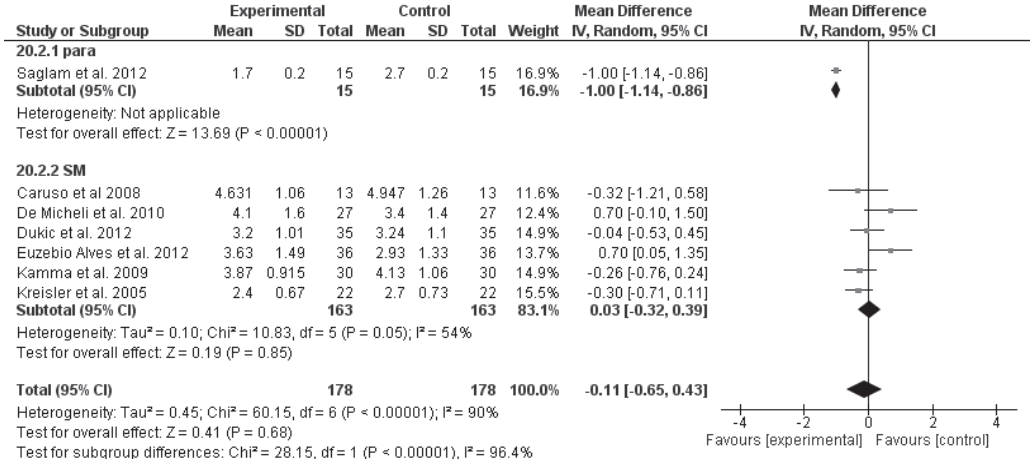
Appendix S6

PPD end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



Appendix S7

PPD end scores and subgroup analysis on the research model used (parallel or split mouth).

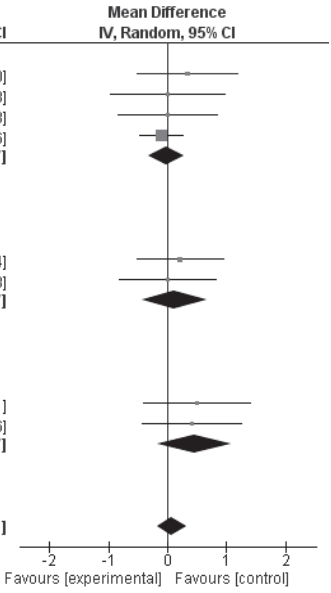


Appendix S8-11 CAL

Appendix S8

CAL baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).

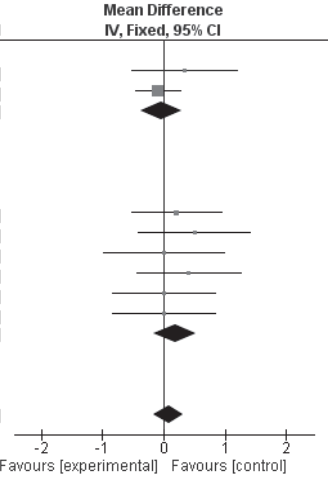
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
26.1.1 subject								
Borrajo et al. 2004	5.12	1.14	15	4.78	1.25	15	7.9%	0.34 [-0.52, 1.20]
Dukic et al. 2012	3.15	2.06	35	3.15	2.11	35	6.1%	0.00 [-0.98, 0.98]
Kamma et al. 2009	7.07	1.71	30	7.07	1.58	30	8.3%	0.00 [-0.83, 0.83]
Saglam et al. 2012	2.7	0.4	15	2.8	0.6	15	43.5%	-0.10 [-0.46, 0.26]
Subtotal (95% CI)			**95**			**95**	**65.8%**	**-0.03 [-0.32, 0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 3 (P = 0.83); I² = 0%								
Test for overall effect: Z = 0.17 (P = 0.87)								
26.1.2 site								
Caruso et al 2008	7.12	0.9	13	6.91	1	13	10.8%	0.21 [-0.52, 0.94]
Kreisler et al. 2005	5.5	1.42	25	5.5	1.57	25	8.4%	0.00 [-0.83, 0.83]
Subtotal (95% CI)			**38**			**38**	**19.2%**	**0.12 [-0.43, 0.67]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.42 (P = 0.67)								
26.1.3 1s1s								
De Micheli et al. 2010	6.9	1.9	27	6.4	1.5	27	6.9%	0.50 [-0.41, 1.41]
Euzebio Alves et al. 2012	6.91	1.94	36	6.5	1.74	36	8.0%	0.41 [-0.44, 1.26]
Subtotal (95% CI)			**63**			**63**	**14.9%**	**0.45 [-0.17, 1.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%								
Test for overall effect: Z = 1.42 (P = 0.15)								
Total (95% CI)			**196**			**196**	**100.0%**	**0.07 [-0.17, 0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 2.89, df = 7 (P = 0.89); I² = 0%								
Test for overall effect: Z = 0.60 (P = 0.55)								
Test for subgroup differences: Chi² = 1.87, df = 2 (P = 0.39), I² = 0%								



Appendix S9

CAL baseline scores and subgroup analysis on the research model used (parallel or split mouth).

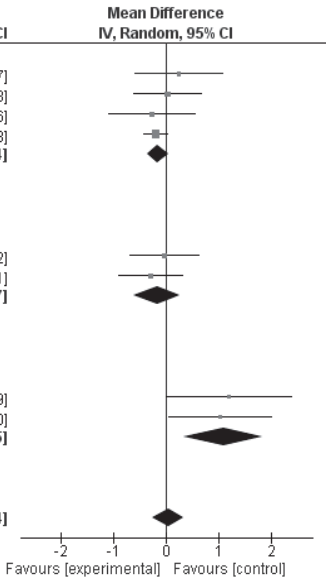
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
21.1.1 para								
Borrajo et al. 2004	5.12	1.14	15	4.78	1.25	15	7.9%	0.34 [-0.52, 1.20]
Saglam et al. 2012	2.7	0.4	15	2.8	0.6	15	43.5%	-0.10 [-0.46, 0.26]
Subtotal (95% CI)			**30**			**30**	**51.4%**	**-0.03 [-0.37, 0.30]**
Heterogeneity: Chi² = 0.86, df = 1 (P = 0.35); I² = 0%								
Test for overall effect: Z = 0.19 (P = 0.85)								
21.1.2 SM								
Caruso et al 2008	7.12	0.9	13	6.91	1	13	10.8%	0.21 [-0.52, 0.94]
De Micheli et al. 2010	6.9	1.9	27	6.4	1.5	27	6.9%	0.50 [-0.41, 1.41]
Dukic et al. 2012	3.15	2.06	35	3.15	2.11	35	6.1%	0.00 [-0.98, 0.98]
Euzebio Alves et al. 2012	6.91	1.94	36	6.5	1.74	36	8.0%	0.41 [-0.44, 1.26]
Kamma et al. 2009	7.07	1.71	30	7.07	1.58	30	8.3%	0.00 [-0.83, 0.83]
Kreisler et al. 2005	5.5	1.42	25	5.5	1.57	25	8.4%	0.00 [-0.83, 0.83]
Subtotal (95% CI)			**166**			**166**	**48.6%**	**0.19 [-0.16, 0.53]**
Heterogeneity: Chi² = 1.25, df = 5 (P = 0.94); I² = 0%								
Test for overall effect: Z = 1.05 (P = 0.29)								
Total (95% CI)			**196**			**196**	**100.0%**	**0.07 [-0.17, 0.31]**
Heterogeneity: Chi² = 2.89, df = 7 (P = 0.89); I² = 0%								
Test for overall effect: Z = 0.60 (P = 0.55)								
Test for subgroup differences: Chi² = 0.79, df = 1 (P = 0.37), I² = 0%								



Appendix S10

CAL end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).

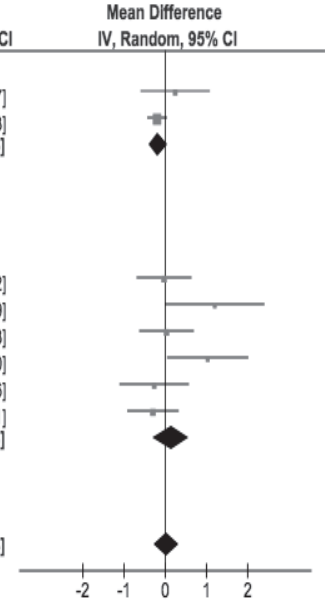
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
26.2.1 subject								
Borrajo et al. 2004	4.17	1.17	15	3.93	1.14	15	9.4%	0.24 [-0.59, 1.07]
Dukic et al. 2012	2.52	1.4	35	2.49	1.38	35	13.0%	0.03 [-0.62, 0.68]
Kamma et al. 2009	4.93	1.624	30	5.2	1.656	30	9.4%	-0.27 [-1.10, 0.56]
Saglam et al. 2012	1.7	0.2	15	1.9	0.4	15	28.5%	-0.20 [-0.43, 0.03]
Subtotal (95% CI)			**95**			**95**	**60.3%**	**-0.16 [-0.36, 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 3 (P = 0.70); I² = 0%								
Test for overall effect: Z = 1.53 (P = 0.13)								
26.2.2 site								
Caruso et al 2008	5.09	0.8	13	5.12	0.9	13	12.9%	-0.03 [-0.68, 0.62]
Kreisler et al. 2005	3.9	1.03	22	4.2	1.04	22	14.0%	-0.30 [-0.91, 0.31]
Subtotal (95% CI)			**35**			**35**	**27.0%**	**-0.17 [-0.62, 0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 0.76 (P = 0.45)								
26.2.3 1s1s								
De Micheli et al. 2010	5.7	2.6	27	4.5	1.8	27	5.3%	1.20 [0.01, 2.39]
Euzebio Alves et al. 2012	5.33	2.13	36	4.3	2.08	36	7.4%	1.03 [0.06, 2.00]
Subtotal (95% CI)			**63**			**63**	**12.7%**	**1.10 [0.34, 1.85]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 2.85 (P = 0.004)								
Total (95% CI)			**193**			**193**	**100.0%**	**0.04 [-0.26, 0.34]**
Heterogeneity: Tau² = 0.07; Chi² = 11.90, df = 7 (P = 0.10); I² = 41%								
Test for overall effect: Z = 0.25 (P = 0.80)								
Test for subgroup differences: Chi² = 10.10, df = 2 (P = 0.006), I² = 80.2%								



Appendix S11

CAL end scores and subgroup analysis on the research model used (parallel or split mouth).

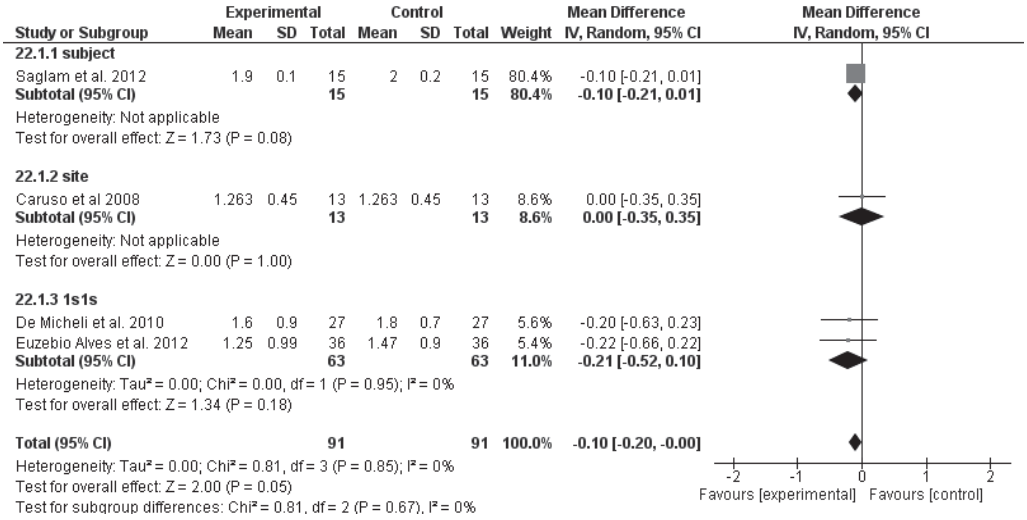
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
21.2.1 para								
Borrajo et al. 2004	4.17	1.17	15	3.93	1.14	15	9.4%	0.24 [-0.59, 1.07]
Saglam et al. 2012	1.7	0.2	15	1.9	0.4	15	28.5%	-0.20 [-0.43, 0.03]
Subtotal (95% CI)			**30**			**30**	**37.9%**	**-0.17 [-0.39, 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%								
Test for overall effect: Z = 1.44 (P = 0.15)								
21.2.2 SM								
Caruso et al 2008	5.09	0.8	13	5.12	0.9	13	12.9%	-0.03 [-0.68, 0.62]
De Micheli et al. 2010	5.7	2.6	27	4.5	1.8	27	5.3%	1.20 [0.01, 2.39]
Dukic et al. 2012	2.52	1.4	35	2.49	1.38	35	13.0%	0.03 [-0.62, 0.68]
Euzebio Alves et al. 2012	5.33	2.13	36	4.3	2.08	36	7.4%	1.03 [0.06, 2.00]
Kamma et al. 2009	4.93	1.624	30	5.2	1.656	30	9.4%	-0.27 [-1.10, 0.56]
Kreisler et al. 2005	3.9	1.03	22	4.2	1.04	22	14.0%	-0.30 [-0.91, 0.31]
Subtotal (95% CI)			**163**			**163**	**62.1%**	**0.14 [-0.29, 0.58]**
Heterogeneity: Tau² = 0.13; Chi² = 9.35, df = 5 (P = 0.10); I² = 46%								
Test for overall effect: Z = 0.65 (P = 0.52)								
Total (95% CI)			**193**			**193**	**100.0%**	**0.04 [-0.26, 0.34]**
Heterogeneity: Tau² = 0.07; Chi² = 11.90, df = 7 (P = 0.10); I² = 41%								
Test for overall effect: Z = 0.25 (P = 0.80)								
Test for subgroup differences: Chi² = 1.55, df = 1 (P = 0.21), I² = 35.4%								



Appendix S12-15 Plaque Scores (Löe & Silness 1964)

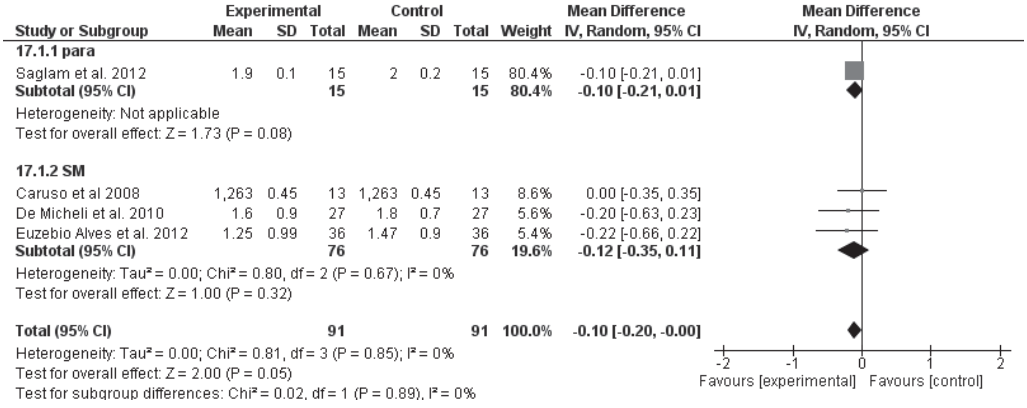
Appendix S12

PS baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



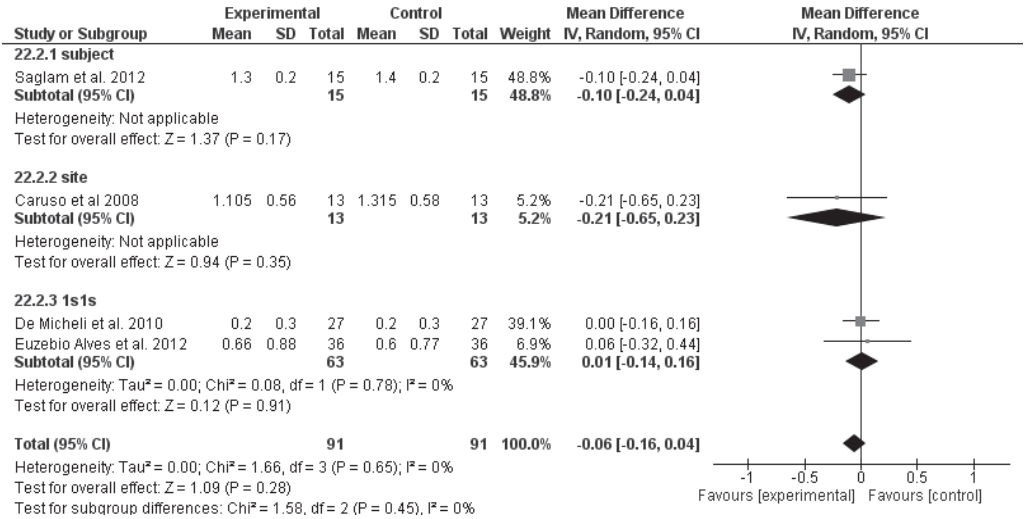
Appendix S13

PS baseline scores and subgroup analysis on the research model used (parallel or split mouth).



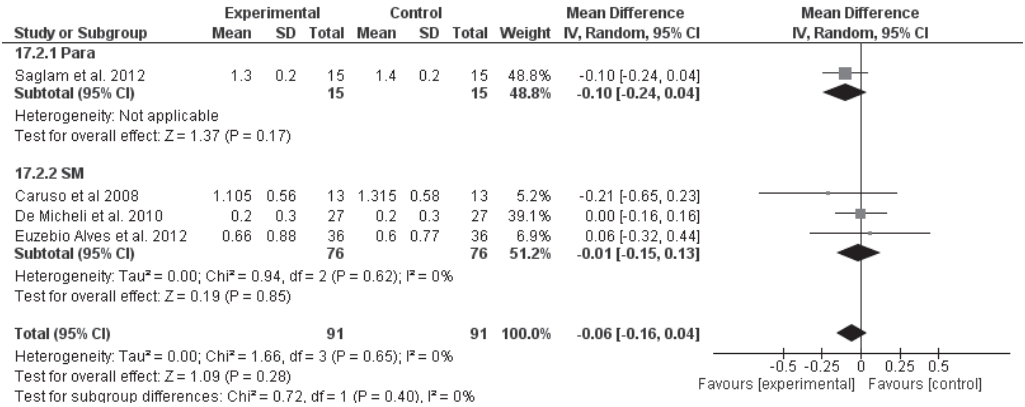
Appendix S14

PS end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



Appendix S15

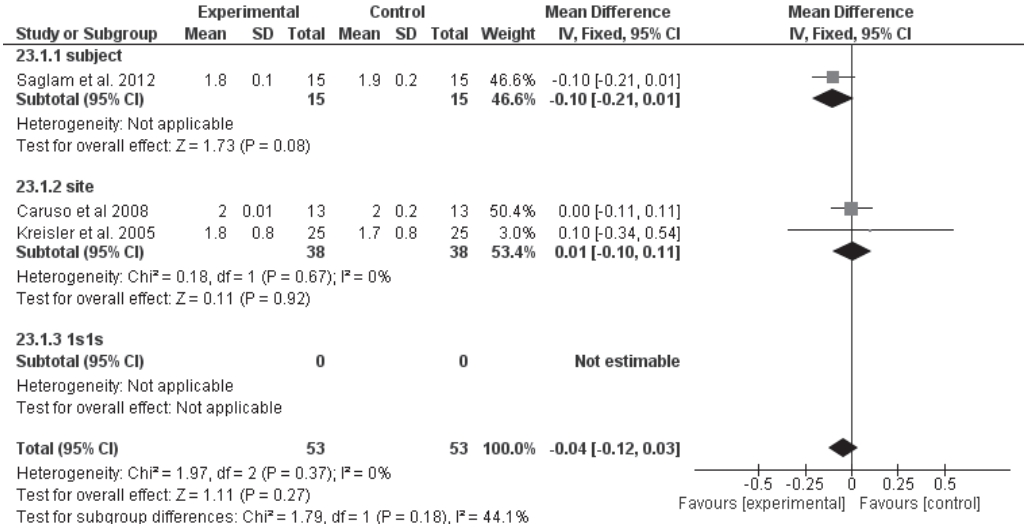
PS end scores and subgroup analysis on the research model used (parallel or split mouth).



Appendix S16-19 Gingival Index (Löe & Silness 1964, Löe 1967)

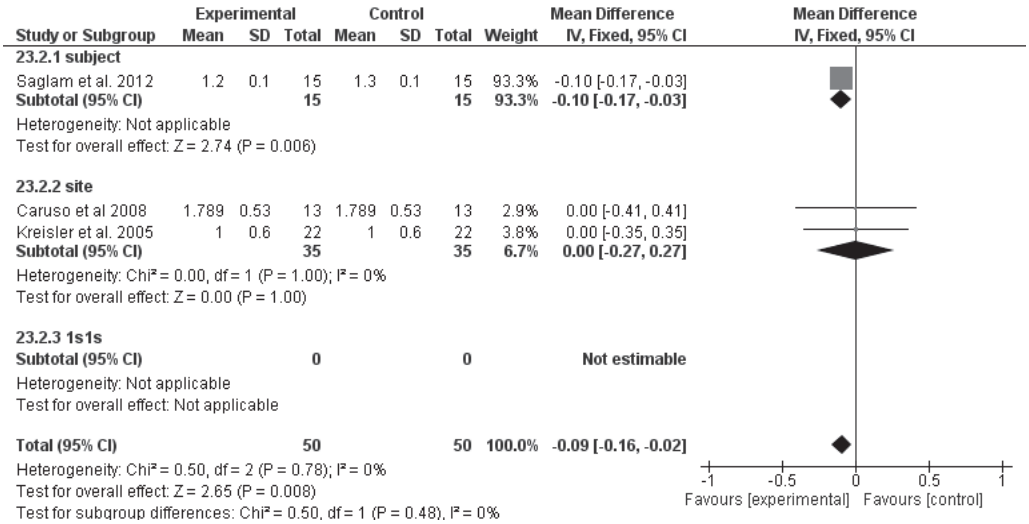
Appendix S16

GI baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



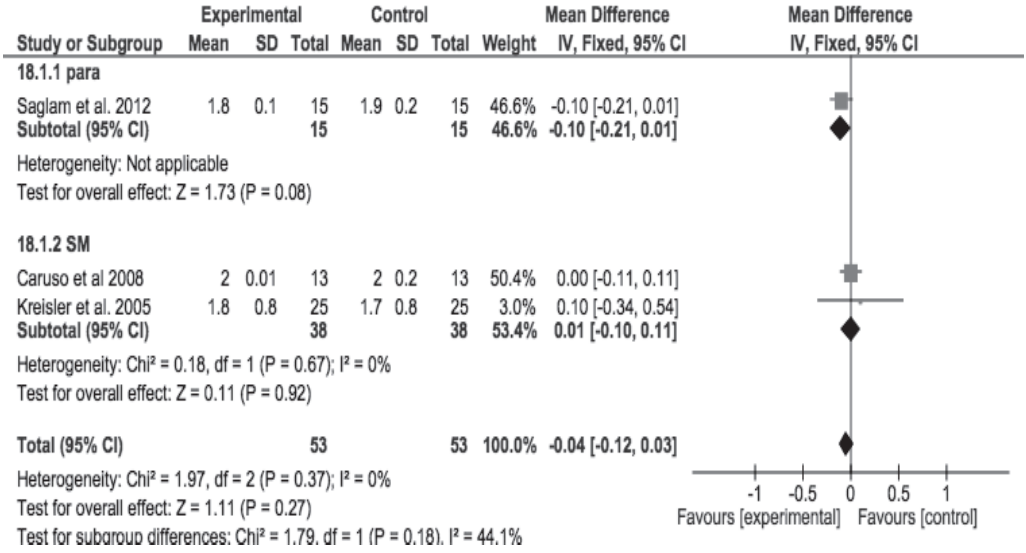
Appendix S17

GI baseline scores and subgroup analysis on the research model used (parallel or split mouth).



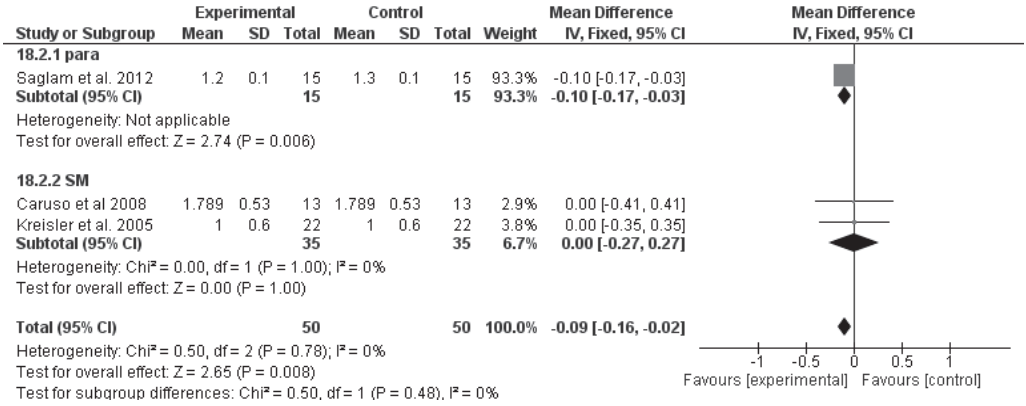
Appendix S18

GI end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



Appendix S19

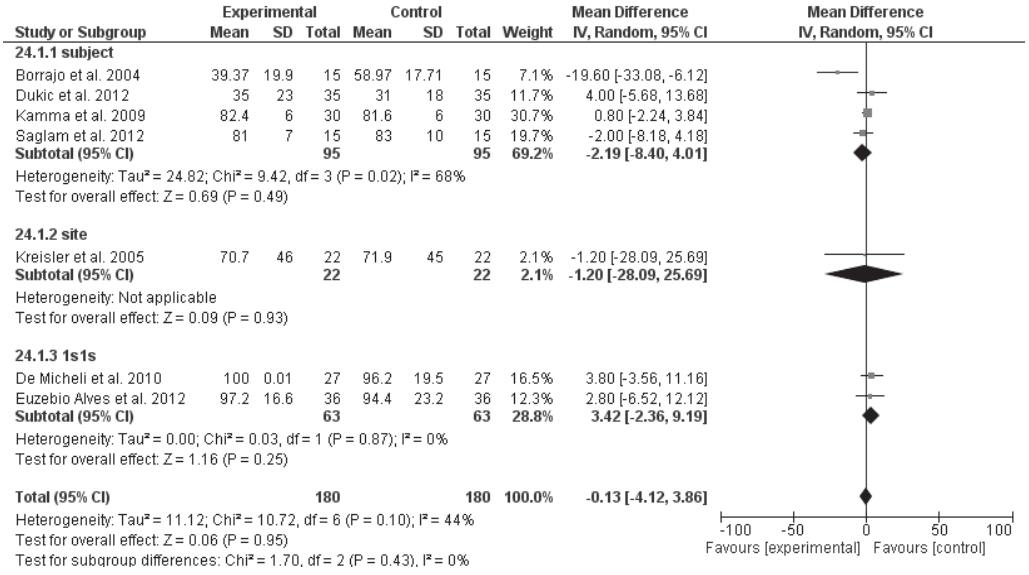
GI end scores and subgroup analysis on the research model used (parallel or split mouth).



Appendix S20-23 Bleeding upon Probing

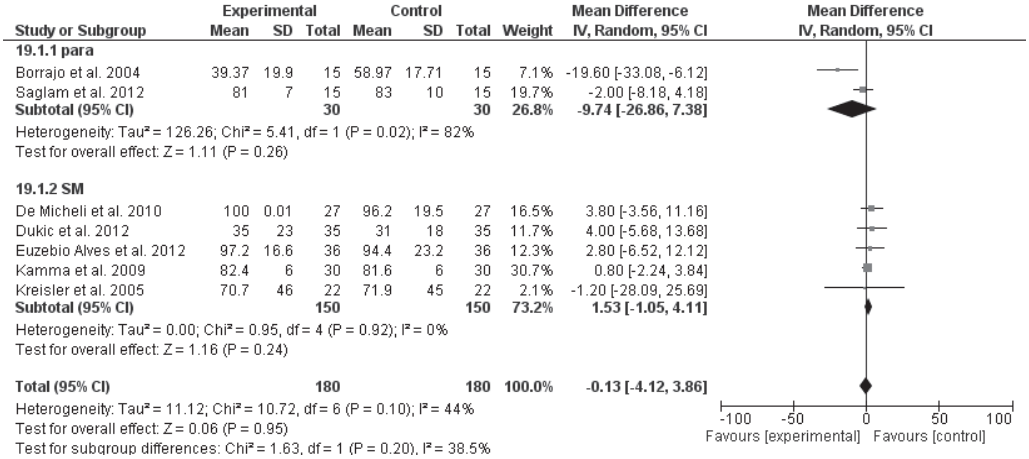
Appendix S20

BOP baseline scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



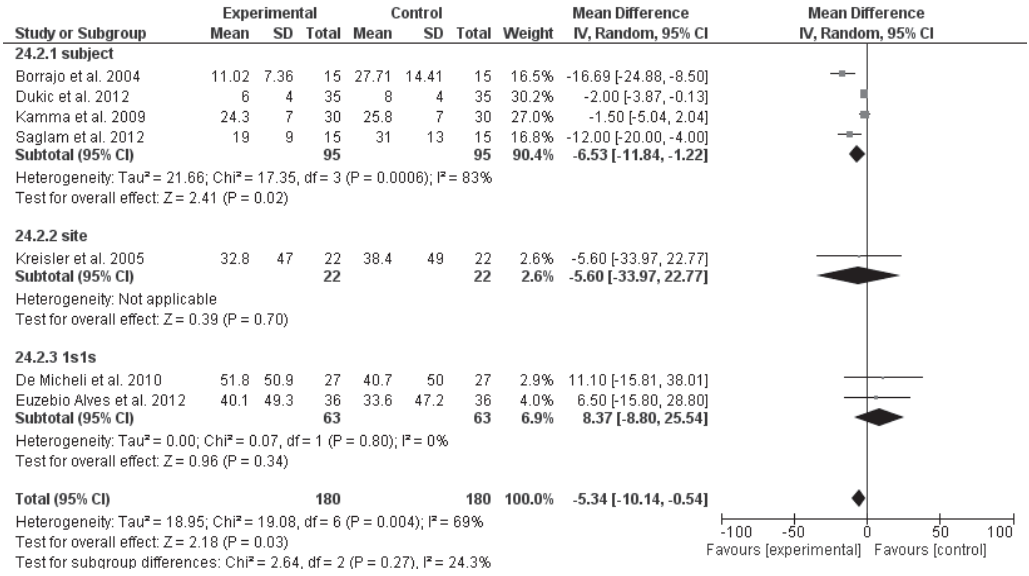
Appendix S21

BOP baseline scores and subgroup analysis on the research model used (parallel or split mouth).



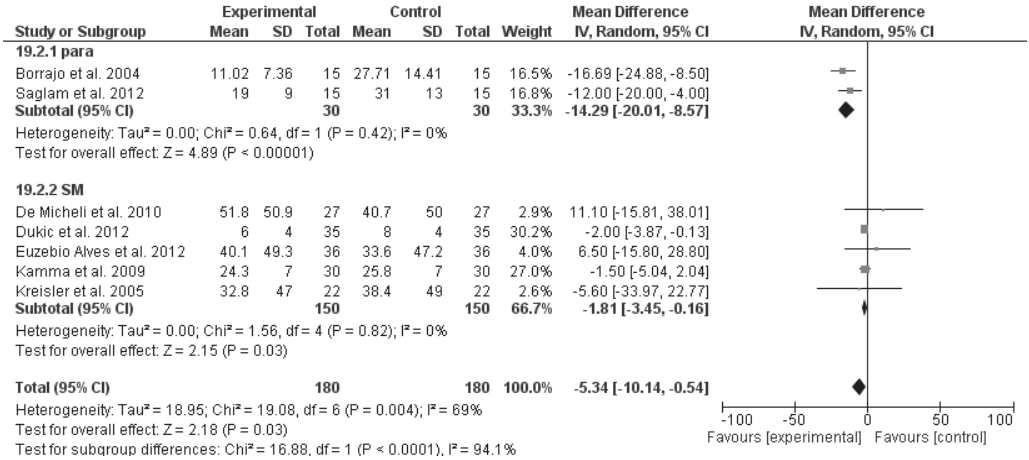
Appendix S22

BOP end scores and subgroup analysis on the basis of level of statistical analysis used in the original study (subject, site, one site within a subject).



Appendix S23

BOP end scores and subgroup analysis on the research model used (parallel or split mouth).



I'm brave to say that I won't take this sort of risk.

Alain Prost

THE EFFECT OF A PULSED ND:YAG LASER IN NON-SURGICAL PERIODONTAL THERAPY: A SYSTEMATIC REVIEW

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KRANENDONK AA
PARASKEVAS S
VAN DER WEIJDEN FA

JOURNAL OF PERIODONTOLOGY
2009 - 80 : 1041-1056

Introduction

The first working laser was created by Theodore Maiman in 1960. This device used a crystal medium of ruby that emitted a coherent radiant light when stimulated by energy. The word "laser" is an acronym for "light amplification by stimulated emission of radiation"; lasers are categorized according to the medium used to provide atoms to the emitting system. Each type of atom can absorb photons of specific wavelengths. Therefore, each medium produces a laser beam with a single, unique wavelength (Miserendino et al. 1987) Light of different wavelengths interacts differently with tissues and does not have the same absorption qualities. The first applications of lasers to dental tissue were reported by Goldman et al. (1964) and Stern & Sognnaes (1972) both articles described the effects of a ruby laser on enamel and dentin.

In 1961, Snitzer published the prototype of the neodymium-doped:yttrium, aluminum, garnet (Nd:YAG) laser, which emits in the infrared range of the spectrum with a wavelength of 1.06 microns. The Nd:YAG laser was further developed by Geusic et al. in 1964. This laser's medium is a crystal of yttrium-aluminum-garnet doped with neodymium. It penetrates to various degrees in pigmented tissues, reaching depths ranging from 0.5 to 4mm as a function of optical scattering, minimal absorption and reflection, and the mode of delivery. The depth of penetration that is characteristic of a wavelength is a critical feature that can influence its usefulness for any particular application. The 1,064-nm Nd:YAG laser light can be transmitted through an optical fiber, such that it can pass through an endoscope or be delivered intraorally using a handpiece. This allows the operator to work in a familiar setting and use contact mode for tactile sensation. The Nd:YAG laser has been recommended for various types of minor oral soft-tissue surgery (Pick & Colvard 1993). It has been prescribed for use in maxillary midline frenectomies, lingual frenectomies, gingivectomies, gingivoplasties, operculum removal, and biopsies of benign lesions (Miserendino et al 1987, Pick & Colvard 1993, White et al. 1991, De Benedittis et al. 2007).

Several advantages of laser treatment over conventional methods include minimal cellular destruction and tissue swelling, hemostasis, increased visualization of surgical sites, sterilization of the wound site, reduced postoperative pain, and high patient acceptance (Myers 1991). In addition, there have been some reports of nerve analgesia after Nd:YAG laser irradiation (Whitters et al. 1995, Gold & Vilardi 1991) showed the efficacy of a low-power pulsed Nd:YAG laser in removing epithelium lining the periodontal pocket in humans with moderately deep pockets. In addition, the Nd:YAG laser has a bactericidal effect, suppressing or eradicating putative

periodontal pathogens from periodontal pockets (Cobb et al. 1992, Ben Hatit et al. 1996).

Laser treatment may serve as an alternative or adjunctive treatment to conventional mechanical therapy in periodontics (Miyazaki et al. 2003). The use of a dental laser in the treatment of periodontitis is based on the purported benefits of subgingival curettage and a significant decrease in subgingival pathogenic bacteria. Such laser therapy is commonly referred to as "non-surgical"(Cobb 2006). A recent narrative review of the literature (Cobb 2006) suggested that the use of the Nd:YAG wavelength for the treatment of chronic periodontitis may be equivalent to scaling and root planing (SRP) with respect to probing depth (PD) reduction.

However, few published data compared the clinical outcomes from treatment with Nd:YAG or carbon dioxide (CO2) laser to those from well-established procedures, such as ultrasonic scaling (US) (Miyazaki et al. 2003). Comparative clinical studies are required to establish the potential of lasers in periodontal therapy. This is particularly true for subgingival applications, such as root debridement, soft tissue curettage, and excisional new attachment. Furthermore, clinical studies are needed to show that laser therapy is effective at treating chronic periodontitis. Systematic reviews aid in clinical decision-making. The value of a good systematic review is that it minimizes bias and provides a comprehensive and contemporary overview. Such analyses are objective in their appraisal of quality, and they are transparent, allowing others to appraise the methodology and quality of the review itself. If such conditions are met, the reader should have greater confidence in the conclusions of the review than other summaries of clinical evidence (Needleman 2002).

A recent systematic review (Schwarz et al 2008) on lasers in non-surgical periodontal therapy developed a search strategy and inclusion and exclusion criteria that eventually picked up only one article on Nd:YAG lasers that met the search criteria. An even more recent review (Karlsson et al. 2008) that evaluated the effect of laser therapy as an adjunct to non-surgical periodontal treatment lacked a reproducible search strategy. Also, it used studies with a duration of ≥12 weeks of follow-up as part of the inclusion criteria. This review also picked up only one article on Nd:YAG lasers, but not the same article as the other review. This is clearly insufficient for making firm statements about the therapeutic effects of this particular laser.

Therefore, the aim of this study was to evaluate, in a systematic manner and after a comprehensive search of the literature, the (additional) therapeutic effects of using a pulsed Nd:YAG laser in the initial treatment of patients with periodontitis.

Materials and methods

Focused Questions

What is the effect of a pulsed Nd:YAG laser in the initial treatment of patients with periodontitis, either as monotherapy or as an adjunct to non-surgical periodontal treatment? How does the pulsed Nd:YAG laser compare to conventional therapy (ultrasonics and/or hand instrumentation) in destroying plaque and in improving clinical parameters of periodontal inflammation and PD?

Search Strategy

Two Internet sources of evidence were used to search for appropriate articles addressing the focused question: the National Library of Medicine (MEDLINE/PubMed) and the Cochrane Central Register of Controlled Trials. Search criteria were designed to include any study that evaluated a pulsed Nd:YAG laser in the initial treatment of patients with periodontitis. The databases were searched up to and including January 2009 using the terms described below. The asterisk (*) was used as a truncation symbol.

Eligibility Criteria

Initially, titles and abstracts resulting from the searches described above were screened independently by two reviewers (DES & FW). Subsequently, the same reviewers screened and selected the full-text articles. The following eligibility criteria were imposed: 1) randomized controlled clinical trials (RCTs) or controlled clinical trials; 2) conducted in humans with good general health (no systemic disorders), ≥18 years of age, and with periodontitis; 3) intervention: use of Nd:YAG laser as monotherapy or as an adjunct to non-surgical periodontal initial therapy; 4) control group: conventional therapy (ultrasonics and/or hand instrumentation) or placebo treatment; 5) evaluation parameters: plaque/bleeding/gingivitis/PD; and 6) the use of statistical analysis.

Only articles written in English were included. Case reports, letters, and historical reviews were excluded. Articles without abstracts, but whose titles suggested that they could be related to the objectives of this review, were also selected, so that the full text could be screened for eligibility. Any disagreements between the reviewers were resolved by discussion. Reference lists of potentially relevant studies and review articles were also searched. After the final selection of the articles by the two reviewers (DES & FW), those that fulfilled the selection criteria were processed for data extraction.

MEDLINE Search

Intervention. <([MeSH terms] lasers OR laser therapy OR [text words] laser) AND ([MeSH terms] OR neodymium OR [substance name] yttrium-aluminumgarnet OR [text words] neodymium OR neodimium OR yttrium aluminum garnet OR aluminum garnet laser OR neodymium YAG OR neodimium YAG OR Nd:YAG OR NdYAG)>
AND
Outcome. <[MeSH] periodontal diseases OR dental deposits OR [text words] papillary bleeding index OR sulcus bleeding OR bleeding on probing OR gingival bleeding OR gingival index OR gingival inflammation OR gingival diseas*OR gingivitis OR periodontitis OR periodontal diseas* OR periodontal pocket OR gingival pocket OR pocket depth OR plaque removal OR plaque index OR dental plaque OR plaque OR dental deposit OR calculus OR clinical attachment loss>.

Cochrane Library Search

Intervention. <([MeSH terms] lasers OR laser therapy OR [text words] laser) AND ([MeSH terms] OR neodymium OR [text words] neodymium OR neodimium OR yttrium aluminum garnet OR aluminum garnet laser OR neodymium YAG OR neodimium YAG OR Nd:YAG OR NdYAG)>
AND
Outcome. <[MeSH] periodontal diseasesORdental deposits OR [text words] papillary bleeding index OR sulcus bleeding OR bleeding on probing OR gingival bleeding OR gingival index OR gingival inflammation OR gingival diseas*OR gingivitis OR periodontitis OR periodontal diseas* OR periodontal pocket OR gingival pocket OR pocket depth OR plaque removal OR plaque index OR dental plaque OR plaque OR dental deposit OR calculus OR clinical attachment loss>.

Assessment of Heterogeneity

Factors that were recorded to evaluate the heterogeneity of the primary outcomes across studies were study design and evaluation period; type of Nd:YAG laser, comparison treatment, and industry funding; and subjects and smoking.

Quality Assessment

Assessment of methodologic study quality was performed as proposed by the RCT checklist of the Dutch Cochrane Center, the CONSORT statement, Esposito et al. (2001), Moher et al.(2001a-c) the Delphi list (Verhagen et al. 1998) and Needleman et al. (2005).

Statistical Analyses

DATA EXTRACTION

From the selected articles, data were extracted that described the clinical effects after the use of a pulsed Nd:YAG laser in the initial treatment of patients with periodontitis compared to control treatment. Means ±SDs were extracted by the authors (DES & FAW). Some of the articles provided standard errors (SE) of the mean. When necessary, the authors calculated SD based on the sample size ($SE=SD/\sqrt{N}$).

DATA ANALYSIS

The studies in the final dataset were few and highly heterogeneous in terms of design, characteristics, energy settings, fiber tips, length of the observation periods, primary outcome variables, and presentation of results. This made it impossible to carry out quantitative analysis of the data and subsequent meta-analysis. Instead, a descriptive manner of data presentation was used.

Results

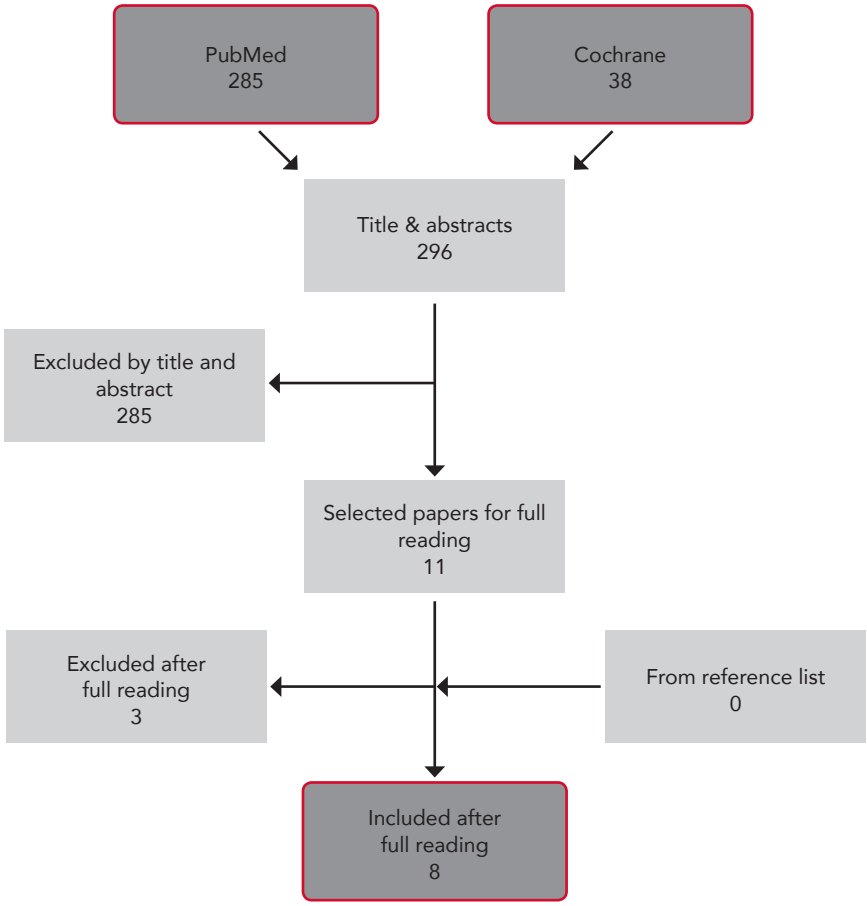
Search and Selection Results

The MEDLINE/PubMed search resulted in 285 citations, and the Cochrane search resulted in 38 citations (Figure 1). After removing duplicate listings of articles present in both searches, 296 titles and abstracts remained to be screened. The screening of titles and abstracts initially resulted in 11 full-text articles. Based on the full texts, three studies were excluded because they lacked a control group (Harris et al. 2004) or statistical analyses (Yukna et al. 2007) or they compared Nd:YAG laser treatment to surgical flap treatment (Mummolo et al. 2008). Finally, eight studies (For details see Table 1) were identified as eligible and were analyzed further.

Study design and evaluation period

All studies had an RCT design. Four studies (III, V, VII, and VIII; Table 1) had a split-mouth design, and two studies (II and IV) had a parallel design. The design was unclear in two studies (I and VI). Three studies (I, II, and VII) had an evaluation period of 4 to 6 weeks, and three studies (III, IV, and VI) had an evaluation period of 12 weeks. Sjöström & Friskopp (VIII) evaluated patients after 4 months. The longest study (6 months) was conducted by Neill and Mellonig (V). When a study presented intermediate assessments regarding the use of the Nd:YAG laser, the authors took the baseline and final evaluations into account for this review.

Figure 1. Search and selection results



Outcome Results

ASSESSMENT OF HETEROGENEITY

Information on the study characteristics is displayed in Table 1.

Table 1. Overview of the selected studies (Nd:YAG laser) and their characteristics, in chronological order

#	Author(s) (year)	Title	Design & evaluation period	Subjects inclusion criteria	Intervention	Subjects (# teeth)	Original authors' conclusions
I	de Andrade et al.	Nd:YAG laser clinical assisted in class II furcation treatment	RCT ? Double-blind 6 weeks	All patients had received previous periodontal treatment (up to four sessions) with the exception of the molars. Chronic periodontitis, class II furcation defects	Nd:YAG + SRP/US SRP/US	17 (34) ? (?) ? (?)	The Nd:YAG laser irration associated with SRP and the isolated conventional treatment demonstrated statistically significant increased clinical conditions with these parameters 6 weeks after the treatment, but no statistically significant differences were observed between the groups.
II	Kara et al.	Effect of Nd:YAG laser irradiation on the treatment of oral maladour associated with chronic periodntitis	RCT Parallel Blinding no 4 weeks	Chronic periodontitis patients (5-7mm), radiographic evidence of bone loss and complaining of oral malodour. No antibiotic treatment within the previous three months, no evidence of systemic disease that may influence oral malodour. Minimum of 20 natural teeth, >3mm.	SRP/US + Nd:YAG SRP/US	60 20 (?) 20 (?)	The data indicated a possible adjunctive role for Nd:YAG lasers in periodontal therapy.

III	Liu et al.	Comparison of Nd:YAG Laser Versus Scaling and Root Planning in Periodontal Therapy	RCT Split- mouth Blinding ? 12 weeks	Individuals with moderate to advanced periodontitis. No periodontal therapy within preceding 6 months, radiographic horizontal bone loss. At least 1or 2 sites of 3 adjacent single-rooth teeth in each quadrant with GI≥2, probing depth of 4 to 6mm, and bleeding on probing.	Nd:YAG Nd:YAG + SRP + Nd:YAG SRP	8 (56) 8(14) 8 (14) 8 (15) 8 (13)	Our data suggest that SRP is more effective than laser therapy at reducing gingival inflammation. No additional benefit was found when Nd:YAG was used secondary to SRP.
IV	Miyazaki et al.	Effects of Nd:YAG and CO2 Laser Treatment and Ultrasonic Scaling on Periodontal Pockets of Chronic Periodontal Patients	RCT Parallel Blinding ? 12 weeks	Seeking for periodontal care, free of systemic complications which could interfere with periodontal healing. No use of antibiotics during the previous 3 months, no periodontal treatment during the previous 6 months.2 or more non-adjacent teeth with interproximal periodontal pockets of ≥5mm.	Nd:YAG US	18 (41) 18 (14) 18 (14)	This study demonstrated that the Nd:YAG was as effective as US in reducing the clinical signs of periodontitis. Both groups showed significant improvements, but no significant difference was observed between the groups.
V	Neill & Mellonig	Clinical Efficacy of the Nd:YAG Laser For Combination Periodontitis Therapy	RCT Split- mouth Double-blind 6 months	Adult periodontitis, with probing depths >4mm and radiographic bone loss.	Nd:YAG + SRP/US SRP/US	10 (186/744‡) 10(91/364‡) 10(49/196‡)	Clinical significance of these findings may suggest that mechanical scaling and root planning therapy alone may not be the most effective. There are several additional areas where the adjunctive use op Nd:YAG may be an advantage over scaling and root planning alone as a mechanical approach to nonsurgical therapy.

VI	Noguchi et al.	Combined effects of Nd:YAG laser irradiation with local antibiotic application into periodontal pockets	RCT ? Blinding ? 3 months	Seeking for periodontal care, no perodontal treatment, >20 teeth, presence of 4 or more non-adjacent single rooth teeth with probing depth >4mm, no systemic complications, no use of antibiotics during the 6 months prior to treatment.	Nd:YAG control group	16 (135) ? (37) ? (32)
VII	Radvar et al.	An evaluation of the Nd:YAG laser in periodontal pocket therapy	RCT Split- mouth Blinding ? 6 weeks	Untreated chronic adult periodontitis, affected teeth of poor prognosis scheduled for extraction.	Nd:YAG (50mJ) Nd:YAG (80mJ) SRP	11 (80) 11(20) 11(20) 11(20)	This study demonstrated that application of Nd:YAG failed to improve the clinical parameters of periodontal disease.
VIII	Sjöström & Friskopp	Laser treatment as an adjunct to debridement of periodontal pockets	RCT Split- mouth Blinding ? 4 months	Referred individuals, healthy from a medical standpoint, smokers and non-smokers. Periodontal breakdown, single-rooted.	Nd:NCG + SRP SRP	26 (960‡) † ?(484‡) ?(476‡)	Nd:YAG treatment resulted in diminished bleeding and enhanced visual control at debridement.

Nd:YAG Nd:YAG laser system
US Ultrasonic Scaler
SRP Scaling and Root Planing with hand instruments
? Unknown/not given
† 1 drop out
‡ # of sites

Type of Nd:YAG laser, comparison, and industry funding

In the identified articles, different brands of Nd:YAG lasers were used as test products. Different energy settings, tips, coolants, contact times, and types and depth of fiber insertions were used (Table 2). The laser used by VIII was a prototype Nd:NCG laser light (1,061nm),which, according to the manufacturer's description, is nearly identical to the Nd:YAG laser (1,064 nm). Four (III, IV, VI, and VII) of the eight studies evaluated the Nd:YAG laser as monotherapy; two of them (studies III and VII) compared laser treatment to manual SRP, one (study IV) compared it to US, and another (study VI) compared it to a control/placebo group in which the fiber was inserted into periodontal pockets, but the sites were not irradiated (sham treatment). Five studies (I, II, III, V, and VIII) included a combined treatment trial that assessed the Nd:YAG laser in combination with supra- and subgingival debridement. Two of them (studies I and II) used a combination of manual and ultrasonic instruments. Study III also evaluated the order of treatment: Nd:YAG laser followed by SRP compared to SRP followed by Nd:YAG laser.

Basic oral hygiene education at baseline, including instructions on toothbrushing, flossing, and the use of an interdental brush, was described in only three studies (II, III, and IV). This instruction was reinforced at all subsequent visits. All studies but three (II, V, and VI) had financial support. The grants originated from funds for the promotion of science from Tanaka Industries, Niigata, Japan (study IV); the Fundação de Amparo a Pesquisa no Estado de São Paulo, Brazil, and Procad/CAPES and Instituto Milenio Fotonica/CNPq (study I); the National Science Council, Taipei, Taiwan (study III); the Scottish Office Home and Health Department (study VII), Edinburgh, United Kingdom; and Public Dental Care, County of Stockholm, Sweden (study VIII). Subjects and smoking. Periodontal patients were used in all studies, the definition of which varied from radiographic information to clinical parameters (Table 1). Three studies (III, VI, and VIII) evaluated single-rooted teeth, whereas one study (I) specifically treated Class II furcation defects. Study VII selected teeth with poor prognosis that were scheduled for extraction. Four studies (II, IV, VI, and VIII) selected subjects in "good general health, with no systemic diseases." The use of antibiotics during the previous months was an exclusion criterion (studies IV and VI). Only study VIII provided information about the smoking habits of the participants; their study population consisted of smokers and non-smokers. However, the effect of smoking on the study outcome variables was not analyzed.

Study quality

Quality assessment is presented in Table 3. The estimated risk for bias was high in seven of eight studies. The risk was considered moderate for study I.

Table 2. Overview of the selected studies and Nd:YAG laser parameters of interest

#	Author(s)	Brand	Energy settings	Tip	Coolant	Contact time	Fiber insertion	Anesthesia
I	de Andrade et al.	ADT-American Dental technology, USA	100 mJ/pulse 1.5 W 15 Hz repetition rate Pulse duration 150 μm Energy density 141.5 J/cm^2	Optical fiber Ø=300μm	?	60sec/ furcation	Parallel alignment	?
II	Kara et al.	Smarty A10, DEKA, Firenze Italy	2.0W 100 mJ	Ø=?	?	90sec	?	Yes
III	Liu et al.	Dentlase DLC8, S.L.T. Compagny, Tokyo, Japan	3.0 W 20 pps=150 mJ 25Hz	Contact optical fiber Ø=400μm	?	?	Parallel alignment	?
IV	Miyazaki et al.	Opelaser Nd, Yoshida , Tokyo, Japan	2.0 Watts 20 pps=100 mJ Total energy dose delivered to each site 240 J	Contact optic fiber Ø=?	?	120sec/ tooth	Parallel alignment	Yes
V	Neill & Mellonig	PulseMaster 1000, American Dental Technologies, Southfield (MI) USA	2.0 W 80 mJ Repetition rate 25Hz	Contact fiber Ø=?	?	Average 120sec	Parallel alignment	Upon request
VI	Noguchi et al.	PulseMaster 600LE, American Dental Technologies, USA	2 W 200 mJ 10 pps	Optic fiber Ø=400μm	?	90sec/tooth	Parallel alignment	No

VII	Radvar et al.	American dental laser, d.lase-300, Sunrise Technology Inc., Fremont (CA), USA	0.5 W 10 pps=50 mJ 62.9 J/cm^2 Pulse duration 150 µm 0.8 W 10 pps=80 mJ 99.5 J/cm^2 Pulse duration 150 µm	Contact optic fiber Ø=320 µm	?	180sec/ tooth	Parallel alignment	Yes
VIII	Sjöström & Friskopp	Genius 9 SDL, Mølsgaard Dental ApS, Copenhagen, Denmark	3 W 250microseconds 60 pps + 7 W 250microseconds 60 pps	Ø=?	Yes	Minimum 60sec	In contact with the surface	Upon request

mJ millijoules
W Watts
pps pulses/sec
? information not given

Table 3. Quality assessment of the studies analyzed

Study / Quality criteria	I de Andrade et al.	II Kara et al.	III Liu et al.	IV Miyazaki et al.	V Neill & Mellonig	VI Noguchi et al.	VII Radvar at al.	VIII Sjostrom & Friskopp
Random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size calculation	?	?	?	?	?	?	?	?
Inclusion/exclusion defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealment	?	?	?	?	?	?	?	?
Blinded to patient	No	No	No	No	No	Yes	Yes	No
Blinded to examiner	Yes	No	?	?	Yes	?	?	Yes
Blinding during statistical analysis	?	?	?	?	?	?	?	?
Balanced experimental groups	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Reported loss to follow-up	?	?	?	?	?	No	?	Yes
#(%) of drop-outs	0 (0)	0 (0)	0 (0)	0 (0)	?	?	?	1 (3.7%)
Treatment identical between groups, except for intervention	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Authors estimated risk of bias*	Moderate	High	High	High	High	High	High	High

Randomization, masking, and losses to follow-up

All studies mentioned random assignment to the different treatment groups, either by subject (II), split-mouth design at quadrants (III, V, VII, and VIII; Table 1), or randomization by site (I, IV, and VI; Table 1). However, the method of randomization was often unclear (studies I, III, IV, V, and VI; Table 1). Only study VIII described that patient assignment was performed by lot. Procedures for allocation concealment were not described. One study (II) mentioned that all clinical evaluations and treatment procedures were done by the same examiner, so no masking was performed. Two studies (I and V; Table 1) self-identified as being double-masked; the others (studies III, IV, VI, VII, and VIII; Table 1) did not specify any such masking. Study VI was the only one that was truly masked in design. In the test and control groups, the fiber was inserted into periodontal pockets, but the sites in the control group were not irradiated (sham treatment). Masking of examiners and participants to protect against performance and measurement bias was assessed, although it is recognized by the authors that masking participants to interventions such as laser treatment is rare and, depending on the design of the trial, often impossible. No loss of subjects to follow-up was reported by three studies (I, III, and IV). Only study VIII lost one subject to follow-up because the person requested to be excluded from the study. The other four studies (II, V, VI, and VII) did not provide any information about losses to follow-up.

Plaque indices and clinical parameters

Various plaque and gingivitis indices were used. Plaque was scored by the Silness and Löe (1964) index in four reports (I, II, IV, and VII); it was unclear which index was used in study III (Table 4). Gingivitis was also assessed by different indices: the gingival index (GI) of Löe and Silness (1963) was used by studies I, II, III, and IV, and Lobene's modified GI (Lobene et al. 1986) was used by study VII (Table 5). Study V did not reference which index was used. For bleeding scores, three studies (IV, VI, and VII) used A measure of bleeding on probing (BOP); two studies (V and VIII) used the gingival bleeding index without reference (Table 6). PD was assessed in all selected studies (Table 7). Clinical attachment level (CAL) was estimated in studies I, II, IV, V, and VI (Table 8). In contrast, gingival recession (Table 9) was measured only in study I. Analyses were performed at the tooth or site level; no study provided a subject-level analysis.

Table 4. Overview of the Selected (Nd:YAG laser) Studies for Plaque Index

#	Author(s)	Brand	Energy settings	Tip	Coolant	Contact time	Fiber insertion	Anesthesia
I	de Andrade et al.	ADT-American Dental technology, USA	100 mJ/pulse 1.5 W 15 Hz repetition rate Pulse duration 150 µm Energy density 141.5 J/cm^2	Optical fiber Ø=300µm	?	60 sec/ furcation	Parallel alignment	?
II	Kara et al.	Smarty A10, DEKA, Firenze Italy	2.0W 100 mJ	?	?	90 sec	?	Yes
III	Liu et al.	Dentlase DLC8, S.L.T. Compagny, Tokyo, Japan	3.0 W 20 pps=150 mJ 25Hz	Contact optical fiber Ø=400µm	?	?	Parallel alignment	?
IV	Miyazaki et al.	Opelaser Nd, Yoshida, Tokyo, Japan	2.0 Watts 20 pps=100 mJ Total energy dose delivered to each site 240 J	Contact optic fiber	?	120 sec/ tooth	Parallel alignment	Yes
V	Neill & Mellonig	PulseMaster 1000, American Dental Technologies, Southfield (MI) USA	2.0 W 80 mJ Repetition rate 25Hz	Contact fiber	?	Average 120 sec	Parallel alignment	Upon request
VI	Noguchi et al.	PulseMaster 600LE, American Dental Technologies, USA	2 W 200 mJ 10 pps	Optic fiber Ø=400µm	?	90 sec/tooth	Parallel alignment	No

VII	Radvar et al.	American dental laser, d.lase-300, Sunrise Technology Inc., Fremont (CA), USA	0.5 W 10 pps=50 mJ 62.9 J/cm^2 Pulse duration 150 µm 0.8 W 10 pps=80 mJ 99.5 J/cm^2 Pulse duration 150 µm	Contact optic fiber Ø=320 µm	?	180 sec/ tooth	Parallel alignment	Yes
VIII	Sjöström & Friskopp	Genius 9 SDL, Mølsgaard Dental ApS, Copenhagen, Denmark	3 W 250microseconds 60 pps + 7 W 250microseconds 60 pps	Flexible optical fiber	Yes	Minimum 60sec	In contact with the surface	Upon request

? not specified/unclear

Table 5. Overview of the Selected (Nd:YAG laser) Studies for Gingival Index

#	Study	Index	Intervention	Mean (SD)			Significant change
				Baseline	End	Difference	
I	de Andrade et al.	Loë & Silness	Nd:YAG + SRP/US	2.17 (0.52)	1.11 (0.85)	-1.06◊	YES
			SRP/US	2.17 (0.63)	0.88 (0.69)	-1.29◊	YES
II	Kara et al.	Loë & Silness	SRP/US + Nd:YAG	1.31 (0.09)	0.08 (0.03)	-1.23◊	YES
			SRP/US	1.30 (0.13)	0.11 (0.04)	-1.19◊	YES
III	Liu et al.	Loë & Silness	Nd:YAG	₪	₪	?	?
			Nd:YAG + SRP	₪	₪	?	?
			SRP + Nd:YAG	₪	₪	?	?
			SRP	₪	₪	?	?
III	Miyazaki et al.	Loë & Silness	Nd:YAG	1.07 (0.47)	0.50 (0.52)	-0.57 (0.65)	YES
			US	0.86 (0.53)	0.43 (0.51)	-0.43 (0.76)	YES
V	Neill & Mellonig	Gingival Index	Nd:YAG + SRP/US	?	?	?	?
			SRP/US	?	?	?	?
VII	Radvar et al.	Modified Gingival Index	Nd:YAG(50mJ)	2.05 (0.56◊)	1.80 (0.64◊)	-0.25 (0.52◊)	NO
			Nd:YAG (80mJ)	1.95 (0.56◊)	1.90 (0.52◊)	-0.05 (0.56◊)	NO
			SRP	1.65 (0.70◊)	1.15 (0.58◊)	-0.50 (0.93◊)	NO

◊ calculated by the authors of this review ₪ insufficient data presented ? unknown

Table 6. Overview of the Selected (Nd:YAG laser) Studies for Bleeding Index

#	Study	Index	Intervention	Mean (SD)			Significant change
				Baseline	End	Difference	
IV	Miyazaki et al.	Bleeding On Probing	Nd:YAG US	1.00 (0.00) 0.86 (0.36)	0.57 (0.51) 0.57 (0.51)	-0.43 (0.51) -0.29 (0.47)	YES YES
V	Neill & Mellonig	Gingival Bleeding Index	Nd:YAG + SRP/US SRP/US	? ?	? ?	? ?	? ?
VI	Noguchi et al.	Bleeding On Probing	Nd:YAG control group	73.0% 65.6%	? ?	? ?	? ?
VII	Radvar et al.	Bleeding On Probing	Nd:YAG(50mJ) Nd:YAG (80mJ) SRP	₪ ₪ 95%	₪ ₪ 50%	? ? 45%	NO NO YES
VIII	Sjöström & Friskopp	Gingival Bleeding Index	Nd:NCG + SRP SRP	₪ ₪	₪ ₪	? ?	YES YES

₪ insufficient data presented ? unknown

Table 7. Overview of the Selected (Nd:YAG laser) Studies for PD (mm)

#	Study	Intervention	Mean (SD)			Significant change
			Baseline	End	Difference	
I	de Andrade et al.	Nd:YAG + SRP/US SRP/US	4.9 (1.3) 4.8 (1.3)	3.1 (1.1) 2.9 (1.0)	-1.8 -1.9	YES YES
II	Kara et al.	SRP/US + Nd:YAG SRP/US	2.80 (0.17) 2.53 (0.19)	1.21 (0.12) 1.27 (0.18)	-1.59◊ -1.26◊	YES YES
III	Liu et al.	Nd:YAG Nd:YAG + SRP SRP + Nd:YAG SRP	? ? ? ?	? ? ? ?	? ? ? ?	? ? ? ?
IV	Miyazaki et al.	Nd:YAG US	6.50 (1.09) 6.86 (2.63)	5.07 (0.83) 5.50 (2.06)	-1.43 (0.94) -1.36 (1.22)	YES YES
V	Neill & Mellonig	Nd:YAG + SRP/US SRP/US	? ?	₪ ₪	-1.7 (1.4) -1.7 (1.6)	? ?
VI	Noguchi et al.	Nd:YAG control group	4.92 (1.12) 5.8 (1.8)	3.35 (1.32) ₪	-1.57 ?	YES NO
VII	Radvar et al.	Nd:YAG(50mJ) Nd:YAG (80mJ) SRP	₪ ₪ ₪	₪ ₪ ₪	? ? ?	NO NO YES
VIII	Sjöström & Friskopp	Nd:NCG + SRP SRP	₪ ₪	₪ ₪	? ?	YES YES

₪ insufficient data presented ? unknown

Table 8. Overview of the Selected (Nd:YAG laser) Studies for CAL (mm)

#	Study	Intervention	Mean (SD)			Significant change
			Baseline	End	Difference	
I	de Andrade et al.	Nd:YAG + SRP/US SRP/US	8.1 (2.1) 7.6 (1.5)	7.1 (2.6) 6.0 (1.9)	-1.0◊ -1.6◊	YES YES
II	Kara et al.	SRP/US + Nd:YAG SRP/US	2.99 (0.34) 2.98 (0.22)	2.01 (0.24) 1.87 (0.14)	-0.98◊ -1.11◊	YES YES
IV	Miyazaki et al.	Nd:YAG US	7.36 (1.69) 8.64 (3.16)	6.86 (1.70) 8.07 (2.90)	-0.50 (0.65) -0.57 (0.85)	YES YES
V	Neill & Mellonig	Nd:YAG + SRP/US SRP/US	? ?	1.1 (1.9) 1.0 (1.7)	? ?	? ?
VI	Noguchi et al.	Nd:YAG control group	5.68 (1.55) 6.6 (2.7)	4.16 (1.88) ₪	-1.52 ?	YES NO

◊ calculated by the authors of this review ₪ insufficient data presented ? unknown

Table 9. Overview of the Selected (Nd:YAG laser) Studies for Gingival recession (mm)

#	Study	Intervention	Mean (SD)			Significant change
			Baseline	End	Difference	
I	de Andrade et al.	Nd:YAG + SRP/US SRP/US	3.3 (1.5) 2.7 (1.3)	3.6 (1.6) 3.5 (1.8)	+0.3 +0.8	NO NO

For abbreviations, see Table 1
◊ calculated by the authors of this review * significant difference from baseline (P<0.05)
₪ insufficient data presented ? unknown

Table 10. Descriptives of the Statistical Analyses

#	Study	Intervention	PI	GI	BI	PPD	CAL	GR	Comparison
IV	Miyazaki et al.	Nd:YAG	?	?	?	O	O	□	US
III	Liu et al.	Nd:YAG	?	?	□	?	□	□	SRP
		Nd:YAG + SRP	?	?	□	?	□	□	SRP
		SRP + Nd:YAG	?	?	□	?	□	□	SRP
VII	Radvar et al.	Nd:YAG (50mJ)	O	O	?	-	□	□	SRP
		Nd:YAG (80mJ)	O	O	?	-	□	□	SRP
VIII	Sjöström & Friskopp	Nd:NCG + SRP	□	□	O	O	□	□	SRP
II	Kara et al.	SRP/US + Nd:YAG	?	O	□	?	-	□	SRP/US
V	Neill & Mellonig	Nd:YAG + SRP/US	□	+	?	?	O	□	SRP/US
I	de Andrade et al.	Nd:YAG + SRP/US	O	O	□	O	O	O	SRP/US
VI	Noguchi et al.	Nd:YAG	□	□	?	?	?	□	Sham treatment

PI = plaque index; BI = bleeding index; GR = gingival recession; ? = information not given; □ = no data available; O = no difference; - = negative significant; difference; + = positive significant difference

Discussion

Most periodontal treatment modalities aim to control disease by reducing the bacterial plaque on the root surface and periodontal tissues to levels compatible with the ability of the host's immune system to control growth. The effectiveness of SRP in the treatment of periodontal disease is universally accepted (Lobene et al. 1986, Axelsson & Lindhe 1981).

Laser energy is capable of ablating and vaporizing residual organic debris, including microbial plaque and probably calculus, and it can disinfect and remove the pocket's sulcular lining (Gold & Vilardi 1994, Cobb et al. 1992, Ben Hatit et al. 1996, Liu et al. 1999, Morlock et al. 1992, Ando et al. 1996). Adjunctive therapy, such as laser energy, aimed at reducing or eliminating bacteria may be useful in reducing PD and BOP. The Nd:YAG laser is effective at melting calculus in vivo and in vitro. Total removal of calculus has not been reported in the literature; Tseng &Liew (1990) noted that the calculus seemed to separate from the underlying root structure after Nd:YAG laser treatment, which facilitated subsequent removal by scaling. It was suggested that SRP after Nd:YAG laser therapy may be more efficient in removing root deposition, resulting in better periodontal health (Liu et al. 1999, Morlock et al. 1992, Tseng & Liew 1990, Tucker et al. 1996, Thomas et al. 1994).

The present review identified eight articles that addressed the clinical outcomes of the Nd:YAG laser in subjects with periodontitis. The data of studies I, II, and IV provided some evidence that the clinical effects of Nd:YAG laser treatment on gingival inflammation and PD are similar to those obtained with conventional SRP/US or US (Tables 5 and 7). In the five articles (I, II, III, V, and VIII) that evaluated the combined treatment of Nd:YAG and supra/subgingival debridement, no evidence was found that using the laser provided additional benefits over those of the conventional approach (ultrasonics and/or hand instrumentation). A gain in CAL is the gold standard when measuring the outcomes of non-surgical periodontal therapy (Cobb et al. 1992). Only five studies (I, II, IV, V, and VI) reported this clinical parameter, and the majority found no differences among laser treatment, conventional periodontal therapy, or sham treatment. Recently, clinical benefits (PD and CAL) were reported for Nd:YAG laser–assisted removal of pocket epithelium after SRP. These were histologically found to be due to new cementum or the attachment of new connective tissue (Mummolo et al. 2008). However, no statistical analysis was provided to support these findings.

Differences in study design and other factors, such as laser energy settings, may also influence clinical outcomes. Given the same wavelength, different laser parameters yield different levels of energy density for varying periods of time (Cobb et al. 1992). This produces different extents of change in the target tissue. Differences in laser energy settings and contact time may explain the varying degrees of success across the studies in eliminating periodontal pathogens. The eight studies used energy settings ranging from 0.5 to 7.0W (50 to 200 mJ; Table 2). The degree of vaporization that takes place in the tissue is proportional to the amount of energy absorbed by the tissue. Because energy is a product of power and duration of exposure (contact time), the penetration depth can be altered by changing the laser's power or the duration of the exposure (De Andrade et al. 2008. Leaderman 1995, Pinero 1998). Other studies demonstrated that laser irradiation at a mean power >3 W was effective at reducing bacterial populations (De Andrade et al. 2008). Therefore, low-energy settings may explain the lack of clinical improvement in the study performed by Raffetto (2004). However, that study used a maximum contact time of 180 seconds per tooth, which was higher than most selected studies (Table 2). Higher-energy settings are not always suitable for laser treatment (Noguchi et al. 2005). The number of articles on the action of high-power lasers on periodontal parameters is modest.

Incomplete removal of microbial residues is another factor that may influence the clinical outcome. This results from incompletely overlapping strokes of the laser probe on root surfaces exposed to periodontitis (Tseng & Liew 1990, Tucket et al. 1996). Therefore, varying tip diameters may account for differences in the outcomes observed in the selected articles. Specifically, a thick laser tip makes deep subgingival application difficult; optical fiber tips, approximately the size of a periodontal probe, may enable the laser tip to access deep periodontal pockets (Raffetto 2004). In all studies, the fiber was moved parallel to the root surface up to the orifice of the pocket. This was done without analgesia in study VI (Noguchi et al. 2005). In one study (Yukna et al. 2007) the fiber was moved laterally and apically along the pocket wall, eventually arriving close to the base of the pocket.

The use of a laser coolant was mentioned in only one (VIII) of the eight selected articles. There are indications that dry laser irradiation heats up the tissue, and a water-based coolant was effective at reducing these thermal effects (Gow et al 1999). The thermal behavior of laser tips also depends on the type of fiber tips used (Verdaasdonk et al. 1991) with transparent contact probes, a large temperature decrease occurs along the surface of the tip, limiting thermal activation at the very tip of the probe.

In addition to the Nd:YAG laser, the laser types most commonly used in dentistry consist of a variety of wavelengths and are delivered as continuous, pulsed, or running-pulse waveforms (Cobb et al. 1992). Although the use of lasers in the treatment of periodontitis has been increasing among practitioners, their efficacy continues to be debated (Parker 2007). Three reviews (Cobb 2006, Schwarz et al. 2008, Karlsson et al. 2008) on lasers in periodontics showed no beneficial effect compared to conventional therapy. This is similar to the conclusions of this systematic review. The consensus report of the Sixth European Workshop on Periodontology (Sanz & Teughels 2008) stated that there is insufficient evidence to support the clinical application of CO2, Nd:YAG, Nd:YAP, or other diode lasers because the available clinical studies used these laser applications as adjuncts to mechanical debridement and did not demonstrate significant added clinical value. This conclusion with respect to the Nd:YAG laser was based on the evaluation of only one article (Miyazaki et al. 2003). Nevertheless, the present review of eight research studies supports the findings of the consensus report.

Conclusions

The majority of the studies analyzed showed no beneficial effect of a pulsed Nd:YAG laser compared to conventional therapy (ultrasonics and/or hand instrumentation) in the initial treatment of patients with periodontitis. The pulsed Nd:YAG laser was assessed as monotherapy and as an adjunct to non-surgical periodontal treatment; efficacy was determined by the extent of plaque removal and the reduction of periodontal inflammation. No evidence exists that the Nd:YAG laser is superior to traditional modalities of periodontal therapy.

Conflict of interest and source of funding statement

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10.

Mechanical Nonsurgical Pocket Therapy

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Advanced Manual Instrumentation

Darby & Walsh

ADJUNCTIVE EFFECT OF A WATER-COOLED ND:YAG LASER IN THE TREATMENT OF CHRONIC PERIODONTITIS

SLOT DE
KRANENDONK AA
VAN DER REIJDEN WA
VAN WINKELHOFF AJ
ROSEMA NA
SCHULEIN WH
VAN DER VELDEN U
VAN DER WEIJDEN FA

JOURNAL OF CLINICAL PERIODONTOLOGY
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Introduction

The goals of treatment of chronic periodontitis generally include reductions in pocket probing depth and supra- and subgingival microbial loads, gains in clinical attachment level and arresting of disease progression. Most treatment modalities used in periodontal therapy attempt to achieve these goals by reducing the amount of bacterial plaque on the root surface to levels compatible with periodontal health. The traditional periodontal treatment of supra- and subgingival debridement (SRP), which may be followed by periodontal surgery (Pihlstrom et al. 1983, Badersten et al. 1984a/b, Ramfjord et al. 1987, Kaldahl et al. 1996), is not always successful in eliminating all deep periodontal pockets around the teeth (Kaldahl et al. 1996). The residual pocket depth is positively related to the risk of future periodontal breakdown (Badersten et al. 1990, Clafey et al. 1990).

For many intraoral soft-tissue surgical procedures, the laser has become a desirable and dependable alternative to traditional scalpel surgery (Cobb et al. 2010). Gold and Vilardi (1994) evaluated the efficacy of a low-power pulsed Nd:YAG laser for removing pocket lining epithelium in humans with moderate periodontitis. The laser proved capable of removing pocket lining epithelium in moderately deep pockets. In addition, the Nd:YAG laser has shown a bactericidal effect (Kranendonk et al. 2010), suppressing and eradicating putative periodontal pathogens from periodontal pockets (Cobb et al. 1992, Ben Hatit et al. 1996).

Debridement of the diseased root surface is usually performed by mechanical scaling and root planing using manual or power-driven instruments. Power-driven instruments such as ultrasonic scalers are frequently used for root surface treatment, as they are effective in removing plaque, calculus and endotoxin, and cause less root surface damage than hand scalers (Torfason et al. 1979, Loos et al. 1987, Folwaczny et al. 2004). Although the data are rather limited, the clinical outcome with the Nd:YAG laser appears to be comparable to the effect of SRP with regard to periodontal inflammation parameters (Slot et al. 2009). Investigators have also proposed using the Nd:YAG laser as an adjunct to SRP (Radvar et al. 1996, Neill & Mellonig 1997). Current evidence suggests that using the Nd:YAG laser for treatment of chronic periodontitis may be equivalent to SRP with respect to the reduction in subgingival bacterial populations (Cobb 2006, Schwarz et al. 2008). However, the Nd:YAG laser is not suitable for root planing or removal of mineralized accretions such as dental calculus (Cobb et al. 2010). Accordingly, this type of laser is indicated as an adjunct to SRP. Furthermore, improper use of the fibre tip may result in unfavourable thermal changes (Aoki et al. 2004, Schwarz et al. 2008).
Among dentists and dental hygienists in the Netherlands, the Genius Nd:YAG-pulsed

laser with water and air coolant (Genius, Mølsgaard Dental, Copenhagen, Denmark) is used as an adjunct to "non-surgical" treatment of periodontitis, as suggested by Lioubavina- Hack (2002). This is a water-cooled laser that releases energy in short interrupted time intervals (pulsed). It has an optical fibre tip that approximates the diameter of a periodontal probe. The flexible fibre optic cable provides good operability, making it suitable for reaching the bottom of the periodontal pocket.

Use of an air–water spray for irrigation during laser irradiation provides a thermal gradient for removal of heat from tissue surfaces. The process of surface cooling is a direct result of the extensive heat capacity of water, which absorbs a significant amount of the surface heat generated by the laser, and thus, effectively limits collateral tissue damage. In addition, due to continual renewal of the air–water spray, simultaneous cooling of the tissue surface occurs by convection. Based on these characteristics, it is theoretically possible to stabilize surface temperatures (Spencer et al. 1996). The water irrigation also reduces the clogging of the probe with debris, thereby preventing a buildup of areas of excessive heat (Qadri et al. 2010). Scientific evidence supporting the use of this Nd:YAG laser brand featuring water and air cooling has, until recently, only been published as abstracts (Lioubavina et al. 1997, Jensen et al. 2003). Two recent papers describing the short-term and the long-term effect of a single laser application in supplement to scaling and root planning showed a positive effect in favour of this laser (Qadri et al. 2010, Qadri et al. 2011) whereas another study did not find such a superior clinical effect (Jensen et al. 2010). A recent "in vitro" study showed that 15 s of this Nd:YAG laser use was effective for total killing of various periodontal pathogens (Kranendonk et al. 2010).

The purpose of this study was (1) to test whether the use of the Nd:YAG laser with water and air coolant adjunctive to SRP results in greater clinical improvements than ultrasonic scaling alone, (2) to investigate the reduction in the number of subgingival microorganisms directly after subgingival SRP with or without adjunctive Nd: YAG laser treatment and (3) to evaluate post-operative experiences and patient comfort with regard to the treatments provided.

Material and Methods

Ethical aspects

The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam (MEC #05/278). All voluntary participants were informed of the outline, purpose and duration of the study and signed an "informed consent" form.

Study population

For the present study, 19 patients (11♂, 8♀) were enrolled from March 2006 to February 2007. All patients had been referred by their general dentists to a clinic specializing in periodontal therapy. The following inclusion criteria were used: healthy, non-institutionalized patients; at least 30 years of age; a minimum of five natural teeth in every quadrant; clinical diagnosis before active periodontal treatment; moderateto- severe generalized periodontitis characterized by the presence of ≥1 site per quadrant with pocket depth >6mm and inter-proximal attachment loss of ≥3mm, presence of bleeding on pocket probing (BOPP) and radiographic evidence of alveolar bone loss; and systemically healthy. Exclusion criteria were professional periodontal therapy before enrollment in the study; antibiotics use for any purpose within 3 months before entering the study; and dental personnel.

Clinical assessments

The following measurements were performed before the initial therapy appointment and after the 3-month evaluation period.

- Probing pocket depth (PPD) using a manual probe (PCPUNC 15mm probe, Hu-Friedy® Hu-Friedy Inc., Leimen, Germany);
- BOPP (Van der Velden 1979);
- Plaque index (Silness & Löe 1964, Danser et al. 2003).

All clinical measurements were taken at six sites (mesio-buccal, buccal, distobccal, mesio-lingual, lingual and distolingual) of each tooth and were rounded off to the nearest millimetre. All clinical measurements were performed by the same investigator, who was blinded to the treatment (WHS). Access to the data of former assessments was not allowed during the course of the study.

Clinical procedure

This study was an examiner-blind, randomized, controlled 3-month clinical trial using a split-mouth design with a treatment protocol similar to Henskens et al. (1996) and Winkel et al. (2001). After establishing eligibility to enter the study and submitting written approval, patients were scheduled for the First session. A medical history form, including smoking habits and history, was filled out. A second investigator performed all treatments (AAK). Local anaesthetics were provided during SRP using ultrasonic and hand instruments and laser treatment. Treatment was performed in two sessions approximately 1 week apart. During each session, teeth in two contra-lateral quadrants were SRP using a piezoelectric ultrasonic unit (Piezon Master,

EMS, Nyon, Switzerland) at a moderate setting and with the appropriate tips for initial therapy (A, P, PS, PL1–5, EMS). In addition, where deemed appropriate by the dental professional, hand instruments were used (204SD, 12/13 11/14 Hu-Friedy® Hu-Friedy Inc.). Depending on the randomization immediately thereafter, all pockets ≥4mm were additionally treated with the Nd:YAG laser immediate following SRP or no additional treatment was provided. The non-laser treated contra-lateral teeth became controls. Randomization was based on a predetermined computer-generated set of random numbers that were obtained via http://www.random.org. The primary investigator and study coordinator (GAW) was responsible for concealing the allocation. Sealed envelopes were prepared that stated which quadrants would receive additional laser treatment. These envelopes were opened only after SRP was finished. Following instrumentation, all supra-gingival surfaces were polished with a rubber cup and point in combination with an abrasive paste (Tri-Fluor-O-Clean, KerrHawe, Bioggio, Switzerland). The time necessary for treatment was recorded after every session. In addition, patients received instruction in personal oral hygiene procedures. After approximately 6 weeks, the level of oral hygiene was evaluated using an erythrosine stain. No other treatment except individual oral hygiene instructions was provided. Subjects were asked to continue their oral hygiene procedures, including both brushing and inter-dental cleaning, in adherence to the given instructions. At the end of the study period (3 months), all clinical measurements were recorded again. Figure 1 shows the flow diagram illustrating the passage of participants through this clinical trial.

Laser treatment

A solid-state crystal Nd:YAG laser (Genius Periodontal A/S, Copenhagen, Denmark) was used as additional therapy in the randomly allocated quadrants after SRP (SRP1Nd:YAG). The details for settings of this water cooled Nd:YAG laser are shown in Table 1. The epithelium lining the inner pocket wall was dampened and the pocket was disinfected using the laser. The fibre tip was held with light pressure in contact with the tissue and parallelly aligned to the tooth. The “perio” setting of the laser was used adjusting power and cooling to allow a smooth instrumentation. The round flexible 0.6mm laser fibre (0.2826mm²) emerging from the handpiece tip (see Figure 2) was adjusted in length to correspond to the periodontal pocket probe charting. Small horizontal excursions of about 2mm along the gingival margin were made, penetrating no deeper into the pocket than the probing depth. The laser was applied for no longer than 60 seconds per site (The tooth was divided into four sites; mb, ml, db, dl). Remnants of gingival tissue were removed using a manual curette. All laser procedures were performed with protective eyewear on the patient, dentist and assistant. At the decision of the operator, the fibre tip was cleaned when visible debris was attached to ensure its optical properties. The used laser fibre tip

was cleaved and discarded. The laser fibre and handpiece were then cleaned. The handpiece was sterilized using an autoclave. Figure 2 shows the fibre tip and the headpiece tip. A mixture of air and water was sprayed over the fibre tip originating from the tip handle circumferential around the fibre.

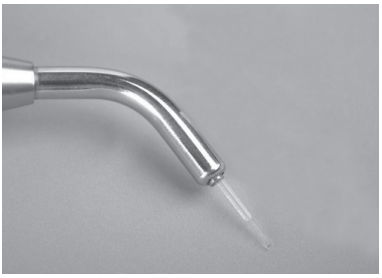
Table 1. Nd:YAG laser parameters and range in the "perio" setting

Wavelength	-	1064
Power*	range 1-12 Watt	6
Water*	range 1-12	5
Air*	range 1-12	5
Frequency	range 10-100 Hz	50
Pulse duration	range 100-800 µsec.	250
Pulse energy	range 400-800 mJ	400
Energy density	J/cm2	142**

* Display settings

** One has to understand that the energy density J/cm2. was calculated. However due to the uncertainty about the actual light-emitting surface and the total area of tissue irradiated one has to interpret this with caution.

Figure 2. Nd:YAG laser fiber tip emerging out of handpiece tip



Microbiological procedures

SAMPLING

The deepest inter-proximal site in each quadrant with BOPP was selected for microbiological sampling (Mombelli et al. 1991). In each quadrant, one pocket as sampled by means of two paper points. Next, samples were pooled for either the quadrants that received SRP alone or those that were treated by SRP1Nd:YAG. Selected sites were sampled at pre-instrumentation, immediately post-instrumentation and 3 months after initial treatment. Sites were subjected to careful removal of supragingival plaque deposits with a scaler. To avoid salivary

contamination, the selected area was isolated with cotton rolls and gently air-dried. Before bacterial sampling, a periodontal probe (PCPUNC 15mm probe, Hu-Friedy®) was inserted in the approximal pocket along the axis of the tooth until definite resistance was met. Two endodontic paper points (size 40#, Johnson & Johnson, Windsor, NJ, USA) were inserted for 10s each into the pocket along the probe, with care taken not to fold or to push them into another area (Rhemrev et al. 2006). The paper points from the selected sites were collected in 1.8ml of reduced transport fluid (RTF) (Syed & Loesche 1972).

CULTURE

Samples were cultured for microbiological analysis within 12h. Samples were vortexed for 30s and 10-fold serially diluted in RTF; 0.1ml of each dilution was plated on 5% horse blood agar plates (Oxoid No. 2, Basingstoke, UK) supplemented with haemin (5 mg/l) and menadione (1 mg/l) for determination of the total anaerobic bacterial counts and specific periodontal pathogens. Samples were subsequently plated on trypticase serum–bacitracin–vancomycin plates (TSBV) for isolation and counting of Aggregatibacter actinomycetemcomitans (Slots 1982). TSBV plates were incubated in air with 5% CO_2 at 37°C for 3 days; blood agar plates were incubated for 14 days at 37°C in 80% N2, 10% CO_2 and 10% H_2. Presence and proportions of the putative periodontal pathogens Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, Fusobacterium nucleatum, Parvimonas micra and Campylobacter recta were determined on the anaerobic blood agar plates (Van Winkelhoff et al. 1985). Identification of the selected bacterial species was based on Gram staining, cell and colony morphology, air tolerance, production of catalase and a number of biochemical reactions (Van Winkelhoff et al. 1986). A. actinomycetemcomitans was identified on the basis of its characteristic colony morphology (star-like inner structure), a positive catalase reaction with 3% hydrogen peroxide and a set of specific enzymes. Total colony-forming units (TCFUs) were estimated on the horse blood agar plates and expressed as the number of viable counts per millilitre of transport medium.

Questionnaire

Immediately after treatment, seven questionnaire forms were provided to each subject, one for immediate postoperative evaluation and one for each day of the following 6 days. Patients were asked to fill out the questionnaire at the end of each day. A visual analogue scale was used to assess patients' perception of pain, sensitivity discomfort, swelling and bleeding during and after treatment. This scale ranged from 0 to 10. Subjects marked a point on a 10-cm-long uncalibrated line with the negative extreme response (0) on the left end and the positive extreme response (10) at the right end. Additionally, the numbers of analgesic tablets taken were assessed.

Statistical analysis

Primary response variables were pocket depth and BOPP. For clinical measurements, a patient-level response variable was calculated for each parameter by computing the mean scores per patient at baseline and after therapy. The % of pockets ≥4mm was enumerated. Furthermore, for pocket probing measurements, an overall mean value of treated sites initially measuring ≥4mm was calculated. Parametric and nonparametric tests were performed where appropriate. Analyses were performed by "intention to treat". P values <0.05 were accepted as significant. For probingdepth reduction, the present design was able to discern a difference of 0.5 between therapies with a standard deviation of 0.7 and a power of ≥80%. Questionnaires were evaluated using either parametric tests comparing outcomes or VAS scales concerning the two treatments. The statistical analysis was performed by an investigator (NAMR), who was blinded to the randomization.

Results

Clinical findings

For the present study, 19 untreated periodontitis patients were enrolled from March 2006 to February 2007. In total, 11 males and eight females with a mean age of 45.3 (±8.67) years (range: 34–62 years) were selected. Ten of the subjects were smokers, three were former smokers and six had never smoked. The subjects were selected from those consulting the Clinic for Periodontology in Utrecht, the Netherlands for treatment of periodontal disease. All enrolled patients completed the 3-month study. At baseline, both contra-lateral quadrants (SRP+Nd:YAG versus SRP) were found to be balanced with respect to the clinical parameters.

The average SRP instrumentation time per quadrant was 33.89 (±5.16) min. The extra time needed for the adjunctive use of the laser was 8.47 (±4.38) min. per quadrant. Table 2 shows the means (SD) of all clinical parameters at baseline and end, comparing SRP+Nd:YAG laser versus SRP. After 3 months, all parameters were improved significantly compared with baseline for both regimens. No statistically significant differences for any of the investigated parameters were found at the baseline and the end-trial between the two treatment modalities. No adverse effects of laser treatment were observed or reported by the patients.

Figure 1. Flowchart depicting subject enrollment and measurements

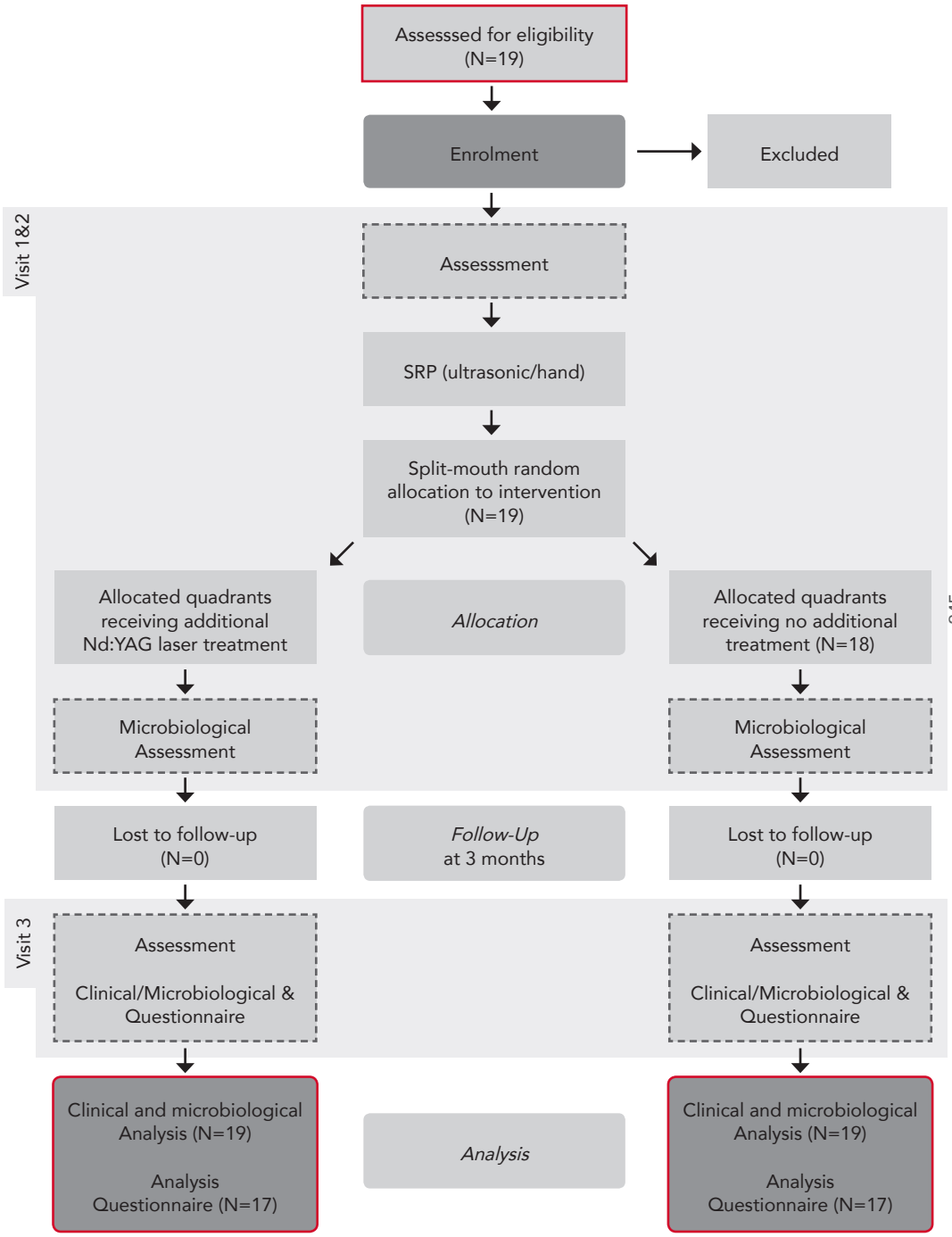


Table 2. Means (SD) of all clinical parameters during the study for both treatment modalities

All subjects (N=19)	SRP + Nd:YAG			SRP			T-test ‡ (P-value)	95% Confidence Interval
	Baseline	3 months	Difference	Baseline	3 months	Difference		
Plaque Index	1.40 (0.28)	1.06 (0.30)*	0.34 (0.33)	1.46 (0.26)	1.12 (0.26)*	0.34 (0.28)	0.947	(-0.12 ; 0.11)
BOPP	1.57 (0.31)	0.81 (0.26)*	0.76 (0.25)	1.58 (0.29)	0.87 (0.26)*	0.71 (0.25)	0.435	(-0.09 ; 0.19)
PD	4.19 (0.69)	3.54 (0.49)**	0.65 (0.43)	4.14 (0.58)	3.52 (0.43)**	0.62 (0.33)	0.617	(-0.09 ; 0.16)
PD of sites ≥4mm	5.23 (0.63)	4.83 (0.39)**	0.40 (0.42)	5.22 (0.57)	4.68 (0.29)**	0.54 (0.40)	0.138	(-0.32 ; 0.05)
% sites PD ≥4mm	28.02 (9.23)	18.68 (9.22)	9.34 (5.21)	28.27 (8.02)	19.67 (7.95)	8.60 (4.46)	0.450	(-2.73 ; 1.26)

* Significantly different from baseline (P<0.05, Wilcoxon's test)

** Significantly different from baseline (P<0.05, Paired t-test)

‡ T-test comparing incremental change from baseline – end for each treatment modality

Microbiological findings

The results of the effects of instrumentation on the total anaerobic counts of the subgingival microflora during the study are presented in Table 3. The mean total anaerobic counts from the selected sites, determined by culture, were not statistically different at any time between the two treatment modalities (Paired T-test). Immediately after instrumentation, both SRP+Nd:YAG and SRP selected sites showed significantly reduced TCFUs at 0.09 x 106 and 0.44 x 106/ml, respectively. However, at 3 months post-treatment, the mean TCFUs of the SRP+Nd:YAG and SRP selected sites had increased to27.59 x 106/ml and 44.93 x 106/ml, respectively. The mean TCFUs 3 month post-treatment was not significantly different compared with pre-instrumentation for both treatment modalities.

Table 3. Mean total CFU/ml (106 ±SD) during the study for both treatment modalities

N=19	SRP+Nd:YAG	SRP	T-test (P-value)	95% Confidence Interval
Pre-instrumentation	59.18 (81.89)	54.03 (83.63)	0.631	(-27.27 ; 16.89)
Immediately post-instrumentation	0.09 (0.34)*	0.44 (1.37)*	0.287	(-0.33 ; 1.05)
3 months post-instrumentation	27.59 (52.15)	44.93 (123.77)	0.576	(-46.56 ; 81.24)

* significantly different from pre-instrumentation (P<0.05, Paired T-test)

Table 4 presents all subjects found to be positive for each of the analysed species, namely A. actinomycetemcomitans, P. gingivalis, P. intermedia, T. forsythia, F. nucleatum and C. recta, at pre-instrumentation, immediately post-instrumentation and at 3 months post-instrumentation. Immediately after instrumentation, all species showed a -decreased prevalence. At 3 months post-instrumentation, there was a noticeable tendency towards relapse to baseline for P. micra and F. nucleatum. The presence of A. actinomycetemcomitans in the SRP+Nd:YAG group was no longer detected in culture immediately post-instrumentation or at the 3-month visit.

Table 4. Prevalence among subject of specific periodontal bacteria during the study for both treatment modalities

N=19	Time of sampling	Periodontal bacteria						
		Aa	Pg	Pi	Tf	Pm	Fn	Cr
SRP + Nd:YAG	Pre-instrumentation	1	5	10	16	14	17	1
	Immediately post-instrumentation	-	3	3	4	8	7	1
	3 months post-instrumentation	-	1	6	10	16	17	-
SRP	Pre-instrumentation	-	8	7	19	18	17	2
	Immediately post-instrumentation	-	4	4	5	6	5	-
	3 months post-instrumentation	-	4	3	7	15	16	2

Questionnaires

Table 5a shows the questions and suggestions related to the two extremes. Table 5b shows the results of the questionnaire. Only 17 subjects returned the questionnaires. Repeated measure analysis between both treatment modalities showed only a significant difference for post-operative pain in favour of SRP. Post-operative experience of pain was more pronounced in the first 3 days for the SRP+Nd:YAG group. Table 6 shows the mean number of analgesics used by patients in each group per day. In the course of the day following treatment, the SRP+Nd:YAG group used 3 x more analgesics than the SRP group. No analgesics were used following either treatment after day 2.

Table 5a. Questions used in the questionnaire with extremes from the VAS score

Paraphrase	Complete question	With extremes	
		From (0)	To (10)
Bleeding	Did you experience any bleeding at the treated sites today?	"no" bleeding	"very much" bleeding
Swelling	Did you experience any swelling in the mouth today?	"no" swelling	"very much" swelling
Post-op pain	Did you experience any post-operative pain in the mouth today?	"no" pain	"very much" pain
Sensitivity	Did you experience any post-operative experience of sensitivity to warm/cold today?	"no" sensitivity	"very much" sensitivity

Table 5b. Mean (SD) VAS score response (0.0–10.0) to the questionnaire presented by regimen

(N=17)	Day	0	1	2	3	4	5	6	RMA P-value
Bleeding	SRP+Nd:YAG	4.21 (3.49)	2.88 (2.88)	2.05 (2.32)	1.45 (1.57)	1.06 (1.38)	0.81 (1.55)	0.58 (1.13)	
	SRP	2.98 (2.69)	2.10 (2.42)	1.08 (1.78)	1.05 (1.84)	0.72 (1.08)	0.32 (0.50)	0.30 (0.45)	0.221
	P-value♦	0.166	0.327	0.116	0.400	0.323	0.105	0.197	
Swelling	SRP+Nd:YAG	3.76 (2.97)	3.05 (2.80)	2.09 (2.02)	1.14 (1.30)	1.20 (1.90)	0.93 (1.82)	0.84 (1.71)	
	SRP	2.01 (2.12)	1.15 (1.66)	0.61 (1.37)	0.84 (1.55)	0.56 (1.21)	0.48 (1.17)	0.33 (0.70)	0.060
	P-value♦	0.003	0.016	0.009	0.551	0.293	0.364	0.210	
Post-op pain	SRP+Nd:YAG	5.89 (2.64)	3.66 (2.95)	2.44 (2.73)	2.71 (2.89)	1.66 (1.79)	1.08 (1.66)	1.05 (1.45)	
	SRP	4.63 (2.96)	1.72 (1.92)	1.04 (1.56)	1.03 (1.53)	0.85 (1.29)	0.67 (1.23)	0.55 (1.19)	0.033
	P-value♦	0.017	0.008	0.066	0.043	0.178	0.313	0.106	
Sensitivity	SRP+Nd:YAG	4.38 (3.77)	3.49 (3.55)	2.26 (2.97)	2.01 (2.95)	1.92 (2.95)	1.95 (3.24)	2.05 (3.16)	
	SRP	3.07 (2.90)	2.12 (2.75)	2.36 (3.00)	1.86 (2.80)	1.65 (2.59)	1.71 (2.52)	1.01 (1.50)	0.588
	P-value♦	0.060	0.029	0.782	0.756	0.502	0.482	0.145	

RMA repeated measure analysis
♦ paired T-test

Table 6. Number of analgesic tablets taken following each treatment

Day	0		1		2	
N=17	# Subjects	# Tablets	# Subjects	# Tablets	# Subjects	# Tablets
SRP + Nd:YAG	12	27	3	5	1	1
SRP	5	9	1	1	1	1

Discussion

The purpose of this study was to test whether use of an Nd:YAG laser with water and air coolant after SRP results in a greater clinical improvement than SRP alone. The appointment protocol suggested by Raffetto (2004) was used, where the tooth and root surfaces were debrided first, followed by laser bacterialreduction and dampening/coagulation of the epithelial tissue. The results clearly show that both SRP and SRP+Nd:YAG treatment resulted in a decrease of all clinical parameters tested. However, the difference between responses to SRP and responses to SRP+Nd:YAG was small and not statistically significant after 3 months.These results are in support of a recent systematic review, which concluded thatthere is limited evidence to support the adjunctive use of a pulsed Nd:YAG laser as compared with conventional therapy alone (SRP, ultrasonics and/or hand instrumentation) in the initial treatment of patients with periodontitis (Slot et al. 2009). Schwarz et al. (2008) in their review also concluded that there is insufficient evidence to support the clinical application of the Nd:YAG laser. The present results now add to the evidence that the Nd:YAG has no adjunctive effect over SRP alone in initial periodontal treatment. This is also supported by the clinical and microbiological outcome of two other recent studies (Gómez et al. 2010, Jensen et al. 2010). The results of two papers describing short-term and long-term effects within the same patient population are, however, in conflict with this conclusion (Qadri et al. 2010, Qadri et al. 2011). The reason for this discrepancy is unclear. It might be attributable to differences in laser settings. Which in the Qadri et al. (2010/2011) studies were lower and set at 4W. Their study was also restricted to mandibular teeth. Furthermore, it is striking that only in the test sites a reduction in plaque scores was observed whereas in control sites no such effect was found. This may have impacted clinical outcomes such as PPD reduction. In the present study, this was not the case where the improvement in plaque control was similar for both treatment modalities.

There was no external control of laser parameters during the treatments within the present experiment design. Because this infrared radiation as well as the effects of laser tissue interactions are not visible, this implies that there was no control in order to ensure the correct working of the tested system. However, before the laser system was set-up for this study, it was serviced and tested to ensure that it worked according to the manufacturers specifications.

The “classical” Nd:YAG laser parameters used in periodontology are between 0.5 and 3W (Ishikawa & Sculean 2007, Slot et al. 2009). The present study used a substantially higher level of 6W (Table 1). In order to limit side effects with this higher power parameter the last provided an air–water coolant simultaneously with laser

activation, which was directed over the tip. A substantial amount of the surface heat, generated by a laser, was therefore dissipated (Spencer et al. 1996).

Generally, subgingival debridement in combination with oral hygiene instruction by itself is an effective treatment modality (Badersten et al. 1981, 1984a/b, Pihlstrom et al. 1981). When an effective treatment modality is used as a golden standard of comparison, it may be difficult to show any adjunctive effect in addition to the original treatment, as was the case with the Nd:YAG laser in the present study (Timmerman et al. 1996). The majority of the treated patients were (former) smokers. This may have had an impact on the clinical outcome. Although this was a split mouth model, this risk factor may cause an underestimation of the magnitude of a potential clinical effect comparing test and control sites (Preber & Bergström 1986). On the other hand, because smoking is a risk factor, and many periodontal patients are (former) smokers (Van der Weijden et al. 2001), the outcomes of this study are applicable to periodontal practice.

Results of microbiological studies are highly dependent on the sampling procedure used. It has been shown that the composition of the microflora may change relative to the distance from the gingival margin (Listgarten 1976, Slots et al. 1979, Magnusson et al. 1984). Treatment causes periodontal tissues to tighten around the teeth (Beardmore 1963). As a consequence, it is more difficult to introduce a paper point to the bottom of a pocket at re-evaluation. To avoid sampling problems, a standardized sampling technique, described by Rhemrev et al. (2006), was used.

Relatively few studies have investigated the microbiological effect of subgingival scaling and root planing directly after completion of the procedure. This aspect was recently investigated by Rhemrev et al. (2006). They observed that mechanical cleaning itself has a limited effect in actually removing bacteria. In agreement with Rhemrev, the present "in vivo" effect does not support the "in vitro" effect as found previously by Kranendonk et al. (2010) where after 15s of laser use total killing of perio pathogens was observed. In the present study, a significant reduction in CFU's was observed between pre- and immediately post treatment. However, no difference in effect between SRP+Nd:YAG and SRP was established. Furthermore, at 3 months post-instrumentation, TCFUs values were not different between treatment and not different from baseline. This result is in agreement with previous studies, which have shown that re-colonization of the subgingival area by microorganisms may occur within 2–8 weeks of treatment (Mousques et al. 1980, Magnusson et al. 1984, Van Winkelhoff et al. 1988, Wade et al. 1992).

Results of the present study show that immediately post-instrumentation, there was a trend towards reduced prevalence of P. gingivalis as compared with pre-instrumentation, whereas Rhemrev et al. (2006) found that all patients positive for P. gingivalis remained culture positive immediately post-instrumentation. Three months post-instrumentation in the present study, a trend towards reduced prevalence of P. gingivalis, P. intermedia and T. forsythia was seen. Rhemrev et al. (2006) had already observed this shift in the composition of microflora at 2 weeks post-instrumentation. It seems feasible to suppose that such a shift lasts for at least 3 months after treatment, a finding in line with the observed clinical improvement in periodontal condition.

In each quadrant, one sample was taken using two paper points, and samples were pooled for either the quadrants that received SRP alone or those that were treated by means of SRP1Nd:YAG. Mombelli et al. (1991) evaluated the feasibility of detecting microorganisms using selected sites in order to indicate increased proportions in periodontitis patients. It was concluded that in some periodontitis patients, the outcome of a test depends greatly upon the number of samples taken and the strategy of site selection. Selection of the deepest pocket in each quadrant was the most efficient method of sampling. In the present study, samples were taken from the deepest pocket in each quadrant for the SRP+Nd:YAG and SRP sites. Whether a pooled sample of two sites is sufficient for assessment of the actual presence of a given microorganism remains a matter of discussion.

Following initial periodontal treatment using hand and ultrasonic instruments with or without the additional use of an Nd:YAG laser, a patient may experience some degree of pain and swelling in addition to post-operative sensitivity to warm and cold temperatures. Harris et al. (2004) performed a retrospective analysis of patients receiving laser sulcular debridement. The four clinicians reported anecdotally that patients seemed to experience less pain and discomfort and recover more rapidly when the laser was included in the treatment protocol than when it was excluded. It is theorized that this pain reduction may be due to the protein coagulum, which is formed on the wound surface and may act as a biological dressing. These anecdotal remarks have not, however, been scientifically validated (Rossmann 2002). In the present study, the post-operative pain as appears from the questionnaire was more pronounced in the SRP+Nd:YAG group. However, it should be emphasized that the patients were not masked with respect to the modality of treatment. This may have affected patients' judgements regarding the novel instrument. On the other hand, on day one the SRP+Nd:YAG group also used more analgesics, which corresponds with the complaint of post-operative pain.

Conclusion

The results of the present study indicate that SRP, with or without the adjunctive use of an Nd:YAG laser, result in a lowered subgingival bacterial load immediately post-instrumentation. In addition, the primary clinical parameters (BOPP, PPD) comparing baseline and end following both treatment modalities showed an improvement. However, at the 3-month evaluation, no additional clinical or microbiological advantage could be established for the water cooled Nd:YAG laser.

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Conflict of interest and source of funding statement

The authors declare that they have no conflict of interest.
This study was self-funded by the Clinic for Periodontology Utrecht, The Netherlands.

Clinical Relevance

SCIENTIFIC RATIONALE FOR THE STUDY

The Nd:YAG laser is capable of removing pocket lining epithelium and has a bactericidal effect, suppressing and eradicating putative periodontal pathogens from periodontal pockets. Investigators have proposed the use of the Nd:YAG laser as an adjunct to ultrasonic scaling and root planing. The cooled Nd:YAG laser allows for higher energy setting without adverse effects and has recently been shown to be effective in bacterial killing.

PRINCIPAL FINDINGS

Results of the present study indicate that subgingival mechanical SRP, especially with the adjunctive use of an Nd:YAG laser, has the effect of lowering the total bacterial load immediately post instrumentation. However, clinical improvement of periodontal status was found to be comparable with or without the adjunctive use of an Nd:YAG laser after initial treatment by SRP.

PRACTICAL IMPLICATIONS

The results of this study are applicable to patients diagnosed with moderate-to-severe periodontitis who are willing to undergo treatment by a specialist. Because clinical results are not improved by adding laser treatment to conventional "non-surgical" periodontal therapy, the use of the Nd:YAG laser as an adjunct to debridement should be questioned.

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11.

Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

Marie Curie

ADJUNCTIVE CLINICAL EFFECT OF A WATER-COOLED ND:YAG LASER IN A PERIODONTAL MAINTENANCE CARE PROGRAMME: A RANDOMIZED CONTROLLED TRIAL

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Introduction

Laser therapy has bactericidal and detoxification effects, and it can remove epithelial lining, granulation tissue, plaque and calculus within the periodontal pocket with low mechanical stress and without leaving a smear layer on root surfaces (Claffey& Polyzois 2008). These effects may potentially improve healing. Among dentists and dental hygienists in the Netherlands, a Nd:YAG laser with water and air coolant is often used as an adjunct to the non-surgical treatment of periodontitis, as suggested by Lioubavina-Hack (2002). In a recent "in vitro" study, this particular Nd:YAG laser has been shown to have a bactericidal effect (Kranendonk et al. 2010). A recent "in vivo" study (Slot et al. 2011) investigated the effect of the watercooled Nd:YAG laser when used for initial periodontal treatment as an adjunct to supragingival and subgingival debridement by scaling and root planing (SRP). Immediately after instrumentation, the total number of colony-forming units (CFU) was significantly reduced compared to the pre-instrumentation baseline for both groups, regardless of the treatment regimen. After 3 months, no added clinical effect was achieved with the additional use of the Nd: YAG laser over SRP alone.

Periodontal stability in the dentition is reflected by a minimal number of residual pockets following the initial periodontal therapy. Periodic monitoring of the periodontal status and appropriate maintenance procedures should be part of a long-term treatment plan in the management of chronic periodontitis (Hancock 1996). In-office periodontal maintenance at 3- to 4-month intervals can be effective in maintaining periodontal stability in most patients (Ramfjord 1993, AAP 1997). The presence of high numbers of residual pockets has been associated with the risk of disease progression (Badersten et al. 1990, Claffey et al. 1990). Lang et al. (1990) suggested that individuals with residual pockets (≥5mm) may be regarded as having a risk for recurrent disease. Therefore, during periodontal maintenance visits, pockets with a probing depth ≥5mm are carefully instrumented (SRP) to remove subgingival biofilm. Under maintenance conditions, it may hypothesized that the bactericidal benefit of the Nd:YAG laser may offer an adjunctive clinical benefit. At present, the adjunctive effect of this water-cooled Nd:YAG laser during periodontal maintenance care is unknown. Therefore, the aim of the this study was to test whether the use of a water-cooled Nd:YAG laser in pockets ≥5mm during a supportive periodontal maintenance care programme (PMC) as an adjunct to hand and ultrasonic instruments would result in greater clinical improvement than obtained with SRP alone.

Material and Methods

Ethical aspects

The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam (MEC# 02/270). All voluntary participants were informed of the outline, purpose and duration of the study and signed an informed consent form. Allocation concealment was achieved by providing the treatment assignment in sequentially numbered opaque sealed envelopes (SNOSE). This study was conducted in accordance with the CONSORT guidelines (Schulz et al. 2010, available at: http://www.consort-statement.org/consort-statement/overview0/).

Study population

For this study, all participants had been referred previously by their general dentists to a clinic specializing in periodontal therapy (Clinic for Periodontology, Utrecht). The final enrolment decision was determined by an experienced periodontist during regular follow-up visits after the patients had been actively involved in a regular supportive PMC for >1 year and had visited a dental hygienist at least once every 4 months. PMC included the reinforcement of oral hygiene instructions based on individual needs regarding optimal plaque control.

The following inclusion criteria were used:

- ≥30 years of age.
- Systemically healthy (not pregnant).
- A minimum of three natural teeth in every quadrant.
- Regarding the clinical diagnosis before active periodontal treatment, moderate-to-severe generalized periodontitis characterized by:
    - presence of ≥1 site per quadrant with a probing pocket depth (PPD) of >6mm and interproximal attachment loss of ≥3mm.
    - presence of bleeding on pocket probing (BOPP).
    - radiographic evidence of alveolar bone loss.
- The following clinical characteristics at the start of the study:
    - presence of ≥2 sites per quadrant with a PPD of ≥5mm and inter-proximal attachment loss of ≥2mm.
    - presence of BOPP.
    - radiographic evidence of alveolar bone loss.

The exclusion criteria were (acute) oral lesions, necrotizing ulcerative periodontitis, antibiotic use for any purpose within 6 months prior to entering the study and orthodontic braces.

Clinical assessments

The following measurements were performed prior to the PMC appointment and after a 6-month evaluation period:

- PPD determined using a manual probe (PQW 10-mm probe with Williams calibration; Hu-Friedy® Hu-Friedy Inc., Leimen, Germany).
- Recession (REC) distance from the marginal gingiva to the cemento–enamel junction.
- BOPP (Van der Velden 1979).

All clinical measurements were obtained at six sites (mesio–buccal, buccal, disto–buccal, mesio–lingual, lingual and disto–lingual) around each tooth and were rounded to the nearest millimeter. All clinical measurements were performed by a calibrated examiner and experienced periodontist who was blinded to the treatment regimen. Access to previous assessment data was not allowed during the course of the study.

Clinical procedure

This study was an examiner-blind, randomized, and controlled 6-month clinical trial using a split-mouth design. After the eligibility to enter the study was established, the patients were scheduled for their first appointment. A medical-history form that included smoking habits and smoking history was completed. An experienced dental hygienist performed all treatments. All residual pockets ≥5mm were supragingivally and subgingivally (SRP) debrided using a piezoelectric ultrasonic unit (Piezon Master; EMS, Nyon, Switzerland) at a moderate setting using appropriate tips. In addition, where deemed appropriate by the dental professional, hand instruments were used (Hu-Friedy®).

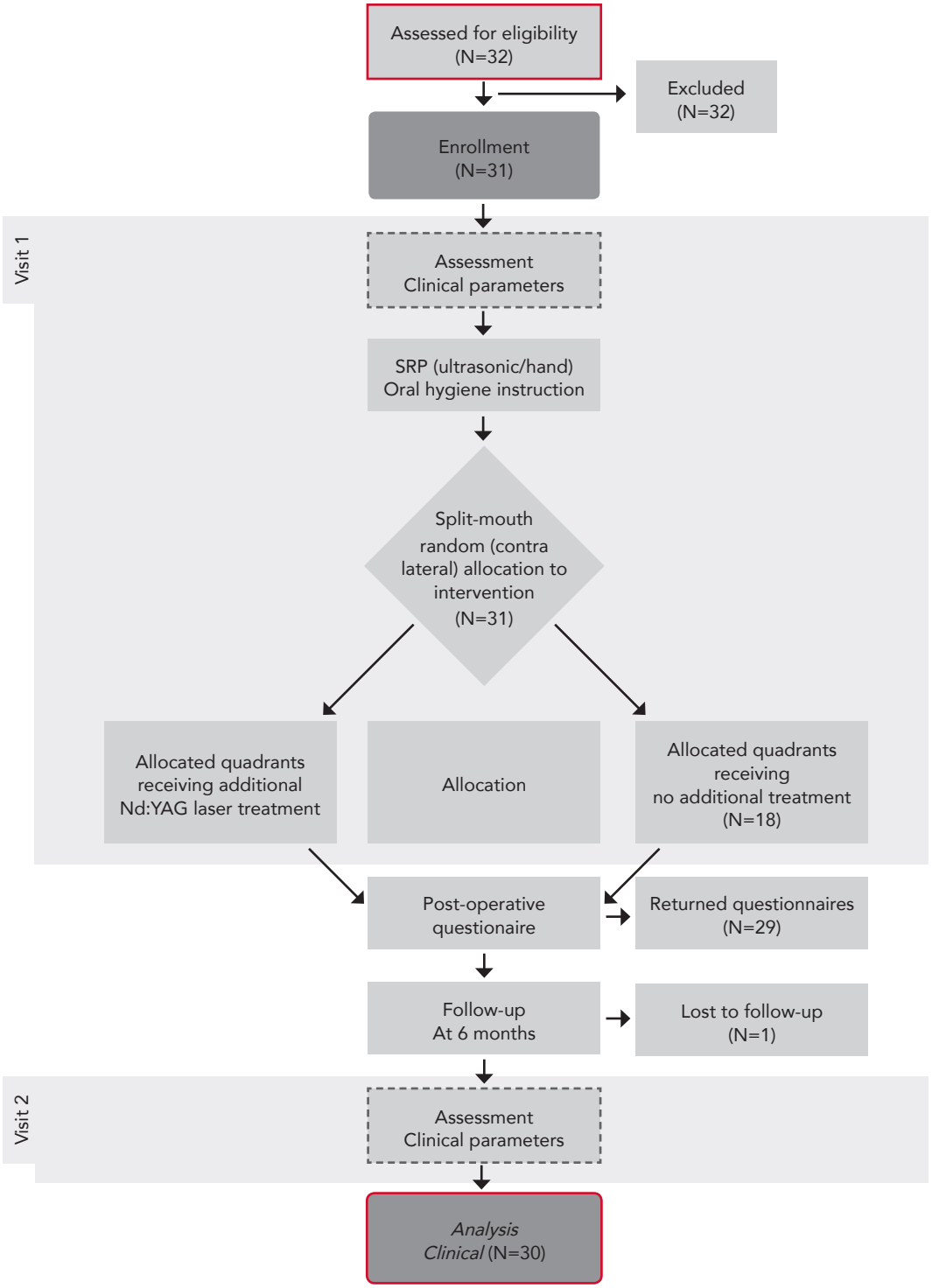
After the completion of SRP, additional laser treatment assignments were revealed to the dental hygienist in an envelope (SNOSE). Immediately thereafter, depending on the randomization, all residual pockets with a depth of ≥5mm among the two randomly assigned contra-lateral quadrants were additionally treated with the Nd:YAG laser. The opposing contra-lateral quadrants received no additional treatment. Randomization was based on a predetermined computer-generated set of random numbers that was obtained via www.random.org.

For additional laser therapy, a solid-state crystal Nd:YAG laser (Genius Periodontal A/S, Copenhagen, Denmark) was used in the randomly allocated quadrants (SRP +Nd:YAG). Before the laser system was set up for this study, the system was serviced and tested to ensure that it worked according to the manufacturer's specifications. The details for the settings of this water-cooled Nd:YAG laser are presented in

Slot et al. (2011). The fibre tip was held with light pressure in contact with the tissue and aligned parallel to the tooth. The "perio" setting of the laser was used to adjust the power and cooling to enable smooth instrumentation. The length of the round flexible 0.6-mm laser fibre (0.2826mm^2) emerging from the handpiece tip was adjusted to correspond to the periodontal pocket probe measurements. Small horizontal excursions were made approximately ±2mm along the gingival margin that penetrated no deeper into the pocket than the probing depth. The laser was applied for no more than 60 seconds per site. Remnants of gingival tissue were removed using a manual curette. All laser procedures were performed with protective eyewear for both the patient and dental hygienist. When debris was visible, the fibre tip was cleaned at the discretion of the operator to maintain its optical properties.

Following instrumentation, all supragingival surfaces were polished In addition, all patients received personalized instruction in oral hygiene procedures, including brushing and inter-dental cleaning. After treatment, the subjects were requested to rinse for 2 weeks, twice daily for 30 seconds, with 15ml of a mouthwash containing 0.12% chlorhexidine (Perio-aid®; Dentaid, Houten, The Netherlands). No other treatment was provided until the next appointment. Six months after this visit, which represented the end of the study period, all clinical measurements were recorded again. Figure 1 presents a flow diagram that represents the passage of the patients throughout this clinical trial.

Figure 1. Flowchart depicting subject enrollment and assessments



Questionnaire

After the treatment, a questionnaire was provided to each subject for postoperative evaluation as a secondary outcome measurement (Table 1). The patients were asked to complete the questionnaires at home at the end of the same day to evaluate their perception of pain, swelling and bleeding after treatment. The patients were asked to indicate the specific quadrants of the mouth where the aforementioned outcomes were observed. In addition, the patients were asked to report the number of analgesic tablets taken. Subjects were asked to return the questionnaire the next day by mail.

Table 1. Questions used for the post-operative questionnaire

Paraphrase	Complete question
Bleeding	Did you experience any bleeding in the treated sites today?
Swelling	Did you experience any swelling in the mouth today?
Post-op pain	Did you experience any post-operative pain in the mouth today?
Analgesics	Did you use any analgesics for pain in the treated sites today?

Power and statistical analysis

Probing pocket depth and BOPP were the primary response variables. For PPD reduction, the present design was able to discern a difference (δ) of 0.5mm between therapies with a standard deviation of 0.7 (as derived from Slot et al. 2011), given a Type I error of $\alpha=0.05$ and a power of ≥80%. For the clinical measurements, a patient-level response variable was calculated for each parameter by separately computing the mean scores per patient at baseline and at the end of the trial for each intervention. The statistical analysis was performed by DES & MFT both of whom were blinded to the randomization. The percentage of pockets with a depth of ≥5mm was enumerated. Furthermore, for the PPD measurements, an overall mean value was calculated for the treated sites initially measuring ≥5mm. Statistical testing for normality with respect to the distribution of the outcome of clinical parameters was performed using the Kolmogorov–Smirnov test. Multivariate analysis was conducted to determine the effect of smoking on treatment outcomes. The periodontal inflamed surface area (PISA) score was also calculated after the PPD data and the incidence of BOPP were entered into a PISA spreadsheet that was publically available from www.parsprototo.info (Nesse et al. 2008). Parametric and non-parametric tests were performed where appropriate with an "intention to treat" approach. $P<0.05$ was defined as significant. The questionnaires were evaluated using non-parametric chi-square tests to compare the outcomes of the two treatment regimens.

Results

Clinical findings

In total, 32 (14♂, 18♀) chronic periodontitis patients enrolled for more than 1 year in PMC were included. One subject failed to appear at the first appointment before the start of the study, whereas another subject was excluded after failing to attend the final assessment because of scheduling conflicts (Figure 1). In total, 13 men and 17 women with a mean age of 48.7 (±11.3) years (range: 39–65 years) completed the study. All enrolled patients completed the study with a mean follow-up time of 6 months. No serious adverse effects of the laser treatment were observed or reported by the patients.

All clinical parameters were normally distributed. Post-hoc analysis revealed that the present study (N=30) was sufficiently powered (β=1.0) to discern a difference of 0.5mm ($P<0.05$) with an average SD of 0.52. At baseline, both sets of contra-lateral quadrants (SRP+Nd:YAG versus SRP) were found to be balanced with respect to the clinical parameters (PPD, BOPP, REC) (Table 2). After 6 months, all of the parameters had significantly improved compared to the baseline for both regimens. No statistically significant differences for the investigated parameters were found at any time between the two treatment modalities. The only significant difference ($P=0.009$) was observed between the groups that manifested as an increase in the number of sites with visible gingival recession relative to the cemento–enamel junction. For the laser-treated quadrants, the number of sites increased by 0.7, whereas in the control quadrants, the number of sites decreased by 0.05. Twelve of the subjects were smokers and had been smoking for up to 40 years with a calculated burden of 42 pack-years. Eighteen of the subjects were non-smokers, among whom 11 were former smokers and quit 1–17 years earlier. An additional seven patients had never smoked. A sub analysis of the impact of smoking on treatment outcome revealed no significant differences with regard to the treatment used.

Table 2. Means (SD) and analyses of all clinical parameters during the study for both treatment modalities for sites with a baseline pocket depth ≥5mm

	SRP+Nd:YAG			SRP				
N=30	Baseline	End	Difference	Baseline	End	Difference	P-value*	95% CI
Mean PPD >5mm	5.39 (0.32)	4.42 (0.60)	-0.97 (0.58)	5.46 (0.36)	4.61 (0.53)	-0.85 (0.45)	0.245	[-0.10; 0.35]
# sites PPD >5mm	11.2 (5.0)	5.6 (3.7)	-5.6 (3.5)	10.6 (5.5)	5.7 (3.6)	-4.9 (3.3)	0.373	[-0.9; 2.2]
Mean BOPP >5mm PPD	0.51 (0.27)	0.49 (0.31)	-0.20 (0.21)	0.51 (0.23)	0.43 (0.25)	-0.07 (0.24)	0.347	[-0.13; 0.04]
Mean REC	0.94 (0.98)	1.00 (0.97)	+0.08 (0.32)	0.81 (0.67)	0.79 (0.79)	-0.02 (0.38)	0.203	[-0.06; 0.25]
# sites REC	5.0 (4.5)	5.7 (5.2)	+0.7 (1.6)	4.8 (3.9)	4.7 (3.9)	-0.05 (1.8)	0.009	[-2.2; -0.2]

* Statistical comparison of the incremental change (difference) between groups (Wilcoxon test)
PPD, probing pocket depth; REC, recession; SRP, scaling and root planing

A similar pattern was observed for the PISA score (Table 3). The intragroup changes were significant, whereas the inter-group comparison failed to show any significant differences between the baseline and the completion of the trial (P=0.210). The mean reduction in the PISA score in the laser-treated quadrants was 12.72mm^2, whereas the equivalent in the control group was 16.90mm^2.

Table 3. Mean (SD) periodontal inflamed surface area (PISA) scores before treatment (base) and at follow-up (end) for both treatment modalities

	SRP+Nd:YAG			SRP			
N=30	Baseline***	End	Difference	Baseline***	End	Difference	P-value*
PISA mm^2	50.40 (49.57)	37.68 (44.29)	12.72 (28.25)	45.03 (37.97)	28.13 (24.46)	16.90 (24.56)	0.210
Within Group**	P=0.009			P=0.001			

* between-group differences (Wilcoxon test)
** baseline-end within group comparisons (Wilcoxon test)
*** baseline comparison between groups. not significant (Wilcoxon test)

Questionnaires

Table 4 shows the answers to questionnaires that were completed by 29 subjects. When post-operative bleeding, swelling or pain was reported on the day of treatment, it was more frequently observed in the quadrants receiving adjunctive laser therapy (P≤0.01). In total, only four patients reported the use of analgesics for continued pain arising from the provided treatment.

Table 4. Results from the post-operative questionnaire

N=29 Paraphrase	N (%) of patients who reported post-operative complaints	# of quadrants associated with post-operative complaints		
		SRP+Nd:YAG	SRP	P-value◊
Bleeding	13 (45%)	14	4	0.010
Swelling	14 (48%)	17	3	0.001
Post-operative pain	24 (83%)	28	11	0.001

◊ Chi-square test

Discussion

The collective evidence gathered in systematic reviews suggests that the effect of the Nd:YAG laser for the treatment of chronic periodontitis may be comparable to SRP with regard to the reduction of subgingival microflora (Cobb 2006, Schwarz et al. 2008) and also with parameters associated with periodontal inflammation (Slot et al. 2009, Cobb et al. 2010). The AAP stated in their Statement on the Efficacy of Lasers in the Non-Surgical Treatment of Inflammatory Periodontal Disease that there is minimal evidence to support use of a laser for the purpose of subgingival debridement, either as a monotherapy or adjunctive to SRP (AAP 2011). This study evaluated the adjunctive effect of treatment with a water-cooled Nd:YAG laser during periodontal maintenance in the clinical setting. However, no adjunctive effect was observed. Thus, based on the present clinical results and those of a previous study (Slot et al. 2011), the water-cooled Nd: YAG laser appears to have no adjunctive beneficial role in subgingival debridement, either during the initial periodontal treatment or during supportive periodontal maintenance care. With respect to the use of other laser types as a non-surgical but supportive periodontal maintenance therapy, recent results from a cohort study (Krohn-Dale et al. 2012) and a multicentre study (Ratka-Krüger et al. 2012) indicate that the Er:YAG (used as a monotherapy during supportive periodontal care) provides clinical and microbiological outcomes similar to those of a traditional (ultrasonic) sonic scaler. The effect of an Nd:YAG laser in supportive periodontal maintenance therapy as monotherapy still needs to be established.

Periodontal inflamed surface area has been proposed as a classification system for periodontitis that quantifies the amount of inflamed periodontal tissue and, as such, indicates the systemic inflammatory burden. PISA probably quantifies the amount of inflamed periodontal tissue for each individual patient more accurately than any other classification technique currently in use (Nesse et al. 2008). The PISA scores support the finding that the Nd:YAG laser does not provide an adjunctive treatment effect over mechanical periodontal therapy.

The increase in number of sites with recession appears to be a potentially adverse effect that does not justify the use of Nd:YAG laser on a routine basis. Among the collective evidence concerning the use of Nd:YAG during non-surgical periodontal therapy (Cobb et al. 2010, Schwarz et al. 2008, Slot et al. 2009), only one systematic review (Slot et al. 2009) reported on gingival recession. From their comprehensive search, only one article was retrieved (de Andrade 2008) that reported on recession in both study groups (i.e., SRP with or without additional Nd:YAG treatment). An increase was observed in the distance of the gingival margin to the cemento–enamel

junction, although statistically significant differences were not observed between the groups. This observation is in line with the present results, where the mean change in recession failed to show differences between the groups. Gingival recession was only assessed in case the gingival margin was located apical to the cemento–enamel junction. As such, no recession was measured when the gingival margin was located coronal to the cemento–enamel junction, which may result in the underestimation of the effect of the laser on gingival recession in the SRP+Nd:YAG-treated quadrants and may have negatively influenced the total clinical attachment loss.

Following the initial periodontal treatment using hand and ultrasonic instruments with or without the additional use of the Nd:YAG laser, a patient may experience a degree of pain and swelling in addition to postoperative sensitivity to high and low temperatures. In a previous study (Slot et al. 2011), post-operative pain determined using a questionnaire was more pronounced in the SRP+Nd:YAG group. Similar observations were evident from this study, where the Nd:YAG-treated quadrants presented with significantly more bleeding, swelling and post-operative pain. Moreover, regarding patient perception, the post-operative experience of bleeding, swelling and pain was more pronounced in those quadrants additionally treated with Nd:YAG laser. Patient comfort and acceptance of dental treatment is not a commonly researched topic in dentistry; however, one study assessed this issue for orthodontic removable retainers (Wong & Freer 2005) and observed a strong relationship between comfort level and compliance. Consequently, it may be assumed that using Nd:YAG laser as an adjunct for periodontal therapy, either during the initial periodontal treatment or maintenance care, may result in patient abstinence from further clinical treatment. Contrary results with the Er:YAG laser show that during supportive periodontal treatment, painful sensations can be reduced as compared to sonic scaler instrumentation (Braun et al. 2010).

Limitations

- The Nd:YAG treatment alone is not evaluated in this study. Monotherapy could hypothetically result in a similar effect as PMC, based on recent work done with the Er:YAG laser (Krohn- Dale et al. 2012, Ratka-Krüger et al. 2012).
- The selected subjects were clients of a private periodontal clinic who, after the completion of active periodontal treatment, were treated in a PMC. Periodontal clinics and their staff are trained to treat and motivate patients with periodontitis and realize a high level of periodontal stability in general (Costa et al. 2012). The present results can therefore be generalized to practices and dental-care professionals with periodontitis patients who are motivated to undergo regular periodontal maintenance care.
- The laser system that was used was serviced and tested before the start of the

experiment. However, there was no external control of the laser parameters during treatment within the present experimental design because the infrared radiation and the effects of the laser–tissue interactions were not visible, which implies that there was no control that ensured the effective performance of the tested system.
- The patients were not blinded with respect to treatment modality, which may have affected the patient assessment of the novel instrument

Conclusion

No significant differences between laser-supported SRP and regular SRP were observed for any of the clinical parameters. An analysis of clinical parameters according to the PISA scores also supports these findings. Consequently, during a PMC, no clinical advantage was achieved with the additional use of the watercooled Nd:YAG laser.

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Conflict of interest and source of funding statement

The authors declare that they have no conflict of interest. This study was self-funded by the Clinic for Periodontology, Utrecht, The Netherlands.

Clinical Relevance

SCIENTIFIC RATIONALE FOR THE STUDY

The Nd:YAG laser has a potential bactericidal effect. At present, the clinical effect of water-cooled Nd: YAG lasers in a periodontal maintenance care programme is unknown.

PRINCIPAL FINDINGS

The adjunctive use of the Nd:YAG laser after SRP during a maintenance care programme did not provide additional benefits. The estimate of the periodontal inflamed surface area (PISA) supports this observation.

PRACTICAL IMPLICATIONS

The results of this study are applicable to patients with diagnoses of moderate-to-severe adult periodontitis who are motivated to attend a maintenance care programme regularly. The clinical results did not show an advantageous effect of adding a laser treatment to conventional periodontal maintenance care. The use of the Nd:YAG laser as an adjunct to the subgingival debridement of residual pockets ≥5mm is therefore not supported by clinical scientific evidence. The Nd:YAG laser treatment alone was not examined.

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12.

There is no evidence. Well that's my two cents.

Caro Emerald

SUMMARY, DISCUSSION AND CONCLUSIONS OF PART II OF THE THESIS

Various laser systems are currently available for intra-oral use. The two most common lasers used in dentistry for periodontal therapy are the Nd:YAG and the diode lasers (Blayden & Mott 2013). The first systematic review (chapter 8) presented in this part of the thesis evaluated the adjunctive effect of the use of a diode laser following non-surgical subgingival debridement during the initial phase of periodontal therapy on the clinical parameters of periodontal inflammation. Three online databases were searched to identify eligible studies with the probing pocket depth (PPD) and clinical attachment loss (CAL) as primary clinical outcome parameters. Independent screening of 416 unique papers resulted in nine eligible publications. The meta-analysis evaluating PPD and CAL showed no significant effect with the addition of laser therapy to conventional treatment. The body of evidence considering the adjunctive use of the diode laser was judged to be "moderate" for changes in PPD and CAL. This systematic review therefore did not provide evidence for the adjunctive use of diode laser in traditional mechanical modalities of periodontal therapy in patients with periodontitis.

During the same time period, Sgolastra and co-workers (2013a) published systematic reviews on laser use in periodontal therapy, and the review that focused on the diode laser included 5 papers. The main reason these authors did not include all available evidence was the strict eligibility criteria such as including only studies that were randomized, with a minimum follow-up of ≥ 6 months, in patients diagnosed with chronic periodontitis. Furthermore, these authors focused on studies reporting data as the mean and standard deviation in order to perform quantitative meta-analysis. Surprisingly, two studies (Aykol et al. 2011, Makhlouf et al. 2012) included did not introduce the diode laser fiber into the periodontal pocket, and one study included maintenance patients (Cappuyns et al. 2012/ Giannopoulou et al. 2012). The latter was an exclusion criteria for the systematic review included in this thesis (chapter 8). The conclusion by Sgolastra et al. (2013a) that the use of a diode laser as an adjunctive therapy to subgingival debridement did not to provide an additional clinical benefit was in line with the conclusion of the chapter on diode lasers (chapter 8). The quality assessment in both systematic reviews had the same rationale but a different approach. Both reviews showed that the majority of the included studies had a high risk of bias. Therefore, improvements in study design and reporting are required for future clinical studies on this topic. In addition, Roncati & Gariffo (2014) performed a systematic literature review on the diode and included the Nd:YAG laser., Their analysis did however not differentiate between the two laser types, which prevents drawing any meaningful conclusion regarding specific laser technologies.

The aim of the second systematic review as presented in chapter 9 was to evaluate after a comprehensive search of the literature, the therapeutic effects of a pulsed Nd:YAG laser in patients with periodontitis. This review evaluated the efficacy of a pulsed Nd:YAG laser in the initial treatment of patients with periodontitis, either as monotherapy or as an adjunct to non-surgical periodontal treatment. Studies were selected with outcome variables on clinical parameters of periodontal inflammation such as plaque, bleeding, gingivitis, probing depth, clinical attachment level, and gingival recession. An extensive search resulted in 296 titles and abstracts. After full-text reading, eight publications met the eligibility criteria. The studies were heterogeneous in terms of study design, participants and laser equipment characteristics, outcome variables and presentation of results. Therefore, it was impossible to carry out quantitative analysis of the data and subsequent meta-analysis. Only a descriptive analysis was possible. The majority of the studies that were analyzed showed no beneficial effect of a pulsed Nd:YAG laser compared to conventional therapy (ultrasonics and/or hand instrumentation) in the initial treatment of patients with periodontitis; either assessed as monotherapy or as an adjunct to non-surgical subgingival debridement. This systematic review therefore suggests that there is no scientific evidence to support the use of the Nd:YAG laser over traditional modalities of periodontal therapy.

More recently, Sgolastra and co-workers published a systematic review on the use of the Nd:YAG laser and included 3 papers (Sgolastra et al. 2014). The main reason for these authors not to include all available evidence was strict eligibility criteria such as excluding non-randomized trials and including only studies with a minimum follow-up of ≥ 3 months and only participants diagnosed with chronic periodontitis. The findings of the meta-analysis of Sgolastra et al. (2014) suggest that use of the Nd:YAG laser as an adjunctive therapy to conventional nonsurgical periodontal therapy could potentially provide additional benefits. The three included studies were not part of the systematic review presented in the chapter on Nd:YAG lasers (chapter 9) because all three were published after the acceptance of the paper presented in the chapter (chapter 9). The two studies presented in the chapter on RCTs of lasers (chapter 10 & 11) were not included in the systematic review by Sgolastra et al. (2014), although they met the eligibility criteria. The argument given for their exclusion was that their use of a low-intensity laser was inappropriate.

Among dental care professionals, the Genius Nd:YAG-pulsed laser with water and air coolant (Genius, Mølsgaard Dental, Copenhagen, Denmark) is used as an adjunct to the "non-surgical" treatment of periodontitis, as suggested by Lioubavina- Hack (2002). This is a water-cooled laser that releases energy in short, interrupted time intervals (pulsed). One paper describing the short-term and another the long-term

effect of a single laser application as an adjunct to scaling and root planing showed a positive effect in favor of the pulsed Nd:YAG laser (Qadri et al. 2010, Qadri et al. 2011). Another study did not substantiate this outcome (Jensen et al. 2010). Therefore, the aim of the designed RCT (chapter 10) was to test whether use of a water-cooled Nd:YAG laser adjunctive to supra- and subgingival debridement with combined hand and ultrasonic instruments results in greater clinical improvement than supra- and subgingival debridement alone. Another objective was to investigate the reduction in the number of subgingival microorganisms. This examiner blinded, randomized and controlled clinical trial used a split-mouth design and was performed in patients diagnosed with moderate-to-severe generalized periodontitis. Immediately following SRP in two randomly chosen contralateral quadrants, all pockets ≥4mm were additionally treated with the Nd:YAG laser. Clinical assessments (plaque index, bleeding on pocket probing, PPD) were performed pre-treatment and at 3 months post-treatment. In each quadrant, one and the same site was sampled for microbiological evaluation at pre-treatment, immediately post-instrumentation and 3 months post-treatment. At the 3-month visit, the clinical parameters had significantly improved for both regimens. No significant differences between treatment modalities were observed for any of the clinical parameters at any time. Immediately following instrumentation, the total colony-forming units for both groups were significantly reduced compared with pre-instrumentation, but no significant differences between treatment modalities were observed. Therefore, it was concluded that three months after SRP, no added effect was achieved with the additional use of the Nd:YAG laser. Microbiological findings reflect these clinical results.

The last chapter (chapter 11) in this section of the thesis evaluated whether the use of a water-cooled Nd:YAG laser as an adjunct to supragingival and subgingival debridement (scaling and root planing, SRP) with hand and ultrasonic instruments during a maintenance care program resulted in clinical improvement compared to SRP alone. The study design was a blinded, randomized and controlled clinical trial using a split-mouth model. The selected patients were originally diagnosed with moderate to severe generalized periodontitis and were enrolled in a periodontal maintenance care program. The clinical characteristics at the start of the study were presence of ≥2 sites per quadrant with a PPD of ≥5mm and an inter-proximal attachment loss of ≥2mm with the presence of bleeding upon pocket probing. Immediately after SRP in two randomly assigned contralateral quadrants, all pockets ≥5mm were additionally treated with a Nd:YAG laser. Clinical assessments (PPD, bleeding on pocket probing) were performed pre-treatment and at 6 months. Based on these assessments, the periodontal inflamed surface area (PISA) was calculated. At 6 months, the clinical parameters had significantly improved for both regimens.

No statistically significant differences between treatment modalities were observed for PPD and bleeding on pocket probing scores at any time. PISA scores supported these findings. Consequently, it was concluded that for residual pockets ≥5mm treated in a periodontal maintenance care program, the adjunctive use of an Nd:YAG laser does not provide a clinically significant additional advantage.

Absence of significant differences can be the result of a study design being underpowered due to an insufficient number of participants. Therefore, sample size calculation (Friedman et al. 1998, Meindert 1986) is an essential part of an RCT in order to minimize the risk of not detecting the effect of the experimental treatment compared to the control treatment. The study size must be determined to ensure a minimal power (typically 0.80) (Leroux & LeSaffre et al. 2009). For both clinical studies included in this thesis, an 'a priori' sample size calculation was performed, and 'post hoc', a detectable difference of 0.5mm in PPD would have been significant. This difference was also considered as clinically relevant. The lack of the potential effect of the water-cooled Nd:YAG laser in both clinical studies therefore cannot be explained by a lack of statistical power.

Because the diode laser and the Nd:YAG may not be effective in non-surgical periodontal debridement, other laser technologies have also been evaluated in a systematic manner. Another type of laser that is frequently used in dental practices and can also be applied in periodontal therapy is the erbium-doped:yttrium-aluminum-garnet (Er:YAG) laser. Its efficacy in debris removal and root smoothing has been proven 'in vitro'. However, the clinical effectiveness of the Er:YAG laser remains controversial. Two systematic reviews concluded that no significant differences were found for any of the investigated clinical parameters, suggesting that the clinical efficacy of the Er:YAG laser was similar to that of SRP (Sgolastra et al. 2012, Zhao et al. 2014).

Antimicrobial photodynamic therapy (PDT) is another novel approach that has been used in several clinical applications, including the treatment of periodontal diseases. The application of PDT is based on the following principle: A photoactivatable agent (photosensitizer) that absorbs light is taken up by bacteria. When the photosensitizer is exposed to light of an appropriate wavelength (such as that emitted by a low-power laser) in the presence of oxygen, it generates singlet oxygen and free radicals that are cytotoxic to microorganisms and their products (Dobson & Wilson 1992, Komerik et al. 2003). The effectiveness of this approach as an alternative to scaling and root planing was systematically reviewed (Atieh 2010, Azarpazhooh et al. 2010, Sgolastra et al. 2013b), and it was concluded that PDT as an independent treatment

or as an adjunct to SRP was not superior to SRP alone. Subsequently, the routine use of PDT for the clinical management of periodontitis cannot be recommended.

Considering all evidence, the cornerstone of management of chronic periodontitis remains non-surgical periodontal treatment (Drisko 2014). In the clinical study of initial periodontal therapy (chapter 3), subgingival debridement was performed using ultrasonics followed by hand instruments under local anesthetic. The treatment was performed in two separate sessions approximately 1 week apart. After treatment, the patients were instructed to rinse for 2 weeks, twice daily for 30 s, with 15 ml of a mouthwash containing 0.12% chlorhexidine (CHX).

Concerning the use of power-driven (e.g. ultrasonics) instrumentation systematic reviews indicated that there is no difference in clinical outcomes compared to use of hand instrumentation (Tunkel et al. 2002, Walmsley et al. 2008). The addition of antiseptic agents to coolants or irrigants does not provide additional clinical benefits (Walmsley et al. 2008). In recent years, different therapeutic strategies have been proposed to improve the results of SRP and, hence, to avoid the need for periodontal surgical interventions in patients with advanced periodontitis. Historically, periodontal therapy protocols involve a staged quadrant scaling at 1- to 2-week intervals. This time interval may result in re-colonization by the bacteria of the instrumented pockets and impaired healing. Therefore, a new approach in which full-mouth non-surgical therapy is completed within two consecutive days has been suggested. Systematic reviews suggest that both the traditional quadrant approach and the more recent approach of full-mouth debridement could be equally effective (Eberhard et al. 2008, Lang et al. 2008, Farman & Joshi 2008). Full-mouth debridement might take less time to complete than quadrant subgingival debridement but might also increase patients' post-operative pain (Matthews 2009). In addition to full-mouth debridement, the use of oral antiseptics such as CHX mouthwash and gel has been suggested. The addition of oral antiseptics to mechanical subgingival debridement offers no advantage over subgingival debridement alone (Eberhard et al. 2008, Lang et al. 2008, Farman & Joshi 2008). Consequently, the protocol outlined in chapter 3 adheres to the current evidence-based standards.

Conventional subgingival debridement is not always successful. Various locally delivered antimicrobial agents and antibiotics as adjuncts to subgingival debridement have been suggested to enhance efficacy, including doxycycline, metronidazole, minocycline, tetracycline, povidone-iodine and CHX. Systematic reviews have been performed to determine the efficacy of currently available, locally delivered anti-infective agents (Hanes & Purvis 2003, Bonito et al. 2005, Kalsi et al.

2011). Based on four included studies, it was determined that local drug delivery combined with subgingival debridement appears to provide additional benefits in pocket depth reduction compared to subgingival debridement alone. More recently, using a different search strategy and selection criteria, Matesanz-Pérez and co-workers (2013) reported data from 52 different investigations and concluded that the subgingival application of antimicrobials caused significant changes in both PPD and CAL. The subgingival application of tetracycline fibers and sustained-release doxycycline or minocycline demonstrated a significant benefit in PPD reduction. The local application of CHX and metronidazole showed only a minimal additional effect compared to the placebo. However, the overall conclusion was that scientific evidence supports the adjunctive use of local antimicrobials with debridement in deep or recurrent periodontal pockets (Matesanz-Pérez et al. 2013).

Povidone-iodine is an antiseptic with a broad antimicrobial spectrum and can be adjunctively used in different concentrations and application modalities with subgingival debridement. A systematic review concluded that povidone-iodine provides a small but significant additional beneficial effect. Enhanced probing pocket depth reductions were observed in particular for single-rooted teeth when the treatment was repeated during the healing stage. The adjunctive use of povidone-iodine during subgingival instrumentation might increase the clinical pocket depth reduction, although the clinical significance was small to moderate (Sahrmann et al. 2010).

Gel vehicles delivering CHX have become available as antimicrobial agents for subgingival application. Based on a systematic review and the limited data currently available, subgingival CHX gel application is not justified in the treatment of chronic periodontitis (Cosyn & Sabzevar 2005). In addition, several local antimicrobial agents, such as a bioabsorbable CHX chip, have been developed to enhance the outcome of non-surgical periodontal therapy. The clinical and microbiological data currently available appear to be limited and conflicting (Cosyn & Wyn 2005). Therefore, the magnitude of the added effect of the CHX chip when used as an adjunct to scaling and root planing requires further elucidation in clinical trials.

When clinical improvements are found with the use of local adjuncts to subgingival debridement, even if statistically significant, the question remains whether these are clinically meaningful. The best interventions are those that achieve improvement in outcome with the lowest costs (Ismail 2010). Economic outcomes are objective measures of the costs, effectiveness relative to costs and return on investment associated with any intervention. Cost effectiveness analysis focuses on the costs of achieving one unit improvement in a clinical outcome or health status. The result is

typically expressed in terms of a ratio in which the denominator is a gain in health from a measure and the numerator is the cost associated with the health gain. The need for cost-effectiveness analysis of laser applications has been proposed in a Consensus Report of the Sixth European Workshop on Periodontology (Sanz & Teughels 2008). Because dental lasers are expensive and their effect either as monotherapy or as an adjunct to non-surgical subgingival debridement is very limited and might even negligible with respect to clinical relevance. It is therefore common sense that the use of lasers for subgingival debridement is not cost efficient and might even increase the costs of the care provided. The AAP states that there is insufficient evidence to suggest that any specific laser wavelength is superior to the traditional treatment methods of the common periodontal diseases, such as periodontitis (AAP 2011). Based on all available evidence and costs, it seems that there is room for an even more firm statement from the AAP regarding lasers in non-surgical periodontal therapy. For those dental care professionals that still cling to using laser technology for non-surgical periodontal treatment, the question asked should be: "Why is it that dental care professionals are among the very few health professionals who can ignore critical evaluation of the scientific literature and treat patients with personal experience as its equal?" Dental care professionals seem to provide laser treatment without critically evaluating whether such treatment is consistent with the best evidence (Spielman & Wolf 2008).

In conclusion, non-surgical periodontal therapy consisting of supra- and subgingival debridement is the basis for periodontal treatment concepts. There is no evidence to support the adjunctive use of the diode or the Nd:YAG laser following traditional modalities of periodontal therapy. Sub-gingival debridement can be performed with manual and power-driven instruments. This treatment can be organized as full-mouth debridement or quadrant-wise scaling and root planing. The scientific observations and evaluations of the excising literature in this thesis support a firm statement to refute the use of laser technologies in non-surgical periodontal treatment based on the lack of clinical efficacy and the potential extra costs.

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Het was zo donker dat ik overal lichtpuntjes zag

Loesje

Nederlandse samenvatting voor leken

Deel 2

Indien gingivitis niet op tijd wordt behandeld, kunnen de bacteriën onder het tandvlees toenemen. Daardoor kan de ontsteking zich uitbreiden met als gevolg dat de ruimte tussen tandoppervlak en tandvlees (pocket) dieper wordt. Door de toenemende pocketdiepte kunnen de bacteriën niet meer met de tandenborstel en andere hulpmiddelen verwijderd worden. Hierdoor kan er schade ontstaan aan het parodontium, welk ontstekingsproces "parodontitis" wordt genoemd. De vezels raken ook betrokken bij de ontsteking en het kaakbot gaat verloren. Dit is een voortschrijdend proces dat veelal onopgemerkt verloopt omdat er zelden pijnklachten zijn. Uiteindelijk kunnen tanden en kiezen los gaan staan. De reeds ontstane schade kan door behandeling niet meer worden hersteld maar slechts tot stilstand worden gebracht.

Parodontitis wordt niet alleen vastgesteld door het beoordelen van het tandvlees qua kleur en consistentie maar ook de pocketdiepte wordt opgemeten. Dit gebeurt met een meetinstrument (pocketsonde) met millimeterverdeling. Daarbij wordt ook de bloedingsneiging genoteerd. Vanaf 4 millimeter spreekt men van een ontstoken pocket. Omdat alleen een klinisch beeld onvoldoende informatie geeft, is het gebruik van röntgenfoto's noodzakelijk omdat het botniveau dan kan worden beoordeeld. Soms is het ook wenselijk om een bacteriologisch onderzoek uit te voeren. Er wordt dan specifiek gekeken welke en hoeveel bacteriën er in de tandplak zitten. De behandeling van parodontitis wordt vormgegeven in een behandelplan en bestaat in eerste instantie altijd uit instructies voor een optimale mondhygiëne en een professionele gebitsreiniging. Het doel is dat er na de behandeling geen verdiepte pockets meer zijn. Het kaakbot dat in het ontstekingsproces verloren is gegaan komt echter niet meer terug.

Tandplak is een kleverig laagje dat zich elke dag vormt en gemakkelijk te verwijderen is met de tandenborstel. Indien het niet goed wordt verwijderd, kan het verkalken tot tandsteen. Om parodontitis succesvol te behandelen moet de oorzaak van de ontsteking (de tandplak) dagelijks grondig worden verwijderd. Professionele gebitsreiniging wordt uitgevoerd door een mondhygiënist, paro-preventie assistent, tandarts of tandarts parodontoloog. Deze verwijdert tandsteen en tandplak onder het tandvlees. Dit kan worden uitgevoerd met handinstrumenten of ultrasone apparatuur of een combinatie ervan. Met handinstrumenten wordt het tandsteen van het tandoppervlak afgeschraapt en met ultrasone apparatuur wordt het tandsteen los getrild. Eventueel kan er een plaatselijke verdoving worden gegeven. Na afloop van de behandeling wordt er gepolijst, dit gebeurt met een borsteltje in

combinatie met een polijstpasta. Door het verwijderen van tandsteen wordt één van de oorzaken van de ernstige tandvleesontsteking aangepakt. Naast een optimale zelfzorg en professionele gebitsreiniging verdwijnt veelal de ontsteking en hecht het gezonde tandvlees zich weer vast aan de tanden en kiezen.

Een laser is een lichtbron die in staat is een smalle coherente bundel licht voort te brengen. Het licht van een laser is daardoor monochromatisch en directioneel, in tegenstelling tot de meeste andere lichtbronnen, die in allerlei richtingen licht uitzenden in een breed spectrum van golflengtes en fasen. Ook zorgt laserlicht voor een lichtbundel die niet of nauwelijks convergeert of divergeert. Het woord "laser" is oorspronkelijk een afkorting van Light Amplification by Stimulated Emission of Radiation, in het Nederlands: lichtversterking door gestimuleerde uitzending van straling. Voor de dentale markt zijn er specifieke lasers en sommige zouden kunnen worden gebruikt voor het verwijderen van tandsteen. De meest gebruikte systemen hiervoor zijn de diode laser en de Nd:YAG laser, tandheelkundige laserapparatuur is kostbaar.

In hoofdstuk 8, het eerste systematische literatuuronderzoek van het tweede gedeelte van dit proefschrift, is het gebruik van de diode laser geëvalueerd. De gevonden studies gebruikten de diode laser als toevoeging aan de professionele gebitsreiniging en vergeleken dit met alleen professionele gebitsreiniging. Er werd specifiek gezocht naar onderzoeken bij proefpersonen met nog niet eerder behandelde parodontitis waarin het effect op de pocketdiepte en niveau van aanhechtingsverlies werd geëvalueerd. Geconcludeerd werd dat het extra gebruik van de diode laser tijdens de professionele gebitsreiniging geen significant positief effect oplevert. Het tweede systematische literatuuronderzoek in hoofdstuk 9 evalueerde het gebruik van de Nd:YAG laser. Ook hier werd gezocht naar onderzoeken bij proefpersonen met nog niet eerder behandelde parodontitis. De Nd:YAG laser kon gebruikt worden als aanvulling op de professionele gebitsreiniging of als monotherapie in plaats van de professionele gebitsreiniging. Het merendeel van de gevonden onderzoeken liet zien dat er geen positief effect was bij het gebruik van de Nd:YAG laser zowel aanvullend dan wel als monotherapie ten opzichte van de normale professionele gebitsreiniging.

Als aanvulling op professionele gebitsreiniging heeft de watergekoelde ND:YAG laser een 10-tal jaren geleden in Nederland veel aandacht gekregen. Omdat hier in de praktijk nog geen onderzoek naar was gedaan is in hoofdstuk 10 een klinisch onderzoek opgezet wat het effect evalueert van het aanvullend gebruik bij professionele gebitsreiniging. De klinische metingen betroffen plakscore, pocketdiepte en bloedingsneiging. Naast de klinische uitkomstmaten

is daarbij ook nog het effect op de samenstelling en aantallen bacteriën in de microflora onder het tandvlees bekeken, zowel voor de behandeling, direct na de behandeling als bij de eindevaluatie. Bij alle proefpersonen met onbehandelde parodontitis werd de professionele gebitsreiniging uitgevoerd in een combinatie van handinstrumenten en ultrasone apparatuur. Hierna werd door het lot bepaald welke twee tegenovergestelde kwadranten (halve kaakhelften, links/rechts, boven/onder) werden behandeld met de gekoelde ND:YAG laser. Na 3 maanden waren alle kwadranten verbeterd qua hoeveelheid plak, bloeding en pocketdiepte. Er was echter geen verschil tussen de kwadranten met en zonder watergekoelde ND:YAG laser. Direct na het toepassen van de professionele gebitsreiniging zowel met en zonder watergekoelde ND:YAG laser werd er wel een significant verschil gezien in het aantal bacteriën in de plak uit de pockets in vergelijking met voor aanvang van de behandeling. Dit effect was echter niet meer zichtbaar na 3 maanden. De microbiologie en de klinische metingen sluiten dus op elkaar aan, waardoor er kon worden geconcludeerd dat de watergekoelde Nd:YAG laser geen effectieve toevoeging is op de conventionele professionele gebitsreiniging.

Het doel van de behandeling van parodontitis is het levenslang behouden van de eigen tanden en kiezen. Om dit te bereiken is regelmatige en intensieve nazorg nodig met als doel het ontstekingsvrij houden van het tandvlees. Om te voorkomen dat er opnieuw parodontitis ontstaat is een goede dagelijkse zelfzorg noodzakelijk. Tijdens de nazorgfase wordt het tandvlees onderzocht en de eventueel aanwezige tandplak en tandsteen professioneel verwijderd. De regelmaat van nazorgafspraken wordt bepaald op individuele indicatie en ligt meestal tussen de 3 tot 6 maanden. In het laatste hoofdstuk, hoofdstuk 11 van dit proefschrift is het gebruik onderzocht van de watergekoelde ND:YAG laser als extra bovenop de professionele gebitsreinigingsprocedures in de nazorgfase. De proefpersonen waren voor aanvang van de parodontale behandeling gediagnostiseerd met parodontitis en waren hiervoor reeds behandeld en bevonden zich minstens 1 jaar in de nazorgfase. Toch hadden zij per kwadrant ondanks eerdere behandelingen minimaal 2 zogenoemde rest-pockets met bloedingsneiging na sonderen. Bij de proefpersonen werd na de professionele gebitsreiniging met de combinatie van handinstrumenten en ultrasone apparatuur door het lot bepaald welke twee tegenovergestelde kwadranten werden behandeld met de gekoelde ND:YAG laser. Vooraf aan procedure werden de pocketdiepte en bloeding na sonderen gemeten, dit werd herhaald na 6 maanden. Op basis van de klinische uitkomstmaten werd ook de PISA berekend, dat is een maat voor het tandvleesoppervlak dat is ontstoken. Zowel de kwadranten met de traditionele professionele gebitsreiniging als die werden behandeld met de gekoelde ND:YAG laser lieten significante verbeteringen zien ten aanzien van pocketdiepte en bloeding na sonderen. Tussen de behandelstrategieën werd echter geen verschil

gevonden. Dit gold ook voor de analyse op basis van de PISA score. Geconcludeerd werd dan ook dat de water gekoelde ND:YAG laser geen toegevoegd effect heeft op rest-pockets in de nazorgfase.

De conclusie van het tweede deel van het proefschrift is dan ook dat de niet chirurgische parodontale therapie door middel van professionele gebitsreiniging met hand en ultrasone instrumenten de basis is van de parodontale behandeling. Er is geen wetenschappelijk bewijs dat het effect van deze behandeling succesvol kan worden aangevuld met de diode dan wel Nd:YAG laser aanvullend op de professionele gebitsreiniging. Parodontologieverenigingen zouden een stevig standpunt in kunnen nemen over deze behandelmogelijkheid daar het gebruik van lasers behandeling duurder maakt maar geen toegevoegde waarde heeft.

Additionele bronnen

- Folder: Parodontitis. Tandvleesontsteking: oorzaak, gevolg en behandeling. (2014) BV diensten NVvP. ISBN 978-90-818530-1-9.
- Folder: Uw schone gebit en een frisse prettige uitstraling. (2006) Paro Praktijk Utrecht. ISBN 978-90-811197-1-9.
- Wikipedia webpagina: http://nl.wikipedia.org/wiki/Laser_%28licht%29 (bekeken op 21 maart 2015).

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