Journal of Clinical Periodontology
Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2009; 36: 661–666 doi: 10.1111/j.1600-051X.2009.01432.x

One-year outcomes of repeated adjunctive photodynamic therapy during periodontal maintenance: a proof-of-principle randomized-controlled clinical trial

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Lulic M, Leiggener Görög I, Salvi GE, Ramseier CA, Mattheos N, Lang NP. One-year outcomes of repeated adjunctive photodynamic therapy during periodontal maintenance: a proof-of-principle randomized-controlled clinical trial. J Clin Periodontol 2009; 36: 661–666. doi: 10.1111/j.1600-051X.2009.01432.x.

Abstract

Background: Single photodynamic therapy (PDT) has been effective in initial periodontal therapy, but only improved bleeding on probing (BoP) in maintenance patients after a single use. Repeated PDT has not been addressed.

Objectives: To study the possible added benefits of repeated adjunctive PDT to conventional treatment of residual pockets in patients enrolled in periodontal maintenance.

Material and Methods: Ten maintenance patients with 70 residual pockets [probing pocket depth (PPD) $\geqslant$ 5 mm] were randomly assigned for treatment five times in 2 weeks (Days 0, 1, 2, 7, 14) with PDT (test) or non-activated laser (control) following debridement. The primary outcome variable was PPD, and the secondary variables were clinical attachment level (CAL) and BoP. These were assessed at 3, 6 and 12 months following the interventions.

Results: Greater PPD reductions were observed in the test (-0.67 ± 0.34; $p = 0.01$) compared with the control patients (-0.04 ± 0.33; NS) after 6 months. Significant CAL gain ($+0.52 \pm 0.31$; $p = 0.01$) was noted for the test, but not in the control (-0.27 ± 0.52; NS) patients after 6 months. BoP percentages dcreased significantly in test (97–64%, 67%, 77%), but not control patients after 3, 6 and 12 months.

Conclusions: Repeated (five times) PDT adjunctive to debridement yielded improved clinical outcomes in residual pockets in maintenance patients. The effects were best documented after 6 months.

Key words: clinical outcomes; PDT; periodontal maintenance; photodynamic therapy; probing depth; RCT; supportive periodontal therapy

Accepted for publication 23 April 2009

Advanced periodontal disease in humans is characterized by the presence of inflammatory lesions leading to loss of periodontal attachment to the tooth. Oral bacteria play a pivotal role in the aetiology of gingivitis and periodontitis (Löe et al. 1965, Loesche & Syed 1978, Syed & Loesche 1978, Genco 1979, Slots 1979, Page & Kornman 1997, Socransky & Haffajee 2002). Hence, plaque control, scaling and root planing (SRP), as well as consequent maintenance with regular recall intervals, may delay or even arrest periodontal progression.

In the treatment of local infections of the oral cavity, anti-infective agents, such as rinsing with disinfectant solutions or administration of local or systemic antibiotics, may be used as supplementary treatment measures.

The adjunctive use of antibiotics in combination with mechanical debridement has been shown to be effective in the elimination of the bacterial periodontal infection (Lindhe et al. 1982, Herrera et al. 2008). However,

Conflicts of interest and source of funding statement

The authors declare that they have no conflicts of interests.
This study was in part supported by HELBOs Photodynamic Systems GmbH, Grieskirchen, Austria, and by the Clinical Research Foundation (CRF) for the Promotion of Oral Health, Brienz BE, Switzerland.

chemotherapeutic therapy may be accompanied by side effects, such as gastrointestinal disorders, or may – at least temporarily – lead to the development of bacterial resistance (Slots & Rams 1990, van Winkelhoff et al. 2000, Feres et al. 2002). For these reasons, patient compliance may also be jeopardized (Bamberger & Dahl 1992).

Therefore, alternatives for an efficient adjunctive removal of periodontal bacteria have been proposed. Such a novel possibility is the application of photodynamic therapy (PDT). In general medicine, PDT has been used in the treatment of neoplasms (Dougherty & Marcus 1992). In dentistry, interest has been in the elimination of various microorganisms.

PDT is based on the principle that a dye, as a photosensitizer, binds to the target cells and is activated by light of an appropriate wavelength. By changing the energy status of the molecules in the photosensitizer, free radicals of singlet oxygen are formed, which are toxic to the cell by destroying the membrane, the mitochondria or the nuclei.

In vitro studies have shown PDT to completely eliminate *Streptococcus sanguis*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* (Dobson & Wilson 1992, Pfitzner et al. 2004). The possibility of the suppression of *P. gingivalis* was also demonstrated in a dog study (Sigusch et al. 2005). In comparing the antimicrobial effects of the administration of chlorhexidine with those of PDT in the treatment of peri-implantitis in an animal model, equal reductions of the bacterial biofilm were documented for the two treatments (Hayek et al. 2005). The elimination of *P. gingivalis*, *Prevotella intermedia* and *A. actinomycetemcomitans* from implant surfaces was also successful in an in vitro study (Haas et al. 1997). Moreover, PDT reduced, but did not eliminate *A. actinomycetemcomitans*, *P. intermedia* and *P. gingivalis* from implant surfaces in a human study (Dörtbudak et al. 2001).

In patients with chronic periodontitis, conventional debridement with or without the adjunctive application of PDT showed better clinical improvements in the group treated using both mechanical debridement and PDT (Andersen et al. 2007).

Compared to SRP alone, the addition of a single application of PDT resulted in higher reductions of bleeding scores, but not in additional improvements in pocket depth reduction and gain of clinical attachment after 6 months (Christodoulides et al. 2008).

Only one recent study reported on the clinical effects of a single application of PDT in maintenance patients and showed a reduction in bleeding on probing (BoP) (Chondros et al. 2008).

In a split-mouth design study of single-rooted teeth in patients with untreated aggressive periodontitis, either SRP or PDT alone or both showed a significant reduction in BoP scores and a decrease in probing pocket depth (PPD) values as well as improvements in clinical attachment levels (CALs). Neither of the two treatments showed superior results after 3 months (de Oliveira et al. 2007).

More recently, patients with chronic periodontitis were treated using conventional subgingival debridement or adjunctive PDT. Clinical outcomes with adjunctive PDT were improved compared with SRP alone after 3 months (Braun et al. 2008).

So far, the role of PDT in the maintenance of residual pockets during supportive periodontal care has not convincingly been elucidated.

The aim of this study was to investigate whether or not PDT added benefits to the conventional treatment of residual pockets in patients enrolled in supportive periodontal therapy (SPT). The null hypothesis is that of no difference in the outcome variables in patients enrolled in SPT between residual pockets treated using repeated PDT or placebo.

Material and Methods

Patients

Patients were recruited from the pool of the Department of Periodontology and Fixed Prosthodontics of the University of Berne, Switzerland. This patient cohort has recently been presented (Matuliene et al. 2008) in a maintenance study of a mean of 11.3 years. The patients had all been previously treated for chronic periodontitis and met the following inclusion criteria:

(1) Age >19 years;
(2) Good general health;
(3) Presence of at least 24 remaining teeth;
(4) History of chronic periodontitis;
(5) Residual PPD $\geqslant 5$ mm with/out concomitant BoP;
(6) Cigarette smoking $\leqslant 10$ cigarettes/day; and
(7) Signed informed consent.

The following conditions led to exclusion from the study:

(1) Use of systemic or local antibiotics in the past 3 months;
(2) Pregnant or lactating females; and
(3) Concomitant participation in other clinical trials.

The study was performed in full accordance with the declared ethical principles of the *World Medical Association Declaration of Helsinki*, V and VI (2002). The protocol was approved by the Ethical Committee of the Canton of Bern (Kantonale Ethikkommission Bern, KEK).

Study design

The study was performed as a randomized-controlled clinical trial using a double-blind design. The allocation to either the test or the control group was performed by random assignment using a randomization table.

Only patients in SPT displaying a single residual PPD of $\geqslant 5$ mm were recruited. A total of 10 patients signed informed consent. Patients were recruited from the SPT clinic during regular visits between March 2005 and July 2006.

On Day 0, all patients were reinstructed in oral hygiene practices. SRP of all sites with PPD of $\geqslant 5$ mm was performed under local anaesthesia using hand instruments. Additionally, all experimental sites were treated with the set-up for PDT including the dye/photosensitizer. In the randomly assigned control sites, the laser was set in a light mode that was not compatible with the photosensitizer (Control Laser tip provided by HELBO® Photodynamic Systems GmbH, Grieskirchen, Austria). Both the patient and the treatment provider were blinded by the power setting of the laser.

Laser therapy

The laser system included a hand-held battery-operated diode laser (HELBO® minilaser 2075 F dent, HELBO® Photodynamic Systems GmbH) with a wavelength of 670 nm and a power density of 75 mW/cm^2, together with phenothiazine chloride as a photosensitizer

(HELBO Blue Photosensitizer, HELBO® Photodynamic Systems GmbH).

The photosensitizer was applied to the bottom of the periodontal pocket and applied in a coronal direction. After 3 min. of action, the photosensitizer was rinsed with distilled water. Following this, the pocket was exposed to the laser light using a fibre optic application for 1 min. (HELBO 3D Pocket Probe, HELBO® Photodynamic Systems GmbH). A registered dental hygienist blinded to the activation or non-activation of the laser tip performed the PDT after intensive training. The determination of PDT or the non-activated laser control therapy was performed by a dental nurse, who was unaware of the study objectives, on the basis of the randomization table.

The procedure was repeated in the same manner after 1, 2, 7 and 14 days. Before the applications, a mechanical disruption of the biofilm was performed with hand instruments.

The patients were observed for 1, 3, 6 and 12 months. Oral prophylaxis procedures using rubber cups and pumice and hygiene instructions were provided at these observation points.

Clinical parameters

The following clinical outcome variables were assessed at baseline (Day 0) and at Days 7 and 14 as well as at Months 1, 3, 6 and 12 by the same, blinded examiner who had also performed the treatment: plaque index (PlI) (Silness & Löe 1964), PPD and CAL in mm, measured as the distance from the cemento-enamel junction to the bottom of the pocket using a calibrated periodontal probe (HAWE Click Probe®, KerrHawe SA, Bioggio TI, Switzerland) with a point diameter of 0.45 mm and standardized to a probing pressure of 0.25 N. Dichotomous BoP was assessed 15 s after probing with a probing pressure of 0.25 N. PPD was the primary outcome variable, and CAL and BoP were the secondary outcome variables.

Periapical radiographs were taken using a film holder and a long-cone technique after 3, 6 and 12 months.

Sample size calculation

The power analysis was performed for a one-way fixed-effects analysis of variance with two levels. The criterion for significance was set at $\alpha = 0.05$ (Type I error) and at $\beta = 0.20$ (Type II error). The ANOVA is non-directional (two tailed), indicating that an effect in either direction will be interpreted.

If an effect of change in PPD of 1 mm is expected, the sample size required is five pairs of patients, assuming that the common standard deviation is 0.5 mm.

Statistical analysis

A patient-level statistical analysis was performed for each of the parameters. A Shapiro–Wilk *W*-test was used to control normal distribution of the data and revealed no evidence for non-normality.

The mean values and standard deviations (mean ± SDs) for the clinical variables were calculated for each treatment, based on the subject as the statistical unit. Student's *t*-test was used for continuous variables (clinical measurements) after the normality of the data distribution had been checked. Likewise, the significance of the difference within each group before and after treatment was evaluated with the paired-samples *t*-test. Ordinal data (BoP and PlI) were analysed with the Mann–Whitney *U*-test (unpaired observations) and Wilcoxon's signed ranks test (paired observations). The level of significance was set at $\alpha = 0.05$ and 0.01.

Results

In total, 10 patients (three women, seven men, aged 40–74 years) were thus selected for the study. All patients met for all observation visits and completed the 12-month study. They were all enrolled in a regular maintenance care programme (Matuliene et al. 2008). Two of the patients were cigarette smokers (Table 1). At baseline, with the exception of CAL data (Table 5), no significant differences in any of the other mean parameters were found between the test and the control patients (Tables 2 and 3).

Table 2 summarizes the mean PlI and mean BoP scores for test and control sites at baseline. The test patients yielded 77% of PlI and the control patients displayed 74% of visible plaque deposits at baseline ($p > 0.05$). The corresponding values for the mean BoP scores were 97% for the test and 84% for the control, respectively ($p > 0.05$).

Table 3 illustrates the mean in the primary outcome variable, the mean PPD for baseline and 3, 6 and 12 months in the test and control patients.

In the test patients, a statistically significant decrease ($p = 0.01$) in mean PPD was observed between baseline (6.08 ± 1.19 mm) and 6 months (5.41 ± 1.09 mm). In the control patients, no statistically significant decreases in mean PPD were observed between baseline (5.97 ± 0.31 mm), 6 months (5.93 ± 0.49 mm) and 12 months (5.90 ± 0.71 mm), respectively. After 6 months, the difference between test and control patients for mean PPD was significant ($p < 0.05$, unpaired *t*-test) (Table 3).

Table 4 compares the changes in mean PPD from baseline to follow-up examinations between test and control groups. The test patients showed significantly higher PPD reductions after 6 months ($p = 0.01$) than did the control patients.

Table 5 shows the means in the secondary outcome variable, the mean CAL for baseline and 3, 6 and 12 months in test and control patients. A statistically highly significant ($p = 0.01$) difference in mean CAL between test and control patients at 6 months (6.18 ± 2.26 mm *versus* 7.82 ± 1.42 mm) was noted.

Table 2. Plaque and bleeding on probing (BoP) percentages at baseline

Baseline	Plaque (%)	BoP (%)
Test (positive)	77	97
Control (positive)	74	84

Table 1. Demographic characteristics of the patient population at baseline

	All	Control group	Test group
N	10	5	5
Gender (m/f)	7/3	4/1	3/2
Mean age (range)	54 years (40–74)	52 years (40–57)	56 years (44–74)
Number of sites	70	31	39
Smoker yes/no	2/8	1/4	1/4

m, male; f, female.

Table 3. Mean pocket probing depths in mm ± standard deviations at baseline and follow-up examinations in test and control groups

	Baseline	3 months	6 months	12 months
Test group	6.08 ± 1.19	5.69 ± 1.34	5.41 ± 1.09*	5.81 ± 1.33
Control group	5.97 ± 0.31	5.68 ± 0.80	5.93 ± 0.49	5.90 ± 0.71

*Statistically significantly different from baseline ($p = 0.01$).

Table 4. Mean changes (decrease: −) in pocket probing depths in mm ± standard deviations from baseline to the follow-up examinations for test and control groups

	3 months	6 months	12 months
Test group	−0.39 ± 0.38	−0.67 ± 0.34*	−0.27 ± 0.43
Control group	−0.29 ± 0.65	−0.04 ± 0.33	−0.07 ± 0.61

*Statistically significantly different from baseline ($p = 0.01$).

Table 5. Mean clinical attachment level in mm ± standard deviations at baseline and follow-up examinations in test and control groups

	Baseline	3 months	6 months	12 months
Test group	6.70 ± 2.17	6.41 ± 2.61	6.18 ± 2.26*	6.79 ± 2.37
Control group	7.55 ± 1.73	7.61 ± 1.92	7.82 ± 1.42	7.76 ± 1.66

*Statistically significantly different from baseline ($p = 0.01$).

Table 6. Mean changes in clinical attachment level (gain: +, loss: −) in mm ± standard deviations from baseline to the follow-up examinations for test and control groups

	3 months	6 months	12 months
Test group	+0.29 ± 0.49	+0.52 ± 0.31*	−0.09 ± 0.41
Control group	−0.06 ± 0.43	−0.27 ± 0.52	−0.20 ± 0.61

*Statistically significantly different from baseline ($p = 0.01$).

Table 6 compares the changes in mean CAL from baseline to follow-up examinations between test and control patients. After 6 months, the test group showed a significantly higher gain ($p = 0.01$) in mean CAL (0.52 ± 0.31 mm) compared with that of the control group (-0.27 ± 0.52 mm).

Table 7 shows the changes in the mean percentage of BoP-positive sites between baseline and after 3, 6 and 12 months in the test and control patients. Test patients yielded a statistically significant reduction in the mean percentage of BoP positive sites after 3 ($p < 0.002$), 6 ($p < 0.001$) and 12 months ($p < 0.03$). However, in control patients, no statistically significant changes ($p > 0.05$) in the mean percentage of BoP-positive sites were observed throughout the observation period. Furthermore, the Mann–Whitney *U*-test revealed significant differences in the mean BoP percentages between test and control patients after 180 days ($p = 0.02$).

Table 8 shows the changes in the mean percentages of sites covered with plaque between baseline and 3, 6 and 12 months in the test and control patients. In both groups, no statistically significant differences were observed throughout the entire observation period.

Discussion

The outcomes of the present double-blinded randomized clinical trial showed that repeated (five times) applications of PDT improved the clinical outcomes after 6 months in the treatment of residual pockets (defined as PPD ⩾ 5 mm) in patients enrolled in a maintenance care programme. PDT was performed adjunctive to the regular debridement at maintenance visits. As opposed to the improved outcomes following adjunctive PDT, this regular maintenance therapy failed to demonstrate improvements in PPD and CAL levels as well as decreasing BoP percentages 3 months later and thereafter. This points to the difficulty of maintaining residual pockets in patients who are otherwise well maintained.

A recent study (Matuliene et al. 2008) demonstrated that compared with PPD ⩽ 4 mm, residual pockets (PPD ⩾ 5 mm) yield a substantially higher risk of disease progression and the loss of the respective tooth (odds ratio: 5 mm: 5.8; 6 mm: 9.3; ⩾ 7 mm: 37.9) within a mean maintenance period of 11.3 years. Because the risks mentioned increased dramatically with increasing PPD, it is evident that residual pockets should be maintained at lower PPD than the 6 mm limit. Hence, it appears reasonable to add clinically effective measures during the debridement of residual pockets in maintenance visits. PDT demonstrated additional benefits and may therefore be recommended for the maintenance debridement of residual pockets. However, it has to be kept in mind that a recent study failed to demonstrate additional clinical benefits in maintenance patients, with the exception of a reduction in bleeding scores (Chondros et al. 2008). The most plausible explanation for this seemingly conflicting result with those of the present study is the fact that the latter study applied PDT only as a single episode. In the present study, the PDT was applied five times in 2 weeks by a registered and routine dental hygienist, resulting in additional positive outcomes, predominantly for pocket reductions that were maintained for 12 months without further interventions.

As opposed to the present study, previous studies focused on untreated periodontal patients and applied PDT in conjunction with initial periodontal therapy (Andersen et al. 2007, de Oliveira et al. 2007, Braun et al. 2008, Christodoulides et al. 2008).

In 10 patients with aggressive periodontitis and a split-mouth design (de Oliveira et al. 2007), significantly improved outcomes (BoP, PPD and CAL) were reported for both test and control sites. The test treatment was PDT alone, while the control treatment constituted of the conventional scaling and root planing (CSR). From this study, it may be suggested that PDT yielded similar outcomes, although the study was not set up to test equality.

In a study with 33 patients suffering from chronic periodontitis (Andersen et al. 2007), CSR alone, PDT alone and the combination of CSR with PDT were tested. CSR with adjunctive PDT

Table 7. Changes in the mean percentages of bleeding on probing+experimental sites from baseline to 3, 6 and 12 months for test and control groups

	Baseline (%)	3 months (%)	6 months (%)	12 months (%)
Test group	97	64*	67*	77*
Control group	84	84	90	87

*Statistically significantly difference from baseline, p90 = 0.0015, p180 = 0.0005, p360 = 0.0273.

Table 8. Changes in the mean percentages of experimental sites covered with plaque from baseline to 3, 6 and 12 months for test and control groups

	Baseline (%)	3 months	6 months	12 months
Test group	77	62	62	59
Control group	74	58	65	61

showed greater CAL gains than did CSR alone or PDT alone, after 3 months (CSR+PDT: 0.86 ± 0.61, 0.36 ± 0.35 and 0.14 ± 0.65, respectively). It is evident that the benefits of PDT alone are negligible from a clinical point of view and hence, PDT should only be considered adjunctive to CSR.

Also, in 20 chronic periodontitis patients and a split-mouth design, the additional clinical benefits of PDT in initial periodontal therapy were tested against CSR alone (Braun et al. 2008). After 3 months, the sites treated with adjunctive PDT showed higher reductions in BoP percentages, PPD and CAL compared with the CSR therapy alone and were judged to improve non-surgical periodontal therapy.

However, a recent study of 24 chronic periodontitis patients and a parallel-group design (Christodoulides et al. 2008) failed to confirm positive effects of an additional single episode of PDT to CSR alone in initial periodontal therapy, with the exception of higher reductions in bleeding scores in the adjunctive PDT sites after 3 and 6 months. The reason for this seemingly controversial result may be the fact that in this parallel-group study, all patients were first debrided according to the concept of full-mouth disinfection (Quirynen et al. 1995). It is reasonable to assume that full-mouth debridement in 24 h may have had effects that overshadowed those supplemented by PDT. Again, it may be speculated that the effects of single-episode adjunctive PDT may not be sufficient to contribute to clinical improvements because CSR alone has been demonstrated to provide long-term success in periodontal treatment (Lindhe & Nyman 1984, Badersten et al. 1987, Greenstein 1992). A reduction in PPD of 1–2 mm (pockets of 4–6.5 mm) and of 2–3 mm (pockets $\geqslant$7 mm) and a CAL gain of 0–1 mm (pockets of 4–6.5 mm) and of 1–2 mm (pockets $\geqslant$7 mm) may routinely be achieved with non-surgical periodontal therapy (Morrison et al. 1980, Badersten et al. 1981, 1984), while the additional benefits in pocket reduction of adjunctive PDT were in the order of magnitude of 0.3–0.5 mm in the above-mentioned studies.

The present study demonstrated in periodontal maintenance patients that PDT may be applied to residual pockets with a clearly documented mean additional benefit of 0.67 mm in PPD reductions, provided that PDT was applied repeatedly. The fact that test and control patients differed significantly in CAL, with the control patients yielding greater attachment loss (Table 5), suggests that a smaller difference in outcomes may be expected if test and control patients do not differ in CAL at baseline.

The beneficial effect was marginally documented after 3 months due to the limited size of this trial. However, after 6 months the positive treatment outcomes in the test patients in reducing BoP and PPD as well as increasing CAL were clearly demonstrated. Also, the outcomes of mean PPD, mean CAL and mean BoP percentage differed significantly between test and control patients at the 6-month evaluation. Although mean PPD and mean CAL no longer differed between test and control patients after 12 months, the repeated application of PDT may be recommended in the management of residual periodontal pockets during supportive therapy.

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Supporting Information

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

Appendix S1. CONSORT Statement 2001.

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Clinical Relevance

Scientific rationale for the study: The role of PDT in the maintenance of residual pockets during supportive periodontal care has not been elucidated convincingly. Only one study reported on the clinical effects of a single application of PDT in maintenance patients. Hence, the present study investigated whether or not *repeated* PDT added benefits to the conventional treatment of residual pockets in patients enrolled in SPT.
Principal findings: Greater PPD reductions were observed in PDT-treated test sites compared with mechanically debrided residual pockets at 6 months. Significant CAL gain and PPD reduction was noted for test, but not for control sites. BoP percentages decreased significantly in test, but not in control sites.
Practical implications: This proof-of-principle study has demonstrated that PDT provided additional clinical benefits compared with conventional instrumentation and may therefore be recommended for the adjunct instrumentation of residual pockets during maintenance debridement.