The Application of Photodynamic Therapy in the Treatment of Periodontal and Peri-Implant Infections

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Running title: Photodynamic therapy in periodontal and peri-implant therapy
Abstract

Antimicrobial photodynamic therapy (PDT) has lately attracted much attention among clinicians for the treatment of pathogenic biofilm associated with periodontitis and peri-implantitis. However, at present, the data from randomized controlled clinical studies (RCTs) are still limited and, to some extent, controversial which makes it difficult to provide appropriate recommendations for the clinician.

Therefore, the aims of the present study were: a) to provide an overview on the current evidence from randomized controlled clinical studies evaluating the potential clinical benefit for the additional use of PDT to subgingival mechanical debridement (i.e. scaling and root planing (SRP)) alone in nonsurgical periodontal therapy and b) to provide clinical recommendations for the use of PDT in periodontal practice.

Based on the available evidence from RCTs the following conclusions can be drawn:

- In patients with chronic periodontitis (ChP) the combination of SRP and PDT may result in substantially higher short-term clinical improvements evidenced by probing depth (PD) and/or bleeding on probing (BOP) reductions compared to SRP alone.
- In patients with aggressive periodontitis (AgP) the use of PDT cannot replace the systemic administration of amoxicillin and metronidazole. Due to lack of data, no conclusions can be made to what extent PDT may replace the use of systemic antibiotics in patients with ChP.
- Limited evidence from one study indicates that PDT may represent a possible alternative to local antibiotics in patients with incipient peri-implantitis.

Key Words: Photodynamic therapy, chronic periodontitis, aggressive periodontitis, peri-implantitis, antibiotics, bacterial biofilm
Biological rationale

Periodontitis is a multifactorial disease which is associated with loss of the supporting tissues (i.e. periodontal ligament and alveolar bone) around the tooth.\(^1\) A major objective of periodontal therapy is to remove soft and hard, supra- and subgingival deposits from the root surface in order to stop disease progression.\(^2\) Numerous studies have reported significant improvements of clinical and microbial parameters following nonsurgical periodontal therapy.\(^3\)-\(^6\)

Despite the fact that non-surgical periodontal treatment may result in significant clinical improvements in the great majority of cases, evidence indicates that none of the currently available instrumentation techniques are effective in completely eliminating subgingival bacterial biofilm.\(^7\) These limitations may be attributed to several factors such as the complex anatomy of teeth (i.e. furcation involvements, root invaginations), presence of intrabony defects, etc., mechanical limitations related to the size of instruments or invasion of periodontal pathogens into the surrounding soft tissues or possible recolonization of periodontal pockets from other diseased sites or intraoral niches.\(^8\) Power-driven instruments (i.e. sonic and ultrasonic scalers) have been introduced to further enhance the effectiveness of scaling and root planing (SRP). However, findings from clinical studies have also shown comparative outcomes following power-driven and manual instrumentation.\(^9\)

Thus, the current evidence indicates that nonsurgical periodontal treatment may result in substantial clinical improvements in the great majority of cases, but none of the currently available instrumentation techniques are able to completely eliminate subgingival bacteria and calculus.\(^7\)

Photodynamic therapy (PDT), also called photoradiation therapy, phototherapy, photochemotherapy, photo-activated disinfection (PAD), or light-activated disinfection (LAD), was introduced in medical therapy in 1904 as the light-induced inactivation of
cells, microorganisms or molecules and involves the combination of visible light, usually through the use of a diode laser and a photosensitizer.\textsuperscript{10} The photosensitizer is a substance that is capable to absorb light of a specific wavelength and transform it into useful energy. Each factor is harmless by itself, but when combined they can produce lethal cytotoxic agents that can selectively destroy cells.\textsuperscript{11}

Thus, PDT has been proposed as a modality to reduce bacterial load or even to eliminate periodontal pathogens.\textsuperscript{12, 13} The action mechanism of PDT has been extensively described previously.\textsuperscript{14} Briefly, upon illumination the photosensitizer is excited from the ground state to the triplet state. The longer lifetime of the triplet state enables the interaction of the excited photosensitizer with the surrounding molecules. It is anticipated that the generation of the cytotoxic species produced during PDT occurs while in this state.\textsuperscript{15, 16} The cytotoxic product, usually singlet oxygen ($^1\text{O}_2$), cannot migrate at a distance more than 0.02 \(\mu\)m after its formation, thus making it ideal for local application of PDT, without endangering distant molecules, cells or organs.\textsuperscript{16}

In vitro studies have revealed that light from a Helium/Neon (HE/Ne) laser or a Gallium-Aluminum-Arsenide (GaAlAs) laser, in combination with appropriate photosensitizers, can achieve a significant reduction in the viability of both aerobic and anaerobic bacteria in a solution of subgingival plaque from patients with chronic periodontitis.\textsuperscript{17, 18} Dobson & Wilson (1992) have shown that bacteria associated with periodontal disease can be killed through photosensitization with Toluidine Blue – O (TBO) and irradiation with a He/Ne soft laser.\textsuperscript{19} Subsequent studies in animals have shown PDT was distinctly advantageous in reducing the periodontal signs of redness and bleeding on probing, and significantly suppressed \textit{P. gingivalis}.\textsuperscript{20}
During the last decade, a considerable interest has evolved in evaluating the use of PDT in the treatment of periodontal and peri-implant infections. However, despite the relatively abundant literature, the data on the clinical relevance of PDT when used in conjunction with mechanical therapy are still controversial and difficult to interpret for the clinician.

Therefore, the aims of this review article are: a) to provide an overview of the current evidence from randomized controlled clinical studies (RCTs) evaluating the potential clinical benefit for the additional use of PDT to mechanical debridement alone in nonsurgical periodontal therapy and b) to provide clinical recommendations for the use of PDT in periodontal practice.

Use of PDT as adjunct to nonsurgical periodontal therapy in patients with untreated chronic periodontitis (ChP)

A total of 18 RCTs have compared the potential additional benefit of PDT to SRP with the use of SRP alone in untreated periodontitis patients (Table 1). Eight out of the 18 studies have reported statistically significantly higher improvements in probing depth (PD) reduction and/or clinical attachment (CAL) gain following SRP + PDT compared to SRP alone,\textsuperscript{21-28 ENREF_22} while the rest of 10 studies have failed to reveal statistically significant differences in these parameters.\textsuperscript{29,30-38} An additional improvement for the reduction of bleeding on probing (BOP) following the use of PDT was reported in 5 out of the 19 papers.\textsuperscript{22, 26, 28, 31, 32} Changes of microbiological parameters were evaluated in 8 of 18 studies. Four studies have found a statistically significant effect of the additional use of PDT on the reduction of periodontal pathogens,\textsuperscript{28, 35, 37, 38} while 4 studies have failed to reveal any differences between the treatments groups.\textsuperscript{31, 33, 36, 39} Three out of the 18 studies have also evaluated the
changes in terms of various inflammatory markers. All three studies have revealed statistically significantly higher reductions in the investigated inflammatory markers following the additional use of PDT (Table 1).

Use of PDT as adjunct to nonsurgical periodontal therapy in patients with Aggressive Periodontitis (AgP)

Two RCTs have compared treatment with SRP + PDT to treatment with SRP alone, and another study has compared SRP alone to PDT alone (i.e. without any mechanical debridement). (Table 2). While one study has found in deep pockets (PD ≥ 7 mm) statistically significant improvements in terms of PD reduction and CAL gain and significantly less periodontal pathogens of the red and orange complex and IL-1β/IL-10 ratio following treatment with PDT, the other study has failed to reveal any statistical significant differences in the evaluated clinical and microbiological parameters between the treatments (Table 2).

Use of PDT as adjunct to nonsurgical periodontal therapy in maintenance periodontitis patients

Eight RCTs have evaluated the potential additional benefit of PDT to SRP as compared with the use of SRP alone in maintenance patients (Table 3). Two out of the 8 studies have reported statistically significantly higher improvements in PD reduction and CAL gain following SRP + PDT compared to SRP alone. An additional improvement for the reduction of BOP was reported in 5 out of the 8 studies.
While three studies have found a statistically significant effect of the additional use of PDT on the reduction of periodontal pathogens,\textsuperscript{46-48} three other studies have failed to reveal statistically significant differences between the treatment groups.\textsuperscript{49-51} Three out of the 8 studies have also evaluated the changes in terms of inflammatory markers.\textsuperscript{47, 50, 52} Two studies have revealed statistically significantly higher reductions in the investigated inflammatory markers following the use of PDT,\textsuperscript{47, 50} while one study detected no differences \textsuperscript{52} (Table 3).

**Use of PDT as an alternative to systemic or local antibiotics**

An extremely important aspect which needs to be kept in mind when considering the use of PDT, is the lack of bacterial resistance which gains even more importance in the light of the worldwide increase in bacterial resistance against antibiotics.\textsuperscript{53} Thus, its repeated application in conjunction with mechanical debridement may represent a valuable future option for treating periodontal and peri-implant infections.\textsuperscript{11, 54} At present, there is however limited evidence on the possibility of PDT to replace systemic or local antibiotics.

A recent RCT study has evaluated the treatment of patients with AgP by means of nonsurgical periodontal therapy in conjunction with either systemic administration of amoxicillin and metronidazole or two-times topical application of PDT.\textsuperscript{55, 56} The results have shown that both treatment protocols resulted in statistically significant improvements in PD reduction, gain of CAL and improvement in BOP compared to baseline. The systemic use of amoxicillin and metronidazole yielded however, at both 3 and 6 months, statistically significantly higher reductions in mean PD compared with the treatment using PDT.\textsuperscript{55, 56} The most important clinical finding was the change in the total number of pockets ≥ 7 mm following both treatment protocols. In the PDT group, the total number of pockets ≥ 7 mm was reduced from 137 to 45 with the
corresponding values of 141 and 3 in the amoxicillin and metronidazole group. Moreover, compared to the results at 3 months, at 6 months, an additional decrease in the number of pockets ≥ 7 mm was measured.\cite{55, 56} On the other hand, the use of PDT has also led to statistically and clinically significant improvements compared to baseline, although the number of residual pockets needing further therapy was substantially higher compared with the use of systemic antibiotics (e.g. 45 vs. 3). The changes in clinical parameters were also accompanied by changes in the concentration of matrix metalloproteinases 8 and 9 (MMP-8 and -9) in the gingival crevicular fluid (GCF).\cite{57} However, while in the antibiotic group, a statistically significant decrease of MMP-8 GCF level at both 3 and 6 months post treatment was observed, these changes were not significant in the PDT group.\cite{57} Taken together, the available data suggest a rather limited clinical benefit of using PDT in the treatment of patients with AgP.\cite{40, 42, 43, 56, 57} Thus, at the time being, PDT cannot be recommended as a replacement for systemic antibiotics in patients with AgP. On the other hand, no studies have compared the use of PDT or systemic antibiotics in conjunction with nonsurgical treatment in patients with ChP. Therefore, at present no conclusions can be made regarding this aspect.

The use of PDT as a potential alternative to local antibiotics has been recently evaluated in a RCT study comparing nonsurgical treatment of incipient peri-implantitis (sites with PD 4-6 mm, BOP positive and radiographic bone loss ≥2 mm) by means of mechanical debridement followed by either use of local antibiotics (e.g. minocycline) or application of PDT. The results at six months and at one year have failed to reveal statistically or clinically significant differences between the two treatment protocols, thus suggesting that PDT may represent a valuable alternative to local antibiotics during nonsurgical treatment of incipient peri-implantitis.\cite{58, 59}
Conclusions

Based on the available evidence from RCTs the following conclusions can be drawn:

- In patients with ChP the combination of SRP and PDT may result in substantially higher short-term clinical improvements evidenced by probing depth (PD) and/or bleeding on probing (BOP) reductions compared to SRP alone.

- In patients with aggressive periodontitis (AgP) the use of PDT cannot replace the systemic administration of amoxicillin and metronidazole. Due to lack of data, no conclusions can be made to what extent PDT may replace the use of systemic antibiotics in patients with ChP.

- Limited evidence from one study indicates that PDT may represent a possible alternative to local antibiotics in patients with incipient peri-implantitis.

Clinical recommendations

1. In patients with ChP, clinicians may consider the use of PDT in conjunction with subgingival mechanical debridement. However, due to limitations in time and costs, the use of PDT appears to be more suitable in the maintenance phase of therapy.

2. At present, the use of PDT cannot be recommended as an alternative to systemic antibiotics in the treatment of AgP or severe cases of ChP.
**Figures 1 and 2: Clinical applications of PDT**

Figure 1. Application of the phenothiazine chloride dye following subgingival SRP

Figure 2. Application of the low level laser light into the pocket
Tables 1, 2 and 3: Randomized clinical controlled studies, with SRP as control group

Table 1. Photodynamic therapy as initial periodontal therapy in patients with ChP (data of 18 studies reported in 19 publications)

<table>
<thead>
<tr>
<th>Study Author Year Country Type</th>
<th>Diagnosis</th>
<th>Patients Female/male Age Smokers</th>
<th>Study duration</th>
<th>Treatment</th>
<th>Photosensitizer Laser</th>
<th>Laser parameters</th>
<th>Microbiology</th>
<th>Immunology</th>
<th>PD reduction (mm) CAL gain (mm) BOP reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Zahrani &amp; Austah (2011)21</td>
<td>ChP</td>
<td>n=17</td>
<td>3 months</td>
<td>Test: SRP + PDT (1x) Control: SRP</td>
<td>Methylene blue (Ondine`s Periowave, Ondine Biopharma, Vancouver, BC) Diode laser</td>
<td>Wavelength 670 nm</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Test: PD: from 5.60±0.83 to 3.84±0.85 * CAL: from 6.30±1.44 to 4.70±1.27 * BOP: from 74.50±21.50 to 41.90±22.30 (n.s.) Control: PD: from 5.35±0.46 3.90±0.75 CAL: from 6.18±1.44 to 4.80±1.45 BOP: from 68.00±23.00 to 45.60 to 19.50.</td>
</tr>
<tr>
<td>Alwaeli et al. (2015)22</td>
<td>ChP</td>
<td>N=16</td>
<td>12 months</td>
<td>Test: SRP+PDT Control: SRP</td>
<td>Phenothiazine chloride Diode Lasers (HELBO, Photodynamic Systems, Grieskirchen, Austria)</td>
<td>Wavelength 660 nm, Output power 100mW Application time: 10s/site, 6 sites/tooth</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Test: PD: 1.51±1.54* CAL: 1.48±1.89* BOP: 25%* Control: PD: 0.66±1.66 CAL: 0.13±1.7 BOP: 54%</td>
</tr>
<tr>
<td>Andersen et al. (2007)23</td>
<td>ChP</td>
<td>N=33</td>
<td>12 weeks</td>
<td>Test 1: PDT Test 2: SRP+PDT Control: SRP</td>
<td>Methylene blue (Periowave) Diode laser (Periowave)</td>
<td>Wavelength 670 nm Energy density 10-20 J/cm² Max. power 150 mW Application time 60s/site</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>Test 1: PD: 0.67±0.44 (n.r.) CAL: 0.14±0.65 (n.r.) BOP: 73% (n.r.) Test 2: PD: 1.11±0.53* CAL: 0.86±0.61* BOP: 59% (n.s.) Control: PD: 0.74±0.43</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>n</td>
<td>Age</td>
<td>Treatment Details</td>
<td>Wavelength</td>
<td>Power</td>
<td>Diameter</td>
<td>Duration</td>
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</table>
| Balata et al. (2013)          | Brazil      | Split-mouth, RCT | 22  | 43.18 (31-62) | Test: SRP (ultrasonic)+PDT  
Control: SRP (ultrasonic)  
Methylene blue 0.005% Low power laser (AsGaAl, Photon Lasell, Sao Paolo, Brazil) | 660nm       | 100mW | 60 μm   | 90s/site  | Not analysed  
CAL: 0.36±0.35  
BOP: 56%  
Test: PD decrease from 5.11±0.56 to 2.83±0.47 (n.s.)  
CAL change from 5.49±0.76 to 3.41±0.84 (n.s.)  
BOP: from 61.58±15.64 to 36.73±19.72 (n.s.)  
Control: PD decrease from 5.15±0.46 to 2.83±0.40  
CAL change from 5.53±0.54 to 3.39±0.51  
BOP: from 62.23±16.91 to 38.49±20.52 | |
| Berakdar et al. (2012)        | Germany     | Split-mouth, RCT | 22  | 59.3±11.7 | Test: SRP+PDT  
Control: SRP  
Methylene blue 0.005%  
Diode laser (Periowave) | 670 nm       | 150 mW | 60s     | Not analysed  | Not analysed  
PD: 2.9±0.8*  
CAL: n.s. changes n.r.  
BOP: from 100% to 13.6% n.s.  
Control: PD: 2.4±0.8  
BOP: from 100% to 22.7%  
CAL gain: n.s. | |
| Betsy et al. (2014)           | India       | Parallel, RCT | 88  | 51/39 39.6±8.7  | Test: SRP+PDT  
Control: SRP  
Phenothiazine chloride trihydrate (freshly prepared, Sigma-Aldrich, USA)  
Diode laser (CNI Opto-electronics Tech., China) | 655 nm, output power 1W  
Power density 60 mW/cm²  
Diameter tip 0.5 mm  
Application time 60s/site | Not analysed  | Not analysed  
PD: from 5.7 (5.0-6.0, 1.0) to 3.0 (2.0-6.0, 1.0)*  
CAL: from 6.5 (5.0-8.0, 1.4) to 4.0 (2.6-7.0, 2.0)*  
BOP: data n.r.  
Control: PD: from 5.5 (4.2-6.0, 1.0) to 4.0 (2.0-6.0, 1.0)  
CAL: from 6.0 (4.2-8.0, 1.7) to 4.5 (2.0-7.0, 2.0)  
BOP: data n.r.  
Test: Median (inter-quartile range) | |
| Braun et al. (2008)           |            |              | 20  | 11/9  | Test: SRP +PDT  
Phenothiazine chloride | 660nm       | Not analysed  | Not analysed  |  
PD: from 3.0 to 2.0  
CAL: from 4.0 to 3.5  
BOP: data n.r.  
Test: Median (inter-quartile range) | |
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>ChP</th>
<th>N</th>
<th>Age (Mean ± SD)</th>
<th>Gender</th>
<th>Duration</th>
<th>Treatment</th>
<th>Control</th>
<th>Device Characteristics</th>
<th>Test Results</th>
<th>Control Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany Split-mouth</td>
<td></td>
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<td></td>
<td></td>
<td>46.6 ± 6.1</td>
<td>no smokers</td>
<td></td>
<td>Power output 100 mW</td>
<td>SRP (HELBO Photodynamic Sys., Austria)</td>
<td>PD: 46.6 ± 6.1 *</td>
<td>CAL: 90 ± 6.1 *</td>
<td>No significant differences between the groups for Aa, Pg, Tf, Td, Pi, Pm, Fn, Cr, En, Ec, Cs</td>
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<tr>
<td>Christodoulides et al. (2008)</td>
<td></td>
<td>Parallel, RCT</td>
<td>ChP</td>
<td>24</td>
<td>13/11</td>
<td>3 smokers</td>
<td>6 months</td>
<td>Test: SRP + PDT</td>
<td>SRP</td>
<td>Wavelength 670 nm Output power 75 mW Application time 60 s/tooth</td>
<td>PD: 3.6 (0.6, 5.3, 3.2)*</td>
<td>CAL: 7.04 (1.63, 9.11, 5.33)*</td>
<td>Not analysed</td>
</tr>
<tr>
<td>Dilsiz et al. (2013)</td>
<td>Turkey</td>
<td>Split-mouth, RCT</td>
<td>ChP</td>
<td>24</td>
<td>14/10</td>
<td>no smokers</td>
<td>6 months</td>
<td>Test 1: PDT + SRP</td>
<td>SRP</td>
<td>Wavelength 808 nm Output power 100 mW Application time 60 s/site</td>
<td>PD: 9.4 ± 0.7</td>
<td>CAL: 5.0 ± 0.5</td>
<td>Not analysed</td>
</tr>
<tr>
<td>Ge et al. (2011)</td>
<td>China</td>
<td>Parallel, RCT</td>
<td>ChP</td>
<td>58</td>
<td>28/30</td>
<td>9 smokers</td>
<td>12 weeks</td>
<td>Test 1: SRP + PDT (once)</td>
<td>SRP</td>
<td>Wavelength 670 nm Output power 140 mW Energy density 21 J/cm²</td>
<td>Not analysed</td>
<td>Not analysed</td>
<td>No significant difference for PD reduction and CAL gain. Significant higher BOP reduction in both test groups compared to the</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>ChP</td>
<td>N</td>
<td>Months</td>
<td>Test:</td>
<td>Control:</td>
<td>Application</td>
<td>Wavelength</td>
<td>Energy Density</td>
<td>Application Time</td>
<td>Results</td>
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<tr>
<td>Luchesi et al. (2013)</td>
<td>Brazil</td>
<td>Parallel, RCT</td>
<td>ChP</td>
<td>37</td>
<td>6</td>
<td>SRP+PDT</td>
<td>SRP+non activated laser</td>
<td>Methylene Blue Diode laser (Thera Lase DMC, Sao Paulo, Brazil)</td>
<td>660 nm, power output 60 mW</td>
<td>129 J/cm²</td>
<td>60s/site</td>
<td>Significant decrease in P.g. and T.f. in PDT group, however no significant differences between the groups.</td>
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<tr>
<td>Lui et al. (2011)</td>
<td>China</td>
<td>Split-mouth, RCT</td>
<td>ChP</td>
<td>50</td>
<td>3</td>
<td>SRP+PDT</td>
<td>SRP</td>
<td>Methylene blue Diode laser (Ezlase, BIOLASE Techn., USA)</td>
<td>940 nm</td>
<td>Energy 1 W</td>
<td>30 s/tooth</td>
<td>4 J/cm² Fibre tip diameter 300 μm</td>
<td>Not analysed</td>
</tr>
<tr>
<td>Mettraux &amp; Hüsler (2011)</td>
<td>Switzerland</td>
<td>Split-mouth, RCT</td>
<td>ChP</td>
<td>19</td>
<td>3</td>
<td>SRP+PDT</td>
<td>SRP</td>
<td>Methylene Blue Softlaser (Lasotronic MED-701, Orcos Medical, Switzerland)</td>
<td>670nm</td>
<td>Energy output 330 mW</td>
<td>31 J/cm²</td>
<td>Application: transgingival 1min/site Fiber tip diameter 8mm</td>
<td>Significant reduction of the total bacterial load in favour to PDT. Significant reduction of T.d. in both groups. Not analysed</td>
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<tr>
<td>Polansky et al.</td>
<td>ChP</td>
<td></td>
<td></td>
<td>58</td>
<td>3</td>
<td>SRP+ + Phenothiazine</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>No significant differences between the groups. Test: PD: 1.59±1.11 (n.s.) CAL: 0.78±1.54 (n.s.) BOP: from 100% to 37.50% (n.s.) Control: PD: 1.50±1.73 CAL: 1.00±1.69 BOP: from 100% to 55% Changes from baseline to 3 m: Test: PD: from 4.7±0.8 to 3.1±0.1 (n.s.) REC: from 0.8±1.2 to 1.8±1.2 (n.s.) BOP from 94±06 to 39±14 (n.s.) Control: PD from 4.5±0.7 to 3.2 ± 0.3 REC from 1.0±1.1 to 1.8±1.3 BOP from 92±10 to 43±12 Test: PD: 2.1±1.4 (n.s.) CAL: 1.5±1.3 (n.s.) Control: PD: 1.5±1.6 CAL: 0.9±1.7</td>
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<td>Study</td>
<td>Country</td>
<td>Design</td>
<td>N</td>
<td>Age (years)</td>
<td>Gender</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
<td>Wavelength</td>
<td>Power Density</td>
<td>Application Time</td>
<td>PD Reduction</td>
<td>CAL Reduction</td>
<td>BOP Reduction</td>
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<td>(2009)&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Austria</td>
<td>Parallel, RCT</td>
<td>36/22</td>
<td>48.7 (25-67)</td>
<td>7 smokers</td>
<td>PDT</td>
<td>Control: SRP (ultrasound)</td>
<td>680 nm</td>
<td>75 mW</td>
<td>60 s/site</td>
<td>difference for the reduction of P.g. between the groups; significant reduction of P.g. at 3 months compared to baseline in both groups.</td>
<td></td>
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<tr>
<td>Queiroz et al. (2014)&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Brasil</td>
<td>Split-mouth, RCT</td>
<td>N=20</td>
<td>46.05±6.38 (35-55)</td>
<td>smokers only</td>
<td>Test: SRP+PDT</td>
<td>Control: SRP</td>
<td>Wavelength</td>
<td>Power Density</td>
<td>Application Time</td>
<td>40 subgingival bacteria were analysed: no significant differences between the groups or the timepoints</td>
<td>Presented in Queiroz et al. 2015&lt;sup&gt;29&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Queiroz et al. (2015)&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Brasil</td>
<td>Split-mouth, RCT</td>
<td>N=20</td>
<td>46.05±6.38 (35-55)</td>
<td>smokers only</td>
<td>Test: SRP+PDT</td>
<td>Control: SRP</td>
<td>Presented in Queiroz et al. 2014&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Significant reduction of IL-1β at 1 wk in favour to PDT. Significant reduction of MMP 8 at 12 wk in favour to PDT.</td>
<td>No significant differences between the groups.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigusch et al. (2010)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Parallel</td>
<td>Parallel, RCT</td>
<td>N=24</td>
<td>32-58</td>
<td>no smokers</td>
<td>Test: SRP + PDT</td>
<td>Control: SRP</td>
<td>Wavelength</td>
<td>Power Density</td>
<td>Application Time</td>
<td>Significant reduction of F.n. in the test group compared to the control group.</td>
<td>Not analysed</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- PD: from 5.79±1 to 4.55±1.14 (n.s.)
- CAL: from 6.60±1.37 to 5.25±1.41 (n.s.)
- BOP: from 100 to 47% (n.s.)
- Control: PD: from 5.53±1.15 to 4.50±1.33
- CAL: from 6.59±1.23 to 5.24±1.48
- BOP: from 100% to 59%

**Assessment:**
- Queiroz et al. 2014: Significant reduction of IL-1β at 1 wk in favour to PDT. Significant reduction of MMP 8 at 12 wk in favour to PDT.
- Sigusch et al. 2010: Significant difference at 12 weeks between the groups regarding mean PD* (data n.r.) Median, interquartile range: CAL: 2.45, 0.68*
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Setting</th>
<th>N</th>
<th>Age (Range)</th>
<th>Sex</th>
<th>Treatment Details</th>
<th>Baseline</th>
<th>Intervention Details</th>
<th>Outcome</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Srikanth et al.  | India   | Split-mouth, RCT | ChP      | 39    | 30-55       |            | Test 1: SRP + PDT  
Test 2: SRP + laser without photosensitizer  
Control: SRP  
Indocyanine green (Aurogreen Aurolabs)  
Diode laser (firm not specified)  
Wavelength: 810 nm  
Power output: 0.7 W  
Application time: 5 s/site  
Significant decrease of the % of viable bacteria in favour to PDT | PD: from 5.81±0.89 to 3.07±0.68 (n.s.)  
CAL: from 5.00±0.80 to 2.53±0.58 (n.s.)  
BOP: n.r.  
Test 2:  
PD: 5.34±0.34 to 3.15±0.43 (n.s.)  
CAL: from 4.57±0.57 to 2.96±0.44*  
BOP: n.r.  
Control:  
PD: from 5.07±0.27 to 3.01±0.21  
CAL: from 4.50±0.50 to 3.10±0.01  
BOP: n.r. | Not analysed |
| Theodoro et al.  | Brazil  | Split-mouth, RCT | ChP      | 33    | 21/12       |            | Test 1: SRP + PDT  
Test 2: SRP + Placebo PDT  
Control: SRP  
Phenothiazine 100 μg/ml  
(Sigma Chemical, St. Louis, USA)  
Diode Laser (BioWave)  
Wavelength: 660 nm  
Power output: 30 mW  
Power intensity: 0.4 W/cm²  
Energy density: 64.28 J/cm²  
Application time: 150 s/site  
Spot size: 0.07 cm²  
A.a., P.g., P.i., T.f., P.n.  
Significant differences in all investigated periodontopathogens in favour to SRP + PDT. | PD: from 5.75±1.44 to 3.42±1.15 (n.s.)  
CAL: from 6.52±2.11 to 4.96±2.07 (n.s.)  
BOP: from 93.9% to 45.5% (n.s.)  
Test 2:  
PD: from 5.88±1.26 to 2.48±1.0 (n.s.)  
CAL: from 6.37±1.56 to 4.38±1.82 (n.s.)  
BOP: from 97% to 39.4% (n.s.)  
Control:  
PD: from 5.81±1.0 to 3.84±0.8 | Not analysed |
n.s.: not significant; n.r.: not reported; REC: recession; IL: Interleukin; MMP: Matrixmetalloproteinases; T.f.: Tannerella forsythia, P.g.: Porphyromonas gingivalis; A.a.: Aggregatibacter actinomycetemcomitans; T.d.: Treponema denticola; F.n.: Fusobacterium nucleatum; P.i.: Prevotella intermedia; C.r.: Campylobacter rectus; E.c.: Eikenella corrodens; P.m.: Parvimonas micra; E.n.: Eubacterium nodatum; C.s.: Capnocytophaga Spp.
Table 2. Photodynamic therapy as initial periodontal therapy in patients with AgP (data of 3 studies reported in 4 publications)

<table>
<thead>
<tr>
<th>Study Author Year Country Type</th>
<th>Diagnosis</th>
<th>Patients Female/male Age Smokers</th>
<th>Study duration</th>
<th>Treatment</th>
<th>Photosensitizer Laser</th>
<th>Laser parameters</th>
<th>Microbiology</th>
<th>Immunology</th>
<th>PD reduction (mm) CAL gain (mm) BOP reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitsazi et al. (2014) Iran Split-mouth, RCT</td>
<td>AgP</td>
<td>N=24 15/9 29</td>
<td>3 months</td>
<td>Test: SRP+PDT Control: SRP</td>
<td>Toluidine Blue photosensitize (Sigma chemical Co., St. Louis, Mo) Diode Laser (HANDY Laser, USA)</td>
<td>Wavelength 670-690 nm Power 75 mW Application time 2 min/site</td>
<td>No significant differences for the levels of A.a. were observed between the groups</td>
<td>Not analysed</td>
<td>Test: PD change: from 5.79±1.06 to 4.29±0.95 (n.s.) CAL change: from 6.58±0.83 to 5.29±1.26 (n.s.) BOP change: from 91.7% to 75% (n.s.) Control: PD change: from 5.45±0.71 to 4.54±0.88 CAL change: from 6.25±0.10 to 5.50±0.18 BOP change: from 100% to 37.5%</td>
</tr>
<tr>
<td>Moreira et al. (2015) Brazil Split-mouth, RCT</td>
<td>AgP</td>
<td>N=20 30.6±4.25 18/2 non smokers</td>
<td>3 months</td>
<td>Test: SRP+PDT Control: SRP</td>
<td>Phenothiazine chloride (HELBO Blue Photodynamic systems, Grieskirchen, Austria) Diode laser (HELBO Minilaser 2075 F, Grieskirchen, Austria)</td>
<td>Wavelength 670 nm Maximum power 75 mW Fiber tip diameter 0.6 Mm Energy density 2.49 J/cm² Application time 10s/site</td>
<td>Significant less periodontal pathogens of the red and orange complex in the test group.</td>
<td>Significant less IL-1/IL-10 ratio in the test group.</td>
<td>No differences between the groups for moderate pockets. In deep pockets (PD&gt;7mm), significant PD decrease and CAL gain in favour to PDT: Test (deep pockets): PD from 7.73±0.87 to 3.77±0.97 * CAL: from 7.84±0.89 to 5.07±0.64* BOP: from 144±60 to 22±13.75 (n.s.) Control (deep pockets): PD: from 7.68±0.92 to 5.12±0.8 CAL: from 7.75±1.21 to 6.00±1.04. BOP: from 154±64.16 to 36±15</td>
</tr>
<tr>
<td>Study</td>
<td>AgP</td>
<td>N=10</td>
<td>3 months</td>
<td>Test: PDT</td>
<td>Control: SRP</td>
<td>Phenothiazine chloride (Helbo blue photosensitizer)</td>
<td>Minilaser (HELBO, Grieskirchen, Austria)</td>
<td>Wavelength 660 nm, Power 0.06W/cm², fluency 212.23 J/cm², Application time 10s/site</td>
<td>40 subgingival species were determined. PDT reduced significantly A.a. compared to SRP; SRP is more efficient for the red complex than PDT. In PDT a recolonisation of T.f. and P.g. was observed. Published in Oliveira et al. 2007</td>
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<tr>
<td>Novaes et al. (2012)</td>
<td>AgP</td>
<td>8/2</td>
<td>31 (18-35) nonsmokers</td>
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<tr>
<td>Brazil</td>
<td>Split-mouth, RCT</td>
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<tr>
<td>Oliveira et al. (2007)</td>
<td>AgP</td>
<td>8/2</td>
<td>31 (18-35) nonsmokers</td>
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<tr>
<td>Brazil</td>
<td>Split-mouth, RCT</td>
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</tbody>
</table>

n.s.: not significant; n.r.: not reported; REC: recession; IL: Interleukin; T.f.: Tannerella forsythia, P.g.: Porphyromonas gingivalis; A.a.: Aggregatibacter actinomycetemcomitans; T.d.: Treponema denticola; F.n.: Fusobacterium nucleatum; P.i.: Prevotella intermedia; C.r.: Campylobacter rectus; E.c.: Eikenella corrodens; P.m.: Parvimonas micra; E.n.: Eubacterium nodatum; C.s.: Capnocytophaga Spp.
Table 3. Photodynamic therapy in Supportive Periodontal Therapy (data of 8 studies reported in 9 publications)

<table>
<thead>
<tr>
<th>Study Author Year Country Type</th>
<th>Diagnosis</th>
<th>Patients Female/male Age Smokers</th>
<th>Study duration</th>
<th>Treatment</th>
<th>Photosensitizer Laser</th>
<th>Laser parameters</th>
<th>Microbiology</th>
<th>Immunology</th>
<th>PD reduction (mm) CAL gain (mm) BOP reduction (%)</th>
</tr>
</thead>
</table>
| Campos et al. (2013) 
Brazil 
Split-mouth, RCT | ChP       | n=13 8/5 48.15±7.53 no smokers   | 3 months      | Test: SRP+PDT  
Control: SRP | Methylene blue  
10 mg/ml Diode laser  
(Thera Laser-DMC, Brazil) | Wavelength 660 nm  
Power output 60 mW  
Energy density 129 J/cm²  
Application time 60s/site | Not analysed | Not analysed | Test: PD: 2.17±0.91*  
CAL: 1.43±1.61*  
BOP: 77.78*  
Control: PD: 1.14±1.53  
CAL: 0.51±0.76*  
BOP: 40% |
| Cappuyns et al. (2012) 
Switzerland 
Split-mouth, RCT | ChP       | N=29 8/21 52 (36-74) 12 smokers | 6 months      | Test 1: SRP+PDT  
Test 2: SRP+Diode Soft Laser  
(DSL) Control: SRP | Phenothiazine chloride  
(HELBO Blue Photosensitizer)  
Diode Laser  
(HELBO Photodynamic Sys) | Wavelength 660 nm  
Power output 40 mW  
Application time 60s/site | A.a. P.g., T.f., T.d., total bacterial load  
No significant difference in the investigated microbiological parameters. However, P.g., T.f., and T.d. were suppressed stronger in the PDT group. | Not analysed | Test 1: PD: from 5.6±1.2 to 3.8±1.2 (n.s.)  
REC: from 0.8±1.3 to 1.0±1.3 (n.s.)  
BOP: at 6m 15% (n.s.)  
Test 2: PD: from 5.5±0.7 to 3.8±1.0 (n.s.)  
REC: from 0.8±1.7 to 1.3±1.8 (n.s.)  
BOP: at 6m18% (n.s.)  
Control: PD: from 5.5±1.0 to 3.6±1.1  
REC: from 0.7±1.3 to 1.0±1.3  
BOP: at 6m 12% |
| Chondros et al. (2009) 
Netherlands 
Parallel, RCT | ChP       | N=24 14/10 50.6±9.2 7 smokers | 6 months      | Test: SRP+PDT  
Control: SRP | Phenothiazine chloride  
(HELBO Blue Photosensitizer)  
Diode laser  
(HELBO minilaser 2075F) | Wavelength 670 nm  
Output power 75 mW/cm²  
Application time 60 s/tooth | A.a., P.g., P.i., T.f., T.d., F.m., F.n., C.r., E.c., C.s.  
Significant reduction of T.d., E.c., C.s. was found in favour of SRP+PDT | Not analysed | Test: PD: 0.8±0.5 (n.s.)  
CAL: 0.7±0.7 (n.s.)  
BOP: from 15±12 to 12±05*  
Control: PD: 0.9±0.8  
CAL: 0.5±0.6  
BOP: from 19±14 to 18±08 |
<p>| Study | Country | Design | N | Age | Follow-up | Test 1 | Test 2 | Control | Wavelength | Power | Application | No changes | Effect | Test 1 | Test 2 | Control | IL-1β | IL-1ra | IL-10 | IL-8 | IL-17 | IFN-γ | IL-4 | See | GIAPPINOULOU et al. (2012)&lt;sup&gt;52&lt;/sup&gt; | Switzerland | Split-mouth, RCT | ChP | 29 | 21 | 8/21 | 52 (36-74) | 6 months | Test 1: SRP+PDT | Test 2: SRP+diode laser (DL) | Control: SRP | Phenothiazine chloride (HELBO Blue Photosensitizer) | Diode Laser (Helbo Photodynamic Sys, Grieskirchen, Austria) | Diode Laser (Helbo Photodynamic Sys, Grieskirchen, Austria) | Analysed in Cappuyns et al. 2012 | Levels of 13 cytokines and 9 acute-phase proteins were measured. No significant differences were observed between the groups at any time point. | Test 1: PD: 1.6±1.20 (n.s.) | CAL: 0.95±1.38 (n.s.) | BOP: from 100% to 28.57% (n.s.) | Test 2: PD: 1.29±1.22 (n.s.) | CAL: 0.69±1.30 (n.s.) | BOP: from 100% to 61.90%* | Kolbe et al. (2014)&lt;sup&gt;47&lt;/sup&gt; | Brazil | Split-mouth, RCT | ChP | 21 | 12/10 | 48.52 (32-75) | 6 months | Test 1: PDT | Test 2: Photosensitizer | Control: SRP | Methylene blue (10 mg/ml) | Diode laser (Thera Lase, Brazil) | Wavelength 660 nm | Power output 60 mW | Energy dose 129 J/cm² | Application time 60 s/site | Lower * levels of A.a. were detected in Test1 and Control groups at 3 as compared to 6 months. Lower * detection frequency of P.g. for Test 1 and Control groups. | Test 1: IL-4 increased <em>in Test 1. IL-10 was reduced <em>in Test 2. Test 1 showed significant reduction of IL-6, IL-1β, IFN-γ. | Test 2: PD: -0.27± 0.43</em> | CAL: -0.09± 0.41</em> | BOP decrease 97-77* | Control: PD: -0.07±0.61 | CAL: -0.20±0.61 | BOP increase 84-87 | LULIC et al. (2009)&lt;sup&gt;45&lt;/sup&gt; | Parallel | RCT | ChP | 10 | 3/7 | 54 (40-74) | 12 months | Test: SRP + PDT | Control: SRP+ Placebo: PDT | Phenothiazine chloride (HELBO Blue Photosensitizer) | Diode laser (HELBO Minilaser 2075 F) | Methylen blue | Diode laser (Periowave, Ondine Biomedical, Vancouver, Canada) | Wavelength 670 nm | Output power density 75 mW/cm² | Application time 60 s/site | Not analysed | Not analysed | Test: PD: -0.27± 0.43* | CAL: -0.09± 0.41* | BOP decrease 97-77* | Control: PD: -0.07±0.61 | CAL: -0.20±0.61 | BOP increase 84-87 | MÜLLER CAMPANILE et al. (2015)&lt;sup&gt;50&lt;/sup&gt; | Switzerland | Split-mouth, RCT | ChP | 27 | 13/14 | 62.8 (37-77) | 6 months | Test1: SRP + PDT (twice) | Test2: SRP + PDT (once) | Control: SRP+ | Wavelength 670 nm | Power output 280 mW | Application time 60 s/site | No significant changes of the microorganisms from baseline to 3 / 6 months in any of the group. | No significant differences between the groups for IL-1β, IL-1ra, IL-8, IL-17, bFGF, G-GSF, GM-CSF, IFN- | Test 1: PD: from 5.9± 0.9 to 3.1±1.0 (n.s.) | CAL: from 2± 1.6 to 4.1±1.6 (n.s.) | BOP: from 16 to 10 sites (n.s.) | Test 2: PD: from 5.9± 0.9 to 3.1±1.0 (n.s.) | CAL: from 2± 1.6 to 4.1±1.6 (n.s.) | BOP: from 16 to 10 sites (n.s.) |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Smoking Status</th>
<th>Duration</th>
<th>Test Group 1</th>
<th>Control Group</th>
<th>Assessment</th>
<th>Not analysed</th>
<th>Laser/Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petelin et al. (2014)</td>
<td>Slovenia</td>
<td>Parallel, RCT</td>
<td>27</td>
<td>12/15 nonsmokers</td>
<td>12 months</td>
<td>US+PDT</td>
<td>SRP</td>
<td>A.a., P.g., P.i., T.f., T.d.</td>
<td>Significant reduction of T.d. + sites and of A.a., T.f., T.d levels in favour to PDT in medium pockets (4-6mm), and of T.d. in deep pockets (&gt;6mm).</td>
<td></td>
</tr>
<tr>
<td>Rühling et al. (2010)</td>
<td>Germany</td>
<td>Parallel, RCT</td>
<td>60</td>
<td>48±8 nonsmokers</td>
<td>3 months</td>
<td>PDT</td>
<td>Ultrasonic debridement</td>
<td>Microbial counts were reduced after treatment but returned to baseline values after 3 months.</td>
<td>No significant differences between the groups: Test:</td>
<td></td>
</tr>
</tbody>
</table>

**Laser Parameters:**
- **Wavelength:** 660 nm for Test 1, 635 nm for Test 2.
- **Output power density:** 60 mW/cm² for Test 1, 100 mW for Test 2.
- **Application time:** 60 s/site for both Test 1 and Test 2.

**Clinical Parameters:**
- **PD:** from 6.3±1.3 to 2.9±1.8 (n.s.) for Test 1, from 3.6±0.2 to 3.0±0.2 (n.s.) for Test 2.
- **CAL:** from 7.9±2.2 to 4.2±2.8 (n.s.) for Test 1, from 7.6±2 to 4.6±2.2 (n.s.) for Test 2.
- **BOP:** from 20 to 7 sites (n.s.) for Test 1, from 25% to 9%* for Test 1, from 3.4±1.5 to 3.4±1.5 (n.s.) for Control.
- **PD:** from 6.3±1.5 to 3.4±1.5 for Control, from 4.2±0.3 to 3.7±0.2 (n.s.) for Test 2, from 3.8±0.2 to 3.3±0.2 (n.s.) for Test 1.
- **CAL:** from 7.6±2 to 4.6±2.2 for Test 2, from 7.9±2.2 to 4.2±2.8 (n.s.) for Test 1.
- **BOP:** from 15 to 10 sites (n.s.) for Test 1, from 23% to 12% (n.s.) for Test 2, from 17% to 9%* for Test 1, from 25% to 9%* for Control.

**Photodynamic Treatment:**
- **Phenothiazine chloride (HELBO Blue Photosensitizer):**
- **Diode laser (HELBO Tera Light):**
- **Energy dose:** 100 mW for Test 2.
- **Application time:** 60 s/site.
n.s.: not significant; n.r.: not reported; REC: recession; IL: Interleukin; b-FGF: basic fibroblast growth factor; G-CSF: granulocyte colony stimulating factor; IFN-γ: interferon γ; MIP-1β: macrophage inflammatory protein 1β; GM-CSF: granulocyte macrophage colony stimulating factor; TNF-α: tumor necrosis factor α; CRP: C-reactive protein; VEGF: vascular endothelial growth factor; T.f.: Tannerella forsythia, P.g.: Porphyromonas gingivalis; A.a.: Aggregatibacter actinomycetemcomitans; T.d.: Treponema denticola; F.n.: Fusobacterium nucleatum; P.i.: Prevotella intermedia; C.r.: Campylobacter rectus; E.c.: Eikenella corroden; P.m.: Parvimonas micra; E.n.: Eubacterium nodatum; C.s.: Capnocytophaga Spp.
References


