Clin Oral Invest (2014) 18:2129–2135
DOI 10.1007/s00784-014-1193-6

ORIGINAL ARTICLE

Six-month results following treatment of aggressive periodontitis with antimicrobial photodynamic therapy or amoxicillin and metronidazole

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Received: 6 October 2013 / Accepted: 16 January 2014 / Published online: 4 February 2014

Abstract
Objective The use of antibacterial photodynamic therapy (aPDT) additionally to scaling and root planing (SRP) has been shown to positively influence the clinical outcomes. However, at present, it is unknown to what extent aPDT may represent a potential alternative to the use of systemic antibiotics in nonsurgical periodontal therapy in patients with aggressive periodontitis (AP). The aim of this study was to evaluate the outcomes following nonsurgical periodontal therapy and additional use of either aPDT or amoxicillin and metronidazole (AB) in patients with AP.
Material and methods Thirty-six patients with AP displaying at least three sites with pocket depth (PD) ≥6 mm were treated with SRP and either systemic administration of AB for 7 days or with two episodes of aPDT. The following clinical parameters were evaluated at baseline and at 6 months: plaque index (PI), bleeding on probing (BOP), PD, gingival recession (GR) and clinical attachment level (CAL).
Results Thirty-five patients have completed the 6-month evaluation. At 6 months, mean PD was statistically significantly reduced in both groups (from 5.0±0.8 to 3.0±0.6 mm with AB and from 5.1±0.5 to 3.9±0.8 mm with aPDT ($p<0.001$)). AB yielded statistically significantly higher improvements in the primary outcome parameter PD ($p<0.001$) when compared to aPDT. The number of pockets ≥7 mm was reduced from 141 to 3 after AB ($p<0.001$) and from 137 to 45 after aPDT ($p=0.03$). Both therapies resulted in statistically significant reductions in all parameters compared to baseline.
Conclusion While both treatments resulted in statistically significant clinical improvements, AB showed statistically significantly higher PD reduction and lower number of pockets ≥7 mm compared to aPDT.
Clinical relevance In patients with AP, the two times application of aPDT in conjunction with nonsurgical periodontal therapy cannot be considered an alternative to the systemic use of amoxicillin and metronidazole.

Keywords Photodynamic therapy · Nonsurgical periodontal therapy · Scaling and root planing · Systemic antibiotics · Amoxicillin · Metronidazole · Randomized controlled clinical study

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Introduction

Nonsurgical periodontal therapy involving scaling and root planing (SRP) aims to remove or disrupt the bacterial biofilm, thus reducing the load of periodontal pathogenic microorganisms [1, 2]. Longitudinal studies have provided evidence for the clinical efficacy of nonsurgical periodontal therapy in the treatment of chronic periodontitis (CP) [3, 4].

Aggressive periodontitis (AP)—although its prevalence is low—is usually characterized by a rapid destruction of periodontal tissue support involving the cementum, periodontal ligament and alveolar bone and deterioration of tooth prognosis eventually leading to tooth loss [5]. In most patients diagnosed with AP, mechanical debridement alone is not

sufficient to reduce inflammation and probing depths. One possible explanation for the more limited response of AP patients to SRP alone is, besides potential local host response deficiencies, the usually high colonization with periodontopathic microorganisms such as *Aggregatibacter actinomycetemcomitans* (*A.a.*) and *Porphyromonas gingivalis* (*P.g.*). It is anticipated that due to their tissue-invading capacity, *A.a.* and *P.g.* cannot or can only partly be eliminated by mechanical therapy alone [6, 7]. It has been repeatedly demonstrated that the adjunctive administration of amoxicillin and metronidazole to mechanical debridement (SRP) is at present the most efficient and accepted modality not only to eliminate or reduce *A.a.* and *P.g.* but also to result in substantial clinical improvements in terms of probing depth (PD) reduction, gain in clinical attachment level (CAL) and decrease of inflammation (e.g. decrease of bleeding on probing (BOP)) [8–11]. Moreover, recent data have also provided evidence for the effectiveness of this antibiotic combination in the treatment of advanced forms of generalized severe CP [12].

Despite the excellent clinical results obtained following the systemic use of amoxicillin and metronidazole in conjunction with SRP, its use is often accompanied by numerous side effects (especially gastrointestinal). Moreover, recent data also indicate that the frequent administration of systemic antibiotics may lead to an increase in the risk of developing resistant strains thus raising new medical problems [13]. Therefore, in order to reduce the problems associated with the use of systemic antibiotics, there is an increasing need for developing new antibacterial strategies which are able to effectively eliminate or reduce the periodontal pathogenic flora.

Photodynamic therapy, also called photoradiation therapy, phototherapy or photochemotherapy, could be such a treatment alternative. It 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 [14, 15]. While each factor is harmless by itself, the combination leads to the release of free oxygen radicals, which in turn can selectively destroy bacteria and their by-products [16, 17]. In the case of the destruction of bacteria, it is called antimicrobial photodynamic therapy (aPDT).

Data from controlled clinical studies have shown that in CP patients, the combination of SRP and aPDT may result in significantly higher PD and/or BOP reductions compared with SRP alone [16, 18–22]. When comparing aPDT with ultrasonic treatment, a recent study yielded some additional benefit over ultrasonic instrumentation alone [23]. A recent meta-analysis suggested that the use of adjunctive aPDT to conventional SRP provides short-term benefits [24]. Moreover, very recent results from a randomized controlled clinical study have also indicated that in patients with incipient peri-implantitis (sites with PD 4–6 mm, BOP+and radiographic bone loss ≥2 mm) the adjunctive use of aPDT to mechanical debridement may lead to comparable clinical and microbiological outcomes [25, 26].

However, at present, it is practically unknown to what extent aPDT may represent a potential alternative to systemic antibiotics when used in conjunction with SRP in patients with AP. Hence, it was the aim of the present study to present the clinical outcomes at 6 months following nonsurgical periodontal therapy in conjunction with either aPDT or amoxicillin and metronidazole in patients with AP.

Materials and methods

Patient selection

The study design, patient population, treatment protocol and the short-term (up to 3 months) results have been previously described [27]. Briefly, the study was an examiner-blind, prospective, randomised, intra-individual comparative, single-centre clinical study. Prior to participation, the purpose and risks of the investigation were fully explained to all participants, and written informed consent was obtained from all patients. The study protocol was approved by the ethical committee of the Bialystok University (approval no. R-I-002/307/2009) and conducted according to the principles outlined in the Declaration of Helsinki on experimentation involving human subjects in the Department of Periodontology, Medical Academy Bialystok, Poland.

Thirty-six patients (24 females and 12 males) suffering from aggressive periodontitis [5] with at least three sites with PD ≥6 mm were recruited for the study and randomized in two parallel groups of 18 patients each.

For entering the study, the patients had to meet the following criteria: (a) no treatment of periodontitis for the last 2 years, (b) no systemic diseases which could influence the outcome of the therapy, (c) no pregnancy and (d) no use of antibiotics for 12 months prior to treatment and (e) no allergy against antibiotics or ingredients of the used photosensitizer. No smokers were included.

The following clinical parameters were assessed at baseline and at 3 and 6 months after active periodontal therapy using the same type of periodontal probe (UNC 15, Hu-Friedy, Chicago, IL, USA): probing pocket depth (PD) and gingival recession (GR). CAL was calculated by adding PD to GR.

All clinical measurements were made at six sites per tooth: mesio-facial (mf), mid-facial (f), disto-facial (df), mesio-lingual (ml), mid-lingual (l) and disto-lingual (dl) by the same calibrated investigator (M.P.). The examiner was not aware, in any of the cases, of the type of treatment rendered. The cemento-enamel junction (CEJ) was used as the reference point. In cases where the CEJ was not visible, a restoration margin was used for these measurements.

BOP and plaque index (PI) at test sites as well as full mouth (full mouth bleeding on probing (FMBOP) and full mouth plaque index (FMPI)) was also assessed at six sites per tooth.

Following one or more appointments including thorough oral hygiene instructions and supragingival scaling and polishing, all pockets ≥4 mm were treated by means of SRP using ultrasonic and hand instruments (by two trained periodontists, A.S. and E.D.). In the aPDT group, the photosensitizer (HELBO® Blue Photosensitizer, Helbo Photodynamic Systems GmbH & Co KG; Wels, Austria) was applied into the pockets from apically to coronally. After 3 min, the pockets were rinsed with sterile NaCl solution and subsequently irradiated with a diode laser tip (HELBO® minilaser 2075Fdent, Helbo Photodynamic Systems GmbH & Co KG; wavelength 660 nm) for 1 min. In the antibiotic group (AB), the patients were prescribed 375 mg of amoxicillin and 250 mg of metronidazole three times daily for 7 days, starting on the day of SRP [8].

Intra-examiner reproducibility/investigator calibration

Five patients, not related to the study, each showing two pairs of contralateral teeth (single- and multirooted) with probing depths more than 6 mm on at least one site of each tooth, were used to calibrate the examiner (M.P.). The examiner evaluated the four teeth (at six sites per tooth) of each patient on two separate occasions, 48 h apart. Calibration was accepted if measurements at baseline and at 48 h were equal to the millimetre at >90 % level. The examiner was not aware of the procedure to be performed.

Statistical analysis

At the start of the study, a significance level of α=0.05, a relevant average difference of 1 mm and a power ($1-\alpha$) of at least 0.90 were set in order to calculate the minimum number of necessary cases (at least seven per group). A power calculation at the end of the study with the given number of cases and the given results yielded a power of 99.6 %.

The null hypothesis to be tested was "no difference in treatment effect of adjunctive use of systemic amoxicillin plus metronidazole compared with aPDT both in addition to SRP". Statistical analysis was performed using IBM SPSS statistics 21 (IBM Company; Armonk, NY, USA). A total of 5,074 sites in all patients were examined; of these, 1,913 exhibited a PD of ≥4 mm which were treated as described above. The statistical unit was the patient. The primary outcome variable was the change in PD. The secondary variables were changes in CAL, GR, BOP, PI, FMBOP and FMPI. Additionally, PD and CAL changes were analyzed for different pocket categories: initially moderate (4–6 mm) and deep (PD ≥7 mm) pockets (in accordance with [10, 11]). The data were checked for normal distribution using the Kolmogorov-Smirnov test. The two groups were compared using Mann-Whitney *U* tests. To compare examination time points (baseline and 6 months), Wilcoxon signed-rank tests were used. For all statistical tests, significance was set at a 95 % confidence level (a=0.05).

Results

Thirty-five (of 36) patients completed the 6-month evaluation period. After the second month following treatment, one patient in the aPDT group decided to discontinue the study without any specific reason.

In all subjects, healing was uneventful. No adverse effects such as discomfort, burning sensation, or pain related to the laser irradiation or side effects by the intake of antibiotics were reported by any of the patients. No teeth were extracted between the baseline and during the entire study period of 6-month evaluation.

Analysis of treated pockets (PD ≥4 mm)

The baseline characteristics of the 35 participants are shown in Table 1. The baseline examination revealed that the two study groups showed similar characteristics for probing depth (PD), CAL, bleeding and plaque scores (PI and FMPI) with no significant differences between the groups (except for BOP and FMBOP) (Table 1).

The clinical outcomes after 6 months (mean±SD) as well as the results of the statistical analysis (both between groups and time points) are displayed in Table 2. Concerning PD, GR and

Table 1 Subject and clinical characteristics at baseline (mean±SD)

Parameter	aPDT (N=17)	AB (N=18)	p value
Age	37.3±8.0	34.7±9.0	0.380[a], n.s.
Female	10 (59 %)	13 (72 %)	0.489[b], n.s.
Male	7 (41 %)	5 (28 %)	
PD (mm)	5.1±0.5	5.0±0.8	0.318[c], n.s.
CAL (mm)	5.7±0.8	5.5±1.1	0.287[c], n.s.
GR (mm)	0.6±0.7	0.5±0.6	0.546[c], n.s.
PI	1.4±0.7	1.7±0.8	0.163[c], n.s.
BOP (%)	70.4±22.4	85.7±15.9	0.025*[,c]
FMPI	1.0±0.7	1.5±0.8	0.057[c], n.s.
FMBOP (%)	52.4±22.7	74.2±20.7	0.005**[,c]
Number of sites with PD ≥7 mm	137	141	0.945[a], n.s.

n.s. not significant

*p<0.05; **p<0.01; ***p<0.001

[a] t test for two independent groups

[b] Fisher's exact test for the 2×2 table, sex by group (aPDT, AB)

[c] Mann-Whitney *U* test for two independent groups

Table 2 CAL, PD and GR (mean±SD) at all treated sites (PD ≥4 mm)

	aPDT (*N*=17)	AB (*N*=18)	*P* value between groups
PD (mm)			
Baseline	5.1±0.5	5.0±0.8	0.318[a], n.s.
After 6 months	3.9±0.8	3.0±0.6	<0.001***,[a]
Base vs. 6 months	<0.001***,[b]	<0.001***,[b]	
GR (mm)			
Baseline	0.6±0.7	0.5±0.6	0.546[a], n.s.
After 6 months	0.7±0.7	0.7±0.8	0.708[a], n.s.
Base vs. 6 months	0.005**,[b]	0.001**,[b]	
CAL (mm)			
Baseline	5.7±0.8	5.5±1.1	0.287[a], n.s.
After 6 months	4.7±1.1	3.6±0.9	0.004**,[a]
Base vs. 6 months	<0.001***,[b]	<0.001***,[b]	

n.s. not significant

*$p<0.05$; **$p<0.01$, ***$p<0.001$

[a] Statistical analysis by Mann-Whitney *U* test for two independent groups

[b] Statistical analysis by Wilcoxon signed-rank test for two dependent groups

CAL, both groups revealed statistically significant changes after 6 months compared to baseline. Comparing the groups, the antibiotic group showed significantly lower PD and CAL after 6 months, while GR was not statistically significantly different ($p=0.708$). BOP, PI at the treated sites as well as full mouth scores (FMBOP and FMPI) are shown in Table 3.

Bleeding and plaque scores decreased statistically significant in both treatments from baseline to 6 months. After 6 months, no statistically significant differences were observed between the groups, while the change from baseline to 6 months was also significantly different between the two groups.

Sub-analysis of moderate and deep pockets

Additionally, PD and CAL changes were analyzed for different pocket categories: initially moderate (4–6 mm) and deep (PD ≥7 mm) pockets (in accordance with [10, 11]). Data are presented in Tables 4 and 5.

Analysis of continued presence of bleeding sites with PD ≥4 mm

Furthermore, the number of pockets with PD ≥4 mm and bleeding on probing (which are perceived as needing further treatment) as well as pockets with PD ≥7 mm were analyzed (Table 6).

At baseline, subjects in aPDT group had 628 sites with PD ≥4 mm and BOP, in AB group 961 sites ($p=0.072$ between groups, n.s.), which could be reduced to 454 sites in aPDT group ($p=0.480$) and 365 sites in AB group ($p<0.001$) at the 6-month evaluation. Subjects in the AB group showed a significantly lower mean number of persisting sites with PD ≥4 mm and BOP compared to the aPDT group ($p<0.001$).

The number of sites with PD ≥7 mm could be reduced from 137 sites to 45 sites in the aPDT group ($p=0.030$) and from 141 sites to 3 sites in the AB group ($p<0.001$), which was significantly lower than in the aPDT group ($p=0.001$).

Discussion

The results of this study have shown that in patients with AP nonsurgical periodontal therapy in conjunction with systemic administration of amoxicillin and metronidazole or followed by two times topical application of aPDT resulted in statistically significant improvements in probing depth reduction, gain of clinical attachment and improvement in BOP compared to baseline. The systemic use of amoxicillin and metronidazole, however, yielded statistically significantly higher reductions in mean PD compared with the treatment using aPDT.

An extremely important finding of the present study was the change in the total number of pockets ≥7 mm following both treatment protocols. In the aPDT 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. It has been shown that on a long-term basis (over more than 11 years) residual deep pockets represent a risk for further attachment and tooth loss, and therefore, such sites may require further treatment such as periodontal

Table 3 BOP and PI at test sites and full mouth (mean±SD)

	BOP		FMBOP		PI		FMPI	
	aPDT	AB	aPDT	AB	aPDT	AB	aPDT	AB
Baseline	70.4±22.4	85.7±15.9	52.4±22.7	74.2±20.7	1.4±0.7	1.7±0.8	1.0±0.7	1.5±0.8
After 6 months	48.0±22.2	32.6±21.0	32.6±19.8	24.3±12.6	0.5±0.5	0.4±0.6	0.3±0.2	0.3±0.5

Statistically significant differences between time points; no statistically significant differences between groups (besides BOP and FMBOP at baseline)

Table 4 CAL, PD and GR (mean±SD) at sites with moderate pockets (PD 4–6 mm)

	aPDT (*N*=17)	AB (*N*=18)	*p* value between groups
PD (mm)			
Baseline	4.6±0.3	4.6±0.3	0.884, n.s.
After 6 months	3.7±0.6	2.9±0.5	<0.001***
Base vs. 6 months	<0.001***	<0.001***	
GR (mm)			
Baseline	0.8±0.9	0.5±0.6	0.363, n.s.
After 6 months	0.9±1.0	0.7±0.8	0.477, n.s.
Base vs. 6 months	0.959, n.s.	0.868, n.s.	
CAL (mm)			
Baseline	5.4±1.1	5.2±0.8	0.473, n.s.
After 6 months	4.5±1.2	3.5±0.8	0.008**
Base vs. 6 months	0.102, n.s.	<0.001***	

surgery [28]. More importantly, compared to the results at 3 months, at 6 months, an additional decrease in the number of pockets ≥7 mm was measured [27]. These findings are of clinical relevance since they indicate that clinical improvements following nonsurgical periodontal therapy can also occur over a longer period (i.e. up to 6 months), thus suggesting that a period of 8 weeks or 3 months following nonsurgical periodontal therapy might be too early for taking the final decision on the need for additional therapy (for example periodontal surgery). Moreover, our findings are in line with those obtained in previous controlled clinical studies evaluating the systemic administration of amoxicillin and metronidazole in conjunction with nonsurgical periodontal therapy in patients with AP and also in patients with advanced CP. Taken together, the present results provide additional evidence on the clinical benefit of the systemic administration of amoxicillin and metronidazole in conjunction with nonsurgical periodontal therapy [10–12, 29–32].

Table 5 CAL, PD and GR (mean±SD) at sites with deep pockets (PD ≥7 mm)

	aPDT (*N*=14)	AB (*N*=13)	*p* value between groups
PD (mm)			
Baseline	7.7±0.63	7.6±0.6	0.707, n.s.
After 6 months	5.5±1.26	3.7±0.9	<0.001***
Base vs. 6 months	<0.001***	<0.001***	
GR (mm)			
Baseline	0.8±0.9	0.8±1.1	0.990, n.s.
After 6 months	0.8±1.0	0.9±1.0	0.914, n.s.
Base vs. 6 months	0.989, n.s.	0.971, n.s.	
CAL (mm)			
Baseline	8.4±1.2	8.4±1.1	0.835, n.s.
After 6 months	6.4±1.5	4.6±1.3	0.002**
Base vs. 6 months	0.005**	<0.001***	

Table 6 Number of sites with PD ≥4 mm at different time points

	aPDT	AB	*p* value between groups
PD ≥4 mm and BOP+			
Baseline	628 (100 %)	961 (100 %)	0.072, n.s.
After 6 months	454 (72 %)	365 (38 %)	<0.001***
Base vs. 6 months	0.480, n.s.	<0.001***	
PD ≥7 mm			
Baseline	137 (100 %)	141 (100 %)	0.945, n.s.
After 6 months	45 (32 %)	3 (2.1 %)	0.001, n.s.
Base vs. 6 months	0.030*	<0.001***	

On the other hand, it is important to point out that also the use of aPDT has led to statistically and clinically significant improvements compared to baseline, although the number of residual pockets needing further therapy was significantly higher compared to the use of systemic antibiotics (e.g. 45 vs. 3). One important aspect which needs to be considered when interpreting the present findings is the fact that until now, no bacterial resistance against aPDT has been reported in the literature, and therefore, its repeated application in conjunction with mechanical debridement may be a possible valuable option to be considered in the future [15, 24]. This possibility may bear clinical relevance, especially in the light of the reported increase of bacterial resistance against antibiotics [13].

The use of aPDT as a potential alternative to local antibiotics has been recently evaluated in a randomized controlled clinical study comparing nonsurgical treatment of incipient peri-implantitis by means of mechanical debridement followed by either the use of local antibiotics (e.g. minocycline) or application of aPDT. The results at 6 months and at 1 year have failed to reveal statistically or clinically significant differences between the two treatment protocols thus suggesting that aPDT may represent a valuable alternative to local antibiotics during nonsurgical treatment of incipient peri-implantitis [25, 26].

To the best of our knowledge, this is the first study evaluating clinically the outcomes following nonsurgical periodontal therapy in conjunction with two times application of aPDT in patients with AP, and the clinical outcomes are in line with previous studies evaluating this treatment modality in patients with chronic periodontitis thus indicating that the effects are not only limited to patients with CP [18–21].

Conclusion

In conclusion, the present data indicate that both treatments resulted in statistically significant clinical improvements, but the systemic use of amoxicillin and metronidazole yielded statistically significantly higher PD reduction and lower number of pockets ≥7 mm compared to aPDT.

Conflict of interest The authors declare that they have no conflict of interest. Helbo Photodynamic Systems GmbH & Co KG, Wels, Austria provided materials for the PDT group. The study was designed, conducted, and analyzed completely independently of Helbo, as was the writing of the manuscript. The authors received no financial support.

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