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Title: Efficacy of mechanical debridement with adjunct antimicrobial photodynamic therapy for the management of peri-implant diseases: A systematic review.

Authors: Fahim Vohra,[1] Mohammad Qasim Al-Rifaiy[1], Graeme Lillywhite,[2] Mohamed Ibrahim Abu Hassan,[3] Fawad Javed[4]*

Affiliations:

1. Department of Prosthetic Dental Sciences, College of Dentistry, King Saud University, Riyadh, Saudi Arabia;

2. Department of Restorative Dentistry, Edinburgh Postgraduate Dental Institute, University of Edinburgh, Edinburgh, UK;

3. Dean Faculty Of Dentistry, Department of Restorative Dentistry, Universiti Teknologi MARA, Shah Alam, Malaysia; and

4. Eng. A.B. Research Chair for Growth Factors and Bone Regeneration, 3D Imaging and Biomechanical Laboratory, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia.

Running title: aPDT and Peri-implantitis

* Corresponding author at: Dr. Fawad Javed. Eng. A.B. Research Chair for Growth Factors and Bone Regeneration, 3D Imaging and Biomechanical Laboratory, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia.

Tel.: +966 50 968 6328 Fax.: +966 114698786

Email: fawjav@gmail.com

ABSTRACT

The aim was to assess whether or not mechanical debridement with adjunct antimicrobial photodynamic therapy (aPDT) is effective for the management of peri-implant diseases. The addressed focused question was "Is mechanical debridement with adjunct aPDT more effective in treating peri-implant diseases as compared to when mechanical debridement is used alone?" PubMed/MEDLINE and Google-Scholar databases were searched from 1994 till April 2014 using different combinations of the following keywords: antimicrobial photodynamic therapy; bone loss; light activated disinfection; mechanical debridement; and peri-implant diseases. Review articles, case-reports, commentaries, letters to the Editor, unpublished articles and articles published in languages other than English were excluded. Twelve studies (six clinical and six experimental) were included. In the clinical and experimental studies, 15-80 implants and 18-150 implants respectively were used. Laser wavelengths, duration of irradiation and power output ranged between 625nm-830nm, 10s-300s, and 30mW-200mW, respectively. Four studies reported mechanical debridement with adjunct aPDT to be effective in the treatment of peri-implant diseases; however, the benefits of aPDT were comparable with conventional treatments. Two studies reported aPDT to reduce bacteria than when laser and photosensitizer were applied alone. In two studies, chemical disinfection and aPDT showed comparable outcomes in terms of bacterial disinfection. In two experimental studies, aPDT was shown to improve bone to implant contact and re-osseointegration. Efficacy of mechanical debridement with adjunct aPDT for the management of peri-implant diseases remains debatable.

Keywords**:** antimicrobial photodynamic therapy; bone loss; light activated disinfection; mechanical debridement; and peri-implant diseases.

1. Introduction

Peri-implant diseases encompass peri-implant mucositis and peri-implantitis which are caused by pathogenic bacteria in the oral biofilm. Peri-implant mucositis is characterized by sore and readily bleeding gingiva with no radiographic evidence of bone loss [1]; whereas, peri-implantitis is characterized by inflammation of peri-implant tissues (including bleeding on probing [BOP] and suppuration) with progressive loss of supporting bone [2, 3]. A variety of treatment strategies have been recommended for the management of peri-implant diseases such as, non-surgical mechanical debridement, surgical debridement (open debridement), chemical disinfection and antibiotic therapy [4-8]. Although studies [9-12] have reported such therapeutic protocols to be useful in the treatment of peri-implant diseases, a complete resolution of the inflammatory condition using these techniques is challenging.

Although studies [13, 14] have reported mechanical debridement with adjunct antibiotic therapy to be useful in the management of peri-implant diseases [15, 16]; bacterial resistance to antibiotics and potential risk of allergic reactions cannot be overruled. With the advent of lasers in modern clinical dentistry [17], contemporary treatment strategies have emerged for the management of oral inflammatory conditions including peri-implantitis [18, 19]. Antimicrobial photodynamic therapy (aPDT) is one of such intervention which involves interaction between a light source and a chemical dye or photosensitizer (PS) in the presence of oxygen, which causes an oxidative burst that kills pathogens, e.g. by destroying their cell walls [20, 21]. Esposito et al. [22], in a one-year follow up randomized clinical trial, showed significant improvement in peri-implant pocket depth (PPD) and stable marginal bone levels following mechanical debridement with adjunct aPDT in patients with peri-implantitis. Moreover, aPDT has also been reported to significantly reduce the counts of pathogens associated with periodontal, endodontic and oral fungal infections [23-28]. Results by

Dortbudak et al. [23] showed a significant reduction in the counts of *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans* around implant surfaces following aPDT. However, some studies [22, 29-31] have reported that the outcomes of mechanical debridement with or without PDT in the management of peri-implantitis are comparable. For example, in studies by De Angeles et al. [29] and Schär et al. [31], peri-implant disease related parameters (such as PPD and Plaque index) showed no significant differences when mechanical debridement was performed either with or without adjunct aPDT. In addition, it has also been reported that complete eradication of biofilm–related microbes following aPDT may be difficult to accomplish [23].

Contentious results [23, 32-34] have been reported regarding the potential role of aPDT as an adjunct to mechanical debridement in the management of peri-implant diseases. Furthermore, oral biofilms (which are composed of multiple bacterial species) have been shown to be more resistant to antimicrobial therapies as compared to planktonic bacteria [35]. Therefore, the aim of the present study was to systematically review whether or not mechanical debridement with adjunct aPDT is effective for the management of peri-implant diseases.

2. Materials and Methods

2.1 Focused question

The addressed focused question was "Is mechanical debridement with adjunct aPDT more effective in treating peri-implant diseases as compared to when mechanical debridement is used alone?"

2.2 Eligibility criteria

The following eligibility criteria were entailed: (a) original studies; (b) clinical and experimental studies; (c) intervention: role of aPDT in reducing peri-implant infection; (d) articles published only in English language. Review articles, case-reports, commentaries, letters to the Editor and unpublished articles were excluded.

2.3 Search strategy

PubMed/Medline (National Library of Medicine, Bethesda, Maryland) and Google-Scholar databases were searched from 1994 till April 2014 using different combinations of the following key words: antimicrobial photodynamic therapy; bone loss; light activated disinfection; mechanical debridement; and peri-implant diseases. Titles and abstracts of studies that fulfilled the eligibility criteria were screened by the authors and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently assessed against the eligibility criteria. Following this, reference lists of original and review studies that were found to be pertinent in the previous step were hand-searched and checked for agreement via discussion among the authors.

The initial search yielded 20 studies. Eight studies, which did not fulfill the eligibility criteria, were excluded (Appendix A). In total, 12 studies [22, 23, 29-38] were included and processed for data extraction.

3. Results

All studies [22, 23, 29-38] were performed at either universities or healthcare centers. Six studies [22, 23, 29-32] were clinical (Table 1) and 6 studies [33-38] had an experimental research design (Table 2). Four experimental studies [33, 34, 36, 37] were performed on animal-models and 2 studies [35, 38] had an in-vitro design.

3.1 Characteristics of clinical studies

In these studies [22, 23, 29-32], patients with peri-implant mucosal inflammation (bleeding on probing [BOP]) and radiographic evidence of crestal bone loss (0.5mm and above), with a minimum of 12 months of implant function, were included. The number of individuals ranged between 15-80 with age ranging between 43-65 years. In these studies [22, 23, 29-32], 15-80 dental implants were followed up for 1week to 52 weeks after treatment of peri-implantitis. PDT was compared to mechanical and surgical debridement and localized antibiotic therapy (minocycline) in two [22, 29] and two [30, 31] studies, respectively. In the study by Dortbudak et al. [23], peri-implantitis was treated by aPDT, in the test-group; whereas in the control groups, peri-implantitis was treated by PS and laser application alone. Deppe et al. [32] investigated the effect of PDT on the management of peri-implantitis in patients with moderate bone loss (< 5mm) and severe bone loss (5-8 mm) (Table 1).

3.2. Laser and photosensitizer related parameters in clinical studies

Diode lasers with wavelengths ranging between 630nm-690nm were used. Power output, energy fluence and duration of irradiation were 100 milliwatts (mW), 3.53 joules per square centimeters (J/cm^2) and 10 seconds (s) - 80s, respectively (Table 3). Toluidine blue (TBO) (0.1 milligrams per milliliter [mg/ml]) and methylene blue (MB) (10 mg/ml) were used as photosensitizers in three [22, 23, 29] and three [30-32] studies, respectively. In these studies [22, 23, 29-32], PS was placed in the peri-implant pockets for one to three minutes (Table 4). In these studies [22, 23, 29-32], frequency of aPDT application ranged from one to four times throughout the study period.

3.3 Outcomes of clinical studies

In four studies [22, 29-31], non-surgical and surgical debridement with adjunct aPDT was reported to be effective in the treatment of peri-implantitis and improve peri-implant inflammatory parameters (PPD, BOP, clinical attachment loss and soft tissue recession); however, in these studies [22, 29-31] , the therapeutic outcomes of mechanical debridement with or without aPDT were comparable. In one study [32], aPDT was ineffective in maintaining crestal alveolar bone levels in patients with severe peri-implantitis (bone loss 5-8mm). In one study [23], aPDT was reported to effectively reduce peri-implantitis bacteria counts compared to when the treatment was performed with PS or laser alone.

3.4. Characteristics of experimental studies.

Amongst the 6 experimental studies[33-38] included in this review, 3 studies [33, 36, 37] were performed on 2-year-old dogs and in one study [34], 150 rats were used (Table 2). In these studies, numbers of implants with peri-implantitis and duration of follow-up ranged between 18-150 implants and 1 week to 20 weeks, respectively. Efficacy of aPDT was compared to mechanical and chemical disinfection (0.12% chlorhexidene) in one [36] and two [33, 38] studies, respectively. Three experimental studies [33, 35, 38] assessed reduction in bacterial count, and in two studies [36, 37] re-osseointegration of implants (bone to implant contact and bone volume) was assessed. Salmeron et al[34] assessed the potential of aPDT in treating peri-implantitis by evaluating the severity of soft tissue inflammation in response to contaminated implant surfaces.

3.5. Laser and photosensitizer related parameters in experimental studies

Diode lasers with wavelengths ranging between 625 - 830 nm were used. The power output, energy fluence and duration of irradiation were 30mW-50mW, 2-45 J/cm^2 and 60s-300s, respectively (Table 3). In four studies [34-37], TBO (0.1 mg/ml) was used and in studies by Hayek et al. [33] and Marotti et al. [38], azulene (25%) and MB (0.01%) respectively, were used as photosensitizers. The incubation period of PS in the region of interest ranged between 1-5 minutes (Table 4).

3.6. Outcomes of experimental studies

Studies comparing PDT and chemical disinfection [33, 38], showed significant reduction of bacterial counts from baseline with no difference between the two groups. In two studies [35, 38], aPDT was more effective in reducing bacterial counts compared to when PS or light were used alone. In the study by Eick et al. [35], aPDT was found to be ineffective in eradicating multi-species bacterial biofilms. In the study by Salmeron et al[34], aPDT application did not reveal significant difference than other groups (application of PS and laser in isolation) in severity of soft tissue inflammation. In two studies [36, 37], treatment of ligature induced peri impantitis using mechanical debridement with adjunct aPDT showed improvement in BIC and BV compared to when mechanical debridement was used alone.

4. Discussion

The present study was based on the hypothesis that aPDT as an adjunct to mechanical debridement is a potential treatment of peri-implant diseases as compared to when mechanical debridement is used alone. The concept of aPDT is based on the interaction of a photosensitizer (e.g. TBO, MB) with light of an appropriate wavelength (for TBO and MB: red light in a wavelength range from 630 nm to 700 nm) in the presence of molecular oxygen.

Due to the absorption of light, the PS is transferred to its triplet state, from where the re-transition to its ground state leads to emergence of either oxygen radicals (type I; due to charge-transfer to a substrate or molecular oxygen) or singlet oxygen (type II; due to energy-transfer to molecular oxygen). Consequently, there is an oxidative burst that kills pathogens, e.g. by destroying their cell walls [20, 21, 39]. In the study by Dortbutak et al. [23] the pathogens existing in the peri-implant sulci of patients with peri-implantitis were significantly reduced following aPDT. Likewise, experimental studies [33, 35, 38] have also reported favorable outcomes of aPDT in terms of minimizing bacterial counts. These results suggest that aPDT may be considered as a useful treatment strategy in the management of peri-implant diseases.

Based on the experimental results [33, 35, 38] it is speculated that aPDT when used as an adjunct to mechanical debridement is more effective in the treatment of peri-implant diseases as compared to when conventional treatment is performed alone. However, clinical studies [22, 29-32] have reported contradictory results. For example, Esposito et al. [22] compared the effect of mechanical and surgical debridement techniques with and without aPDT in patients with peri-implantitis. In this study [22], peri-implant inflammatory parameters (PPD and plaque and bleeding scores) were investigated at baseline and 52 weeks after the respective treatments. Interestingly, the results showed a comparable reduction in peri-implant inflammatory parameters when conventional treatments were performed either with or without aPDT [22]. Similar results were reported by De Angelis et al. [29]. An explanation in this regard may be derived from the fact that severity of peri-implantitis most probably varied among all the clinical studies [22, 23, 29-32]. For example, in the studies by Schär et al. [31] and De Angelis et al. [29], the mean PPD was 4.29mm and 6.34mm, respectively. Moreover, in the study by Deppe et al. [32], there was no significant effect of aPDT in patients with severe peri-implantitis (PPD 5-8mm) as compared to those with

moderate peri-implantitis (PPD 3-5mm). Therefore it is hypothesized that the efficacy of mechanical debridement either with or without aPDT is governed by the severity of peri-implant diseases.

It is noteworthy that the frequency and duration of aPDT (1- 4 times and 10s-80s, respectively) considerably varied among the clinical studies [22, 23, 29-32]. In addition, a standardized test-group (mechanical debridement with adjunct aPDT) and control-group (mechanical debridement alone) was also missing in most of the clinical studies [23, 30-32]. In addition, other critical parameters that influence the overall efficacy of laser therapy include fiber diameter and method of laser application [40]. It has been reported that the diameter of fiber used influences the power density and energy output [41, 42]. It is pertinent to mention that none of the studies included in the present review reported the diameter of the fiber used; which makes it arduous to determine the actual amount of light energy delivered during aPDT. Therefore, the clinical efficacy of aPDT as an adjunct to mechanical debridement techniques in the treatment of peri-implant diseases remains debatable. However, in ~66% studies [22, 23, 29, 32, 33, 36-38], the laser was applied circumferentially around the implant surface in a manner that the laser path was situated around the peri-implant defect. This may be advantageous in the sense that circumferential movement of the fiber within the region of interest may enhance interactions between the PS and laser thereby enhancing the overall effectiveness of aPDT.

It is well known that habitual tobacco smoking and systemic disorders such as (poorly controlled diabetes and acquired immunodeficiency syndrome) jeopardize periodontal health [43]. Moreover, habitual tobacco smoking has also been reported to compromise the outcomes of periodontal surgical interventions [44]. In the present systematic review, smokers were included in two studies [22, 29], both of which reported mechanicall debridement either with or without aPDT to yield comparable outcomes. It is likely that outcomes of aPDT in

smokers were compromised and could have influenced the overall efficacy of aPDT. Chronic hyperglycemia has been associated with an increased formation and accumulation of advanced glycation end products in the body tissues including those of the periodontium [45, 46]. These end products have been reported to impair fibroblastic growth and proliferation [47] and impair healing [48] in diabetic patients. Therefore it is possible that the outcomes of peri-implant disease therapy (regardless of the technique used) are compromised in patients with chronic hyperglycemia as compared to normoglycemic individuals. In all the clinical studies [22, 23, 29-32] patients with systemic disorders were excluded therefore further randomized controlled trials are needed to assess the efficacy of aPDT in the treatment of peri-implant diseases in immune compromised patients.

With recent advancements in aPDT, new photosensitizers (such as safranine O and perinaphthenone derivative) have emerged which have shown pronounced bactericidal effects against pathogenic bacteria such as *P. gingivalis* [25, 27]. However, to our knowledge from indexed literature, efficacy of these newly introduced photosensitizers for the management of peri-implant diseases is not yet investigated. Therefore further studies are needed to assess the efficacy of these photosensitizers against pathogens associated with peri-implant diseases.

5. Conclusion

Efficacy of mechanical debridement with adjunct aPDT for the management of peri-implant diseases remains debatable.

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Conflict of interest statement

None declared

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Appendix A: List of excluded studies. Reason for exclusion is shown in parenthesis.

a) N. Mohanty, M. Jalaluddin, S. Kotina, S. Routray And Y. Ingale, Photodynamic therapy: the imminent milieu for treating oral lesions, *J. Clin. Diagn. Res.,* 2013, **7,** 1254-1257. (Focused question not answered)
b) R. Thierbach And T. Eger, Clinical outcome of a nonsurgical and surgical treatment protocol in different types of peri-implantitis: a case series, *Quintessence. Int.,* 2013, **44,** 137-148. (Focused question not answered)
c) A. Al-Ahmad, C. Tennert, L. Karygianni, K.T. Wrbas, E. Hellwig And M.J. Altenburger, Antimicrobial photodynamic therapy using visible light plus water-filtered infrared-A (wIRA), *J. Med. Microbiol.,* 2013, **62,** 467-473. (Focused question

not answered)

d) K. Subramani And D. Wismeijer, Decontamination of titanium implant surface and re-osseointegration to treat peri-implantitis: a literature review, *Int. J. Oral. Maxillofac. Implants.,* 2012, **27,** 1043-1054.(Review paper)

e) H. Gursoy, C. Ozcakir-Tomruk, J. Tanalp And S. Yilmaz , Photodynamic therapy in dentistry: a literature review, *Clin. Oral. Investig,,* 2013, **17,** 1113-1125. (Review paper).

f) J. Meyle, Mechanical, chemical and laser treatments of the implant surface in the presence of marginal bone loss around implants, *Eur. J. Oral. Implantol.,* 2012, **5,** 71-81. (Review paper)

g) S. Rajesh, E. Koshi, K. Philip And A. Mohan, Antimicrobial photodynamic therapy: An Overview, *J. Indian. Soc. Periodontol.,* 2011, **15,** 323-327. (Review paper).

h) C. Bories, X. Struillou, Z. Badran And A. Soueidan, Peri-implantitis: tools and techniques for disinfecting the implant surface, *Schweiz. Monatsschr. Zahnmed,* 2011, **121,** 341-355. (Paper not in English)

Table 1. General characteristics of clinical studies that fulfilled the eligibility criteria.

Authors	Patients	Mean age in years (range)	Gender (% female)	Study groups	Number of implants (*n*)	Assessed Parameters	Follow up (in weeks)	Study outcome
Esposito et al. [22]	80	65.49 (36-80)	53	Group 1: MD + PDT Group 2: SD + PDT Group 3: only MD Group 4: only SD	31 9 30 10	PPD, Pl, BS.	52 weeks	Outcomes of groups 1 and 2 were comparable to groups 3 and 4
Dörtbudak et al. [23]	15	43 (NA)	53	Group 1: No treatment Group2: Dye application Group3: PDT	15 15 15	Counts of gram negative bacteria	NA	Highest bacterial reduction occurred in group 3 compared to other groups.
De Angelis et al. [29]	80	65.49 (36-80)	53	Group 1: MD+ PDT Group 2: SD + PDT Group 3:MD alone Group 4: SD alone	31 9 30 10	PPD, Pl, BS.	16 week	Outcomes were comparable when debridement was performed either with or without PDT

Bassetti et al. [30]	40	58 (27-78)	50	Group 1: MD + PDT Group 2: MD + antibiotic§	43 24	PPD, CAL, BS, Pl and gingival recession,	52 weeks	Outcomes for group 1 and 2 were comparable.
Schär et al. [31]	40	58 (27-78)	50	Group1: MD + PDT Group 2: MD + antibiotic§	43 24	PPD, CAL, BS, Pl and gingival recession	24 weeks	Outcomes for group 1 and 2 were comparable.
Deppe et al. [32]	16	NA	NA	Group 1: PI with < 5 mm bone loss Group 2: PI with 5-8mm bone loss (PDT was performed in both groups)	10 8	BS, PPD and CAL.	24 weeks	PDT halted bone loss only in group 1. Soft tissue response in both groups was comparable.

NA: Not available PDT: photodynamic therapy, PPD: Peri-implant probing depth, Pl: plaque scores, BS: bleeding scores, MD: mechanical debridement, SD: surgical debridement CAL: clinical attachment level, PI: peri-implantitis, Gram negative bacteria: *Aggregatibacter Actinomycetemcomitans*, *Prevotella intermedia* and *Porphyromonas gingivalis*. § Localized application of 1mg of minocycline hydrochloride microspheres

Table 2. General characteristics of experimental studies that fulfilled the eligibility criteria.

Authors	Subjects	Mean age (in years)	Gender	Study groups	Number of implants	Assessed Parameters	Follow up	Study outcome
Hayek et al. [33]	9 dogs	4	NA	Group 1: MD + CHX (control)	9	Pathogenic bacterial counts	24 hours	Microbial reduction in both groups was comparable.
				Group 2: MD+ PDT (test)	9			
Salmeron et al. [34]	150 rats	NA	Male	Group 1: Sterile discs (negative control)	30	Severity and area of soft tissue inflammation.	12 weeks	Severity of soft tissue inflammation was comparable in groups 3,4 & 5.
				Group 2: Contaminated discs (control)	30			
				Group 3: Gp2 + laser	30			
				Group 4: Gp2 + TBO	30			
				Group 5: Gp2 + PDT	30			
Eick et al.. [35]	NA	NA	NA	Group 1: Biofilm + PDT 60 seconds	Number of implants used was unclear	Disinfection of PI microbes and biofilm (bacterial counts).	NA	Group 6-treatment protocol was less effective against multi specie biofilms than.uni-specie biofilms.
				Group 2: Biofilm + PDT 30 seconds				
				Group 3: Biofilm				

				(control)			
				Group 4: Biofilm + LED 60 seconds			
				Group 5: Biofilm + TBO			
				Group 6: Biofilm + H_2O_2 + PDT			
Shibli et al. [36]	5 dogs	2	Male	Group 1: MD + GBR (control)	20	BIC, BV.	20 weeks	BV and BIC were significantly higher in group 2 as compared to group 1.
				Group 2: MD + GBR + PDT (test)	20		
Shibli et al. * [37]	6 dogs	2	Male	Group 1: CPTi implants + treatment	9	BIC, BV.	20 weeks	BV and BIC significantly improved in all groups.
				Group 2: TPS implants + treatment	9		
				Group 3: HA implants + treatment	9		
				Group 4: MAE implants + treatment	9		

Marotti et al. [38]	NA	NA	NA	Group 1: No treatment (negative control) Group 2: CHX (0.12%) (positive control) Group 3a: PDT 3 minutes Group 3b: PDT 5 minutes Group 4a: Laser 3 minutes Group 4b: Laser 5 minutes	NA	Bacterial count	NA	Group 2 and 3 yield comparable outcomes in terms of reducing bacterial counts. Group 3 was more effective in reducing bacterial counts than group 4.

H_2O_2: Hydrogen per oxide NA : Not available PDT: photodynamic therapy, TBO: toluidine blue O, PI: peri-implantitis, GBR: guided bone regeneration, MD: mechanical debridement, BIC: bone to implant contact, BV: bone volume , CHX: chlorhexidine, TPS: titanium plasma sprayed, Ti: titanium, MAE: 3 threads machined, remaining acid-etched, HA, hydroxyapatite, CPTi: commercially pure titanium surface, LED: light emitting diode. * All groups were treated by MD+GBR+PDT

Table 3. Laser parameters of studies that fulfilled our eligibility criteria.

Authors e al.	Wavelength (in nm)	Energy fluence (in J/cm^2)	Power output (in mW)	Power density (in mW/cm^2)	Duration of irradiation (in seconds)
Esposito et al. [22]	630	NA	NA	NA	80
Dörtbudak et al. [23]	690	NA	NA	NA	60
De Angelis et al. [29]	630	NA	NA	NA	80
Bassetti et al. [30]	660	3.53	100	60	10
Schär et al. [31]	660	3.53	100	60	10
Deppe et al. [32]	660	3.53	100	60	60
Hayek et al. [33]	660	7.2	40	NA	180
Salmeron et al. [34]	660	45	30	NA	60
Eick et al. [35]	625-635	2	NA	NA	60
Shibli et al. [36]	830	4	50	NA	80
Shibli et al. [37]	685	200	50	NA	80
Marotti et al. [38]	660	7.2 and 12	30	NA	180 and 300

NA : Not available J/cm2: Joules per square centimeters nm: Nanometers

mW: Milliwatts mW/cm^2: Milliwatts per square centimeters

Table 4. Characteristics of photosensitizers used in studies that fulfilled our eligibility criteria.

Authors et al.	Site of application	Type of PS	Pre-irradiation time (in minutes)	Concentration/s of PS used
Esposito et al. [22]	Peri-implant pocket	TBO	NA	0.1mg/ml
Dörtbudak et al. [23]	Implant and peri-implant bone	TBO	1	0.1mg/ml
De Angelis et al. [29]	Peri-implant pocket	TBO	NA	0.1mg/ml
Bassetti et al. [30]	Peri-implant pocket	MB	3	10 mg/ml
Schär et al. [31]	Peri-implant pocket	MB	3	10 mg/ml
Deppe et al. [32]	Peri-implant pocket	MB	3	10 mg/ml
Hayek et al. [33]	Experimental peri-implant defect	azulene	5	0.01%
Salmeron et al. [34]	Ti discs	TBO	1	0.1 mg/ml
Eick et al. [35]	Ti wells and discs	TBO	1	0.1 mg/ml
Shibli et al. [36]	Experimental peri-implant defect	TBO	1	0.1 mg/ml
Shibli et al.[37]	Experimental peri-implant defect	TBO	1	0.1 mg/ml
Marotti et al. [38]	Implant surface	MB	5	0.01%

Ti: Titanium MB: Methylene Blue NA : Not available

TBO: Toluidine Blue PS: Photosensitizer