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Role of Photodynamic Therapy and Diode Laser as an Adjunct to Non-Surgical Periodontal Therapy

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INTRODUCTION

Chronic periodontitis is a multifactorial inflammatory disease involving bacterial biofilm as the focal aetiology. It is characterized by progressive destruction of supporting structures of teeth [(1)]. Mechanical periodontal therapy is the first line treatment, which includes subgingival scaling and root surface debridement. Non-surgical therapy has proven to be effective in reducing probing pocket depth (PPD) and gain in clinical attachment level (CAL) in mild to moderate periodontal cases [(2)]. However, it is difficult to achieve complete elimination of pathogenic bacteria, particularly present in deep periodontal pockets and within periodontal tissues [(3)]. Consequently, recolonization of pathogenic microflora occurs after traditional root surface debridement (RSD) [(4)]. In order to prevent this phenomenon, supplementary mechanisms of elimination of pathogenic biofilms are desired.

Laser assisted pocket disinfection is gaining popularity as the use of Laser along with SRP showed improvement in clinical parameters. The efficacy of Laser is enhanced by the addition of photosensitizers referred as photodynamic therapy (PDT), essentially a non – invasive treatment strategy. The photosensitizer gets activated on focusing with light of appropriate wavelength, leading to transfer of electrons and resulting in formation of singlet oxygen [(5)]. Thus, formed singlet oxygen has a short radius of action of about 0.02 µm with half – life of about <0.04 ms and is highly cytotoxic causing irreparable damage to the cell membrane. As the reaction occurs in a confined space, this property makes it suitable for therapeutic application in localized sites without affecting the distant cells.

PDT has several advantages as it is non- invasive and has localized zone of action, has the ability to inactivate endotoxins such as lipopolysaccharides (LPS), destruction of bacteria, prevents development of resistant strains even on repeated application. However, the therapeutic effect of PDT depends on choosing the appropriate light source of recommended wavelength for adequate tissue penetration and further, tissue oxygenation is imperative to the photodynamic effect.

Literature evidence showed improvement in clinical parameters like probing pocket depth, clinical attachment level and bleeding on probing [(6)] using PDT as adjunct to SRP. Though there is a dispute among studies in concerning effectiveness of PDT as an adjunct to periodontal therapy, a recent systematic review by Christopher et al, 2015 [(7)], suggested that adjunctive photodynamic therapy using diode laser showed beneficial effects when compared with Laser as a sole agent.

The aim of the present study was to systematically review the "Efficacy of Photodynamic Therapy and Diode Laser as an adjunct to non- surgical therapy in treatment of periodontitis".

MATERIALS AND METHODS

SEARCH STRATEGY

To find the information from databases i.e., MEDELINE/ PubMed, Cochrane library, Embase, Scopus and Google Scholar were searched using the following key words: photodynamic inactivation, photodynamic therapy, photodynamic antimicrobial therapy, lethal photosensitization, diode laser and periodontitis, bacteria. Data was searched from time period 1990 till January 2019 for relevant articles.

ELIGIBILITY CRITERIA

Inclusion criteria consisted of title / abstracts mentioning randomized controlled trial design with intervention in periodontitis subjects, treatment regimen including PDT using Diode lasers compared to Scaling and Root planing (SRP), trials mentioning details of PDT application including dye being used, laser energy settings, number of applications (single and / or multiple). Studies with minimum of 3 months follow-up assessing clinical parameters like probing pocket depth (PPD), clinical attachment level (CAL), bleeding index and plaque scores were considered. Additionally, investigations quoting changes in microflora (Porphyromonas gingivalis (P.g), Actinobacillus actinomycetemcomitans (A.a), Tannerella forsythia (T.f), Treponema denticola (T.d)) were also included. Studies using light source other than diode laser, studies in foreign language and with incomplete abstracts were excluded.

The quality of included studies was assessed based on: masking of intervention, masking of randomization, masking of outcome assessment, similarity in test and control groups at the start of the treatment and completeness of follow-up.

RESULTS:

In the Preliminary search 50 articles were included following application of selection criteria 17 articles were eligible for this systematic review. Among these 17 articles, 12 articles were employed single application and

5 were multiple application; 13 articles assessed clinical and microbial parameters (CP+MP) whereas 3 articles assessed only clinical parameters (CP) and 1 article evaluated microbial parameters alone; 8 articles with 3 months follow up, 7 articles with 6 months follow up and 2 articles with 12 months follow up. (Figure 1).

Photosensitisers (PS) used in these studies were either Methylene Blue (MB), Toluidine Blue O (TBO), Indocyanine Green dye (ICG), Phenothiazine chloride (PTC) and Curcumin. Primary outcome measures included in most of the studies were probing pocket depth reduction and clinical attachment level gain, which were defined as the difference between CAL and PPD levels, respectively, at baseline and at the end of follow-up. Among the clinical parameters change in bleeding on probing (BoP) was considered as the secondary outcome measures. Twelve studies assessed the effect of adjunctive use of PDT in treating chronic periodontitis subjects and five studies assessed the adjunctive use of aPDT in non – surgical periodontal therapy to aggressive periodontitis. (Table 1: describes the outcomes of the clinical and microbial parameters of the included studies)

DISCUSSION

Effect of PDT on clinical parameters – outcome

In twelve studies [9-13,15-17,19,20,22,23] investigating chronic periodontitis subjects, PDT + SRP showed significant reduction in PD, CAL and BoP in test sites. Also, no adverse effects have been reported in any of the studies.

However, on comparison with control group, three studies [13,15,17], showed significant reduction in PPD and CAL gain following single application of PDT, whereas, six studies [9-12,16,19] reported that single application of PDT to SRP showed no additional benefit in reduction of PD or gain in CAL when compared to SRP alone.

Three [20,22,23] studies assessed the multiple applications of PDT compared to SRP in treating chronic periodontitis patients and had concluded, that multiple applications of PDT showed significant reduction in PPD and CAL gain when compared to SRP alone for a short duration of time but failed to show beneficial results at a long term follow up.

Five [8,14,18,21,24] studies assessed the efficacy of PDT in treating aggressive periodontitis subjects. Three [8,14,18] studies employed single application of PDT and two [21,24] employed multiple application of PDT. The single application studies suggested that there is no additional benefit achieved on using PDT as an adjunct to SRP. Whereas, Moreira et al [21], assessed the efficacy of multiple application of PDT in aggressive periodontitis subjects, showed a higher PD reduction and CAL gain at 3 months follow up period in deeper pockets compared to SRP. Sreedhar et al [24], compared the effect of SRP alone, single application of PDT and multiple application of PDT in aggressive periodontitis subjects and concluded that multiple application showed significant reduction in PPD, BoP and CAL gain at 3 months follow up.

Based on the outcomes of individual studies the statistically significant improvement in PD and CAL with PDT as an adjunct to SRP were considered to signify questionable additional benefits.

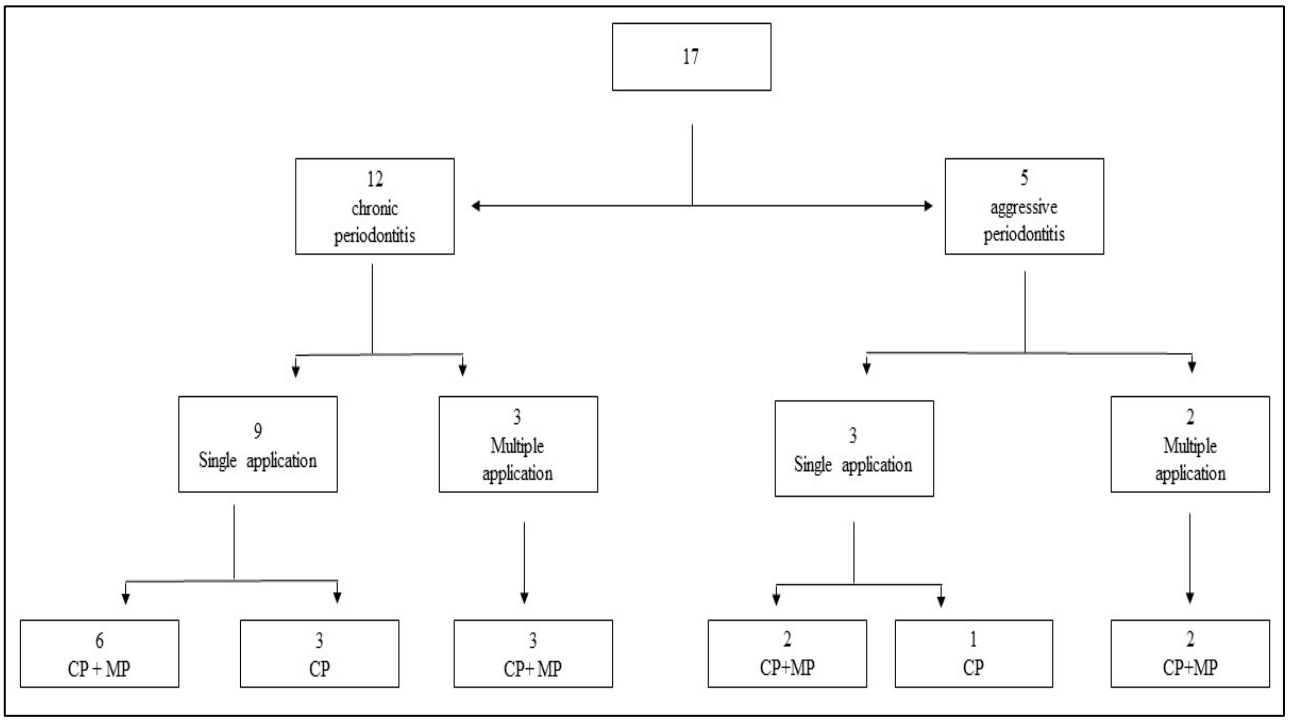

FIGURE 1: Details of included studies

TABLE 1: CLINICAL AND MICROBIAL PARAMETERS OF INCLUDED STUDIES

AUTHOR (YEAR)	PDT PROTOCOL EMPLOYED	OUTCOME
de Oliveira et al (2007) [8]	Diode laser 660 nm (fiber -optic applicator- 600-μm diameter), 60mW/cm2, 10seconds – laser application PS: Phenothiazine (10 mg/ml)	Subjects: aggressive periodontitis n = 10 (split mouth design) Test=PDT & Control=SRP Similar outcomes in both groups at end of 3 months follow up (P >0.05).
Christodoulides et al (2008) [9]	670 nm, 75 mw/cm2, 1 min- laser application PS – TBO	PDT + SRP group showed no improvement in PPD reduction and CAL gain but showed significant reduction in BoP compared to SRP alone. Test group showed significant changes in BoP (P <0.001). A.a, P.g, T.f counts were comparable among both the groups at 24 weeks follow up
Polansky et al (2009) [10]	Diode laser 680 nm (fiber-optic tip - 300μm diameter), 60 seconds – laser application PS - PTC	Subjects: (n=58) chronic periodontitis patients Test group= SRP+PDT Control group = SRP Similar outcomes for both the groups at the end of 3 month follow up (P>0.05). BoP values were significant for the test groups (P<0.05) Significant reduction of P. gingivalis observed in both the groups (Test group: p=0.020; control group: p=0.042) P.g, T.f, and T.d counts were comparable among both groups at 3 months follow-up.
Chondros et al. (2009) [11]	670 nm, 75 mw/cm2, 1 min- laser application PS – PTC (10 mg/ml)	Subjects: Chronic periodontitis Test (n=12) =SRP + PDT Control (n=12) = SRP Test group failed to result in additional improvement at 3 & 6 months follow up. (P>0.05). BoP values were significant with respect to test sites (P<0.05). PDT+SRP group showed increase in T.d counts A.a, P.g, and T.f counts were comparable among both groups at 24 weeks follow-up
Ruhling et al. (2010) [12]	635 nm, 100 mw/cm2, 1 min- laser application, PS – Tolonium chloride	Subjects: Chronic periodontitis Test group (n=25) = PDT Control group (n=29) = Ultasonic debridement (UST) Similar outcomes for both the groups (P>0.05) and 30-40% reduction of microbial count was presented immediately following application but reverted to baseline values at 3 months follow up.
Cappuyns et al. (2012) [13]	660 nm, 40 mw/cm2, 1 min - laser application, PS – PTC (0.1 mg/ml)	Subjects (n=32): Chronic periodontitis Three groups: group 1: SRP; group 2: Diode laser; group 3: PDT Statistically significant reduction in PPD and BoP at the end of 6 months in aPDT group (P<0.05) and PDT group suppressed P.g, T.f, T.d counts at the end of 6 months follow up.
Novaes Jr et al (2012) [14]	Diode laser 660 nm, 0.06 W/ cm2, 10 s – laser application, PS – PTC	Subjects: aggressive periodontitis n = 10 (split mouth design) Test group: SRP + PDT Control group: SRP Test group showed significant reduction in Aa counts whereas control group showed reduction in P.g, T.f and T.d at 3 months follow up.
Theodoro et al (2012) [15]	Diode laser 660 nm, 400 mw/cm2, 150 s - laser application, PS - TBO	Subjects: (n=33) Chronic periodontitis Group 1: SRP; Group 2: SRP+ irrigation with TBO; Group 3: PDT. PDT group showed significant improvement in clinical parameters (P<0.05) PDT + SRP group showed significant reduction in Aa, P.g, and T.f counts compared with PS and control group at 24 weeks follow-up

AUTHOR (YEAR)	PDT PROTOCOL EMPLOYED	OUTCOME
Balata et al (2013) [16]	Diode Laser 660 nm, 100 mw/cm2, 320 J 1 min laser application, non-contact	Subjects (n=22) Chronic periodontitis Test group = SRP + PDT Control group = SRP Similar outcomes for both the groups at 6 months follow up (P>0.05).
Alweli et al (2013) [17]	Diode Laser 660 nm, 100 mw/cm2, 1 min laser application, PS - PTC	Subjects (n=16): Chronic periodontitis Test group = SRP + PDT Control group = SRP Test group showed Significant reduction in PPD, BoP and gain in CAL 3, 6- and 12-months period (P<0.05).
Chitsazi et al (2014) [18]	Diode laser (fiber-optic tip), 690nm, 75mW, 120 secs-laser application, PS - TBO	Subjects (n=24): Aggressive periodontitis Control = SRP; Test = SRP+PDT Both the groups showed similar results in terms of PPD reduction and CAL gain (P>0.05) A.a counts were comparable among both groups at 12 weeks follow-up
Kolbe et al (2014) [19]	660 nm, 60 mw/cm2,129 J, 1minute laser application, PS – MB (10 mg/ml)	Subjects (n=22): Chronic periodontitis Test group (SRP+PDT) and control group (SRP) Bothe the groups showed similar outcomes at the end of 3 months follow up. A.a, P.g, and T.f counts were comparable among both groups at 3 months whereas recolonization occurred at 6 months follow up
Petelin et al (2014) [20]	Diode Laser – 660 nm, 60 mW/cm2 (fiber optic tip), 1 minute – laser application, PS – PTC, frequency of PDT application- 3 (1st, 3rd and 7th day after ultrasonic debridement)	Subjects: (n=27) chronic periodontitis Test group = PDT Control group = SRP Multiple applications of PDT showed Significant reduction in BoP (P<0.05) at 3 and 12 months. Test group showed significant reduction in A.a, P.g, T.f, and T.d counts compared with control (SRP) group at 6 months follow up
Moreira et al (2014) [21]	Diode laser 670 nm (fiber -optic tip 600-μm diameter) 75mW, 10 secs – laser application, PS-PTC (10 mg/ml), frequency of application- 4 (Baseline, 2, 7 and 14 days)	Subjects (n=20): Aggressive periodontitis Test group = PDT + SRP Control group= SRP Treatment group showed significantly higher reduction in PPD and CAL gain at 90 days follow up compared to control (SRP) group (P<0.05). A.a, P.g, T.f, and T.d counts significantly reduced in test group (PDT+SRP) at 12 weeks follow-up
Birang et al (2015) [22]	Diode laser 810 nm (fiber-optic tip 300-μm diameter) 0.5W/cm2, 10 secs – laser application, PS – ICG (1 mg/ml), frequency of application - Applied at baseline and 2 weeks later	Subjects (n=20): Chronic periodontitis Multiple application of PDT showed significant reduction in PPD, CAL gain, BOP (P<0.05). But only for a short period of time. A.a, P.g, and T.d counts were comparable among all groups at 3 months follow-up.
Carvalho et al (2015) [23]	660 nm, 40 mw/cm2, 90 J 1-minute laser application, PS – MB, frequency of application- 4 (baseline, 3, 6 and 9 months)	Subjects (n=34): Chronic periodontitis Test (n=18) = PDT; Control (n=16) = SRP Similar outcomes for both the groups at 12 months follow up (P>0.05). A.a, P.g, T.f, and T.d counts were comparable among both groups at 12 months follow-up
Sreedhar et al (2016) [24]	Diode laser 810 nm, continuous mode, 30 secs – laser applications, PS – TBO, frequency of application - (0, 7th and 21st day)	Subjects (n=15): Aggressive periodontitis Group 1: SRP; Group 2: SRP + PDT (single application); Group 3: SRP + PDT (Multiple application) Group 3 showed significant reduction in PPD and BoP and CAL gain at 3 months follow up compared to SRP alone and single application of PDT (P<0.05). PDT group showed reduction in level of A.a, P.g, Pi compared to other groups at 3 months follow up.

Effect of PDT on microbial parameters

Single and multiple application studies reporting the periodontal pathogen profile, showed significant reduction in the counts of four periodontal pathogens. Among the nine studies[9-13,15-17,19] which assessed the efficacy of single application of PDT treating chronic periodontitis subjects, three [9,18,19] studies showed that the microbial counts for A.a, P.g, T.f organisms were comparable among both the test and control groups at all follow ups. Theodoro et al [15], evaluated the efficacy of SRP, TBO photosensitizer alone and single application of PDT and reported significant reduction in counts of Aa, P.g, T.f and T.d following single application of PDT over a period of 6 months follow up compared with PS and control group (SRP). Whereas, Kolbe et al [19], evaluated the effect of PDT as an adjunct to SRP and the author reported significant reduction of Aa counts at 3 months follow up. P. gingivalis levels were less regularly identified in PDT group compared to other groups during follow up. Nevertheless, these levels cannot be maintained over a period of 6 months where bacterial recolonization was evident in all the groups. A contradictory finding was reported by Chondros et al [11], 2009 where, the authors observed an increase in Treponema denticola counts during 6 months follow up subsequent to single application of PDT.

Effect of multiple application of PDT on microbial parameters, reported significant reduction in microbial count of red and orange complex bacteria compared to SRP. Petelin et al [20], concluded that there is no recolonization of periodontal pathogens in the deep pockets even at 6 months follow up following multiple applications of PDT compared to control group. Whereas, Birang et al [22] and Carvalho et al [23], suggested that Aa, P.g, T.d, T.f counts were comparable among both the groups following multiple application of PDT.

Moreira et al [21] and Sreedhar et al [24], investigated the efficacy of multiple applications of PDT in aggressive periodontitis subjects and reported significant reduction of A.a, P.g, T.f and T.d over a 3 month follow up.

On interpreting data from the previous clinical trials its evident that in patients with chronic periodontitis and aggressive periodontitis, the adjunctive usage of PDT to conventional therapy may be beneficial in terms of reducing the periodontal pathogens in deeper pocket sites.

The included studies in this systematic review had various divergences as in terms of laser energy being used ranging from 0.5 to 2 W, duration of laser exposure about 10 seconds to 150 seconds, the PS being used. Further, method of collection of microbial samples, microbial analysis employed varied among studies. Hence, we were not able to arrive at meta-analysis using the outcomes of these enlisted studies.

CONCLUSION

Photodynamic Therapy is emerging as a beneficial treatment strategy in treating chronic periodontitis subjects. The outcome of various clinical trials suggest that PDT presented similar improvement in terms of clinical parameters compared to SRP. Also, the bactericidal effect of PDT showed inconsistent results. Therefore, development of new photosensitizers and proper standardization of protocol is necessary in future to achieve better clinical and microbial outcomes.

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