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Effects of Photodynamic Therapy with Laser Photobiomodulation as an Adjunct to Scaling and Root Planing: Systematic Review

Efeitos da Terapia Fotodinâmica com Fotobiomodulação Laser Adjuvante a Raspagem e Alisamento Radicular: Revisão Sistemática

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Abstract

Scaling and root planing is the gold standard procedure in the periodontal disease treatment. Although this therapy has the ability to reduce or eliminate periodontopathogens through periodontal instrumentation, sometimes the response to treatment may not promote the complete eradication of pathogens, affecting the healing process and leading to the presence of residual periodontal pockets. The aim of this study was to analyze the effectiveness of photodinamic therapy with laser photobiomodulation and as an adjunct to scaling and root planing (having as a conductive agent a fiber optic tip radiating inside the periodontal pocket), compared to scaling and root planing alone in patients with periodontitis on randomized trials. This systematic review was carried out complying with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The databases used were *Pubmed*, *Lilacs, Biblioteca Virtual em Saúde - Odontologia* and *Medline*. "Periodontal Disease" OR "Periodontal Treatment" AND "Photodinamic Theraphy" were the descriptors used. A total of five articles were included. Two studies have shown superior results in relation to the referred association; a study indicated benefits in biochemical and/or microbiological aspects; it suggests, however, that clinical relevance needs to be better evaluated; two studies did not reveal benefits that categorize photodynamic therapy + scaling and root planning as superior to conventional treatment. The association in question, when well standardized and performed, can result in promising responses in the control of periodontal disease; however, the clinical benefits that demonstrate its superiority will certainly be subject to new researches.

Keywords: Photochemotherapy. Periodontal Debridement. Periodontal Diseases. Periodontal Attachment Loss.

Resumo

A raspagem e alisamento radicular é o procedimento padrão-ouro no tratamento da doença periodontal. Embora essa terapia seja capaz de reduzir ou eliminar os periodontopatógenos por meio da instrumentação periodontal, algumas vezes a resposta ao tratamento pode não promover completa erradicação dos patógenos, afetando assim, o processo de cicatrização e levando à presença de bolsas periodontais residuais. O objetivo do presente estudo foi analisar a eficácia da terapia fotodinâmica com fotobiomodulação laser adjuvante a raspagem e alisamento radicular (tendo como agente condutor uma ponta de fibra óptica que irradia o interior da bolsa periodontal), em comparação com a raspagem e alisamento radicular isoladamente em pacientes com periodontite, avaliados em estudos clínicos randomizados. Esta revisão sistemática foi realizada de acordo com as recomendações Principais Itens para Relatar Revisões sistemáticas e Meta-análises. As bases de dados utilizadas foram Pubmed, Lilacs, Biblioteca Virtual em Saúde - Odontologia e Medline. "Doença periodontal" OR "Tratamento periodontal" AND "Terapia fotodinâmica" foram os descritores utilizados. Um total de cinco artigos foram incluídos. Dois estudos mostraram resultados superiores em relação à referida associação; um estudo indicou benefícios nos aspectos bioquímicos e/ou microbiológicos; sugere, no entanto, que a relevância clínica precisa ser melhor avaliada; dois estudos não revelaram benefícios que categorizassem a terapia fotodinâmica + raspagem e alisamento radicular como superiores ao tratamento convencional. A associação em questão, quando bem padronizada e realizada, pode resultar em respostas promissoras no controle da doença periodontal; entretanto, os benefícios clínicos que demonstram sua superioridade certamente serão alvo de novas pesquisas.

Palavras-chave: *Fotoquimioterapia. Desbridamento Periodontal. Doenças Periodontais. Perda da Inserção Periodontal.*

1 Introduction

The use of lasers in the medical and dental fields is growing exponentially due to its wide spectrum of therapeutic possibilities[1,2]. In dentistry, lasers are devices with widely recognized applicability. They are classified as high and low power, or surgical and non-surgical, respectively. High-powered lasers are indicated for soft and hard tissue surgery, in addition to having an antimicrobial, coagulation and hemostasis effect. Low-power lasers are indicated for analgesia, intensify the repair of wounds and act effectively in inflammatory processes[3-5].

A growing therapeutic measure in recent years is called Photodynamic Therapy (PDT), and consists of the association of Low Power Laser Therapy (LLLT), in most cases, with a photosensitizing agent (PS). Its mechanism consists of the photosensitizing agent activation, which, by absorbing photons from the LLLT light source, causes the electrons to pass to an excitation level and form reactive species of molecular oxygen with short life, called singlet oxygen. This

leads microorganisms to develop lethal changes in proteins and / or in the plasma membrane, generating a decrease in the microbial load at the site[6-9]., in addition toto reducing the number of liposaccharides that foster and synthesize pro-inflammatory cytokines. This therapy has been shown to be effective against different types of bacteria when there is an adequate association of the laser wavelength and the concentration of a compatible non-toxic photosensitizer, with a high capacity to absorb photons and to penetrate bacterial cells through membrane permeability[10]. However, the membrane of Gram-negative bacteria is difficult to penetrate, due to its thick layer of liposaccharides and lipoproteins[11,12].

Among the dental specialties that can benefit from the use of PDT, it is possible to mention Periodontics. Periodontal disease is caused by the presence of bacteria species in dental support tissues, with consequent bacterial biofilm agglomeration, inflammatory and immunological factors exacerbation, in addition to the loss of conjunctive and bone insertion[13]. To restrain this infectious process, scaling and root planing (SRP) is the procedure considered the gold standard, in addition to the use of antimicrobial solutions[14] and surgical therapeutic resources.

Although conventional SRP therapy has the ability to reduce or eliminate periodontopathogens through periodontal instrumentation associated with effective control of dental biofilm, in deeper places where the operator's reach is limited, the response to treatment may not promote complete eradication of pathogens. In addition, rapid microbial recolonization after periodontal treatment can affect the healing process and lead to the presence of residual periodontal pockets[15]. This factor is justified by the ability of bacteria to penetrate gingival epithelial cells, allowing them to escape from the host[16,17].

Although there is a recognized relevance of the theme, this scenario is conducive to the carrying out of research with factors that can contribute to the SRP. The PDT method associated with non-surgical periodontal treatment has advantages such as reduced morbidity, greater comfort in the postoperative phase, in addition to being a less invasive practice when compared to traditional surgical treatment methods. Thus, the use of PDT as an exclusive protocol can generate preferable results in clinical and patient performance, and consequently better antibacterial solutions[18,19].

In this perspective, the objective of this paper has been to carry out a systematic literature review through randomized clinical trials comparing the combined effect of photodinamic therapy and laser photobiomodulation with the use of fiber optic tip as a conductive agent for irradiation inside the periodontal pocket, as adjuvant to scaling and root planing in patients with periodontitis.

2 Material and Methods

2.1 Eligibility criteria

This is a systematic literature review, which was carried out according to the notification items for systematic review and meta-analyses Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[20], and the review was registered a priori at the PROSPERO.

2.2 Inclusion and non-inclusion criteria

Only randomized clinical studies that included the proposed methodology (association of PDT with SRP treatment, using LLLT with fiber optic tip radiating the interior of the periodontal pocket) were included in the present study, and only those written in the English language, published in the last 10 years and related to normoreactive human patients.

In contrast, the non-inclusion criteria established were the following: works that did not present their respective abstracts on the search platforms; studies whose therapeutic approach covered other agents associated with PDT; studies with PDT application in different clinical situations or where patients had a history of harmful habits; studies that did not report the photosensitizer concentration; protocols that did not inform the defined dosimetry of the apparatus, did not specify or imply the quantity and/or location of the points of LLLT application and somehow did not provide the PDT usage protocol.

2.3 Search strategies and research information

The electronic databases *PubMed, Lilacs*, *Biblioteca Virtual em Saúde* – Odontologia [Virtual Health Library – Dentistry] (BVS) and MEDLINE were used in March 2020, by crossing the Decs/Mesh descriptors through the Boolean operators AND and OR, according to the following strategy: "Periodontal Disease" OR "Periodontal Treatment" AND "Photodinamic Theraphy". In order to maximize the evaluation, PICO strategy was used (P – population: patients with periodontitis; I – intervention: PDT associated with LLLT (using fiber optic tip inside the periodontal pocket) in the treatment of SRP; C – comparison – only with the SRP; O – Outcomes: does the PDT associated with the SRP show better results?). For this purpose, the relevant and specific question of the present study was: "Can the PDT protocol with low power laser using a fiber optic tip inside the periodontal pocket in association with the SRP obtain superior results in relation to the exclusive use of SRP?".

2.4 Selection of studies

All the selected articles were tabulated in the Microsoft Word program (version 2010). In the first stage, two previously calibrated reviewers, D.A.S and C.S, performed the search regadless of the databases mentioned above. In case of disagreement between them, a third author was called (J.B.L.D). The inclusion and non-inclusion criteria were applied for the reading of titles and abstracts. Duplicate articles were considered only once. In the second stage, the complete texts were read and selected. The analysis of

agreement between the two reviewers concerning the included studies was performed by using the Cohen's Kappa test, which presents the following parameters: light (0.00 to 0.20), regular (0.21 to 0.40), moderate (0.41 to 0.60), high (0.61 to 0.80) and almost perfect (0.81 to 1.00). The value of the Cohen's Kappa coefficient in the present study was >0.82, with concordance classified as almost perfect.

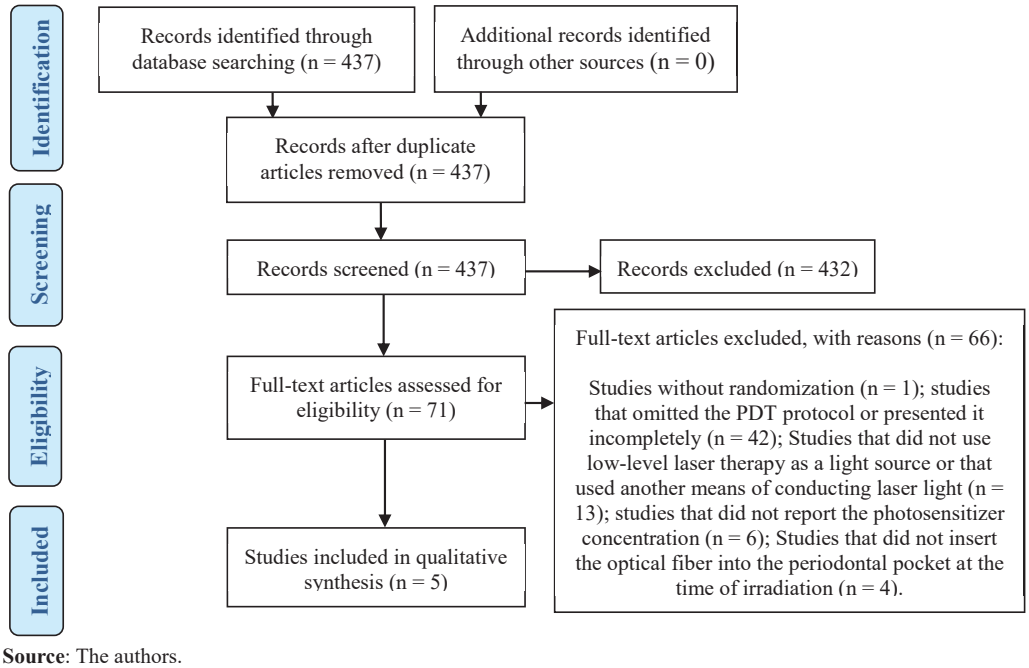
2.5 Data extraction

The following data were extracted: citation (author/year), publication type, study design, aim/study objectives, study duration, duration of participation, population description, total number of the study participants, method of recruitment, age, gender, follow-up method, subgroups measured, subgroups reported, oral/dental status reported, co-morbidities, disease definition, measurements, outcome, unit of measurement, statistical analysis and the study conclusions by the author(s).

3 Results and Discussion

Initially, a total of 437 articles with the proposed theme were selected, all of them from PubMed, given that the LILACS, *Biblioteca Virtual em Saúde* – Odontologia (BVS) [Virtual Health Library – Dentistry] and MEDLINE platforms had zero articles related to the chosen descriptors. No duplicate articles were found on the search platform. After the first analysis, 432 journals were outside the inclusion criteria (98 literature reviews; 99 were laboratory studies; 5 did not present their respective abstracts on the search platform; 1 did not have PDT as a topic; 1 was written in another language; 162 applied PDT in other clinical situations and/or in patients with a background of systemic diseases or harmful habits; 6 did not report the photosensitizer concentration; 1 did not present randomization; 19 did not report the complete dosimetry used; 5 did not specify or imply the amount and/or location of application points; 9 used red LED light; 1 used violet-blue LED light; 3 used another means of conducting laser light; 4 did not insert the fiber optic tip into the periodontal pocket at the time of irradiation; 18 did not provide the use protocol of the PDT). It is worth mentioning that even the studies that fitted in several simultaneous non-inclusion criteria were allocated and categorized in only one of them. In short, a total of 5 articles were selected for the present study after the search refinement, as shown in the flowchart of figure 1, based on the PRISMA model[20].

Figure 1 - Flowchart of identification of selected articles.



Source: The authors.

After analyzing the data, it can be observed that in the last 10 years, the most relevant clinical studies, according to the criteria established for the present work, were published between the years 2012–2019, the year of greatest rise being 2012 (n=2). The total number of patients in all the articles analyzed was 118. The average of the study samples among all the clinical trials was 23.6 ± 4.1; standard deviation (SD): 9.18. Most of the population studied was male (n = 62), with an average of 12.4 ± 3.34, SD: 7.46, for men and of 11.2 ± 1.82, SD: 4.08, for women, per study. The average age of the individuals was 41.8 ± 5.07, SD: 11.3. Two studies reached superior results regarding the association of PDT with SRP, when compared to conventional SRP; one study reported benefits in terms of biochemical and/or microbiological aspects; it suggests, however, that its clinical relevance needs to be better assessed; two studies did not verify any additional benefit in the PDT + SRP association which might categorize it as superior to the conventional SRP. The general descriptions of the main findings of the present systematic review are summarized in Table 1.

Table 1 - Summary of selected articles

Author/ Year	Sample	Study	Results
Al-Khureif et al. (2019)	(n = 17) At least one periodontal location with PPD and clinical insertion of ≥5mm.	Randomized controlled clinical trial of whole mouth.	The moderate PPD significantly reduced in both groups, but the deep pockets had a more significant improvement with the use of PDT.
Carvalho et al. (2015)	(n = 34) Loss of proximal insertion ≥ 5 mm in more than 30% of the teeth.	Randomized controlled clinical trial.	PDT has failed to demonstrate any bacteriological benefit in the treatment of residual pockets.
Kolbe et al. (2014)	(n = 22) With at least 3 residual pockets ≥ 5 mm with BoP.	Prospective randomized controlled study.	PDT as monotherapy has advantages in the inflammatory cytokines modulation and can be used as a therapeutic to treat residual pockets, with indication for supportive periodontal treatment.
Campos et al. (2012)	(n = 13) Presence of at least 2 residual pockets ≥ 5 mm, BoP in uniradicular teeth under periodontal therapy.	Blind randomized clinical study.	PDT in addition to SRP can be a therapeutic alternative.
Giannopoulou et al. (2012)	(n = 32) Under maintenance care and with persistence of sites with PPD > 4 mm and positive BoP ┗.	Randomized clinical study with parallel design and divided mouth.	Groups B and C promoted changes in the levels of cytokines and acute phase proteins, levels similar to SRP. However, no additional benefits can be found through SI€ and PDT when compared to SRP.

Source: Research data.

The present study focused on conducting a systematic literature review in order to contrast the effects of laser photobiomodulation associated with PDT (having as the conducting agent the optical fiber tip radiating the interior of the periodontal pocket) as a complementary treatment to the SRP, with the following basic periodontal profile: patients with periodontal disease and the treatment described and evaluated through randomized clinical trials.

Periodontal disease is an oral pathology resulting from the action of periodontopathogenic microbial agents in dental support tissues, which leads to the bacterial biofilm agglomeration, immunoinflammatory factors exacerbation, in addition to loss of conjunctiva and bone insertion[13]. It is worth mentioning that the term "chronic periodontitis" is no longer used after the publication of the "2018 classification of periodontal and peri-implant diseases and conditions: a practical guide and key points", which classifies periodontal disease by "stage" (severity of the disease) and "degree" (evidence or risk of its progression)[22].

The conventional procedure in the treatment of periodontal disease is called SRP. Its focus is to mechanically reduce the local microbial load, which is carried out through the mechanical removal of microbial deposits that cause inflammation and periodontal infections, and may also be associated with antimicrobial solutions[14]. In some cases it is not possible to achieve complete disease stabilization and / or prevent the systemic spread of these microorganisms. This factor is justified by the bacteria's ability to penetrate gingival epithelial cells, allowing them to escape from the host and be resistant to antiseptic and antibiotic treatments. In view of this, the TFD proposal has been gaining ground in the dental field by allowing a reduction in morbidity and greater comfort in the patient's postoperative period, in addition to being a less invasive procedure when compared to traditional treatment methods. Therefore, it can be considered that PDT is characterized as a current therapeutic resource that has the ability to enhance the conventional periodontal treatment, with consequent better clinical performance and regression of the periodontal patient's pathological condition [16-19,23].

The effectiveness of photodynamic therapy depends on the ability to provide light to all the target tissues. To circumvent this problem, it was opted for the use of optical fibers, light-conducting devices that can be coupled to lasers for endoscopic or interstitial application[24]. The lateral emission profile of the fiber ends can be of particular benefit for applications for disinfecting periodontal pouches. As the laser energy is emitted along the entire length of the fiber side, a more uniform irradiation (aiming at the complete scanning of the interior of the periodontal pocket) would be achieved[25].

Based on this principle, Al-Khureif et al.[26] intended to evaluate the efficacy of PDT and antimicrobial therapy on the clinical and immunological results of periodontal disease treatment in stage 3 or 4 / Grade C, over a period of 6 months, as adjuncts to plan with ultrasonic devices. This research was carried out with 17 patients who presented the referred periodontal profile and with at least 20 teeth in the mouth. Participants were divided into two groups: Group 1 - received treatment with PDT (PS: phenothiazine chloride (10mg/ml). 670nm diode laser (red); power: 75mW; power density: 0:25 mW; flow per location: 2.49 J/cm^2; and per tooth: 14.94 J/cm^2) + SRP; Group 2 - submitted to antibiotic therapy with metronidazole and amoxicillin (500mg) orally, 3 times a day, for 7 days + RAR. Both groups had a significant decrease in BoP, probing depth (PPD) and gain in clinical insertion (CAL).

During the 3-month period, there was a noticeable reduction in the rate of bleeding on the probe (BoP), as well as a significant reduction in deep periodontal pockets in group 1. However, as far as immunological patterns are concerned, group 2 showed a certain advantage with antimicrobial therapy, by increasing the levels of IL-10; therefore, group 1 had no significant effect on the levels of cytokines in the gingival fluid. In general, the moderate probing depth reduced significantly in both groups, whereas the deep pockets had a more significant improvement with the use of PDT.

Accordingly, a study was conducted with thirteen patients with periodontitis who had at least two residual periodontal pockets ≥ 5 mm with the presence of SS. Patients underwent subgingival SRP in a single session, and after three months they were randomly allocated to receive one of the following treatments: SRP + PDT (PS: methylene blue (10 mg / ml); Diode laser λ 660 nm (red); power: 60 mW; energy density: 129 J/cm$^{2)}$ or SRP alone. Among the results obtained, it is noteworthy that in the three-month evaluation, the reductions in PPD and the gains in CAL were statistically significant in the PDT + SRP group, with a greater reduction in PPD and BoP, and gain of CAL compared to the SRP group. The sites treated by the associated therapy produced a statistically significant reduction in the percentage of sites with PPD <5 mm without BoP after 3 months (72.22%) compared to sites treated only by conventional SRP (40%)[27].

Kolbe et al.[28] evaluated the clinical, microbiological and immunoinflammatory aspects in 22 patients treated with the following monotherapies during periodontal maintenance: SRP with curettes, application of photosensitizing agent without laser irradiation and PDT (PS: methylene blue 10mg / ml; Diode laser λ 660 nm (red); power: 60 mW; energy density: 129 J/cm$^{2)}$. These patients were reassessed after 3 and 6 months. Due to that, it was concluded that there was a significant reduction in the number of sites with PPD ≥ 5 mm and with BoP ┗ in both PDT and SRP protocols with curettes (14.28% and 19.04%, respectively) at the 3rd and 6th month, this reduction being higher than the isolated protocol with photosensitizer (42.85%). At the end of the 3-and-6-month period, reductions in PPD and CAL were achieved in all the experimental protocols when compared to mean values at baseline. However, no difference in PPD or CAL was observed between the groups along the study. When performing the Polymerase Chain Reaction exam, it was identified that the anti-inflammatory levels of IL-4 increased only in the PDT protocol at the 6th month after treatment. The intergroup analysis showed that reduced levels of IL-10 were detected in the photosensitizing group at the 6th month when compared to the PDT and SRP protocols. Regarding proinflammatory mediators, IL-6 levels decreased in 6 months, and IL-1β levels decreased at the 3rd and 6th months only in the PDT protocol. As for the microbiological tests, significant reductions in the levels of A. *actinomycetemcomitans* were identified after 3 months in the PDT and SRP protocols, although this reduction was not maintained in 6 months. In addition, P. gingivalis was detected less frequently in the PDT protocol at the 3rd and 6th months. Regarding the intergroup analyses, P. *gingivalis* was identified in a smaller amount in the PDT protocol when compared to other therapies in the post-three-month follow-up.

However, there are still controversies in the literature regarding the effectiveness and real benefits of PDT when applied to routine periodontal treatment. To analyze the effectiveness of PDT as a treatment for residual pockets in patients with periodontitis, 34 patients were used with the minimum of 10 teeth in the mouth and 4 sites with PPD ≥ 4mm. Initially, the oral environment of all the patients was adjusted using ultrasonic devices and hand instruments. After 45 days, the 4 sites with residual pocket were selected, provided that at least 1 site had PPD ≥ 5 mm. Having done that, they were divided into Control Group (CG) and Test Group (TG). The TG was submitted to the usual PDT protocol (PS: 0.01% methylene blue; Diode laser λ 660 nm (red), for 90s; energy density: 90 J/cm^2; power: 40 mW), and in the CG the irrigation was performed with saline solution, and the laser light was not activated. The treatment performed in the pre-study phase resulted in improvements in both groups in terms of PPD, CAL and BoP. Subsequently, at the 3rd, 6th and 12th month, there was no significant change in CAL between TG and CG. In PPD and BoP there was a big change, after the same period. Both groups showed a decrease in the amount of residual pockets, with no statistical difference between the groups. It can be concluded that in this photosensitizer protocol employed, PDT has not proven to have clinical privileges for the residual pockets treatment in patients with periodontitis[29].

Maintaining a similar conception, Giannopoulou[30] evaluated the local level of the host's immune-inflammatory response to the residual pockets treatment through three different modalities: SRP, subgingival irradiation (Diode laser λ 810 nm - infrared; power: 100 mW; irradiation time: 60s) and PDT (PS: phenothiazine chloride 100 mg/mL; Diode laser λ 660 nm (red); power: 100 mW; energy density: 3 J/cm; irradiation: 1' per tooth) in 32 patients under periodontal maintenance during the 6-month period. After this period, only 9% of the sites treated with SRP, 25% with SI and 9% with PDT still had PPD^{H} greater than 4 mm. Approximately half of the sites had positive BoP at the 6th month, regardless of the therapeutic modality, with no significant differences in the clinical parameters between the groups. According to the analyses of proinflammatory cytokines and proteins from pathological amyloid deposits, which inhibit fibrinolysis, all the therapeutic modalities showed a reduction during the period of 14 days to 2 months after the treatment. However, the authors reported that, as for the levels of proinflammatory cytokines and of proteins in the acute phase, no significant

differences were observed between the treatment modalities. Given that, within the limits of the study, no additional benefits could be found in subgingival irradiation and PDT when compared to conventional SRP.

4 Conclusion

The association of PDT and laser photobiomodulation with conventional periodontal treatment, when well standardized and performed, can result in promising responses in the periodontal disease control. Results such as regression of periodontal pockets, reduction in the probing depth, in the clinical attachment level and mainly the decrease in bleeding rates at probing were observed.

Although there is no unanimity in the literature, the association of PDT, under the use of optical fiber, with SRP as therapeutic measures has promising effectiveness for the treatment of patients with periodontal disease. However, the clinical benefits that categorize the superiority of the use of PDT and SRP, when compared to conventional treatment, will certainly still be the target of further research.

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