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Effect Of Photodynamic Therapy On Non-Surgical Periodontal Therapy In Chronic Periodontitis Patients: A Randomized Clinical Trial

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Abstract

Aim: *Chronic periodontitis is an inflammatory condition affecting oral health due to bacterial biofilms and host immune responses. Although scaling and root planing (SRP) reduce bacterial load, deep-seated pathogens necessitate additional therapies. This randomized controlled split-mouth clinical study examined locally delivered unactivated methylene blue versus methylene blue activated as a photosensitizer in antimicrobial photodynamic therapy (APDT), combined with SRP.*

Materials and Methods: *Twenty patients with chronic periodontitis with pocket depth of ≥5mm at 3 different sites, were divided into three groups: Group I (SRP only), Group II (SRP with unactivated methylene blue), and Group III (SRP with laser-activated methylene blue). Each patient had two test sites and one control site. Test sites received SRP with activated methylene blue and laser therapy, while the other received SRP with unactivated methylene blue. The control site underwent SRP alone. Clinical parameters such as plaque index (PI), gingival index (GI), probing pocket depth (PD), clinical attachment level (CAL), and microbiological profiles were measured at baseline and after three weeks.*

Results: *Results showed that PDT with activated methylene blue led to significant improvements in plaque reduction, gingival health, and pocket depth compared to other groups. The improvement in CAL were non-significant between groups. Activated methylene blue in PDT significantly reduced levels of spirochetes and motile rods at three weeks and increased beneficial coccoid cells without adverse effects, minimizing microbial recolonization.*

Conclusion: *The study concluded that PDT with activated methylene blue has superior antimicrobial efficacy for managing chronic periodontitis compared to SRP alone or SRP with unactivated methylene blue.*

Keywords: *Antimicrobial Photodynamic Therapy (aPDT), Methylene Blue (MB), Diode Laser, Photosensitizer, Chronic Periodontitis, Non-Surgical Periodontal Therapy*

INTRODUCTION

Periodontitis is a chronic inflammatory disease that affects the structures supporting the teeth, including the periodontal ligament and alveolar bone. Ranking as the sixth most common human disease globally, it arises from specific bacteria in dental biofilm. The host's immune response to bacterial toxins triggers gingival inflammation, pocket formation, and heightened tooth mobility, ultimately causing the destruction of periodontal tissues. [1,2]

Traditional treatments like scaling and root planing (SRP) effectively removes periodontopathogens, but it is less effective in deep pockets, often leaving residual pathogens that continue to cause disease.[3] Moreover, the reliance on antibiotics carries risks of adverse effects and increasing bacterial resistance.[6]

Considering these challenges, innovative therapeutic approaches such as Antimicrobial Photodynamic Therapy (aPDT) have emerged as adjuncts to SRP. By utilizing photosensitizers like methylene blue and specific wavelengths of light, aPDT generates reactive oxygen species that effectively target and kill

bacterial cells.[4] With minimal side effects and promising clinical and microbiological outcomes, aPDT represents a safer, non-invasive alternative for periodontal therapy. [5]

Photodynamic Therapy (PDT) is driven by three core elements: light, a photosensitizer, and oxygen. Antimicrobial Photodynamic Therapy (aPDT) harnesses singlet oxygen and free radicals, generated through a precisely light-activated photosensitizer, to destroy microbial cells with precision. The process begins with a low-power laser or light of an optimal wavelength to excite the photosensitizer. Upon activation, the photosensitizer transitions to a singlet state and, through intersystem crossing, reaches a long-lived triplet state. This state initiates a photochemical reaction producing cytotoxic singlet oxygen, free radicals, and superoxide that eliminate microbes effectively.[7]

Photosensitizers in antimicrobial PDT (aPDT), such as phenothiazines (e.g., toluidine blue O and methylene blue), can target both Gram positive and -negative bacteria due to their positive charge. Methylene blue is a potent redox indicator and photosensitizer that effectively inactivates both gram-positive and gram-negative periodontopathic bacteria. It targets mitochondria with or without photostimulation, generating oxidative species upon light exposure. This process damages mitochondrial macromolecules, evidenced by increased lipid peroxidation and protein carbonyls. Methylene blue creates a pro-oxidant environment, depletes glutathione (GSH), and disrupts bioenergetics by uncoupling oxidative phosphorylation, inactivating complex I, complex II, and F1FO–ATP synthase, thereby reducing ATP production. Its multifaceted antimicrobial mechanism makes it a powerful adjunct in periodontal therapy. [7,8] Initially investigated over a century ago for selective toxicity, PDT's use for infectious diseases decreased with the development of antibiotics in the 1940s. Now, with the rise in antibiotic resistance, PDT is gaining renewed interest as an effective, non-invasive method for eliminating microbes in clinical treatments.[7] Through this study, we aim to further elucidate the efficacy of this treatment, providing clinicians with robust, evidence-based insights to guide informed decision-making in periodontal therapy. Hence this study explores the comparative efficacy of methylene blue—both activated as a photosensitizer and unactivated—as adjunctive therapies to SRP, providing valuable insights into optimizing periodontal treatment strategies.

METHODS AND MATERIALS

The present study was a randomized clinical trial conducted on 20 patients at 60 sites.

Inclusion and Exclusion Criteria

Patients with periodontal pocket depths of ≥5mm and bleeding on probing at a minimum of three different sites, good systemic health, and over 20 natural teeth. We excluded patients who had recent periodontal treatment, were on certain medications, had systemic diseases, or used tobacco and alcohol. These patients were divided into three groups: Group I: SRP only (control), Group II: SRP with unactivated methylene blue and Group III: SRP with laser-activated methylene blue (photodynamic therapy).

Preparation of Methylene blue Solution

A methylene blue (MB) solution, with a concentration of 100 µg/ml, was employed as a photosensitizer. The solution was prepared using commercially available methylene blue powder. Specifically, 5 mg of MB powder was dissolved in 50 ml of distilled water. For application the solution was transferred in a cartridge or syringe first and was injected into the deepest part of the periodontal pocket and then while extruding, the needle was slowly drawn out till it reached the superior portion of the pocket.

Light Source (Diode Laser)

In this study, a diode laser with a wavelength of 810 nm, with an aiming beam wavelength of 630-670 nm at 1.8 watts was used. After five minutes of methylene blue application, irradiation of the inner and outer pocket mucosa around each tooth and the dental root with the laser was done. The optical fibre was introduced into the pocket and moved circularly in a deep-to-cervical direction and smoothly over the outer gingiva (one minute inside and one minute outside the pocket per tooth). Irradiation was done in the inner pocket with repeated passages of the fibre tip in contact mode for two seconds each, and the outer pocket with repeated passages of the fibre tip in non-contact mode for two seconds each. Local anaesthesia was not required for this procedure.

CLINICAL EXAMINATIONS

All parameters were evaluated at baseline and three weeks following specific treatment. The parameters assessed included the Plaque Index (PI), as defined by Silness and Loe (1964), the Gingival Index (GI), as

established by Loe and Silness (1963), Probing Pocket Depth (PPD), and Clinical Attachment Level (CAL).

The plaque score was obtained by adding the scores from the four areas of the tooth and dividing by four. GI was measured based on gingival consistency, colour and bleeding on probing; severity of gingivitis is assessed. The gingival index score was calculated by combining tooth scores from four areas and dividing by four to give a tooth score.

Probing Pocket Depth (PPD) is the distance between gingival margin and the bottom of the probable pocket and recorded to the nearest whole millimetre. Clinical Attachment Level (CAL) is the distance from Cemento-Enamel Junction (CEJ) to the base of the pocket. First the distance from the CEJ to the gingival margin was measured with the probe. CAL was calculated based on the assessments of probing pocket depth and gingival margin location at the selected site using the formulae CAL = PPD – GM. All the clinical measurements were assessed using a UNC-15 manual probe that has markings from 1-15 at 1 mm interval. It has colour coding at markings 5, 10 and 15 The apical margin of the acrylic splint was used as the fixed reference point.

Administration of Methylene Blue

Methylene blue was administered to the periodontal pocket using a syringe for standardization. Patients were advised to avoid using any interdental aids, chew hard or sticky foods for a week in the treated area, and not to use mouthwash or antimicrobial agents.

Microbiological Sampling Technique

A clean periodontal curette was inserted through the sulcus or pocket orifice to collect bacterial contents when no detectable supragingival microbial accumulations are present. The sample was suspended in saline by agitating the instrument's tip in 0.5–1 ml of solution in a screwcap vial. Sample preparation and examination was done within an hour to prevent clumping and loss of bacterial motility. One drop of suspension was placed on a microscopic slide and covered with a cover slip. Excess fluid was removed by pressing the slide on an absorbent surface. The slide was examined using dark field microscopy at 10X magnification.

Protocol

Clinical parameters were meticulously documented for the patient on the first day, and subgingival samples were promptly acquired for microbiological analysis using a dark field microscope. A thorough oral prophylaxis, incorporating scaling and root planing (SRP) with ultrasonic scalers and curettes, was executed. Impressions were secured for stent fabrication. Follow-up sessions were decisively arranged for three days later, with random selection of three distinct sites per individual.

After 3 days, one site was used as a control group (Group I). In second and third site 1ml unactivated Methylene Blue was directly administered in the periodontal pocket by using a 2ml syringe. One site was categorized under Group II. At the alternate site, unactivated methylene blue was activated using laser light transmitted through an optical fibre. That site was categorized under Group III. Patients had follow-ups scheduled after three weeks.

After a span of 3 weeks the clinical parameters were again recorded, and the bacterial samples were taken from the sulcus or subgingival areas with the tip of curettes. They were subjected to microbiological analysis, to arrive at the result.

Both clinical parameters and microbiological examinations were done at baseline visit and 3 weeks after specific treatment. All the data from both the clinical & microbiological parameters were sent for statistical analysis.

Fig 1. Baseline

Fig 2. Methylene Blue Solution Delivery after 3 Days

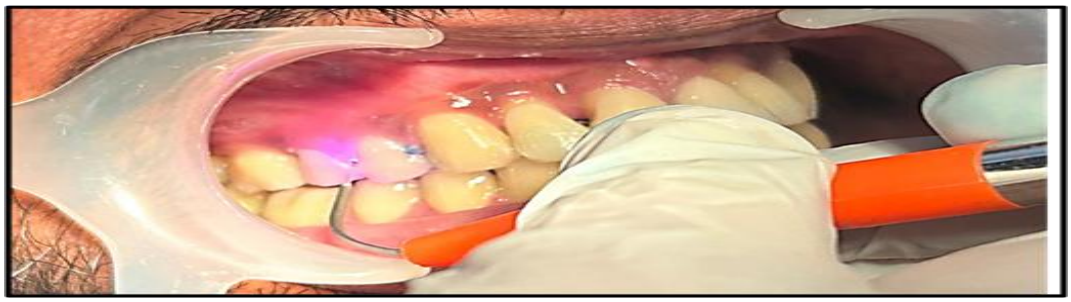

Fig 3. Laser Activation of Methylene Blue

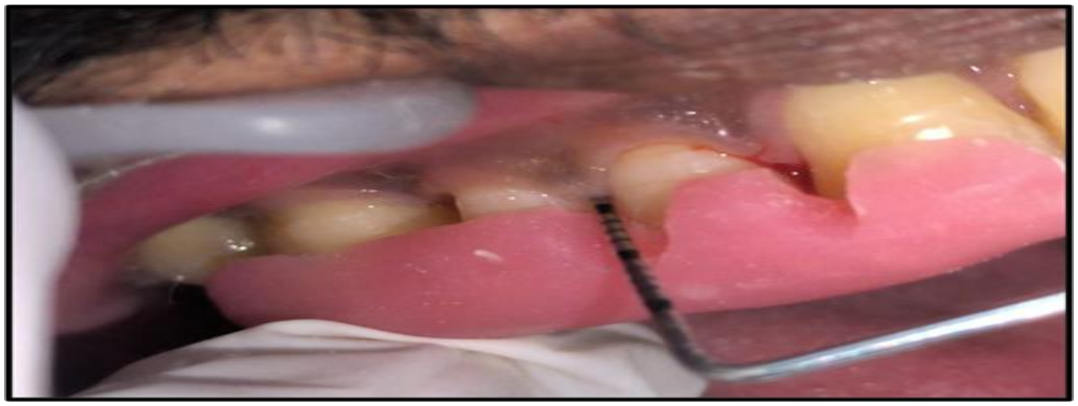

Fig 4. After 3 Weeks

STATISTICAL ANALYSIS

The statistical analysis was carried out using Jamovi (Version 2.6.26; Jamovi Project, 2024). The descriptive statistics were calculated as mean and standard deviation. Prior to analysis, the normality testing of data was carried out using Shapiro-Wilk test which showed that the data deviated from normal distribution ($p<0.05$). Thereafter, the intergroup comparisons of study parameters among the three groups were done using Kruskal-Wallis test. The level of significance for the present study was set at a p-value of less than 0.05.

RESULTS

The study involved 20 participants aged between 25 and 65 years who met the inclusion and exclusion criteria. Parameters such as Plaque index (PI), Gingival index (GI), Clinical Attachment Level (CAL), and Pocket Depth (PD) were measured at baseline for all three groups before periodontal therapy, indicating that the baseline parameters were similar.

Intragroup comparison of PD, CAL PI, and GI showed a statistically significant difference from baseline to 3 weeks ($P < 0.001$) in all the 3 groups suggestive of the fact that both conventional and activated methylene blue with Laser as an adjuvant therapy were effective ($P < 0.001$).

Intergroup comparison of the PI, GI, PD after treatment have shown a statistically significant reduction in the Group III compared to Group I & Group II at 3 weeks. Group III (SRP + activated methylene blue in aPDT) demonstrated the most pronounced improvements across all clinical and microbiological

parameters. Group III showed the most substantial gain in clinical attachment levels (CAL), though the difference did not reach statistical significance compared to other groups. Group II (SRP + unactivated methylene blue) outperformed SRP alone but was less effective than activated methylene blue in achieving comprehensive periodontal health. SRP alone (Group I) showed limited efficacy in microbial reduction and clinical healing compared to adjunctive treatments.

The comparison of microbiological profile among the study groups at various time periods. The statistical analysis was carried out using Kruskal-Wallis test which showed that there was a statistically significant difference among the groups in spirochetes at 3rd week ($p<0.001$), motile rods at 3rd week ($p<0.001$) and coccoid cells at 3rd week ($p<0.001$). No statistically significant difference was observed at baseline ($p>0.05$). This indicates that activated methylene blue significantly reduced pathogenic bacteria (spirochetes and motile rods) while promoting beneficial microbial shifts (coccoid cells). This shows that laser when used as an adjuvant to SRP is more effective in reducing the PI, GI, PD than when using SRP alone.

Table 1: Intergroup Comparison of Plaque Index & Gingival Index at Various Time Periods

Clinical Parameter	**Group**	**Baseline**	**3rd Week**	**P-Value**
PI	**Group I**	2.813 ± 0.291	1.88 ± 0.222	
	Group II	2.888 ± 0.172	1.55 ± 0.208	
	Group III	2.900 ± 0.205	1.00 ± 0.00	<0.001*
			Baseline	**3rd Week**
	Group I vs Group II		0.839	
	Group I vs Group III		0.539	
	Group II vs Group III	**P- Value**	0.836	<0.001*
		Baseline	**3rd Week**	**P-value**
GI	**Group I**	2.83 ± 0.36	1.98 ± 0.16	
	Group II	2.88 ± 0.28	1.59 ± 0.26	
	Group III	2.95 ± 0.13	1.00 ± 0.00	<0.001
			Baseline	**3rd Week**
	Group I vs Group II		0.989	
	Group I vs Group III		0.634	
	Group II vs Group III	**P-Value**	0.682	<0.001

***Statistically significant ($p<0.05$, Kruskal-Wallis test)**

Table 2: Intergroup Comparison of Pocket Depth & Clinical Attachment Level at Various Time Periods

Clinical Parameter	**Group**	**Baseline**	**3rd Week**	**P-Value**
PD	**Group I**	5.313 ± 0.352	3.362 ± 0.417	
	Group II	5.300 ± 0.368	3.500 ± 0.493	
	Group III	5.338 ± 0.327	2.848 ± 0.474	<0.001*
			Baseline	**3rd Week**
	Group I vs Group II		0.992	0.656
	Group I vs Group III		0.960	0.006
	Group II vs Group III	**P- Value**	0.914	<0.001*
		Baseline	**3rd Week**	**P-value**
CAL	**Group I**	5.74 ± 1.42	4.83 ± 1.38	
	Group II	5.71 ± 1.38	4.71 ± 1.23	
	Group III	6.14 ± 1.32	3.81 ± 1.25	0.033*
			Baseline	**3rd Week**
	Group I vs Group II		0.999	0.990
	Group I vs Group III	**P-Value**	0.417	0.059
	Group II vs Group III		0.356	0.069

Table 3: Intergroup Comparison of Microbiological Profile at Various Time Periods

	Group	Mean	SD	p-value
Spirochetes (Baseline)	**Group I**	38.50	6.39	0.274
	Group II	39.15	6.18	
	Group III	41.35	6.89	
Spirochetes (3rd week)	**Group I**	22.65	7.18	<0.001*
	Group II	21.30	7.18	
	Group III	13.30	4.71	
Motile Rods (Baseline)	**Group I**	34.50	5.44	0.293
	Group II	34.85	5.31	
	Group III	36.15	4.50	
Motile Rods (3rd week)	**Group I**	23.70	3.21	<0.001*
	Group II	22.65	3.75	
	Group III	13.40	2.16	
Coccoid Cells (Baseline)	**Group I**	34.30	9.07	0.541
	Group II	35.35	8.82	
	Group III	36.70	9.08	
Coccoid Cells (3^{rd} Week)	**Group I**	54.95	7.46	<0.001*
	Group II	52.60	7.05	
	Group III	72.30	9.88	

DISCUSSION

The findings of this study underscore the therapeutic potential of activated methylene blue in antimicrobial photodynamic therapy (aPDT) as an adjunct to scaling and root planing (SRP) for the management of chronic periodontitis. By analysing and interpreting the data from clinical and microbiological perspectives, the discussion provides deeper insights into the results and their implications, contextualizing them within existing literature.

Activated methylene blue used in aPDT exhibited the most significant improvements across all evaluated clinical parameters, including plaque index (PI), gingival index (GI), pocket depth (PD), and clinical attachment level (CAL), when compared to unactivated methylene blue or SRP alone. This highlights the ability of aPDT to enhance the outcomes of mechanical periodontal debridement.

The reduction in plaque scores observed in Group III demonstrates the effectiveness of activated methylene blue in targeting bacterial biofilms. Studies indicate that aPDT-mediated oxidative reactions rely on the cellular uptake of a photosensitizing dye, followed by irradiation with a visible light source. This process results in cellular damage within organelles sensitized by dyes. [8, 9] Methylene blue reduces mitochondrial membrane potential, thereby increasing its permeability. Additionally, singlet oxygen generated by aPDT may reach DNA and compromise the nuclear membrane of microbes. [10] These findings are consistent with previous studies, such as those by Fontana et al. (2009) [11] and Giannelli et

al. (2012) [3], which reported comparable clinical outcomes when combining PDT with conventional periodontal therapy.

The improvements in gingival health, indicated by reduced GI scores, are due to the anti-inflammatory effects of aPDT. Ana Pejcic et al [12] found that laser therapy reduces inflammation by regulating immune cells, enhancing blood circulation, reducing edema, normalizing vessel permeability, suppressing inflammatory mediators, lowering cytokine production, and inhibiting T and B lymphocytes. These actions lead to less swelling, faster healing, and overall anti-inflammatory benefits. Another study by Ana Pejcic et al [13] showed increased GI values in the conventional treatment group, unlike SRP alone, where subgingival pathogens may prolong inflammation.

The reduction in PD and improvement in CAL further demonstrate the enhanced ability of aPDT to promote periodontal healing. The greater reduction in PD and CAL gain observed in Group III compared to Groups I and II can be associated with the deeper bacterial decontamination achieved by activated methylene blue. Dong Xue et al. (2017) [14] found that while Photodynamic Therapy (PDT) adds short-term benefits to Scaling and Root Planing (SRP), its long-term efficacy remains uncertain, with no substantial clinical attachment level gain observed after 6 months. Similarly, Katsikanis et al. (2020) [15] reported notable pocket depth reductions for both laser treatments and antimicrobial PDT, showing significant improvement in clinical parameters at 3 and 6 months, with the diode group yielding greater PD reduction for deep pockets at 3 months.

From a microbiological standpoint, Group III exhibited a substantial reduction in spirochetes and motile rods, alongside a significant increase in coccoid cells, suggesting a beneficial shift in subgingival microbial composition. In contrast, SRP alone (Group I) showed a more limited reduction in periodontopathogenic bacteria, consistent with the limitations of mechanical debridement in accessing deep periodontal pockets. The bactericidal mechanism of aPDT, driven by singlet oxygen and free radicals, likely explains these results. The light-activated methylene blue targets both Gram-positive and Gram-negative bacteria, effectively reducing the microbial load.[7] This is particularly important for pathogens like spirochetes, which are implicated in the progression of periodontitis. Additionally, the ability of aPDT to inactivate bacterial endotoxins, such as lipopolysaccharides, further enhances its therapeutic efficacy.[7]

Notably, unactivated methylene blue (Group II) achieved better microbiological outcomes than SRP alone, albeit less pronounced than activated methylene blue. This may be due to the inherent antimicrobial properties of methylene blue, which disrupts bacterial membranes even without light activation. Recent evidence (Zhang et al., 2023) [16] corroborates this finding, emphasizing methylene blue's antibacterial potential in its unactivated state.

SRP, although effective in reducing bacterial loads, showed limitations in achieving complete periodontal healing. Residual pathogens may persist in connective tissues or dentinal tubules, contributing to inflammation and disease recurrence. The modest improvements in Group I (SRP alone) emphasize the need for adjunctive treatments to enhance the depth of bacterial decontamination and improve clinical outcomes. Haffajee et al. (1997) [17] reported similar challenges, noting that bacterial recolonization often occurs within weeks of SRP. The study confirmed the safety of activated methylene blue in aPDT, with no adverse effects reported in any of the groups. This finding is significant, as it highlights the potential of aPDT to provide effective microbial control without contributing to antibiotic resistance or causing tissue damage. Patient tolerance to aPDT was excellent, likely due to the non-invasive nature of the treatment and the absence of thermal effects associated with low-level diode lasers.

The superior outcomes achieved with activated methylene blue in aPDT underscore its potential as a standard adjunctive therapy in periodontitis management. By integrating aPDT into clinical protocols, periodontal practitioners can improve treatment efficacy, reduce disease recurrence, and potentially delay the need for surgical interventions in advanced cases.

Moreover, the cost-effectiveness of methylene blue, coupled with its safety profile, makes it a feasible option for widespread clinical adoption. Future advancements in photosensitizer formulations and laser technologies may further enhance the accessibility and effectiveness of aPDT.

While the study demonstrated significant short-term benefits of aPDT, its long-term efficacy remains unaddressed. Future research should explore the sustainability of clinical and microbiological improvements over extended follow-up periods. Additionally, larger sample sizes and multi-center trials would strengthen the generalizability of the findings.

The role of repeated aPDT sessions in maintaining periodontal health also warrants investigation. Muzaheed et al. (2020) [18] found that multiple aPDT applications resulted in more sustained reductions in pathogenic bacteria compared to a single session. Evaluating this approach in clinical settings could further refine treatment protocols.

CONCLUSION

Activated methylene blue in aPDT is a safe, effective, and clinically significant adjunct to SRP in the management of chronic periodontitis. Its ability to enhance clinical and microbiological outcomes provides a compelling case for its inclusion in periodontal treatment protocols. By addressing the limitations of mechanical debridement and harnessing the targeted antimicrobial action of aPDT, this approach holds promise for transforming the landscape of non-surgical periodontal therapy.

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