

Applications of Lasers in Refractory Periodontitis: A Narrative Review

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ABSTRACT

Objective: The purpose of the study is to evaluate the various lasers in dentistry and to investigate if it can be used for treatment of refractory periodontitis. **Methods:** The study followed partially the PRISMA guidelines as it is a narrative review. A number of articles were selected from a period of 1980 to 2020 from databases, PubMed, PubMed central, Cochrane and Scopus. Articles related to the effects of lasers on periodontitis both refractory and aggressive were investigated. **Results:** After reviewing the literature, 70 articles were found, related to application of lasers in periodontal diseases. Out of the 70, 11 articles pertained to the effect of laser for the treatment of Refractory and inflammatory periodontitis. 5 articles related to experimental animal models, one pertaining to in-vitro and six studies related to in-vivo in human cohorts. **Discussion:** It was found that lasers if used in controlled parameters by incorporating laser assisted treatment such as Photodynamic therapy and low level laser therapy can be of use as an adjunct therapy for treatment of refractory periodontitis. The use of different wavelengths in the initial and maintenance phase of periodontal disease plays a positive role. The presence of in-vitro and animal model studies is one of the limitation to this study. The available studies have shown marked reduction in inflammation and better clinical and microbiological parameters. The drawback of this study is the limited literature involving laser management for refractory periodontitis in human cohorts. **Conclusion:** Different wavelengths of laser and choice of laser assisted periodontal treatment plays an important role in the overall progress and prognosis of periodontal disease activity.

KEYWORD: Laser, periodontal disease, refractory periodontitis

INTRODUCTION

Light amplification by stimulated emission of radiation is what the acronym LASER stands for.^[1,2] The first laser was built by Theodore H. Maiman in 1960. The emission of the laser as a natural process was hypothesized by Einstein via a derivation of Planck’s law of radiation.^[1-3] The three characteristic features of lasers that make it characteristic from natural light is collimation which ensures beam divergence and parallelism; coherent, where the light is related to each other in speed; and most importantly monochromatic, where the laser waves have the same

energy and frequency. This is further attributed to Einstein’s theory of spontaneous and stimulated emission of radiation.^[1-3]

LASER HISTORY

Although “light therapy” was written in ancient Indian and Persian texts as a form of therapy for the treatment of skin ailments, serious consideration to the use of lasers in modern medical treatment started

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with the treatment of lupus vulgaris by Finsen in 1903. The use of laser in soft and hard tissues and its documentation was done by Miaman in 1963.^[1] The introduction of lasers as a treatment modality to the public was in 1959.^[4] The use of lasers in various dental conditions such as bleaching, cavity cutting, soft-tissue excision, biopsy, periodontal decontamination, and more so in more advanced treatment procedures such as low-level laser therapy (LLLT) and photodynamic therapies have brought a broader picture in dental treatment.^[4] It has thereby reduced treatment time, increased efficiency, and most importantly brought about patient comfort.^[4-7] In the early 1960s, the use of lasers in medical conditions brought about unlimited applications, but none of these applications were specific to a condition. This led to researches being conducted to gradually localize specific applications of lasers related to dentistry.^[8] During this period, the use of lasers such as ruby for caries removal was used, but it caused irreversible damage to the pulp due to which the use was discontinued.^[5]

RATIONALE

The discovery of newer wavelengths with relation to Nd:YAG (neodymium-doped yttrium aluminum garnet), erbium lasers, both the YAG (doped yttrium aluminum garnet) and Cr:YSGG (chromium-doped yttrium, scandium, gallium, garnet), and argon lasers proved to be effective in routine dental treatment, such as endodontic therapy, and prosthetic treatment.^[5,9]

The first laser introduced in the year 1990 by Myers was approved by the Food and Drug Administration (FDA). This approval was taken into consideration that the laser can be used in soft-tissue surgeries as it reduced treatment time, provided adequate hemostasis, and provided better wound healing. This mode of application either as a therapeutic, photodynamic, or low level provided effective and lasting treatment outcomes. Furthermore, the FDA specific also approved the use of laser in dental practice as safe and effective.^[10]

TYPES OF LASERS

The lasers have been classified and graded according to the lasing medium it emits and also the presence of active medium [Table 1]. They are also categorized as hard- and soft-tissue lasers depending on their application on tissues; furthermore, they are also segregated depending on wavelengths.^[10] The FDA categorized therapeutic laser as lasers emitting energy less than 500 mW.^[1] The first gas laser was the He-Ne (helium-neon) that can operate at different wavelengths, but the majority of lasers can operate at 633nm wavelengths. The CO₂ lasers are quite effective and are currently used as both hard and soft tissue, although the primary chromophore being hydroxyapatite. The CO₂, which is the 10,600nm, is primarily a soft-tissue laser and the recently introduced ionized CO₂ is both a hard-tissue and soft-tissue laser.^[11,12] Chemical lasers such as hydrogen fluoride laser and deuterium fluoride lasers are used in industrial applications. Excimer lasers are used in ophthalmic conditions; they work on the principle of population inversion.^[10] Solid-state lasers such as Nd:YAG, erbium, and holmium are common dopants that are used in dentistry. Fiber lasers such as erbium and ytterbium are common in such lasers where the laser light is directed via an optical fiber. Photonic crystal lasers are based on nanostructures and the density of the optical states. Semiconductor lasers are diodes, which is the most commonly used in dentistry. It is used in various wavelengths, namely 810, 940, and 980 nm.^[11-13] Dye lasers use organic dye and dye-doped polymers as laser media. Free electron lasers generate coherent wavelengths from microwave to soft X-rays. Exotic media is a pursuit by the military all over the world for gamma-ray laser.^[14,15]

Furthermore from the dental application, hard lasers such as CO₂, Nd:YAG, and erbium-doped yttrium aluminum garnet laser (Er:YAG) are used for both hard and soft tissues. Cold lasers comparatively are used for soft tissues and comprise diode lasers. The ionized CO₂ 9300nm and the super pulsed Nd:YAG, which is the latest entry among the plethora of dental laser devices, offer excellent soft-tissue and hard-tissue

Table 1: Laser types

Laser types	Gas laser	Chemical laser	Excimer	Solid	Photonic crystal lasers	Semiconductor	Liquid
	He-Ne	HF	Argon Fluoride	Nd:YAG	Nano-based crystal	Diode	Organic dye
	CO ₂	Deuterium fluoride	Xeno-fluoride krypto fluoride	Diode holmium:YAG Er:YAG Er:YSGG		Hybrid silicon	

He = helium, Ne = neon, HF = hydrogen fluoride, Nd = neodymium, YAG = yttrium aluminum garnet, Er = erbium, YSGG = yttrium scandium gallium garnet

cutting and ablation with limitless possibilities. Although both work on different affinity levels, with CO₂ being hydrophilic and Nd:YAG, the principle chromophore being pigmented tissue. Both these lasers provide effective surgical cutting, and most importantly coagulation of the tissue.^[14,15]

The erbium laser comprising Er, Cr:YSGG, and Er:YAG works by absorbing its principle chromophore water and its high affinity for hydroxyapatite makes it best for treatment of hard tissues and also ablation of soft tissue.^[14,15] The diode laser works by absorbing its principle chromophore pigmented cells mainly hemoglobin. It does not work in tissues where the predominant chromophore is hydroxyapatite and water. The application of diode in various soft-tissue procedures such as depigmentation, biopsies, and preprosthetic surgical procedures such as frenectomies, gingivectomy, vestibuloplasty, crown lengthening, and troughing along with the cost of the laser unit being economical makes it the first choice for dentists in routine practice. Its use in photobiomodulation and treatment of lesions of herpetic origin gives it an added advantage.^[14,15]

The recent introduction of LLLT in the treatment of various dental conditions has proven to accelerate wound healing coupled with biostimulatory effects and also reduction in pain levels has shown superior therapeutic effects for the patients. It eliminates the side effects seen with conventional techniques of surgical origin such as inflammation and edema.^[16] The ability to provide therapeutic effects with lower thermal generation such as capacity for cellular regeneration, biostimulation, and anti-inflammatory effects gives this treatment option an adjunctive status with relation to routine dental treatments. Studies of a randomized clinical trial have been done recently with relation to temporomandibular joint disorders, dry socket, third molar extractions, and lesions of herpetic nature. Many studies have reported superior patient outcomes in terms of healing, pain reduction, and regeneration of tissues. Although LLLT has various advantages, studies have also reported failures attributed to LLLT as a contraindication in the treatment of malignancies as it induces cellular growth and also in patients with hematological disorders as it can induce blood flow.^[16-20]

The incorporation of various laser wavelengths such as CO₂, erbium, diode, Nd:YAG, and holmium YAG for use in routine dental procedures such as soft- and hard-tissue surgeries, TMJ disorders coupled with dental examinations such as caries detection, implant, and pocket decontamination gives the dentist and periodontist in providing near predictable results.^[21]

LASER PHYSICS AND DOSING

It is based on the Amdt-Schutz principle.^[22,23] In a dental laser, the unit comprises an active lasing medium, and two mirrors and an energy source. For a dental laser, the light from the unit reaches the tissue either by a fiber optic cable, hollow waveguide, or a cooling system. The lasing is done using either by a contact or a noncontact mode. The dose is dependent on the correct parameter, failure to which the effect does not result. The biostimulation effect of LLLT results in deposition of energy within the tissues, resulting in stimulation of mast cells causing an increase in hydrostatic pressure, edema absorption, and corresponding anti-inflammatory effect. The biostimulatory effect also results in the production of tropocollagen molecules resulting in the formation of extracellular matrix and collagen. Analgesic effect of LLLT is performed by inhibiting nociceptive signals.^[24,25]

The wavelengths in the electromagnetic spectrum used in dentistry are classified as follows: visible spectrum (visible 400–750nm), infrared that ranges in the nonionizing part of the spectrum from 750nm, and ultraviolet range (400–750nm in the ultra-spectrum range).

CALCULATING DOSING

The dosing is calculated by multiplying the energy in mW with the time in seconds; further, the product is divided by the area needed to be radiated. Care should be taken to provide the target area with an optimum density as longer exposure can result in adverse effect. Depending on the surface texture of the tissue and keratinization, the dose needs to be calculated. Thicker the tissue, higher the power as more energy will be needed to ablate the tissue; conversely thinner the tissue, power needs to be reduced and exposure time also correspondingly reduced to avoid necrosis. Further, focal spot needs to be considered, if the area is large, the radiation should be of diffuse in nature, so the tip of the laser should be some distance away so as to maximize irradiation. In smaller areas, the focal spot size should be focused in a smaller setting. Cooling mechanisms have to be instituted to avoid any flare-ups. Irrigation with saline or distilled water will avoid any mishaps of this nature. In acute inflammation, lasing can be done using higher energy and more sessions. In chronic conditions where the infection has already set in and is of stubborn nature, more sessions will be required and the patient will have to be put on a recall phase for a longer time frame. In treatment involving photodynamic therapy (PDT) and LLLT, single and multiple sessions are required, with the latter session more commonly seen.^[17]

BIOLOGICAL EFFECTS OF LASER

Laser applications in dentistry are wide and it is not the dentists alone who use it. It is used routinely by oral and maxillofacial surgeons, ear nose throat surgeons, and dermatologists especially when it is of multidisciplinary nature. Researchers have seen that using lasers reduces the growth of pathogenic bacteria in periodontal pockets and diseased sites and also a reduction in edema.^[26] The properties of laser which dictate its effect on tissues are namely reflection, transmission, absorption, and scattering. Reflection and scattering are not favorable as it can cause damage to the operator's eyes. Transmission moves from a level of tissue to a deeper zone. This if not used properly can induce collateral damage to underlying tissues. The desired effect is absorption in laser treatment of target tissues, where the energy is collectively absorbed owing to the collimative property as it travels as a narrow beam. Absorption will also depend on either of the chromophore such as water or pigment content. The effect of the laser is mostly of a oxidative-reduction reaction, similar to release of free radicals where the cells are alkalized and have normal morphological characteristics.^[26] The basic function in any cellular process is the increase in the production of adenosine triphosphate within the mitochondria, which is the storehouse of energy in any cell in eukaryotes. This is done by inhibiting cytochrome by nitric oxide. By providing laser energy, in treatment using low-level laser, the cells receive energy to produce adenosine triphosphate (ATP), which is the basis of the photochemical theory and is currently the most accepted. The ability of the laser energy to initiate the production of photoreceptors such as cytochrome c-oxidase will lead to increase in production of ATP.^[25,26]

The current use of lasers ranges from 488 to 10,600 nm, all within the nonionizing radiation segment. The effects of these lasers are beneficial and not destructive such as necrosis, mutagenic effects on DNA, and extracellular material degradation. Some of the lasers are in the visible spectrum. Argon produces a blue light at 488 nm; it is used for bleaching of teeth. At 514 nm, it produces green light. Nd:YAG also produces green light at 532 and at 655 nm; it produces a blue light for caries detection. Diodes work in a wavelength ranging from 810, 930, 980, and 1064 nm. The 810 nm, a surgical diode laser, comes in the range between 800 and 830 nm. The erbium YAG works in a 2940 nm wavelength and the Er, Cr:YSGG works at 2780 nm wavelength. The CO₂ and the nonionized version work at 10,600 and 9,300 nm, respectively.^[24-26]

OBJECTIVES

Our objective in this study was to evaluate if there was adequate literature related to the management of refractory periodontitis using lasers. Our search was to evaluate studies related to human cohorts, if there was any intervention done, whether the study involved comparisons among periodontal diseases or among lasers, and the outcome of the study and the design of the study.

MATERIALS AND METHODS

ELIGIBILITY CRITERIA

Articles studying the effects of lasers on periodontitis, both refractory and aggressive, were investigated. Articles only in English language were selected by typing the keywords refractory periodontitis, PDT, LLLT, aggressive periodontitis diode, systemic, inflammatory periodontal diseases, erbium, neodymium, and carbon dioxide lasers were taken into consideration and included in the study.

INFORMATION SOURCES

The study followed partially the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines as it is a narrative review. A number of articles were selected from a period of 1980 to February 2020 from databases, PubMed, PubMed Central, Cochrane, and Scopus.

SEARCH CRITERIA

The search for the articles was limited to the keywords used for the study and the articles were localized based on these criteria [Table 2].

STUDY SELECTION

Aggressive periodontitis and inflammatory periodontal conditions were included in the study as the pathogenesis of the condition mimics refractory cases and so does the time frame for treatment due to the unpredictable nature of the disease. The studies were further filtered and only those studies pertaining to the management of refractory cases were included in the study. Those studies which had laser management for conditions such as chronic periodontitis and other periodontal conditions were excluded from the study.

DATA COLLECTION PROCESS

The data were extracted from the articles where the emphasis was given to laser management to periodontal disease condition.

DATA ITEMS

After reviewing the literature, 130 articles were found related to gingivitis and mild–moderate periodontitis.

Of the 130 articles, 70 articles were related to periodontitis. The search was further filtered using keywords pertaining to Refractory and Aggressive periodontitis. Of the 70, 39 articles did not fulfill the inclusion criteria and 20 did not have full texts. A total of 11 articles were found which pertained to the effect of laser for the treatment of Aggressive and Refractory periodontitis. Among the 11 articles, 5 were related to experimental small animal models, one was pertaining

to *in vitro*, and six studies were related to *in vivo* in human cohorts [Figure 1 and Table 2].

RISK OF BIAS

To standardize studies, relevant literatures pertaining to the effect of lasers on dental inflammatory and chronic conditions were chosen. Study outcomes in experimental animal models, *in vitro* and *in vivo* that were relevant to inflammatory and refractory periodontitis cases were considered.

Table 2: List of studies related to refractory and aggressive periodontitis

Author	Laser used	Type of study	Periodontal condition
Chiang <i>et al.</i> ^[27]	810 diode	<i>In vitro</i>	Refractory periodontitis
Malanotte <i>et al.</i> ^[28]	830 diode	Experimental	Inflammatory Periodontitis
Akram <i>et al.</i> ^[29]	810, 830 diode	Experimental	Inflammatory periodontitis
Takasaki ^[30]	810, 830, 930 diode	Experimental	Inflammatory periodontitis
Murakami-Malaquias-da-Silva ^[31]	830 diode	Experimental	Inflammatory Periodontitis
Zhang ^[32]	650 diode	Experimental	Inflammatory Periodontitis
Al Habashneh <i>et al.</i> ^[33]	635 LED	<i>In vivo</i>	Refractory periodontitis
Shiau ^[34]	810, 910 diode	<i>In vivo</i>	Inflammatory periodontitis, Refractory periodontitis
Ren <i>et al.</i> ^[35]	940 diode	<i>In vivo</i>	Inflammatory Periodontitis
Chandra and Shashikumar ^[36]	808 diode	<i>In vivo</i>	Inflammatory periodontitis
Talmac <i>et al.</i> ^[37]	940 diode Er, Cr:YSGG-10 Hz, 1.5 W, 140 µs pulse length	<i>In vivo</i>	Aggressive periodontitis

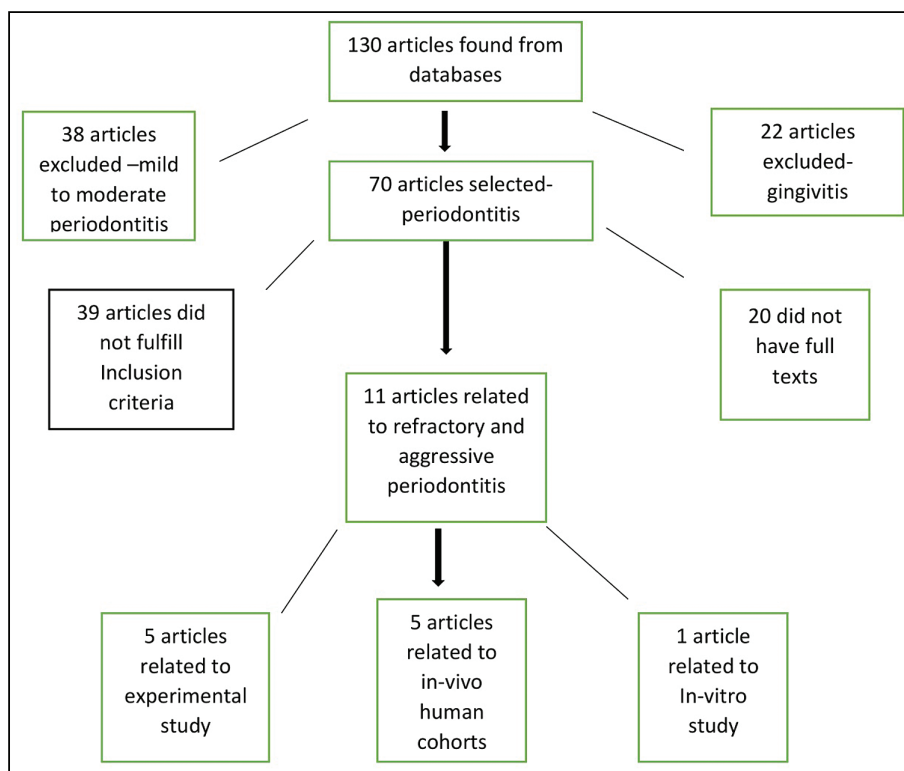


Figure 1: Flow diagram for data collection

DISCUSSION

PRIMARY OUTCOME

Periodontitis is an inflammatory disease of the gingiva and periodontal tissues that spreads to the supporting structures. It is initiated by specific pathogenic bacteria present within plaque biofilms that release enzymes causing an immunomodulatory mechanism resulting in host–parasite interaction and subsequently loss of attachment and bone loss.^[38,39] The objective of the various treatment modalities is to halt the progression of disease and this is achieved by adequate instrumentation of the root surface, elimination of the bacterial biofilms, and instituting recall program which is the cornerstone for controlling and stabilizing the disease. The presence of anatomic factors such as root convergence, depressions in the root, and furcation involvement produces challenges to the dentist to eliminate the offending biofilm. This situation results in recolonization of the biofilm, which results in disease progression and also delayed healing.^[40-42] The term refractory denotes patients who do not respond to periodontal treatment or show delayed healing or destruction of periodontal tissues in the worst cases.^[22] Currently, the pathological process involved in refractory periodontitis is not understood yet and various factors such as host immune response, systemic factors, genetic, environmental, and local factors have been implicated in the pathogenesis of the disease. The clinical characteristics to confirm a case of refractory periodontitis suggested by Kornman^[43] were as follows:

1. The disease was prevalent in multiple sites.
2. Progression is seen in sites that have had no disease in the past.
3. Disease progression is not arrested by periodontal treatment.

Table 3: Laser Treatment modalities for periodontal therapy

Type of laser	Subgingival decontamination	Intraoperative procedure
Diode ^[11,13-15,20,23,25, 36, 37, 44,45]	√	√
Nd:YAG ^[14,15]	√	
Er:YAG ^[14,37,46]	√	
Er:YSSG ^[14,37,46]	√	
CO ₂ ^[12,14]		√

Table 4: Nonsurgical laser-assisted options for periodontal treatment

Laser-assisted options	Chronic periodontitis	Aggressive periodontitis	Refractory Periodontitis
PDT ^[31,50-57,59,61, 63,65,66]	√		√
LLLT ^[16,18,19,21,27,28,32,35,58,60,62,64, 67]	√	√	

PDT = photodynamic therapy, LLLT = low-level laser therapy

Various nonsurgical periodontal therapies such as root surface debridement, local delivery of medications, and adjunctive use of antibiotics for treatment of diseased pockets have been routinely performed [Table 3]. Nevertheless, the use of antibiotics has its drawbacks, in the development of antibiotic resistance and also the development of opportunistic pathogen that can result in secondary infections.^[47-49]

SECONDARY OUTCOME

Surgical periodontal therapy could only be carried out once the disease slows down or shows mild progression, which was difficult to see clinically in a refractory case.

Lately, the use of laser treatment as an adjunctive treatment modality combined with nonsurgical periodontal therapy has gained importance. One of the laser-assisted treatments that is used as an adjunctive therapy is PDT. This therapy is based on the principle that laser light mediates the activation of photosensitizing agent to produce free oxygen radicals to kill pathogens.^[50,51] It offers a noninvasive, safe, low cost, and localized treatment during the initial and maintenance phase of refractory periodontitis.^[29,33,52]

PDT not only has antimicrobial effects but also eliminates endotoxins secreted by gram-negative microorganisms such as lipopolysaccharide (*Aggregatibacter actinomycetemcomitans*) and gingipains (*Porphyromonas gingivalis*). It also tends to reduce the biologic activity of mononuclear cells responsible for the production of pro-inflammatory cytokines.^[30] It is believed to have biomodulatory effects as documented by earlier studies,^[34,53] thereby reducing the activation of inflammatory cytokines such as tumor necrosis factor alpha and interleukin 1 beta (IL-1β). Evidence of vasodilation and formation of collagen has also been observed.^[54-58] The positive effects of PDT have also been documented in *in vitro* and study involving experimental animal models.^[59,60] Although PDT shows promising results, given the problems that refractory cases show, it may not be suitable for all cases.^[31,61-64]

LLLT is one of the other laser therapies that has been used as an adjunctive therapy in periodontitis cases [Table 4]. The aim of this treatment is to induce regeneration of cells, as it acts on the fibroblastic proliferation and moreover has a direct effect on the

Schwann cells, which has an anti-inflammatory role and secretes neurotrophic effect for nerve regeneration. A study by Malanotte *et al.*,^[28] and a similar study in experimental animal model showed that in mice induced with periodontal disease and nerve injury, the degree of nerve regeneration showed promising results, but the inflammatory component had not reduced. Furthermore, the study showed protection of cells against oxidative stress.^[32,67] Ren *et al.*,^[35] in a study on periodontally compromised patients showed benefits in pain relief and slowing of inflammation in the early stages of periodontal inflammation.

The use of diode as an adjunct to scaling and root surface debridement is becoming increasingly evident with numerous studies showing beneficial results. Diode has been used routinely in periodontal pocket decontamination after the initial phase of scaling and root surface debridement and also during the maintenance phase. Although the 810, 940, and 980 nm have been recognized for routine periodontal therapy, the 1064 nm has rarely been used. Recent addition of a system that emits blue radiation with a wavelength of 445 and 532 nm have been used.^[68] The 980-nm diode is absorbed by water, which makes it safer than the 810 nm and other wavelengths.^[33] 940 nm has shown better efficacy and safety than other wavelengths in one of the studies.^[44] In another study by Katsikanis *et al.*,^[65] significant pocket depth reduction was evident after a period of 3 months.

Nd:YAG has been a popular choice for periodontal pocket decontamination as it is approved by FDA to perform a laser-assisted new attachment procedure (LANAP). In a study by Chandra and Shashikumar^[36] involving type 2 diabetes patients with periodontal disease, there was a significant improvement in clinical and microbiological parameters even after 3 months using LANAP and scaling followed by root surface debridement, when compared to scaling and root surface debridement alone. Further study by Martelli *et al.*^[69] on 2683 patients using perioplast (periodontal biological laser-assisted therapy) where Nd:YAG and scaling followed by root surface debridement showed a significant improvement in microbiological parameters.

Er:YSGG and Er:YAG have also shown positive improvement in clinical parameters.^[45] Sezen *et al.*^[46] in a randomized clinical trial found significant improvements in clinical inflammation when combined with nonsurgical periodontal therapy. In aggressive periodontitis that shows an almost similar destructive pattern of inflammation, if not more, the use of Er:YSGG along with scaling and root surface debridement showed decrease of pro-inflammatory

cytokines IL-1 β when compared with scaling and root surface debridement.^[37,46] Comparing erbium lasers with diodes and Nd:YAG, it was found that diodes were superior to Nd:YAG and erbium to show significant improvements in clinical parameters. Nd:YAG was better than erbium when used as a monotherapy.^[70]

No data of CO₂ used as an adjunct laser therapy for the treatment of periodontitis were reported, although its use in preprosthetic treatment due to periodontal conditions has been seen and also for oral surgical procedures.

Refractory periodontitis cases have been maintained using nonsurgical periodontal treatment protocols in a study by Chiang *et al.*^[27] In cases where there is no clinical attachment gain, open flap debridement along with laser-assisted treatment has shown significant improvements in experimental and chronic periodontitis cases.^[66]

LIMITATION

The drawback of this study is the limited literature involving laser management for refractory periodontitis in human cohorts.

CONCLUSION

The application of lasers in refractory periodontitis cases has potential for better healing and stabilizing the periodontal apparatus. All the laser wavelengths have specific treatment outcomes. Selection of the right laser device is essential to provide a refractory patient with a fair-to-good prognosis outcome. The use of laser-assisted periodontal treatment has certainly brought about changes in treatment ideology and hope to bring promising results in refractory periodontitis cases in the near future.

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CONFLICTS OF INTERESTS

There are no conflicts of interest.

AUTHORS CONTRIBUTIONS

S R V: Conceptualization, methodology, validation, investigation, resources, writing original draft and supervision. **M S & J N:** Methodology, investigation, resources, writing-review and editing. **E A:** Investigation, resources and writing-original draft. **A H:** Investigation, resources and validation. **M J:** Methodology, writing-reviewing and editing. **S A F:** Resources and writing-reviewing and editing.

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

No clinical study was carried out, so no patient declarations of consent are needed or appropriate.

PATIENT DECLARATION OF CONSENT

Not applicable.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the article.

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