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Laser Applications in Regenerative Endodontics: A Review

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Abstract

Introduction: Developing regenerative endodontic treatment (RET) is an exciting approach to managing immature permanent teeth with pulp necrosis. RET is usually performed in two clinical steps: disinfection (first step) and tissue engineering (second step). Recently, laser therapy has entered the field of RET. This study aimed to provide an overview of the literature that employed laser therapy for root regeneration.

Methods: A comprehensive search was performed on four databases, including PubMed, Web of Science, Scopus, and Google Scholar. The searched keywords were laser, regenerative endodontics, immature permanent teeth, and dental pulp necrosis, and related English-published articles were included up to October 2023.

Results: Thirteen studies utilized a laser for RET. In the first step of RET, both high-power and low-level lasers (through photodynamic therapy [PDT]) may be applied for canal disinfection. In contrast, regenerative procedures in the second step of RET are just accelerated by low-power lasers (biostimulation). The literature does not support the benefit of laser-assisted irrigation in improving the clinical success of RET. There is some evidence that laser-assisted disinfection with a diode laser may provide comparable results to triple antibiotic paste in reducing bacterial counts in root canals while providing slightly better clinical and radiographic outcomes. PDT may be an effective and suitable adjunct to conventional disinfection methods in immature, necrotic teeth.

Conclusion: Low-power lasers may be beneficial tools for improving the results of regenerative endodontics through chemical disinfection in the first step (PDT) or by biostimulation in the second step of RET.

Keywords: Disinfection; Laser; Pulp necrosis; Regenerative endodontics; Tissue engineering.

Introduction

Endodontic therapy of immature permanent teeth with necrotic pulp is a challenging issue in dentistry. Loss of pulpal vitality in open-apex teeth prevents root formation and leads to short roots and fragile dentin walls.[1] Traditionally, apexification with calcium hydroxide (Ca(OH)2) or mineral trioxide aggregate (MTA) has been applied to stimulate the formation of apical barriers. However, this approach does not have the potential to survive the damaged tissue, and thus, it leads to a reduction in fracture resistance of the root.[1,2] Recently, regenerative endodontic treatment (RET) has gained much attention as a new extension of root canal therapy for replacing the necrotic tissue with a vital and functional pulp–dentin complex in immature, permanent teeth.[3,4]

Regenerative endodontics usually involves two clinical steps. In the first step, disinfection of the root canal is carried out, and the tooth is temporarily sealed for 1 to 4 weeks.[5] Two critical aims must be followed in the root canal disinfection step, including the optimal removal of the microorganisms and smear layer and the minimal disruption of vital tissues. Usually, regenerative endodontics is performed with minimal or no instrumentation of the dentinal walls because of concerns about future root fractures. Instead, robust disinfection protocols, including chemical irrigation and intracanal medicaments, are followed to eradicate bacterial biofilms in the dentinal tubules.[5] Sodium hypochlorite (NaOCl), ethylenediaminetetraacetic acid (EDTA), and chlorohexidine have been recommended as root canal irrigants. However, these substances could decrease the success rate of RET due to their cytotoxic effects at higher concentrations. Intracanal medicaments such as triple antibiotic paste and calcium hydroxide could provide antibacterial and anti-inflammatory properties. However, they may also lead to some adverse effects like bacterial resistance and damage to vital tissues.[6]

The second step of RET benefits from the adult stem cells in the tooth and oral environment, such as stem cells of the apical papilla, dental pulp stem cells, stem cells of

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human exfoliated deciduous teeth, periodontal ligament stem cells or bone marrow stem cells.[7] A scaffold (matrix) is provided for stem cells either by inducing blood clots through over-instrumentation or by transferring platelet-rich plasma or platelet-rich fibrin (PRF) into the canal. Scaffolding guides cell orientation, organization, and proliferation while enhancing nutrient and gaseous exchanges.[8] Another essential element for root regeneration is the growth factors, which are signaling proteins that regulate the proliferation, differentiation, and maturation of cells. Dentin has been known as a primary reservoir of signaling proteins. It is assumed that the growth factors/cytokines are fossilized into dentin during mineralization. They can be solubilized and released by several methods, such as chemical treatment with EDTA, calcium hydroxide, or acid etching.[9,10] The assembly of a sufficient source of stem cells, scaffolds, and growth factors has been known as the biological basis of RET and the tissue engineering triad. It has been demonstrated that the intentional manipulation of these three elements can result in the regeneration of tissue function.[11] At the final stage of RET, coronal sealing of the scaffold is conducted with a biocompatible material, such as MTA.[12]

Laser therapy is becoming a very popular adjunct in different branches of dentistry and has recently entered the field of regenerative endodontics. In the first step of RET, both high-power and low-power lasers (through the process of photodynamic therapy [PDT]) can be applied for eradicating microorganisms, whereas regenerative procedures in the second step of RET are just accelerated by low-power lasers.[6,13-15] There is limited information concerning the benefits of laser therapy in enhancing the success rate of RET.[7] Furthermore, the treatment result mainly depends on the selected parameters, such as wavelength, power, energy, and energy density; thus, choosing an appropriate protocol is crucial for achieving successful outcomes.[16] The present study aimed to provide an overview of the literature that employed laser therapy for root regeneration, focusing on the appropriate laser protocols in different steps of RET.

Materials and Methods

Search keywords included laser, regenerative endodontics, immature permanent teeth, and dental pulp necrosis in the following combination: (laser AND regenerative endodontics) OR (laser AND immature permanent teeth) OR (laser AND dental pulp necrosis). We found related English-published articles through electronic databases, including PubMed, Web of Science, Scopus, and Google Scholar, up to October 2023. Then all the reference lists of the related articles were checked to identify the potentially eligible studies. Finally, the included studies were reviewed and placed in the categories of RET steps, including the first step (root disinfection) and the second step (tissue engineering). Studies involving apexification, vital pulp therapy, and primary dentition, and studies other than the English language were excluded.

Results

Laser Applications in the First Step of Root Disinfection

Proper root canal disinfection has a crucial role in the success rate of treatment, as inflammation and infection could disrupt regenerative procedures.[6] A variety of high-power lasers can be applied for canal disinfection, including neodymium-doped yttrium, aluminum, garnet (Nd:YAG) laser (1064 nm), neodymium-doped yttrium aluminum perovskite (Nd:YAP) laser (1340 nm), different wavelengths of high-power diode lasers (780-980 nm), erbium-doped yttrium, aluminum, garnet (Er:YAG) laser (2940 nm), and erbium, chromium-doped yttrium, scandium, gallium, garnet (Er,Cr:YSGG) laser (2780 nm). Wavelengths in the visible and near-infrared range, such as diode and Nd:YAG lasers, exhibit more profound bactericidal effects on dentin.[6,17,18] On the other hand, mid-infrared lasers like the erbium family have high absorption in water and hydroxyapatite and thus create a superficial effect on dentin. Erbium lasers can only be applied to remove the smear layer and surface microorganisms. Low-level lasers are also applied in the root disinfection step through PDT.[6, 17]

Briefly, lasers can eradicate microorganisms through three different mechanisms: laser-assisted disinfection (LAD), laser-activated irrigation (LAI), and PDT.

Laser-Assisted Disinfection

The irradiation from high-power lasers in the near-infrared range can be used for destroying microorganisms and reducing the bacterial load in infected root canals.[15] The Nd:YAG laser shows the highest penetration depth in dentin and thus provides more excellent bactericidal effects, but the risk of thermal damage to neighboring tissues is greater with Nd:YAG than with the diode laser.[19,20]

In a clinical study, Mekkawi et al[21] investigated the effect of a diode laser on the pathogenesis of immature teeth with necrotic pulp in comparison to the conventional technique of revascularization using triple antibiotic paste. They assigned 30 immature necrotic maxillary anterior teeth, whose ages ranged between 8 and 16 years, into three groups (n = 10). The teeth in group 1 underwent disinfection by triple antibiotic paste and revascularization with the standard method. In group 2, the teeth were disinfected by the diode laser and then underwent standard revascularization treatment. A diode laser (980 nm) was used for canal disinfection at 1.5 W power and 50 Hz frequency for 5 seconds. In group 3, the teeth were disinfected by the triple antibiotic paste followed by revascularization with the standard method, and then the diode laser was applied. Bacterial sampling cultures

were taken during pretreatment and after completing root canal disinfection procedures (posttreatment), and the bacterial counts were calculated. The results showed no significant difference in the percent change of microbial load between the triple antibiotic paste and laser disinfection groups. The authors concluded that laser irradiation could be a suitable alternative to triple antibiotic paste for the eradication of root canal infection in regenerative endodontic therapy while providing the benefit of no tooth discoloration as opposed to triple antibiotic paste.

In a randomized clinical trial with two parallel groups, Divya et al[11] assigned 18 children with necrotic, immature permanent teeth into two groups. The American Association of Endodontics (AAE) recommendations were followed when doing regenerative endodontics on the patients. Group A served as the control, whereas the patients in group B received further disinfection with a high-power diode laser. The laser device had an 810 nm wavelength and ran at the power of 1 W, with a 20 ms pulse length and 20 ms interval duration. After inserting the optical fiber tip (200 μm) 1 mm shorter than the working length, we irradiated the laser for 15 seconds with the irrigant in the canal. The patients were recalled at 1, 3, and 6 months posttreatment, and the results revealed a significant decrease in the bacterial counts after disinfection in both groups ($P=0.02$ for group A and $P=0.007$ for group B). At the 3-month follow-up, group A (control) showed a significant increase in tooth mobility. However, the LAD group showed no change in tooth mobility over the follow-up periods, suggesting a favorable clinical outcome. At the 6-month follow-up, the LAD group demonstrated much superior periapical healing in comparison to group A.

In a case series study by Doddamani et al,[22] four cases with necrotic young permanent teeth underwent regenerative endodontic therapy. In the first session, gentle irrigation was done with 1.5% NaOCl, and then a diode laser (810 nm) was irradiated to disinfect the canal with a power of 1 W, a 20 ms pulse length, and a 20 ms rest period. The optical fiber tip (200 microns) was inserted 1 mm shorter than the working length, and laser irradiation was performed for 15 seconds with the irrigant in the canal, followed by irrigation with 17% EDTA. The access cavity was sealed with a glass ionomer, and the patients were recalled one to four weeks later for a second appointment. During this visit, blood clot formation, collagen plug insertion, and MTA sealing were carried out. The 12-month follow-up with CBCT examination revealed a decrease in the extent of the peri-radicular radiolucency and an increase in the root length and dentin thickness in the sagittal plane.

In a recent pilot trial, Liu et al[23] compared the effect of an Nd:YAP laser with a triple antibiotic paste on pulp regenerative therapy of 66 teeth diagnosed with acute or chronic apical periodontitis. Thirty teeth were in the experimental (laser) group, while 36 teeth were in the control (triple antibiotic paste) group. In both groups, the canals were irrigated for five minutes with 2.5% sodium hypochlorite, then for 5 minutes using 17% EDTA, and finally with 50 mL of 0.9% saline injection without doing root canal preparation. Following this, the teeth in the control group received a triple antibiotic paste, whereas those in the experimental group were exposed to irradiation from a Nd:YAP laser (wavelength: 1.34 μm) at a frequency of 30 Hz and pulse energy of 100 mJ using a 0.32 mm optical fiber tip. The root canal was filled with a 0.9% saline solution. The fiber was inserted into the canal, one mm from the root tip, and it was moved up and down along the canal walls for 30 seconds. In both groups, the pulp cavity was sealed using glass ionomer cement. The clinical examination revealed the disappearance of clinical symptoms 2 weeks following therapy in all teeth. The follow-up at 24 months after regeneration therapy revealed the achievement of the primary goal in 34 out of 36 teeth in the control and 29 out of 30 teeth in the experimental group. The secondary goals including root canal wall thickening, root lengthening, and apical foramen closure were attained on radiographs in 31 and 27 teeth in the control and experimental groups, respectively. On the other hand, the tertiary goal was observed in just four teeth in the control and four in the experimental group. There was no significant difference between the two groups in any of the evaluated parameters, suggesting that Nd:YAP laser irradiation may be considered a suitable alternative to the triple antibiotic paste during the disinfection step of regenerative endodontic therapy.

Laser-Activated Irrigation

Laser-activated irrigation (LAI) is accomplished by erbium family lasers. It is well-known that erbium lasers produce their effects through the photoablation phenomenon. In this process, water within the dental tissue turns into steam and explodes, thus splitting off parts of the tooth structure.[24-26] In LAI, laser energy is transferred to the irrigation solution using different fiber tips, such as those with lateral emission. Subsequently, the vapor bubbles at the site of irradiation explode and create a secondary cavitation effect, as well as causing rapid motion of the irrigant in the root canal.[27,28] Therefore, two mechanisms may be involved in the cleaning mechanism of erbium lasers, including the increase in the flow velocity of the solution and the generation of physical forces on the root canal walls that could be effective for biofilm removal. The antibacterial effect of erbium lasers is confined to surface areas close to the canal lumen.[24,27]

Photon-induced photoacoustic streaming (PIPS) is a novel type of LAI technology, which has demonstrated more encouraging results for the removal of biofilms and the smear layer.[29] This technique is based on

producing cavitation phenomena and acoustic streaming in intracanal fluids, which are brought about by the photomechanical effects of erbium lasers at low settings. PIPS differs from previous methods in that the laser tip is positioned in the coronal section of the root canal, thus preventing damage to the canal walls and the periapical tissues, while providing an increased cleaning rate of the canal walls in comparison to traditional methods.[29-31]

The ShockWave Enhanced Emission Photoacoustic Streaming (SWEEPS) technique has been proposed recently for the Er:YAG laser to promote the cleaning and disinfection of canals in endodontic treatments.[31] In contrast to the PIPS mode which emits single pulse energy (50 μs super short pulse), the SWEEPS technique is based on producing shorter double pulses (25 μs ultra-short pulse). Because of its shorter pulse duration, the peak power of each pulse is doubled at the same energy, creating a more massive bubble explosion.[32] Moreover, the second pulse shoots into the liquid at an optimal interval from the first pulse, that is when the first bubble is nearing the end of its collapse.[33,34] These pairs of consecutive laser pulses produce shock waves and enhance fluid flow and photoacoustic currents, which eventually contribute to optimal root canal cleansing and disinfection.[31,32]

Yu et al[35] described a case with periapical periodontitis treated with revascularization assisted with Er:YAG laser irrigation. Following the removal of necrotic pulp, the canal was rinsed with 0.5% sodium hypochlorite (NaOCl) solution. Next, the Er:YAG laser was applied to induce the PIPS process at settings of 20 mJ, 15 Hz, and 50 μs using a radial fiber tip. The fiber tip was maintained within the pulp chamber, and laser irrigation was performed through 4 cycles of 20-second irradiation, followed by 5-second off cycles. The canal was then filled with a triple-antibiotic paste. After two weeks, the medication was removed, and the concentrated growth factor (CGF) was transferred into the root canal. MTA was placed on the CGF, and the tooth was restored with glass-ionomer cement. The 11-month follow-up indicated apical closure, and after four years, the pulp regained its vitality.

An in vitro study by Rahmati et al[36] evaluated the effect of dentin conditioning by different endodontic irrigants (EDTA, MTAD, and QMix), compared to the Er:YAG laser, on the adherence of stem cells to dentin. Forty dentin specimens were prepared and divided into five groups: control, irrigation with EDTA, irrigation with MTAD, irrigation with QMix, and Er:YAG laser irrigation. In the laser group, the samples were exposed perpendicularly to the Er:YAG laser at the energy of 25 mJ and frequency of 15 Hz for 20 seconds. The stem cells were isolated from third molar tooth buds and cultured on dentin specimens for three days. SEM micrographs were obtained, and the number of flat (firmly attached) versus round (weakly attached) cells was counted. The least number of flat cells (representing lower cell adhesion to dentin) was present in the MTAD group, indicating that MTAD is not a suitable irrigant for endodontic regenerative procedures. Other modalities (including Er:YAG laser irradiation) induced cell adhesion rates comparable to each other and significantly greater than that of the MTAD group.

Photodynamic Therapy

Photo-activated disinfection (PAD) or photodynamic therapy (PDT) or is a novel approach that is increasingly used in medicine and dentistry for killing microorganisms and tumor cells. In this process, a light-absorbing material or photosensitizer (PS) is placed in the target area and activated by a low-intensity light source with a specific bandwidth. The reactive oxygen species (ROS) are produced in this process and destroy microorganisms without exhibiting toxicity to normal cells.[37,38] The coordination between the photosensitizer and the light source is a critical factor in attaining the success of PDT.[6]

Johns et al[39] reported successful regenerative therapy for a 9-year-old boy with pulp necrosis of two upper central incisors. Following canal irrigation with 20 mL of 5.25% NaOCl, rinsing with normal saline, and drying, the canal was filled with 0.5 ml tolonium chloride (0.01% w/v in aqueous solution) as the photosensitizer for 2 minutes (pre-irradiation time). A diode laser (660 nm, 40 mW) was used for illumination using a 300 μm diameter fiber tip. The fiber was inserted into the canal and moved spirally from apical to cervical. This motion was repeated approximately ten times every minute. After that, the canal was rinsed with a sterile saline solution to wash out the photosensitizer. PRF was condensed into the canal as a scaffold for the revitalization of the pulp. Finally, MTA was applied directly over the PRF at a thickness of 3 mm. After 6 and 10 months, the clinical and radiographic examinations revealed no sensitivity to percussion or palpation and the occurrence of root lengthening, regression of the preapical lesions, apical closure, and continued dentinal wall thickening.

A case report study by Rahim et al[40] revealed the efficacy of PAD as a novel method to help regenerative endodontic therapy in a fractured central incisor of an 8.5-year-old girl. The canal was gently irrigated with 1.5% sodium hypochlorite solution (NaOCl) for 5 minutes, then dried with paper points. PAD treatment was performed by a 635 nm diode laser to activate the Aseptim solution (PS) for 150 s. The PS was then removed with saline, and finally, the canal was irrigated with 20 ml of 17% EDTA. Bleeding was induced, and a resorbable matrix and then a white MTA were placed. The tooth was restored with permanent filling two days later. Clinical examination indicated no adverse signs and symptoms at 3, 6, 9, and 12 months. The radiographic examination revealed increased root length and apical thickness at six months and apical closure at the 12-month follow-up.

In a comparative in vivo study, Emam et al[41] classified

30 cases with immature, infected teeth into three groups according to the disinfection protocol employed. In group 1, Ca(OH2) was injected into the canal after drying. In group 2, azulenocyanine (photosensitizer) was inserted into the canal and distributed by an endodontic file for 60 seconds. The photosensitizer was activated by a 940 nm diode laser applied in cycles 4×2 mm/s for canal disinfection. In group 3, Azulenocyanine was activated similarly to group 2, and then Ca(OH)2 was injected after drying the canal with paper points. The patients were followed for 3-6, 6-9, and 9-12 months, and the results showed a significantly higher increase in root length in group 3 than in either group 1 or group 2 in the 3-6 months follow-up. In contrast, the increase in dentin thickness was not significantly different between the three groups over the experiment.

Kaur et al[42] also reported regenerative treatment for a 9-year-old boy with two nonvital central incisors. The necrotic tissue and debris were removed by minimal mechanical instrumentation and irrigation with 3% NaOCl, followed by sterile saline rinsing. The subsequent irrigation was carried out by 17% EDTA, followed by normal saline, and the canal walls were dried by paper points. A concentration of 6.25 μg/mL methylene blue was inserted in the root canal as the photosensitizer and left for 2 minutes, and then it was illuminated by a diode laser (810 nm) operating at the power of 2.5 W. The laser fiber moved spirally from apical to cervical to provide equal light diffusion. These motions were repeated six to ten times a minute. Following disinfection, PRF was transferred into root canals up to the apical end and confined below the cementoenamel junction. PRF was covered by a 2-mm thick coating of MTA. After 20 minutes, to allow for the setting of MTA, the tooth was permanently restored with glass–ionomer cement and composite resin. At 6- and 12-month follow-ups, there was no pain, tenderness to percussion, or tooth mobility, and an improvement in the tooth color was observed. A radiographic examination revealed partial apical closure, root lengthening, regression of the periapical lesion, and increased thickness of the dentinal walls.

In a prospective clinical study, Dragana et al[43] evaluated the effectiveness of PDT and high-power diode laser in treating 39 young permanent teeth with chronic periapical periodontitis (CPP). They assigned permanent anterior or the first premolar teeth with CPP to the control, PDT, and high-power diode laser (DL) groups. Conventional endodontic treatment was performed in all groups. In the PDT group, the root canals were filled with the photosensitizer phenothiazinium chloride (10 mg/mL). The photosensitizer remained for 3 minutes, then eliminated by paper points and saline. After drying with additional paper points, the canals were exposed to the diode laser radiation (660 nm, 100 mW) for 60 seconds at continuous-wave mode using a 450 μm fiberoptic tip (total energy 6 J). In the DL group, the diode laser (Biolase) was irradiated for 20 seconds, and the treatment was repeated three times, with 10-second rest intervals in between. After canal drying, a 200 μm fiberoptic tip was positioned 1 mm above the working length and irradiated while being moved in an apical-coronal direction. The physical parameters of the laser were λ = 940 nm at a peak power of 1 W in continuous wave. Bacterial identification and quantification were accomplished after accessing the canal, after standard canal preparation, and after PDT or DL procedures. The results showed that before the treatments, the root canals included 202 isolates from 13 different bacterial species. All three groups showed a successful reduction in the microbial load following conventional endodontic therapy; however, no species was completely eradicated. Adjunctive PDT and DL treatments resulted in the complete elimination of 8 and 6 bacterial species, respectively. Complete microbial eradication was observed in about 54% of root canals in the PDT group and 31% in the DL group. The remaining canals showed fewer bacterial colonies after adjunctive PDT or DL treatments. The radiographic analysis six months after endodontic treatment demonstrated that PDT and DL caused a significantly greater reduction in the diameter of periapical lesions in comparison to the control group.

Laser Applications in the Second Step of RET: Tissue Engineering

The second step of RET is based on tissue engineering principles, consisting of the triad assembly of dental stem cells, scaffolds, and growth factors. These elements may be stimulated by applying low-power lasers (also called cold or soft lasers) to enhance regenerative procedures.[7,13]

Low-level laser therapy (LLLT), low-power laser therapy, or photobiomodulation therapy (PBMT) are interchangeable words to describe the process of stimulating biological tissues through energy emitted from low-power, non-ionizing light sources such as lasers or light-emitting diodes in the visible and near-infrared spectrum (600 nm-1000 nm).[44] The absorption of laser energy leads to photochemical changes that create alterations at the molecular, cellular, and tissue levels. Several studies demonstrated that LLLT can enhance cell function and ATP production, relieve pain, resolve inflammation, and accelerate wound healing.[45-49] Different lasers, such as GaAlAs, GaAlInP, GaAs, and helium-neon lasers, may be applied for LLLT. LLLT may serve as the fourth element of tissue engineering by stimulating the growth of seeded stem cells and optimizing the environmental conditions through the improved blood supply. LLLT may also be capable of stimulating growth factors, thus leading to enhanced cell proliferation and differentiation.[7,13]

Arany et al[50] investigated the effect of low-power laser

therapy as a minimally invasive method for activating an endogenous latent growth factor complex, transforming growth factor beta-1 (TGF-β1), which in turn, controls the differentiation of dental stem cells to improve tissue regeneration. The study was conducted in 2 phases: in vitro (human dental stem cells) and in vivo (mouse and rat experiments). During the in vitro phase, a low-power GaAlAs diode laser (810 nm) was used with a fiber delivery system (400 μ). The laser was applied in a continuous-wave mode, and various energy densities (J/cm^2) were produced using different spot sizes. In all experiments, the treatment duration was kept constant (5 minutes). The authors postulated that LLLT generates ROS and, in this way, activates latent TGF-β1 (LTGF-β1) through a particular methionine (at position 253) on the latency-associated peptide. Laser-activated TGF-β1 was capable of differentiating human dental stem cells in vitro. In the in-vivo part of the study, the use of a GaAlAs laser (810 nm) was investigated on exposed maxillary first molars of mice or rats. One tooth was considered as the control and the other tooth as the experimental (laser) group. In the experimental group, the laser ran at a power of 0.01 W/cm^2 and a duration of 5 minutes for a total dosage of 3 J/cm^2. In the control group, calcium hydroxide dressing was employed to induce tertiary dentin production. Both teeth received a filling. The animals were treated once and followed for eight weeks (mice) or 12 weeks (rats). Micro-computed tomography (μCT) and histology assessments revealed that the amount of tertiary dentin produced in the laser group was significantly higher than in the control group after 12 weeks ($P=0.0469$). The tertiary dentin produced by laser treatment had a similar composition to the samples treated with calcium hydroxide. This work demonstrated the impact of lasers on regenerative treatments through the stimulation of growth factors.

The effect of biostimulation on the pulp regeneration of immature dog teeth was investigated by Fouad et al.[51] Sixty root canals were assigned to two experimental groups. Group 1 underwent disinfection by double antibiotic paste (DAP) and was then subjected to biostimulation. In group 2, DAP was applied without subsequent biostimulation. Laser therapy in group 1 was performed every other day for seven sessions using an 808 nm diode laser applied on the buccal side. The laser operated at 300 mW power, continuous wave mode, and 90 seconds, giving an energy density of 27 J/cm^2. Six samples with periapical infection were considered positive control and did not undergo any treatment, whereas six normal teeth served as negative control and were left intact for normal maturation. The treatments were followed up for 1 (subgroup A), 2 (subgroup B), and 3 (subgroup C) months. In addition to the radiographic examination, the canals were also examined histologically for the presence or absence of signs of life or growth. In the radiographic examination, group 1 showed a marked increase in the length and thickness of the root and a decrease in the apical diameter. Root maturation was also observed in group 2 but to a lower extent. The difference between groups 1 and 2 reached statistical significance in subgroup C. Histological analysis at the 3-month posttreatment evaluation (subgroup C) revealed a significantly greater score of vital tissue infiltration and new hard tissue formation and a statistically lower inflammatory score in teeth exposed to RET with subsequent biostimulation as compared to RET without biostimulation.

Table 1 summerizes the results of the studies that employed lasers in different steps of RET.

Discussion

Every year, millions of immature permanent teeth develop irreversible pulpitis or necrosis due to severe tooth decay or dental trauma. Since the introduction of RET, many teeth have survived via this approach. The primary (necessary) goal of RET is to improve the clinical and radiographic symptoms of the necrotic tooth. The secondary (desirable) goal is the deposition of minerals and continued maturation of the root (increase in thickness and length of the root). The achievement of the tertiary goal (positive sensitivity tests) has been reported in only a few cases.

Proper sterilization of the root canal is an essential step to achieving successful root regeneration. In RET, canal instrumentation is a double-edged sword. On the one hand, it cleans the dentin walls, and on the other hand, precision instrumentation can weaken the thin walls of immature teeth and increase their susceptibility to fracture. Moreover, the original tooth stem cells in the apical region may be destroyed by instruments used to cause bleeding into the canal. Therefore, chemical disinfection methods are the primary means of canal sterilization in immature necrotic teeth. The primary drawback of chemical rinsing solutions is that their bactericidal effect is restricted to 100 μm from the canal lumen, while bacteria can infiltrate dentinal tubules over 1000 μm. Lasers may be employed to improve the effectiveness of conventional canal sterilization methods through a variety of mechanisms, including LAD, LAI, and PDT.

Near-infrared lasers are ideal for LAD due to their superior penetration depth and extremely thin and flexible fiber optic light delivery systems. Of all the lasers on the market, the Nd:YAG laser has the most bactericidal effect and can reach dentin depths of over 1000 μm. The diode laser has a lower penetration depth than the Nd:YAG laser, but it also exhibits optimal bactericidal effects. As a result of its versatile applications, affordable cost, and decreased chance of an unintentional temperature rise,[52] the diode laser may be more frequently used for canal disinfection. Since most diode lasers are chopped lasers, there would be no pulse noise to be heard, and thus,

Table 1. The Results of Studies Employing Laser Therapy for Regenerative Endodontic Treatment

Author	Study Design	Treatment Step	Laser Settings	Method of Evaluation	Follow-ups	Main Results
Mekkawi et al[21]	Clinical trial	First step/ LAD	Diode (980 nm), 1.5 W, 5 seconds, 50 Hz	Microbial assessment	Assessments: Before and after disinfection	No significant difference was found in the percent change of the microbial load between the triple antibiotic paste and laser disinfection groups.
Divya et al[11]	RCT	First step/ LAD	Diode (810 nm), 1 W, 15 seconds, 20 ms pulse length, 20 ms interval, 200 µm fiber tip	Microbial, clinical, and radiographic assessments	1, 3, and 6 months	There was a significant reduction in the bacterial count after disinfection in both the laser and control groups. The application of laser led to a more successful clinical outcome at 3 months, and a better periapical healing score at 6 months, compared to the control group.
Doddamani et al[22]	Case series	First step/ LAD	Diode (810 nm), 1 W, 15 seconds, 20 ms pulse length, 20 ms interval, 200 µm fiber tip	Radiographic assessment	12 months	CBCT examination at 12 months revealed a reduction in the size of the peri-radicular radiolucency and an increase in the root length and dentin thickness.
Liu et al[23]	Pilot clinical study	First step/ LAD	Nd:YAP (1340 nm), 0.32 mm fiber tip, 100 mJ, 30 Hz, 30 seconds	Clinical and radiographic assessments	Every 3-6 months until 24 months	At 24 months, the primary goal was achieved in 34/36 teeth in the control (triple antibiotic paste) and 29/30 teeth in the laser group. The secondary goals (radiographic assessment) were attained in 31/36 teeth in the control and 27/30 in the laser group. No significant difference was found between the two groups in any of the parameters.
Yu et al[35]	Case report	First step/ LAI (PIPS)	Er: YAG (2940 nm), 20 mJ, 15 Hz, 50 µs, four cycles of 20-second irradiation, each followed by a 5-second off-cycle	Clinical and radiographic assessments	3, 6, 11, 22, 39, and 53 months	Apical closure was observed at 11 months. At the latest follow-up at 53 months, the tooth remained asymptomatic and fully functional, and it responded positively to both electric pulp testing and cold testing.
Rahmati et al[36]	In vitro	First step/ LAI	Er:YAG (2940 nm), 25 mJ, 15 Hz, 20 seconds	SEM	Assessment: After three days of cell culture	Er:YAG laser showed a comparable cell adhesion rate to EDTA and QMix irrigants, whereas the MTAD irrigant showed the weakest adherence of stem cells to dentin.
Johns et al[39]	Case report	First step/ PDT	Diode (660 nm), 40 mW, 300 µm fiber tip, spiral movement from apical to cervical 10 times per minute	Clinical and radiographic assessments	6 and 10 months	There was no sensitivity to percussion or palpation tests. Radiographic examination revealed continued thickening of the dentinal walls, root lengthening, regression of the peri-apical lesion, and apical closure.
Rahim et al[40]	Case report	First step/ PDT	Diode (635 nm), 150 seconds	Clinical and radiographic assessments	3, 6, 9, and 12 months	Clinical examination indicated no adverse signs and symptoms up to 12 months. There was an increase in root length and apical root thickness at six months and apical closure at the 12-month follow-up.
Emam et al[41]	In vivo	First step/ PDT	Diode (940 nm), cycles 4 × 2 mm/ second	Radiographic assessment	3-6, 6-9, and 9-12 months	At 3-6 months, there was a significantly higher increase in root length in group 3 (calcium hydroxide and PDT) than in either the calcium hydroxide group or the PDT group. The increase in dentin thickness was not significantly different between the groups.
Kaur et al [42]	Case report	First step/ PDT	Diode (810 nm), 2.5 W, spiral movement from apical to cervical 6 to 10 times per minute	Clinical and radiographic assessments	6 and 12 months	There was no pain and tenderness on percussion and no mobility. The radiographic assessment showed continued thickening of the dentinal walls, root lengthening, regression of the periapical lesion, and partial apical closure.
Dragana et al[43]	Prospective clinical study	First step/ PDT and LAD	PDT group: Diode (660 nm), 100 mW, CW, 60 seconds, 450 µm fiber tip, 6 J. LAD group: Diode (940 nm), 1 W, CW, three times of 20 seconds irradiation followed by 10 seconds rest intervals, 200 µm fiber tip	Microbial and radiographic assessments	Microbial experiments: After canal access, after canal preparation, and after PDT and LAD treatments Radiographic examination: 6 months	Chemo-mechanical treatment decreased the CFU count in all three groups, but complete eradication was not observed for any of the microbial species. Adjuvant PDT and LAD resulted in complete bacterial elimination from 53.8% and 30.8% of root canals, respectively, whereas the rest of the canals showed a reduced number of bacterial colonies. PDT and LAD induced a significantly higher reduction of peripheral lesion diameter than the control at six months.

Table 1. Continued.

Author	Study Design	Treatment Step	Laser Settings	Method of Evaluation	Follow-ups	Main Results
Arany et al[50]	In vitro and animal study	Second step	In vitro: Diode (810 nm), 400 µm fiber tip, CW, 5 minutes Animal: Diode (810 nm), 0.01 W/cm^2, 5 minutes, 3 J/cm^2	Biochemical and molecular analysis, histological and µCT assessments	8 and 12 weeks	In vitro: Laser therapy induced ROS, which activated latent TGF-β1. The laser-activated TGF-β1 was capable of differentiating human dental stem cells. Animal: Rat teeth demonstrated a significantly higher volume of tertiary dentin formation in the laser than in the control group in µCT evaluation after 12 weeks. The composition of tertiary dentin was similar between the two groups.
Fouad et al[51]	Animal study	Second step	Diode (808 nm), 300 mW, 90 seconds, CW, 27 J/cm^2	Radiographic and histological assessments	1, 2, and 3 months	In the 3-month subgroup, the laser-treated teeth showed a significantly higher increase in root length and thickness compared to the control teeth. Histological analysis at the 3-month posttreatment revealed a significantly greater score of vital tissue infiltration and new hard tissue formation, and a lower inflammatory score in teeth exposed to RET with subsequent biostimulation as compared to the RET without biostimulation.

LAD, Laser-assisted disinfection; LAI, Laser-assisted irrigation; PDT, Photodynamic therapy; Er,YAG, Erbium-doped yttrium aluminum garnet; PIPS, Photon-induced photoacoustic streaming; Nd:YAP, Neodymium-doped yttrium aluminum perovskite; CW, Continuous-wave; ms, Milliseconds; SEM, Scanning electron microscopy; TGF-β1, Tumor growth factor-beta 1; CBCT, Cone-beam computed tomography; ROS, reactive oxygen species; µCT, micro-computed tomography.

during laser application, there would be no difference between the damp versus dry condition of the canal. The present literature involves a few articles that used diode lasers for supporting the canal disinfection of necrotic immature teeth. These studies did not show a significant superiority of LAD over the standard technique in reducing the bacterial count after disinfection.[11,21] However, significantly better periapical healing scores and a more successful clinical outcome were observed in teeth subjected to additional laser disinfection.[11] The Nd:YAP laser also proved to be a suitable alternative to the triple antibiotic paste for canal disinfection during pulp regenerative therapy.[23]

Laser-assisted irrigation can be accomplished by erbium lasers. The mechanism of LAI is mainly through producing bubble explosion and physical rinsing of the superficial dentin layers, and the results are assumed to be comparable to chemical rinsing solutions.[24,27] Erbium lasers are only effective for the removal of the smear layer and surface microorganisms, and thus, they are not usually selected for solitary canal sterilization. The literature contains a few studies on the use of erbium lasers for improving canal disinfection, and there is no clear evidence that LAI is effective in promoting canal disinfection in teeth requiring regenerative procedures. Laser irrigation by erbium family lasers appears to provide negligible benefit over the conventional method of canal disinfection, while the sophisticated instruments used in this process and the lack of enough flexibility in the laser delivery system can make the procedure difficult in young patients.

PDT is now famous for eradicating microorganisms in medicine and dentistry. This technique is safe, and the singlet oxygen and free oxygen radicals produced in this process can provide a solid bactericidal effect against different microorganisms.[53] Furthermore, some photosensitizers, such as curcumin and erythrosine, demonstrate bactericidal effects when applied without light irradiation.[6,54] The literature provides some evidence that PDT may be an effective and suitable adjunct to standard endodontic treatment in necrotic, immature permanent teeth by creating a significant reduction in the microbial load and enhancing the healing of periapical lesions.[43]

In the tissue engineering step, LLLT has the potential to improve dental tissue regeneration through stimulating stem cells and growth factors. The evidence to support the effectiveness of LLLT in the second step of RET, however, is limited.[13] Several in vitro studies evaluated the effect of LLLT on the growth of stem cell cultures, but the results are not directly applicable to the clinical setting. Most of these in vitro experiments employed the diode laser with a wavelength of 660 nm, 810 nm, or 980 nm, among which 660 nm was the most popular wavelength.[13] The major challenge in this procedure is selecting the ideal energy

and energy density to stimulate cell metabolism and proliferation without inducing phototoxicity. Additionally, the administration of LLLT below the therapeutic window range is ineffective.[7,55] Another issue is the distance between the laser tip and cell culture, which could cause beam divergence and make the calculation of the spot size and energy density inaccurate.[56] According to the results of in vitro experiments, LLLT at doses between 1 and 7 J/cm^2 may be able to stimulate stem cell proliferation, but further research is necessary to confirm these benefits in the clinical setting.[57,58] The results of an animal study revealed the beneficial effects of laser therapy on root maturation and hard tissue formation in dogs subjected to RET with subsequent biostimulation compared to the group that did not get biostimulation treatment.[51] LLLT also proved effective in activating growth factors in laboratory and animal experiments.[50]

Most studies in the field of laser application in RET are case reports and case series with only a few clinical trials. Indeed, the number of cases needing tooth regenerations is usually limited, which makes it impossible to conduct extensive clinical trials. Furthermore, there still needs to be a unique protocol for performing RET, which makes comparing different studies difficult. At present, it is clear that in most cases, revitalization occurs instead of true regeneration, and it needs to be defined how laser therapy can help achieve actual regeneration. Further high-quality randomized controlled trials with long-term follow-ups are warranted to assess the effect of additional laser irradiation on the success of root maturation in necrotic teeth with open apices. It is also required to compare different laser parameters to attain an optimal protocol of laser irradiation for the treatment of immature necrotic teeth.

Conclusion

The available literature does not support the benefit of laser-assisted irrigation in improving the clinical success of regenerative endodontic therapy. There is some evidence that LAD with a diode or a Nd:YAP laser provides comparable results to triple antibiotic paste in reducing the bacterial count in necrotic root canals while providing slightly better clinical and radiographic outcomes than that of the standard technique without laser irradiation. PDT may be an effective and suitable adjunct to conventional methods of canal disinfection in immature permanent teeth with pulp necrosis.

According to the present literature, low-power lasers may be beneficial tools for improving the results of regenerative procedures through chemical disinfection in the first step (PDT) or by biostimulation (PBMT) in the second step of RET

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Competing Interests

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