Photodynamic Therapy in Endodontic

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ABSTRACT

The use of photodynamic therapy dates to 1900s. it was earlier used as a therapy in various cancer and tumor treatments. The application of photodynamic therapy was introduced in few decades. Due to its several favorable features, it has drawn attention in endodontic treatment. Many studies have demonstrated its use in root canal treatment. PDT has shown promising results in vitro and in vivo in eliminating microorganisms from endodontic space. The current review compiles the efficiency, extent, application, and limitations of PDT as an adjunct in endodontic procedures. We analyzed literature from 2015-2022 related to photodynamic therapy in endodontics. We concluded that PDT is a promising and beneficial approach but requires further research to overcome obstacles of application in clinical use.

INTRODUCTION

Microorganisms play a major role in development of pulpal and periapical pathology. Complete decontamination of root canal is one of the primary challenges in Success of endodontic treatment. Despite scientific and medicinal developments, endodontic failure is prevalent and can be linked to persistent and secondary infections, which is associated with protective mechanism used by microorganisms such as biofilm formation (Jiao et al., 2019). Furthermore, anatomical variations and complexity of root canals may add to the limited elimination of the root canal pathogenic flora. However, chemico-mechanical therapy with medicaments such as sodium hypochlorite have shown to reduce the microbial activity but the penetration of these irritants into the dentinal tubules is limited to some extent. Microorganisms associated with root canal pathology can penetrate further deeper into the tubules and accessory canals that it could be difficult to eliminate them (Hoedke et al., 2017). High power lasers were another approach to achieve complete decontamination in endodontic treatment which led to 99% of microorganism elimination by the photothermal effect and denaturation of protein (Bordea et al., 2020). However, damages to dental and periradicular tissues, such as carbonization of dentin and cementum, root resorption, ankylosis and periradicular necrosis, are seen to be associated with use of high-power lasers in some cases (Sarda et al., 2019).

To overcome the challenges of endodontic treatment and limitations of conventional methods, researchers have developed interest in use of photodynamic therapy (PDT) in endodontic. Earlier PDT were successfully applied several types of cancer (Dos Santos et al., 2019), photo inactivation of microorganisms and in treatment of localized microbial infection (Niculescu & Grumezescu, 2021). From last decades, the area of application for PDT has been shown great interest and its indications are expanded. It represents promising alternative to overcome obstacles of antibiotic resistance by various microorganism, it is unlikely to develop resistance to PDT
"Antibacterial photodynamic therapy: overview of a promising approach to fight antibiotic-resistant bacterial infections", 2015). The technique of PDT is nonresistant, minimally invasive and repeatable (Niculescu & Grumezescu, 2021). The principal mechanism behind PDT is based on the fact that light can be used to excite a photosensitive non-toxic dye (photosensitizer) at the target tissue to without causing many effects on surrounding tissues. The interaction between photosensitizers and low intensity visible light in presence of oxygen produces some cytotoxic species which causes damage to microorganism by irreversible oxidation of various cell components (Carvalho et al., 2022). The objective of this paper is to review the available dental literature that represents the indication and applications involving antimicrobial effects of PDT and its extent in endodontic therapy in complete decontamination of the root canal system.

BACKGROUND

It dates to 1900 when it was realised by researchers that light when interacts with certain dye could cause antibiotic effect (Baltazar et al. 2015). It was also realized that in the presence of oxygen the interaction between dye and white light can be used as a therapy in cancer and tumor (Dos Santos et al., 2019). However with advent on medications and antibiotics the investigations on photodynamic therapy decreased progressively (Santezi et al. 2018). Later, when resistance against antibiotics was increasing rapidly the attention in PDT was again came into focus and since than it has been gaining interest and growing rapidly in various medical specialties (Soukos & Goodson 2011).

Moreover, the application in oral cavity has been introduced in last few decades. Various studies were reviewed for the role of PDT in dentistry and it was demonstrated that the PDT effectively decrease cell viability of microbial cells (Carrera et al., 2016). It also disrupts oral biofilm by directly affecting g polysaccharides present in extracellular matrix disrupting colonization. Thus it has major advantage in inhibiting plasma exchange which would have otherwise caused the antibiotic resistance (Jiao et al., 2019)

The mechanism of action of PDT involves the absorption of photons from light source by photosensitizers; this will cause electrons to enter in exited state known as triple state. In the presence of oxygen the photosensitizer will return to basic state, transferring energy to substrate, producing free radicals such as superoxide or singlet oxygen leading to irreversible oxidative damage to various cellular components (Abrahamse & Hamblin, 2016).

PDT is highly promising therapy as it does not cause damage to human normal cells in low concentration and it can be repeated considerable times without producing any additive effects (Soukos NS 2011). Due to its mode of action PDT has greater advantage of hindering microbial resistance, as interaction between highly reactive oxygen and organic molecules is nonspecific. PDT could be an excellent tool to produce significant intracanal microbial reduction. It can disrupt biofilm by eradicating pathogens. The ease of application and lower cost as compared to lasers make it a potent root canal disinfectant (Chiniforush et al., 2016).

METHOD

A pertinent literature review was conducted on online databases such as Web of Science (WOS), Google scholar, and PubMed to search for photodynamic therapy in endodontics. Multiple terms were implied in the search including “photodynamic therapy in Endodontics” OR “photochemotherapy in endodontics” AND “photodynamic antimicrobial chemotherapy” OR light activated disinfection OR photodynamic inactivation OR photoactivated disinfection AND endodontics. To manage the extent of search the search terms were entered with Boolean operators OR and AND. Additional studies were included by searching randomly on the databases. We then checked the reference lists of the original and review articles that the initial search had yielded to identify additional full-text articles. The articles in English language between years 2015-2022 were considered. The articles included were Studies that compared the effect of PDT with conventional techniques in endodontics, in vitro and ex vivo studies, studies evaluating the efficiency and efficacy of PDT in endodontic disinfection and review articles. Studies based on animals were not included in this review.
A total of 39 studies were identified for this review. Of them, 27 remained after removing duplication. Finally, 19 articles were kept as remaining have only abstract or no relevance to the study hypothesis.

RESULTS

A total of 19 articles were included for evaluation. Data extracted from the search and review summarized and compiled in table 1, specifying the study title, study design, treatment modality, type of light source or wavelength used, evaluation of clinical outcome.

Table: 1 study findings and their design

<table>
<thead>
<tr>
<th>Articles Reviewed</th>
<th>Study Design</th>
<th>Sample Size (n)</th>
<th>Treatment Modality</th>
<th>Light Source and Wavelength</th>
<th>Results</th>
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<tr>
<td>De Miranda, R.G.; Colombo, A.P.V. Clinical and microbiological effectiveness of photodynamic therapy on primary endodontic infections: A 6-months randomized clinical trial. Clin. Oral. Investig. 2018, 22, 1751–1761.</td>
<td>Randomized controlled clinical trial</td>
<td>2 groups of 16 patients each</td>
<td>Primary endodontic infections treated with CMD + CaOH in control group and with CMD+PDT+CaOH in PDT group</td>
<td>Diode laser (660 nm) for 5 min</td>
<td>Statistically significant improvement Periapical Index Score at 6 months</td>
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<td>Rabello, D.G.D.; Corazza, B.J.M.; Ferreira, L.L.; Santamaria, M.P.; Gomes, A.P.M.; Martinho, F.C. Does supplemental photodynamic therapy optimize the disinfection of bacteria and endotoxins in one-visit and two-visit root canal therapy? A randomized clinical trial. Photodiagn. Photodyn. Ther. 2017, 19, 205–211</td>
<td>Case series</td>
<td>2 groups of 12 patients each</td>
<td>Primary endodontic infection treated in Three visits with PDT in 1 visit and PDT+CaOH in 2 visits</td>
<td>Diode laser (660 nm) for 2 min</td>
<td>significant reduction of bacteria is seen with PDT 1 visit as compared to control group but not significant in 2 visits with calcium hydroxide</td>
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<tr>
<td>Asnaashari, M.; Ashraf, H.; Rahmati, A.; Amini, N. A comparison between effect of photodynamic therapy by LED and calcium hydroxide therapy for root canal disinfection against Enterococcus faecalis: A randomized controlled trial. Photodiagn. Photodyn. Ther. 2017, 17, 226–232.</td>
<td>Case series</td>
<td>20 patients</td>
<td>Persistent endodontic infection treated either in 2 sessions with CaOH intracanal medicament or in a single visit with adjunctive aPDT</td>
<td>LED (620–640 nm) for 60 s</td>
<td>Decrease in number of colonies was more evident in aPDT group</td>
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| Chiniforush, N., Pourhajibagher, M., Shahabi, S., Kosarieh, E., & Bahador, A. (2016). Can antimicrobial photodynamic therapy (APDT) enhance the endodontic treatment? Journal of Lasers in Medical Sciences, 7(2), 76–85. https://doi.org/10.15171/jlms.2016.14 | Review Article | nil | N/A | N/A | it was concluded that aPDT should be applied in combination with conventional mechanical debridement and irrigants. However, it is also important to note that the success rate is critically dependent on the type of the PS,
<table>
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<tr>
<th>Name</th>
<th>Type</th>
<th>Patients</th>
<th>Treatment</th>
<th>Laser</th>
<th>Outcome</th>
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<tr>
<td>Author(s)</td>
<td>Study Type</td>
<td>Teeth/Patients/Groups</td>
<td>Description</td>
<td>Light Source</td>
<td>Result</td>
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<td>Zorita-García, M.; Alonso-Ezpeleta, L.Ó.; Cobo, M.; Del Campo, R.; Rico-Romano, C.; Mena-Álvarez, J.; Zubizarreta-Macho, Á.</td>
<td>Quasi-controlled clinical trial</td>
<td>42 teeth from 33 patients</td>
<td>Photodynamic therapy in endodontic root canal treatment significantly increases bacterial clearance, preventing apical periodontitis. Quintessence Int. 2019, 50, 782–789.</td>
<td>LED (630 ± 20 nm) for 2 cycles of 30s each</td>
<td>Significant reduction in CFU/tooth was achieved after aPDT application in all cases.</td>
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<td>Sarda, R., Shetty, R., Tamrakar, A., &amp; Shetty, S. (2019).</td>
<td>Comparative study</td>
<td>120 unrooted teeth with 2 groups of 60 each further divided into 6 subgroups</td>
<td>Antimicrobial efficacy of photodynamic therapy, diode laser, and sodium hypochlorite and their combinations on endodontic pathogens. Photodiagnosis And Photodynamic Therapy, 28, 265-272. <a href="https://doi.org/10.1016/j.pdpdt.2019.09.009">https://doi.org/10.1016/j.pdpdt.2019.09.009</a></td>
<td>low intensity wavelength</td>
<td>A significant reduction (98%) in the E. faecalis count was observed when the NaOCl was used in combination with the diode laser or PAD</td>
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<td>Conejero, M.J.; Almenar, A.; Forner, L.; Sanz, J.L.; Llena, C.</td>
<td>Retrospective study</td>
<td>100 teeth treated with conventional CMD and 114 teeth received adjunctive aPDT</td>
<td>Retrospective clinical evaluation of root canal treatment with or without photodynamic therapy for necrotic teeth and teeth subjected to retreatment. J. Oral. Sci. 2021, 63, 163–166</td>
<td>LED (360 nm) for 30s</td>
<td>success rate was more i.e. 97.2% with CMD+ aPDT as compared to CMD group which is 94.7%. Duration of Periapical healing was 15 ± 9.33 months in CMD+ aPDT group as compared to CMD group which was 20.35 ± 22.1 months.</td>
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<td>it revealed many in vitro studies demonstrated positive results, but fewer in vivo investigations are needed on the use of antimicrobial PDT in root canal treatment.</td>
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<td>Diogo, P., Fernandes, C., Caramelo, F., Mota, M., Miranda, I., &amp; Faustino, M. et al. (2017). Antimicrobial Photodynamic Therapy against Endodontic Enterococcus faecalis and Candida albicans Mono and Mixed Biofilms in the Presence of Photosensitizers: A Comparative Study with Classical Endodontic Irrigants. Frontiers In Microbiology, 8. <a href="https://doi.org/10.3389/fmicb.2017.00498">https://doi.org/10.3389/fmicb.2017.00498</a></td>
<td>a comparative study</td>
<td>strains of C. albicans and E. faecalis</td>
<td>efficacy of aPDT with the Zn(II)chlorin e6 methyl ester (Zn(II)e6Me) activated by red light against monospecies and mixed biofilms of Enterococcus faecalis and Candida albicans</td>
<td>LED light for 60s and 90s with wavelength of 627nm for TBO, TMPyP, and Zn(II)e6Me and wavelength of 55nm was used for RB</td>
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<td>The organization of biofilms and the normal microbial cell ultrastructure were extensively damaged by the presence of Zn(II)e6Me. aPDT with Zn(II)e6Me showed to be an efficient antimicrobial strategy</td>
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<td>successfully interpreted that aPDT has emerged as an alternative to antimicrobial regimes and mechanical removal of biofilms</td>
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<td>regression of periapical radiolucencies and progression of bone formation suggests that Passive ultrasonic Irrigation (PUI) and aPDT associated with endodontic retreatment can improve disinfection</td>
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<td>Mustafa, M., Alamri, H., Almokhatieb, A., Alqahtani, A., Alayad, A., &amp; Divakar, D. (2021). Effectiveness of antimicrobial photodynamic therapy as an adjunct to mechanical instrumentation in reducing counts of Enterococcus faecalis and Candida albicans from C-shaped root canals. Photodermatology, Photoimmunology &amp;Amp; randomized controlled trial</td>
<td>60 teeth with C-shaped root canals</td>
<td>treatment of periodontally hopeless molars with Mechanical instrumentation (MI) and aPDT as an adjunct</td>
<td>MI followed by diode laser of 665 nm</td>
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<td>MI with adjunct aPDT is more effective in reducing count of E faecalisand C albicans from C-shaped root canals</td>
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DISCUSSION

Root canal is a complex structure. Morphological variations, incomplete penetration of medicaments in the root canal, biofilm formation causes great challenge in complete decontamination of the structure. Poor disinfection and incomplete debridement is directly related to residual infections and endodontic treatment failure ((Bordea et al., 2020)). Many conventional methods can be used to reduce microbial load in root canal such as medicaments, irrigants. But, complete microbial elimination may not be possible with these techniques especially in obstructive root canal morphology, hence to overcome the limitations and extent of conventional treatment PDT can be applied as adjuvant to the treatment. (LIMA et al., 2019)

The efficiency of PDT in decontaminating and eradication of microorganism in the endodontic space (ES) is based on three factors which are interconnected to each other i.e. a low-intensity light source (laser), a non-toxic dye capable to absorb light (photosensitizer), and oxygen. The mechanism of PDT is based on the principle that photosensitizer gets absorbed by the microbial cell, and the activated light of certain wavelength has affinity towards cell wall, causing microbial death by apoptosis (Stájer et al., 2020) (Plotino et al., 2018). The energy from the activated photosensitizer is transferred to the oxygen in ES, where it will produce various cytotoxic elements such as free radicles and singlet oxygen which will destroy various cellular components. The mechanism of photochemical process of PDT can occur by two types: type I, involves electron transfer; and type II, involves energy transfer. In the entire process it difficult to differentiate between both the types of mechanism but type II is majorly responsible for microbial cell damage (Abrahamse & Hamblin, 2016). Moreover, the treatment is minimally invasive, repeatable without causing any harm to adjacent tissues and non-resistant (Carvalho et al., 2022), makes PDT more potent adjuvant.

Obstructive root canal morphology offers great challenge to clear root canal as the risk of instrument breakage is high (Alrahabi et al., 2019). This often leads to incomplete debridement and persistent infections. A study has demonstrated significant reduction in microbial load from C shaped canals with mechanical irrigation along with aPDT (Mustafa et al., 2021). Reoccurrence of endodontic infection is also associated with Bacterial resistance to certain antibiotics, and biofilm formation (Diogo et al., 2017). Histological studies have shown endodontic biofilms constitutes multiple organisms and could be more resistant to antibiotics (Tennert et al., 2015). To overcome the obstacles of biofilm eradication, some authors have insisted on use of triple antibiotic paste comprising of ciprofloxacin, minocycline and metronidazole in residual infections to efficiently reduce bacteria but the risk of developing antimicrobial resistance still persists (Mohammadi et al., 2019). Since the mechanism of as interaction between highly reactive oxygen and organic molecules is nonspecific.
the risk of resistance become minimal. Various studies have demonstrated promising results of implementing aPDT as an adjunct to conventional methods and antibiotics treatment (Garcez et al., 2015), particularly for teeth undergoing endodontic retreatment (Asnaashari et al., 2017) (Rabello et al., 2017) (Chiniforush et al., 2016). In a study by Tennert et al 2015 shown photodynamic effects of PDT significant reduce upto 99% in colony formation in experimentally induced infections in root canals of extracted teeth (Tennert et al., 2015). A systemi review (Bordea et al., 2020) has confirmed role of PDT in eliminating endodontic biofilms from root canals. In an in vitro study author demonstrated better penetration of biofilm using a diode laser with silver nanoparticles and indocyanine green (Afkhami et al., 2017).

Various authors have shown in vivo (Rabello et al., 2017) (Plotino et al., 2018) and in vitro (Asnaashari et al., 2017) (Soares et al., 2016) bacterial load reduction and improved periapical healing with the use of PDT in endodontic treatment. Zorita-Garcia et al. (Zorita Garcia et al., 2017) performed microbiological clinical study in forty-two necrotic single rooted posterior teeth in three steps. Evaluation done after each step. After first step i.e. root canal access, a mean value of 113.5 ± 130 colony forming units (CFU) per tooth was detected. After second step of CMD, the mean CFU per tooth decreased to 26.52 ± 72, which came down to to 4.2 ± 13 CFU/tooth after third step of aPDT application.

Numerous studies have demonstrated reduction in microorganism and elimination of residual infection not only results in healing of periapical lesions but also promotes bone formation. Vieira et al. used quantitative real-time polymerase chain reaction (qPCR) to improve microbiological detection in a study on 19 teeth that needed periapical surgery. The result revealed application of aPDT has significantly reduced bacterial and streptococci levels and high healing rates were reported in a mean follow-up of 16 months (Vieira et al., 2018). Another author analyzed aPDT as an adjunctive disinfection method during endodontic retreatment in the tooth with apical root perforation. Before Obturation and during apicectomy before sealing the root end, all the residual bacteria were eliminated by using aPDT. In a twelve-month follow-up successfully healed lesion with neobone formation was confirmed in CBCT (Abu Hasna et al., 2020). Leading to more complex cases, Moreira et al. (Moreira et al., 2015) demonstrated application of aPDT in two failed cases of endodontic retreatments and persistent sinus tract. aPDT was given via sinus tract for seven to ten sessions. Successful healing of sinus tract and periapical bone repair was confirmed with CBCT. Efficient eradication of microorganisms promotes faster healing and provides better treatment outcomes, as demonstrated in a randomized controlled clinical trial by De Miranda et al. (De Miranda & Colombo, 2017) in necrotic teeth which were treated with aPDT. Lower periapical index (PAI) scores at the 6-month follow-up and better healing of periapical region was observed. Conejero et al (Conejero et al., 2021) analyzed two groups in a retrospective clinical study. The group with conventional CMD had greater periapical healing time (20.35 ± 22.1 months) as compared to the second group which received aPDT as an adjunctive therapy which resulted in shorter periapical healing time (15 ± 9.33 months).

The efficiency of PDT depends on the ability to excite PS in the target without causing harm to surrounding tissues. Furthermore, biological factors such quality and delivery of the photosensitizer and concentration of oxygen, physical factors such as the light flux at the target and the transfer of energy of the photosensitizer; and chemical factors such as oxidizing effect plays vital role in efficiency of the therapy (Asnaashari et al., 2016). The literature survey revealed that most commonly applied PS in endodontic studies is toluidine blue (TBO) or methylene blue (MB). They have amphiphilic nature and thus facilitate staining of both gram-positive and gram-negative bacteria associated with endodontic infections. PS reported in literature range between 10 to 100 μg/mL for TBO and 6.25 to 25 μg/mL for MB (Chiniforush et al., 2016). Appropriate delivery and duration of PS is needed for proper staining of microbes followed by suggested irradiation. Pourhajibagher et al. (Pourhajibagher & Bahador, 2018) applied 60s of PS application followed by 30s irradiation to reduce high concentrations of bacteria, and Kosareih et al. (Kosarieh et al., 2016) revealed better penetration of PS in dentinal tubules when pre irrigation of the root canal with 17% EDTA for 2 min is done. Shahbazi et al (Shahbazi et al., 2022) treated three pateints with PDT and concluded that efficient root canal disinfection can be obtained by using 635-nm LED with a mean power density of 3 W/cm² to activate low viscosity 0.1 mg/mL Toluidine Blue agent during two 30-second periods. A study performed to the changes in the region of root canal, two groups of teeth were analyzed, one group received conventional treatment and other group received PDT (toluidine
blue for 5 min pre irradiation followed by low-level red diode laser of wavelength 660 nm, activated continuously for 5 minutes using optical fiber. The result revealed higher smear layer retention in the control group and considerable dentinal tubules opening in the teeth that received PDT, which can be masked by the benefits of the technique (Lacerda et al., 2016).

The duration of endodontic treatment is an important factor to reduce bacterial contamination. The single visit endodontic treatment allows prompt coronal restoration. The efficiency of aPDT in single visit as compared to calcium hydroxide application in two visits was revealed by Asnaashari et al. by a randomised controlled trial in endodontic retreatment cases (Asnaashari et al., 2017). Furthermore, comparison between the antimicrobial effect of aPDT with CaOH intracanal medicament between appointments in one-visit versus two-visit cases. Significant bacterial reduction was expressed in one-visit cases but no further significant reductions was expressed in the two-visit approach (Rabello et al., 2017).

Carvalho et al 2022 reviewed the literature and found that PDT is minimal invasive, effective, risk free for patients, and does not cause bacterial resistance, hence making it potent treatment tool (Carvalho et al., 2022).

Even though it was revealed with great literature the PDT is a beneficial treatment adjunct for endodontic procedure, its application is limited by classic PSs. Most of the PSs applied in endodontic space are highly susceptibility to aggregate and degrade in aqueous solutions (Chen et al., 2020). Further, classic PS classic photosensitizers has certain limitations on cellular uptake, penetration depth and light absorbance clinical applicability still requires protocol formation for common use (Niculescu & Grumezescu, 2021). Another drawback is complex multiple scheduling of procedures. However, to overcome these limitations and enhance biocompatibility and further penetrating capability of PS, integration with nanotechnology was also demonstrated (Alfirdous et al., 2021), but further research is needed in this context.

Although interest in investigations on aPDT has attained greater pace in last few decades but it still lacks high level evidence to achieve the position of standard care (Niculescu & Grumezescu, 2021).

**CONCLUSION**

Complete disinfection of root canal is essential for successful endodontic treatment. PDT along with various available treatment methods significantly lowers the microbial load from endodontic space, promotes healing and bone formation. However, further studies are required to determine combinations of parameters such as PS concentration, exposure, preirradiation duration, dosage energy, so that maximum output from PDT can be obtained.

**References**


