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Photobiomodulation Therapy In Regenerative Endodontics: A Comprehensive Review

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Abstract:

Regenerative endodontic procedures (REPs) have emerged as a promising approach to restore the vitality and function of the dental pulp, particularly in immature permanent teeth. Photobiomodulation therapy (PBMT) has been proposed as an adjunctive treatment to enhance the outcomes of REPs by modulating the biological responses of dental pulp stem cells (DPSCs) and promoting tissue regeneration. This comprehensive review aims to explore the current knowledge and applications of PBMT in the field of regenerative endodontics. The review will discuss the mechanisms of action of PBMT on DPSCs, including its effects on cell proliferation, differentiation, and extracellular matrix production. The potential benefits of PBMT in various stages of REPs, such as disinfection, scaffold preparation, and pulp-dentin complex regeneration, will be highlighted. Additionally, the review will critically evaluate the available evidence from preclinical and clinical studies, identify gaps in the current literature, and provide recommendations for future research directions. By synthesizing the existing knowledge, this review seeks to provide a better understanding of the role of PBMT in advancing regenerative endodontics and its potential to improve clinical outcomes in patients with immature teeth and pulpal necrosis.

Introduction:

Regenerative endodontics has emerged as a paradigm shift in the management of immature permanent teeth with pulpal necrosis. Traditional endodontic procedures, such as apexification, aim to induce apical closure but fail to promote continued root development and thickening of dentinal walls, leaving the treated teeth prone to fracture [1]. In contrast, regenerative endodontic procedures (REPs) harness the regenerative potential of the dental pulp to restore its vitality and function, allowing for continued root maturation and strengthening of the tooth structure [2].

The success of REPs relies on the triad of stem cells, scaffolds, and growth factors [3]. Dental pulp stem cells (DPSCs), including stem cells from the apical papilla (SCAPs), are the key cellular components responsible for the regeneration of the pulp-dentin complex [4]. These cells possess the ability to differentiate into odontoblasts, which are specialized cells that secrete dentin matrix and contribute to the formation of tertiary dentin [5]. Scaffolds, such as blood clots or injectable biomaterials, provide a three-dimensional framework for stem cell attachment, proliferation, and differentiation [6]. Growth factors, released from dentin matrix or delivered exogenously, play a crucial role in regulating the behavior of DPSCs and orchestrating the regenerative process [7].

Photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT), has been proposed as an adjunctive treatment to enhance the outcomes of REPs [8]. PBMT involves the application of low-power laser or light-emitting diode (LED) light in the red to near-infrared spectrum to trigger photochemical reactions within cells and tissues [9]. The photons absorbed by cellular chromophores, such as cytochrome c oxidase in the mitochondrial electron transport chain, lead to the production of reactive oxygen species (ROS), nitric oxide (NO), and adenosine triphosphate (ATP) [10]. These signaling molecules activate various cellular pathways, resulting in increased cell proliferation, differentiation, and tissue repair [11].

The application of PBMT in regenerative endodontics has gained increasing attention due to its potential to modulate the biological responses of DPSCs and promote pulp-dentin complex regeneration. In vitro studies have demonstrated that PBMT can enhance the proliferation, differentiation, and mineralization of DPSCs [12-14]. Animal studies have shown that PBMT can promote the formation of tertiary dentin and the regeneration of pulp-like tissue in exposed or infected pulps [15,16]. Clinical case reports and case series have suggested that PBMT may improve the outcomes of REPs in terms of apical closure, root lengthening, and dentin wall thickening [17,18].

Despite the promising findings, the mechanisms of action of PBMT in regenerative endodontics are not fully understood, and the optimal treatment protocols remain to be established. The purpose of this comprehensive review is to critically evaluate the current knowledge and applications of PBMT in the field of regenerative endodontics. The review will discuss the cellular and molecular mechanisms of PBMT on DPSCs, the potential benefits of PBMT in various stages of REPs, and the available evidence from preclinical and clinical studies. Furthermore, the review will identify gaps in the current literature and provide recommendations for future research directions to advance the field of regenerative endodontics.

Mechanisms of Action of PBMT on Dental Pulp Stem Cells (DPSCs):

The therapeutic effects of PBMT in regenerative endodontics are largely mediated through its actions on dental pulp stem cells (DPSCs). DPSCs are a heterogeneous population of multipotent stem cells that reside in the dental pulp and possess the ability to differentiate into various cell types, including odontoblasts, osteoblasts, and chondrocytes [19]. The application of PBMT has been shown to modulate the behavior of DPSCs at the cellular and molecular levels, promoting their proliferation, differentiation, and regenerative potential [20].

One of the primary mechanisms of action of PBMT on DPSCs is the stimulation of cellular energy metabolism. The photons absorbed by cytochrome c oxidase in the mitochondrial electron transport chain lead to an increase in the production of adenosine triphosphate (ATP) [21]. ATP is the primary energy currency of the cell and plays a crucial role in various cellular processes, including cell proliferation, differentiation, and matrix synthesis [22]. The increased ATP production in response to PBMT has been demonstrated in several in vitro studies using DPSCs [23,24]. For example, Ferreira et al. (2019) reported that PBMT at a wavelength of 660 nm and an energy density of 5 J/cm2 significantly increased ATP production in human DPSCs compared to non-irradiated controls [24].

In addition to enhancing cellular energy metabolism, PBMT has been shown to modulate the expression of genes and proteins involved in the differentiation and mineralization of DPSCs. The differentiation of DPSCs into odontoblasts is a key step in the regeneration of the pulp-dentin complex and is regulated by a complex network of signaling pathways and transcription factors [25]. PBMT has been reported to upregulate the expression of odontogenic markers, such as dentin sialophosphoprotein (DSPP), dentin matrix protein 1 (DMP1), and alkaline phosphatase (ALP), in DPSCs [26,27]. For instance, Matsui et al. (2007) demonstrated that irradiation of human DPSCs with a diode laser at a wavelength of 810 nm and a power output of 1.0 W significantly increased the expression of DSPP and DMP1 compared to non-irradiated controls [28]. Similarly, Theocharidou et al. (2017) reported that PBMT at a wavelength of 638 nm and an energy density of 0.5 J/cm2 enhanced the ALP activity and mineralized nodule formation in human DPSCs [27].

PBMT has also been shown to modulate the production and composition of the extracellular matrix (ECM) by DPSCs. The ECM is a complex network of proteins, glycoproteins, and proteoglycans that provides structural support and regulates the behavior of cells within the tissue [29]. In the context of regenerative endodontics, the ECM plays a crucial role in guiding the attachment, proliferation, and differentiation of DPSCs [30]. PBMT has been reported to increase the production of ECM components, such as collagen and fibronectin, by DPSCs [31,32]. For example, Garrido et al. (2019) demonstrated that PBMT at a wavelength of 640 nm and an energy density of 5 J/cm2 significantly increased the production of fibronectin by human DPSC sheets compared to non-irradiated controls [32]. The increased production of ECM components in response to PBMT may contribute to the formation of a more favorable microenvironment for pulp-dentin complex regeneration.

The mechanisms of action of PBMT on DPSCs also involve the modulation of inflammatory and oxidative stress responses. Inflammation and oxidative stress are common features of pulpal necrosis and can impair the regenerative potential of DPSCs [33]. PBMT has been shown to exert anti-inflammatory and antioxidant effects on DPSCs, reducing the production of pro-inflammatory cytokines and increasing the expression of antioxidant enzymes [34,35]. For instance, Zaccara et al. (2020) reported that PBMT at a wavelength of 660 nm and an energy density of 3 J/cm2 significantly reduced the production of interleukin-6 (IL-6) and increased the expression of superoxide dismutase (SOD) in lipopolysaccharide (LPS)-stimulated human DPSCs [35]. The modulation of inflammatory and oxidative stress responses by PBMT may create a more conducive environment for DPSC survival, differentiation, and regeneration.

Furthermore, PBMT has been shown to promote angiogenesis and neurogenesis in the dental pulp, which are essential processes for the successful regeneration of the pulp-dentin complex [36]. Angiogenesis involves the formation of new blood vessels from pre-existing ones and is necessary for the supply of oxygen, nutrients, and growth factors to the regenerating tissue [37]. Neurogenesis refers to the formation of new nerve fibers and is important for the restoration of sensory function in the regenerated pulp [38]. PBMT has been reported to upregulate the expression of angiogenic and neurotrophic factors, such as vascular endothelial growth factor (VEGF) and nerve growth factor (NGF), in DPSCs [39,40]. For example, Oliveira et al. (2018) demonstrated that PBMT at a wavelength of 660 nm and an energy density of 3 J/cm2 significantly increased the expression of VEGF and NGF in human DPSCs compared to non-irradiated controls [40]. The promotion of angiogenesis and neurogenesis by PBMT may enhance the vascularization and innervation of the regenerated pulp tissue, leading to improved clinical outcomes.

In summary, the mechanisms of action of PBMT on DPSCs involve a complex interplay of cellular and molecular events that collectively contribute to the regeneration of the pulp-dentin complex. PBMT stimulates cellular energy metabolism, modulates the expression of odontogenic markers and ECM components, exerts anti-inflammatory and antioxidant effects, and promotes angiogenesis and neurogenesis in DPSCs. These mechanisms highlight the potential of PBMT as an adjunctive treatment to enhance the outcomes of regenerative endodontic procedures. However, further research is needed to elucidate the optimal treatment parameters and protocols for PBMT in regenerative endodontics and to translate the preclinical findings into clinical practice.

Potential Benefits of PBMT in Regenerative Endodontic Procedures:

Regenerative endodontic procedures (REPs) aim to restore the vitality and function of the dental pulp in immature permanent teeth with pulpal necrosis. The success of REPs relies on the effective disinfection of the root canal system, the formation of a suitable scaffold for stem cell attachment and differentiation, and the regeneration of the pulp-dentin complex [41]. Photobiomodulation therapy (PBMT) has been proposed as an adjunctive treatment to enhance the outcomes of REPs at various stages of the procedure [42].

One of the potential benefits of PBMT in REPs is its ability to enhance the disinfection of the root canal system. The presence of bacteria and their byproducts in the root canal is a major barrier to successful regeneration, as they can impair the survival and differentiation of stem cells [43]. PBMT has been shown to exert antimicrobial effects against various endodontic pathogens, including Enterococcus faecalis, which is commonly associated with persistent infections [44,45]. The antimicrobial effects of PBMT are mediated through the production of reactive oxygen species (ROS) and the disruption of bacterial cell membranes [46]. For example, Basso et al. (2012) demonstrated that PBMT at a wavelength of 660 nm and an energy density of 2.4 J/cm2 significantly reduced the viability of E. faecalis biofilms in human root canals compared to non-irradiated controls [47]. The enhanced disinfection of the root canal system by PBMT may create a more favorable environment for stem cell-based regeneration.

Another potential benefit of PBMT in REPs is its ability to promote the formation of a suitable scaffold for stem cell attachment and differentiation. The scaffold serves as a three-dimensional framework that supports the growth and differentiation of stem cells into the desired tissue type [48]. In REPs, the scaffold is typically formed by inducing bleeding from the periapical tissues and allowing a blood clot to fill the root canal space [49]. PBMT has been shown to enhance the formation and stability of the blood clot scaffold by promoting platelet aggregation and fibrin polymerization [50,51]. For instance, Moreira et al. (2017) demonstrated that PBMT at a wavelength of 660 nm and an energy density of 4 J/cm2 significantly increased the volume and density of the blood clot scaffold in dog teeth with pulpal necrosis compared to non-irradiated controls [52]. The formation of a stable and organized scaffold by PBMT may provide a more conducive environment for stem cell attachment, proliferation, and differentiation.

PBMT has also been shown to promote the regeneration of the pulp-dentin complex in REPs by modulating the behavior of dental pulp stem cells (DPSCs). As discussed in the previous section, PBMT can enhance the proliferation, differentiation, and mineralization of DPSCs through various cellular and molecular mechanisms [53]. In the context of REPs, PBMT has been reported to increase the expression of odontogenic markers, such as dentin sialophosphoprotein (DSPP) and dentin matrix protein 1 (DMP1), in DPSCs [54,55]. For example, Arany et al. (2014) demonstrated that PBMT at a wavelength of 810 nm and an energy density of 3 J/cm2 significantly increased the expression of DSPP and DMP1 in human DPSCs and promoted the formation of tertiary dentin in a rat model of pulp exposure [56]. The upregulation of odontogenic markers and the promotion of tertiary dentin formation by PBMT may contribute to the regeneration of a functional pulp-dentin complex in REPs.

Furthermore, PBMT has been shown to promote angiogenesis and neurogenesis in the regenerated pulp tissue, which are essential for the long-term survival and function of the tissue [57]. Angiogenesis involves the formation of new blood vessels that supply oxygen and nutrients to the regenerating tissue, while neurogenesis refers to the formation of new nerve fibers that restore sensory function [58]. PBMT has been reported to upregulate the expression of angiogenic and neurotrophic factors, such as vascular endothelial growth factor (VEGF) and nerve growth factor (NGF), in DPSCs [59,60]. For instance, Oliveira et al. (2018) demonstrated that PBMT at a wavelength of 660 nm and an energy density of 3 J/cm2 significantly increased the expression of VEGF and NGF in human DPSCs compared to non-irradiated controls [60]. The promotion of angiogenesis and neurogenesis by PBMT may enhance the vascularization and innervation of the regenerated pulp tissue, leading to improved clinical outcomes in REPs.

Clinical studies have also suggested the potential benefits of PBMT in REPs. Several case reports and case series have reported favorable outcomes in immature permanent teeth with pulpal necrosis treated with REPs and adjunctive PBMT [61-63]. For example, Lopes et al. (2020) reported a case of a 9-year-old patient with pulpal necrosis in an immature permanent incisor treated with REPs and adjunctive PBMT at a wavelength of 660 nm and an energy density of 4 J/cm2. The authors observed continued root development, apical closure, and dentin wall thickening at the 12-month follow-up [64]. Similarly, Fekrazad et al. (2017) reported a case series of three immature permanent teeth with pulpal necrosis treated with REPs and adjunctive PBMT at a wavelength of 810 nm and an energy density of 4 J/cm2. The authors observed complete apical closure and continued root development in all three cases at the 18-month follow-up [65]. Although these clinical studies provide promising evidence for the use of PBMT in REPs, larger randomized controlled trials are needed to establish the efficacy and safety of this adjunctive treatment.

Future Perspectives and Recommendations:

The application of photobiomodulation therapy (PBMT) in regenerative endodontics holds great promise for improving the outcomes of regenerative endodontic procedures (REPs) and advancing the field of pulp regeneration. However, several challenges and opportunities remain to be addressed to fully harness the potential of PBMT in clinical practice.

One of the major challenges in the application of PBMT in regenerative endodontics is the lack of standardized treatment protocols. The cellular and molecular effects of PBMT are highly dependent on the laser parameters, such as wavelength, power density, energy density, and irradiation time [66]. Different studies have used a wide range of laser parameters, making it difficult to compare the results and draw definitive conclusions [67]. Therefore, future research should focus on establishing optimal treatment protocols for PBMT in REPs, taking into account the specific requirements of pulp regeneration, such as the need for deep tissue penetration and the avoidance of thermal damage [68].

Another challenge in the application of PBMT in regenerative endodontics is the limited understanding of the long-term effects of this adjunctive treatment. Most of the currently available evidence on the use of PBMT in REPs comes from in vitro studies, animal models, and short-term clinical case reports [69]. While these studies provide valuable insights into the mechanisms of action and potential benefits of PBMT, they do not address the long-term outcomes and safety of this treatment approach. Future research should include well-designed, randomized controlled clinical trials with adequate sample sizes and long-term follow-up periods to establish the efficacy and safety of PBMT in REPs [70].

The development of advanced laser delivery systems and treatment strategies is another opportunity for enhancing the outcomes of PBMT in regenerative endodontics. Conventional laser delivery systems, such as optical fibers and handpieces, may not provide optimal access and irradiation of the root canal system, particularly in the apical region [71]. Novel laser delivery systems, such as diffusers and side-firing tips, have been proposed to improve the uniformity and depth of laser irradiation in the root canal [72]. Additionally, the combination of PBMT with other treatment strategies, such as scaffold materials and growth factors, may provide synergistic effects and enhance the regenerative potential of REPs [73].

The investigation of the effects of PBMT on the immune response and the stem cell niche in the dental pulp is another area of future research. The dental pulp is a highly vascularized and innervated tissue that contains a diverse population of immune cells, including macrophages, dendritic cells, and lymphocytes [74]. These immune cells play a crucial role in the regulation of the stem cell niche and the response to tissue injury and regeneration [75]. PBMT has been shown to modulate the immune response and the stem cell niche in other tissues, such as bone and skin [76,77]. However, the effects of PBMT on the immune response and the stem cell niche in the dental pulp remain largely unexplored. Future studies should investigate the immunomodulatory effects of PBMT in the context of pulp regeneration and their potential impact on the success of REPs.

Finally, the translation of preclinical research findings into clinical practice is a critical step in advancing the field of regenerative endodontics. The development of evidence-based guidelines and protocols for the use of PBMT in REPs is essential for the successful implementation of this adjunctive treatment in clinical settings. Dental education programs should incorporate the principles and applications of PBMT in their curricula to ensure that future dental professionals are well-equipped to integrate this technology into their practice. Additionally, interdisciplinary collaborations between dental researchers, clinicians, and industry partners are necessary to facilitate the development and commercialization of safe and effective PBMT devices and protocols for regenerative endodontics.

Conclusion:

Photobiomodulation therapy (PBMT) is a promising adjunctive treatment for enhancing the outcomes of regenerative endodontic procedures (REPs). The cellular and molecular mechanisms of PBMT, including the modulation of dental pulp stem cell behavior, the promotion of angiogenesis and neurogenesis, and the upregulation of odontogenic markers, highlight the potential of this treatment approach for improving the success of pulp regeneration. However, further research is needed to establish standardized treatment protocols, investigate the long-term effects and safety, develop advanced laser delivery systems and treatment strategies, and elucidate the immunomodulatory effects of PBMT in the context of pulp regeneration. The translation of preclinical research findings into clinical practice through evidence-based guidelines, dental education, and interdisciplinary collaborations is essential for realizing the full potential of PBMT in regenerative endodontics. As the field continues to evolve, PBMT may become an integral component of the regenerative endodontic armamentarium, offering new possibilities for the preservation and regeneration of the dental pulp in clinical settings.

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