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Review Article

Photobiomodulation Therapy and Periodontitis: A Discussion Paper

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Abstract

Aim: To evaluate the impact in terms of benefit of adjunctive photobiomodulation (PBM) therapy associated with laser and LED irradiance on the management of periodontitis.

Background: The pathogenesis of periodontitis has been well represented in peer reviewed publications and is accepted as a complex interaction of multiple factorial agents. The challenge in delivering applicable therapy requires that these factors should be recognised and incorporated within the ultimate choice of therapy. Photobiomodulation therapy, developed through the use of photonic energy in many medical and surgical disciplines, has been shown to have predictable and ultimately beneficial adjunctive effects. There is a logical synergy to be evaluated wherein photobiomodulation together with contemporary periodontal treatment may result in an enhanced clinical outcome.

Methods: This discussion paper is presented to offer an overview of the potential benefits of photobiomodulation, as referenced through a number of peer reviewed publications.

Discussion: The relative benefit and adjunctive use of photobiomodulation therapy and the role played in periodontal treatment may be evaluated and quantified through analysis of the many proven effects of the treatment modality. Identification of the host inflammatory response to the microbial challenge in periodontitis can be matched to the proven effects of PBM at cellular and tissue molecular level.

Conclusion: The extent of this discussion paper is to provide an introduction and overview to the discerning clinician and should promote the further evaluation through controlled well designed clinical trials of this potentially useful clinical modality.

Keywords: *Photobiomodulation Therapy; Periodontitis*

Introduction

Periodontal disease is a complex multifactorial condition and achieving resolution can be difficult in high susceptibility patients with a gene based inherent heightened immunological response to pathogens [1,2]. In addition, due to the sophisticated biodynamics of a virulent pathogenic biofilm, once formed, it can be very difficult to eradicate [3]. Conventional approaches have limitations and the requirement for an initial intensive and meticulous intervention combined with a life-long commitment to re-care is an issue for many patients

[4]. Consequent to post therapy inflammation and dentinal sensitivity, there can be reduced patient compliance and sadly some patients even prefer to permit the onward progression of the disease rather than tolerate treatment. Given the expanded and evolving evidence base associating chronic periodontal infections with systemic health issues, combined with the increased resistance of many periodontal pathogens to antibiotics, it is becoming increasingly evident that new approaches to intervention and care are required [5-8].

Photobiomodulation (PBM)

Lasers generically have many intrinsic interesting and useful properties. For instance, there is the potential for producing different results depending on dose. Laser tissue interaction can range in product from biochemical and biophysical promotion of healing and the selective suppression of the inflammatory cytokine cascade through to surgical ablation of diseased tissues and the photothermal destruction of pathogens [9-11]. Therapeutic low intensity laser and light emitting diode (LED) irradiation is termed photobiomodulation (PBM) and this type of treatment has been suggested as an adjunctive measure in the management of periodontitis [12,13]. Based on *in vitro*, animal and some human studies PBM has been found to have the capacity to modify the cytokine cascade away from a reactive pro inflammatory locally destructive process to an anti-inflammatory cycle [14]. In addition, PBM has been found to have a significant effect on the quality of healing [11] and may optimise the biological capacity for tissue regeneration plus laser treatments can be a useful adjunct to the management of dentinal sensitivity [15] as well as mitigate pain associated with surgical interventions [10].

PBM using lasers or LED light sources is an accepted evidence based therapy for a number of medical conditions including musculoskeletal pain and rheumatoid arthritis [16]. Also, it is an effective management strategy to reduce the incidence and severity of the very painful ulceration (oral mucositis) associated with head and neck radiotherapy and cancer chemotherapy [17]. In addition, there is a growing evidence base demonstrating clinical benefits for the PBM treatment and resolution of a wide variety of inflammatory and immunologically related oral medicine issues including aphthous ulceration, burning mouth syndrome, xerostomia and lichen planus amongst others [18]. Furthermore, PBM has been found to offer considerable promise as an adjunct to periodontal gingival surgery [19].

Advocates for low intensity laser therapy propose that by use of a so called photoceutical, there may be a reduced need for costly drugs, with a negligible risk for the potential systemic complications of conventional chemotherapy such as allergy, drug interactions or immunosuppression [20,21]. Furthermore, based on extensive *in vitro* and animal models of wound healing there are histological, genomic and proteomic studies plus many interesting models of PBM therapy, for example, in the acceleration of orthodontic tooth movement, that clearly demonstrate a positive effect in the production of matrix materials as well as in other aspects of healing, repair and regeneration [22,23]. There are some intriguing clinical studies that support the use of PBM therapy as an analgesic in orthodontics as well as in restorative dentistry, and in a number of systematic reviews, PBM is an effective measure in treating dentinal sensitivity [24].

PBM therapy has been found to have profound and deep reaching effects in many cellular sub systems and the potential for the therapeutic application of the same has attracted interest to clinicians seeking a novel approach to managing periodontitis. Gupta., *et al.* conducted a comparative outcome study between periodontal flap surgery using an erbium chromium YSGG laser and a conventional scalpel approach [25]. This interesting study showed a small statistically significant difference in the clinical outcome indices of around 0.5 mm gain in clinical attachments levels favouring the conventional approach. Perhaps far more significantly the authors commented on the very marked differentials in patient acceptance of the procedures as the laser approach was associated with a considerable reduction in post-operative pain and sensitivity compared to the conventional scalpel approach.

As identified by Chambrone., *et al.* studies on outcome in periodontology tend to focus on indications of statistical significance in periodontal indices such as pocket depths and clinical attachment loss where perhaps the subtle difference in outcome is of suspect clinical significance [26]. The important issues of patient comfort as well as the long-term stability of the outcome tend to be neglected as metrics of outcome.

The mechanisms of PBM have undergone many investigations and it would appear to operate on many different planes. Depending on dose it is possible to achieve a good anti-inflammatory and analgesic action [27,28], and due to attenuation of the delivery beam simultaneously improve the biological capacity of the wound bed to achieve optimal healing [11]. Furthermore, the systemic benefits associated with the adjunctive use of lasers and light photo-therapy has been proposed as a possible mechanism for both reducing risk and affecting patient morbidity [20].

Red to near infrared wavelengths of coherent laser light have the potential for optical penetration into tissues, up to 3 - 5 cm in depth [29,30]. Consequent to the selective absorption of the applied photonic energy by cellular organelles and sub structures, including the cell membrane, as well as cupric-ferrous containing protein clusters, low levels of LED and laser energy trigger a range of anti-inflammatory and pro-healing regulatory events. There are marked changes in cellular physiology which can result in the manufacture and release of extracellular signals including nitric oxide and tissue growth factors such as tissue growth factor B1(TGF-β1) and vascular endothelial growth factor (VEGF) [31,32]. Nitric oxide is a vasodilator which helps enhance the availability of the peripheral circulation as well as improve lymphatic drainage [33,34]. TGFβ1 is associated with an increase in the formation of secondary dentine and VEGF promotes the growth of new blood vessels at a wound site.

In addition, there are highly significant changes in gene transcription factors that positively affect the rate of mitosis as well as the manufacture of other matrix materials such as collagen and bone [35-37]. Furthermore, there is a major step difference in the manufacture of ATP resulting in a highly energized and more stress resilient cell in an aerobic cycle of metabolism.

The resultant effects of PBM are wide ranging from vasodilatation and analgesia, improved lymphatic drainage and angiogenesis, to the activation and inactivation of specific cytokines which are central to the inflammatory, healing and regeneration sequence associated with wound resolution. Exposure to the correct dose of low level of laser energy can have a profound anti-inflammatory effect due to the up regulation of specific antagonists to interleukin-1β and tissue necrosing factor- alpha (TNF-α). These are key pro-inflammatory cytokines which in turn stimulate the release of prostaglandin E2 (PGE_2) and modulate the transcription factors for nuclear factor кappa B which on exposure to PBM results in reduced osteoclast activation [38-40].

The downstream effects of PBM therapy include an increase in the numbers of osteoblasts and fibroblasts, a more active immune response to infection and the selective inhibition of PGE-2 production by cyclooxygenase-2 (COX-2) as well as the selective apoptosis of pro inflammatory cells [41].

Due to the potential for enhanced healing and reduced inflammation plus the ability to modulate the key cytokines involved in the destructive processes of periodontitis there are some clinical studies exploring the potential benefits of PBM in the management of periodontitis. Studies by Aykol., *et al.* and Qadri., *et al.* measured a statistically significant improvement in probing pocket depths, clinical attachment loss and gingival inflammation in test groups treated with the low level Diode laser at a dose in the range 2-5J/cm^2 [42,43]. *in vitro* and *in vivo* animal studies demonstrate that there are effects on the expression of interleukins viz. IL-1, IL-6, IL-8 and TNF-α, all of which are suppressed by PBM. In consequence, PBM could prove of value in promoting healing and reducing inflammation as well as alleviating post-operative pain. The clinical studies of Aykol and Qadri however show only a small improvement in clinical parameters and the adjunctive value of this interesting treatment strategy have yet to be proven.

The potential for lasers to modulate the cytokine cascade towards an anti-inflammatory pathway was the subject of an interesting paper by Pesevska., *et al.* in a human histology study. The outcome clearly demonstrated a marked reduction in TNF-α in human papillae biopsies post laser irradiation. TNF-α is a key cytokine involved in the destructive histopathological sequence that cumulates in bone loss [39].

Pesevska., *et al.* used 80 patients in a parallel study divided into four groups. The measured clinical parameters were taken by two calibrated blinded periodontists and the choice of subjects, for excisional papilla biopsy, were randomly assigned. The results demonstrated a highly statistically significant change in TNF-α in the laser test subjects. The test group given a series of ten daily Diode laser treatments achieved the optimum results. The positive outcome of the therapy is very promising; however, this is a short-term study. The researchers in this elegant study set out well defined boundaries with good scientific controls and a clear idea of the test subject. The laser parameters are presented in a well presented table and there is sufficient information to permit later researchers to either repeat the study or use the template for further investigations.

Turning this interesting study into something clinically applicable however takes some careful consideration. TNF-α forms in response to lipopolysaccharide (LPS) stimulating a cell mediated immune response to a bacterial challenge. If there is a failure to eliminate the bacterial challenge, then the intervention with the laser is bound to fail. There would in this event be at best a short-term effect, as more TNF-α is manufactured in response to a continued or recurrent bacterial challenge. To translate this reported adjunctive use of PBM therapy to a treatment protocol with a demonstrable long-term clinical gain has yet to be determined.

In a more recent study Pesevska used a similar model of human papilla biopsies employing genomic and proteomic analyses to investigate the effects of the application of low levels of near infrared (NIR) lasers to COX-2 activity. The outcome clearly demonstrated the suppression of COX-2 activation [41]. This outcome is further supported by *in vitro* studies that similarly describe the suppression by NIR exposure of the activation and production of other pro inflammatory markers including IL-1 and IL-6.

The expanded knowledge base on the physiology and biochemistry of the inflammatory cascade and its modulating factors have opened the possibility of additional clinical pathways to explore in the search for further effective tools to eliminate inflammation and the associated destructive sequence in the periodontium.

The potential benefits of photo medicine via laser biomodulation are presently one of the aspects of laser use which are attracting a high level of current interest within the dental laser community [44-46]. To date however, the merits of the periodontal use of lasers in this respect has been shown to be only of marginal and temporary clinical benefit. Perhaps in conjunction with stem cell research and the selective use of tissue growth factors, PBM is an area which may in the fullness of time evolve into a routine clinical measure.

Future Trends

Current efforts to incorporate photomedicine into periodontal care are attempts to capitalise on the existing evidence base that shows the potential for some improvements in clinical indices and a reduction in the histochemical markers associated with inflammation. Although there are many anecdotal clinical reports of positive clinical outcomes, the evidence base of this approach currently is weak and in need of further studies. In recognition of the proven potential for phototherapy in reducing inflammation, promoting healing as well as reducing pain and post-operative sensitivity the adjunctive incorporation of photomedicine into periodontology offers considerable merit. The challenge remains however of establishing agreed evidence based clinical protocols.

Notwithstanding the high quality and volume of *in vitro* and animal model research, PBM therapy in periodontology can only be viewed at present as indicative to the potential for human clinical gains pending suitable well designed blinded controlled clinical trials.

Conclusion

The extent of this discussion paper is to provide an introduction and overview to the discerning clinician and should promote the further evaluation through controlled well designed clinical trials of this potentially useful clinical modality.

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