

Photodynamic Therapy: Is It More Effective Than The Current Standard Of Care?

An evidence-based study of the literature

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Abstract

Mechanical debridement is currently considered as the first line of defense against periodontitis. Often we need to add antibiotics to the armamentarium to treat this disease. Technological advancements are not very uncommon in many fields including dentistry. Our project was based on the comparison of efficacy of a new product, Periowave™ which is based on the principle of photodynamics with the standard treatment of periodontitis.

A comprehensive computer-based search combined the following databases into one search: Pubmed, Google, Ovid and Cochrane. In addition, hand searches were done for several journals not cataloged in the databases, and the reference lists from published articles were checked. Since this is a fairly new device, our database search turned no published studies and our focus turned towards the principle of photodynamic therapy (PDT). We did a literature review again regarding PDT. All studies had to use some form of laser for treatment, there had to be a pre-established diagnosis of periodontitis, all studies had to be *invivo*, and all studies had to be randomized controlled. We had a total of 1363 articles but after excluding the articles that did not meet the criteria we had four papers left.

In conclusion there is a great need to develop an evidence-based approach for the use of lasers for the treatment of periodontitis. The literature review revealed that there is presently insufficient evidence to suggest that any specific wavelength of laser is superior to the traditional modalities of therapy.

KEY WORDS: *Periowave, Photodynamic therapy, and Laser in periodontitis / periodontology.*

A wide range of persistent human infections are due to microbial biofilms. Microorganisms grow in biofilms stuck to a solid surface where they multiply and form microcolonies embedded in extracellular polymeric matrix which includes water and nutrient channels. Periodontal diseases result from accumulation of subgingival bacterial biofilms on tooth surfaces. There is reduced susceptibility of these biofilms to antimicrobial agents (1).

The rapidly increasing emergence of antibiotic resistance amongst pathogenic bacteria may bring an end to the period extending for the last 50 years, called the antibiotic era. Bacteria replicate very rapidly and a mutation that helps the microbes survive in the presence of antibiotics will quickly become predominant throughout the microbial population (2).

Although mechanical removal of the periodontal pathogens is the current gold standard of treatment, antibiotics are also known to be effective. However, development of resistance in the target organisms is a problem associated with the use of such drugs. The use of photoactivatable compounds or photosensitizers (PS) to cause photodestruction of oral bacteria has been demonstrated, indicating that photodynamic therapy (PDT) could be a useful alternative to mechanical means as well as antibiotics in eliminating periopathogenic bacteria (1).

Light alone or in combination with chemical compounds has been used for a long time to induce a therapeutic effect. Psoralens and light were used in ancient India, China and Egypt for treatment of vitiligo and psoriasis (3). Moreover PDT is a treatment modality for cancer and other diseases (2). Its use as a

therapeutic approach is based on previous studies where a specific non-toxic dye PS accumulates preferentially in targeted tissues or organisms. PDT involves delivering visible light of appropriate wavelength to excite PS molecule to excited singlet state. This excited state then may undergo intersystem crossing to the slightly lower energy, but longer lived, triplet state, which may then react further by one of the two pathways known as type I and type II photoprocesses, both of which require oxygen. Type I pathway

involves electron-transfer from the PS triplet state with the participation of a substrate to produce radical ions that can then react with oxygen to produce cytotoxic species (superoxide, lipid-derived radicals). Type II pathway involves energy transfer from the PS triplet state to ground-state molecular oxygen (triplet) to produce excited-state singlet oxygen, which can oxidize many biological molecules such as proteins, nucleic acid and lipids, and can lead to cytotoxicity (2).

Methods

A systematic search was conducted to find articles pertaining to the research question.

Search Strategy

The following keywords and phrases were used for the search: Periowave™, Photodynamic therapy, and Laser in periodontitis / periodontology. Four databases were used to locate relevant articles namely, PubMed (1966-2006), Ovid/Medline (1996-2006), Cochrane (1995-2006) and Google Search which yielded 309, 0, 14 and 1,040 articles respectively. In addition to the electronic databases, textbooks in Periodontology, Journal of Periodontics and expert opinion of a Periodontologist was consulted.

Measures used to determine relevance of material

Our inclusion criteria involved studies that used some form of laser for treatment, a pre-established diagnosis of periodontitis, *invivo* studies, all studies had to be randomized controlled trials, and in English. We had a total of 1363 articles and only those articles relevant to our inclusion criteria were selected

(Table 1). A total of 32 articles remained which were analyzed and an additional 25 articles were eliminated at the abstract stage based on the previously mentioned criteria. The seven articles that remained were reviewed and subjected to a Checklist to Assess Evidence of Efficacy of Therapy or Prevention (Table 2). Discussion among the authors was carried out to critically appraise the remaining 7 articles and four articles were unanimously accepted. Most of the articles scored at least $\geq 11/19$ on the checklist. Furthermore, the articles were graded according to the Canadian Task Force (CTF) For Preventive Health Care (Tables 3a & 3b).

Table 1

Review of evidence	
Abstracts matching the title in Pubmed (1996-2006)	309
Abstracts matching the title in Ovid/medline (1996-2006)	0
Abstracts matching the title in Cochrane (1995-2006)	14
Abstracts matching the title in Google	1040
Articles rejected based on title	1331
Articles rejected based on abstract review	25
Articles rejected based on full text review	3
Total Remaining	4

Table 2. Checklist to Assess Evidence of Efficacy of Therapy

1. <u>Was the study ethical?</u>
2. <u>Was a strong design used to assess efficacy?</u>
3. <u>Were outcomes (benefits and harms) validly and reliably measured?</u>
4. <u>Were interventions validly and reliably measured?</u>
5. <u>What were the results?</u> <ul style="list-style-type: none"> • Was the treatment effect large enough to be clinically important? • Was the estimate of the treatment effect beyond chance and relatively precise? • If the findings were “no difference” was the power of the study 80% or better?
6. <u>Are the results of the study valid?</u> <ul style="list-style-type: none"> • Was the assignment of patients to treatments randomized? <ul style="list-style-type: none"> • Were all patients who entered the trial properly accounted for and attributed to its conclusion? <ul style="list-style-type: none"> i) Was loss to follow-up less than 20% and balanced between test and controls? ii) Were patients analyzed in the groups to which they were randomized? <ul style="list-style-type: none"> • Was the study of sufficient duration? • Were patients, health workers, and study personnel “blind” to treatment? • Were the groups similar at the start of the trial? <ul style="list-style-type: none"> • Aside from the experimental intervention, were the groups treated equally? • Was care received outside the study identified and controlled for?
7. <u>Will the results help in caring for your patients?</u> <ul style="list-style-type: none"> • Were all clinically important outcomes considered? • Are the likely benefits of treatment worth the potential harms and costs?

Table 3a. Grades of Recommendations

A	The CTF concludes that there is good evidence to recommend the clinical preventive action.
B	The CTF concludes that there is fair evidence to recommend the clinical preventive action.
C	The CTF concludes that there is conflicting evidence neither recommending nor favoring the clinical preventive action.
D	The CTF concludes that there is fair evidence to recommend against the clinical preventive action.
E	The CTF concludes that there is good evidence to recommend against the clinical preventive action.
I	The CTF concludes that there is insufficient evidence to make a recommendation.

Table 3b. Quality of Published Evidence

I	Evidence from at least 1 properly randomized controlled trial (RCT).
II-1	Evidence from well-designed controlled trials without randomization.
II-2	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
II-3	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Results

There were 4 published clinical trials matching the inclusion criteria using laser for treatment of periodontitis. When viewed as a collective body of

evidence they provide conflicting results. In the study done by Qadri et al (4), 17 patients in the age group of 35-70 for 6 weeks were studied. The results showed a difference in probing depth

(PD), gingival index (GI) and plaque index (PI) of test and control groups which favored adjunctive use of the laser with scaling and root planing (SRP) versus SRP alone. Two other studies done by Yilmaz et al and Ambrosini et al (5,6) reported no difference in PD, bleeding on probing (BOP) and clinical

attachment loss (CAL) of test and control groups. Moritz et al (7) suggested that use of laser as an adjunct to SRP can decrease BOP and PD and bacterial count, however there was an evidence of an increase in Actinomyces Actinomycetemcomitans (AA) count in some patients.

Table 4

RESULTS (RCT Studies)

Author/ Year of Study	Population (Age, Sex, Location)	Intervention or Test treatment (number studied)	Control Treatment (number studied)	Outcome	Critical Appraisal Comments/Strength of Study/Conclusions
Ambrosini et al- 2005, 3 months	30 pts, 20-60 yr old (sex not specified), France	SRP+PDT (30 pts)	SRP (30 pts)	No significant difference b/w treatment groups. P>0.05	RCT, single blind, split mouth. This study scored 11 on the checklist and level of evidence is I-E.
Qadri et al- 2005, 6wks	17 pts, 35-70yrs, 10 women, Sweden	SRP+PDT	SRP	Differences in PD, GI & PI but no difference in subgingival microbata, decrease in GCF(p=0.01) P<0.001	RCT, double blind, split mouth. This study scored 15 on the checklist and level of evidence is I-A.
Moritz et al- 1998, 6 months	50 pts (age & sex not specified), Austria	SRP+PDT (37 pts)	SRP+H2O2 rinses	Differences in PD, BOP, overall reduction in bacterial count but increase in AA in some pts.	RCT. This study scored 12.5 on checklist and level of evidence is I-B.
Yilmaz et al- 2002 , 32 days	10 pts (age of pts not specified), Turkey	SRP, SRP+PDT, PDT, OHI	OHI, SRP	SRP and SRP+PDT showed similar findings, while the effects of SRP alone were similar to OHI	RCT, split mouth. This study scored 11 on checklist and level of evidence is I-C.

Discussion

Systemic antibiotics have been used as an adjunct to scaling and root planing but there are quite a few disadvantages. First, systemic administration can cause adverse effects such as GIT disturbances and allergic reactions. Second, some antibiotics are taken up by mineralized tissues. Third, patient compliance can be a factor in the ineffectiveness of the therapeutic regimen. Finally, the development of resistant organisms is probably the most serious concern of all

(8). PDT on the other hand does not have any of the aforementioned drawbacks.

Photodynamics involves the application of a dye to the treatment area (the dye is referred to as a photosensitizer because the dye after absorbing the light sensitizes the organisms to visible light inducing damage) then light is applied to the dye which results in the production of free oxygen radicals. These oxygen radicals

are cytotoxic and destroy cellular constituents.

Periowave™ is a photodynamic disinfection system developed by Ondine Biopharma Corporation that utilizes low intensity lasers and wavelength-specific, light-activated compounds to specifically target and destroy microbial pathogens and reduce the symptoms of disease (10). The photosensitive compounds are topically applied in the gingival sulcus and the laser is used to activate the compounds and complete the disinfection.

In November 17, 2005 the first regulatory approval for photodynamic disinfection therapy from Health Canada was announced (9). Also it received company-wide ISO-13485 certification of quality management standard for medical device companies. Based on the evidence to date, treatment of periodontal diseases using PDT of any type is still considered experimental.

Health Canada's approval of Periowave™ has been deemed by the manufacturing company as a "significant milestone in paving the way for near term revenue generation and longer term growth (10)." The fact that Health Canada granted a medical license for Periowave™ for its clinical use and importation of the device in the country may imply positively to its efficacy. Health Canada's Medical Licensing Division is responsible for the grant of licensure to products intended for medical and dental use. "Medical devices are classified into one of Classes I to IV by means of the classification rules set out in Schedule 1, where Class I represents the lowest risk and Class IV represents the highest risk." (11). According to the criteria set forth in Schedule 1, Periowave™ is classified as a Class II medical device. Under the

Medical Devices Regulations, manufacturers of Class II devices are not required to submit review information.

Instead, they must attest that they have evidence to support the safety and effectiveness requirements of the Regulations which are the following (11):

- (a) a description of the medical conditions, purposes and uses for which the device is manufactured, sold or represented;
- (b) a list of the standards complied with in the manufacture of the device to satisfy the safety and effectiveness requirements;
- (c) an attestation by a senior official of the manufacturer that the manufacturer has objective evidence to establish that the device meets the safety and effectiveness requirements;
- (d) an attestation by a senior official of the manufacturer that the device label meets the applicable labeling requirements of these Regulations;
- (e) in the case of a near patient in vitro diagnostic device, an attestation by a senior official of the manufacturer that investigational testing has been conducted on the device using human subjects representative of the intended users and under conditions similar to the conditions of use; and
- (f) a copy of a quality system certificate certifying that the quality system under which the device is manufactured satisfies National Standard of Canada CAN/CSA-ISO 13488-98, Quality systems -- Medical devices -- Particular

requirements for the application of ISO 9002, as amended from time to time.

It is clear upon reviewing the above conditions that no third-party review is required to be submitted for the granting of licensure but merely an attestation by a senior official of the manufacturer that the device meets the eleven safety and effectiveness requirements laid out in sections 10 to 20. The mere fact that Periowave™ has been approved by Health Canada does not mean much in the perspective of efficacy. Efficacy has to be judged by means of an independent, unbiased, and scientifically proven method such as a double blind randomized control trial. At this moment in time as there are no published studies involving Periowave™ it is quite early to claim against or in the favor of the efficacy of Periowave™. However, the principle of photodynamics is biologically plausible and the numerous studies done on the principle of photodynamics do show that it might have a certain place as a part of an armamentarium to combat periodontal diseases, especially chronic periodontitis.

Conclusion

Based on these articles one must conclude that there is a great need to develop an evidence-based approach to the use of lasers for the treatment of periodontitis. It would be prudent to say that there is insufficient evidence to suggest that PDT is superior to the traditional modalities of periodontal therapy. On a technology assessment table PDT/Periowave™ will be clearly identified as a more costly treatment but with a questionable efficacy (Table 5). Everything new is not always better so

an astute clinician should critically appraise all the literature before making a dramatic change from the current standard of treatment.

Table 5

Technology Assessment Table (Periowave™)			
Comparative Outcomes With New Maneuver			
Relative Cost of New Maneuver	Better	Same	Worse
	Less		
	Same		
	More	???	???

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Regulation current to February 21, 2006.