Managing Peri-Implantitis and Peri-Mucositis with Direct Medication Delivery

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Abstract

Background: Periodontal disease and peri-implantitis/perimucositis are a host inflammatory response to the biofilm in the gingival sulcus or periodontal pocket. Some patients with a propensity for gum disease may not respond to mechanical treatments like scaling / root planing and surgery as the treatments leave the bacteria that caused the disease in the gingival tissue, on the surface of the roots of the tooth or implant. Mechanical treatments may foster biofilm regeneration, introduce the bacteria, toxins and host inflammatory products into the systemic circulation resulting in an increased incidence of bacteremia. This three part study demonstrates effective biofilm control using a direct medication delivery method by three different practitioners for three different patients.

Method: Direct medication delivery uses hydrogen peroxide gel (Perio Gel) and a sub-clinical dose of doxycycline (Vibramycin, Pfizer) delivered subgingival and interproximal using custom formed medical devices (Perio Tray [Perio Protect LLC St. Louis, MO.]) Hydrogen peroxide forms oxygen that approaches hyperbaric oxygen when generated within the Perio Tray. The method was used in accordance with the patient’s conditions and the treatments were modified as healing occurred. Direct medication was used first to control the biofilm and debride the wound and mechanical means to remove biofilm deposits were used where needed. Three cases are presented to demonstrate efficacy, bacterial changes and clinical and radiographic improvements with treatment.

Results: Use of direct medication delivery demonstrated a resolution of peri-implantitis/mucositis and periodontal disease with decreased pocket probing depth and bleeding upon probing. A pre-treatment salivary DNA analysis showed a pathogenic biofilm constituency compared to a post-treatment salivary analysis showing a less virulent population. Implants with bone loss were shown to increase threads coverage with direct medication delivery. Pathogen specific DNA analysis before, during and after treatment demonstrated a significant decrease in the virulence and the number of bacteria demonstrating an ability to modify the cause of disease and managing the cause over time.

Conclusion: Direct medication delivery of hydrogen peroxide gel and doxycycline using custom formed medical devices were effective in treating periodontal disease, peri-implantitis and perimucositis. Direct medication delivery demonstrated a significant modification in the biofilm by decreasing number and virulence of bacteria, improved tissue responses and decreased pocket probing depth and bleeding upon probing. An implant that suffered bone loss was treated by direct medication delivery and the bone loss was reversed as exposed implant threads were recovered by new bone.

Keywords: Biofilm, Peri-implantitis / Perimucositis, Direct Medication delivery, Perio Protect Method, Perio tray, Perio gel, Bone Reformation
Introduction

Treatment of periodontal disease is important as the World Health Organization Report of 2003 and 2006 shows between 85 to 90% of people world-wide have some form of periodontal disease1. The American Academy of Periodontology, when citing a Center for Disease Control study, state that almost 50% of Americans have moderate to severe periodontal disease which increases with age2. The bacteria responsible for periodontal disease are part of the cause of peri-implantitis and perimucositis3, and effectively treating the cause of periodontal disease, peri-implantitis and perimucositis is important4. These same bacteria are also related to systemic disease, such as cardiovascular disease5, pregnancy complications6, arthritis7, Alzheimer’s disease8 and other systemic inflammatory dysfunctions9. The biofilm control for peri-implant disease has emerged as an ever increasing problem as the number of implants to replace missing teeth has increased and the prevalence of mucositis was evident in 80% of the subjects and in 50% of the implants10. These same authors reported peri-implantitis existed in 28% to 56% of the patients involving 12% to 48% of the implants11.

Successful biofilm control for periodontal disease and perimucositis / peri-implantitis disease must coincide with guidelines for similar chronic inflammatory wounds. Wound Care Guidelines by the Wound Healing Society12 delineate specific steps for the medical community in wound management. The steps include; diagnosis, infection control, wound bed preparation, wound care management, long-term management and prevention. These same steps in medical treatment are applied for both acute and chronic wounds in dental treatments with direct medication delivery when used for periodontal disease, peri-implantitis and perimucositis.

Wounds are usually classified as either acute or chronic. Acute wounds which are predominantly caused by planktonic bacteria can be treated with antibiotics. Antibiotics are less effective against chronic wounds. Most chronic wounds like periodontal disease are caused by micro-organisms that live in a biofilm and the nature of the biofilm makes it more difficult to manage when compared to planktonic bacteria13. Antimicrobial wound management involving biofilm control requires the ability of the medication to penetrate the biofilm matrix with sufficient effectiveness to modify the microenvironment in order to alter the biofilm. The biofilm is seldom completely eradicated during treatment and the biofilm continues to regrow, resulting in a need for medication re-application14.

Medical wound care guidelines for biofilm infections recommend the use of topically applied antimicrobials in place of antibiotics prior to wound debridement15. Hydrogen peroxide gel is an antimicrobial wound debridement agent that follows medical guidelines in chronic wound management as it begins the infection control and debridement when delivered with a direct medication method. The ability to reapply the medication through direct medication delivery is an infection control mechanism that can be part of treatment as well as long-term wound management. Long term care involves using directed medications on a prescribed basis guided to the cause of the infection as part of a prevention technique.

The biofilm invasion and persistence in the gingival tissue results in a chronic inflammation related to host risk factors as components of pathogenicity16. Treating the subgingival biofilm reduces host responses in both periodontal disease17 and implant infections18. Comparison of host responses involved evaluating bacteria associated with peri-implantitis compared with periodontitis pathogens. The biofilm in peri-implantitis was more complex than periodontitis as the primary bacteria were Gram-negative obligate anaerobes, but peri-implantitis demonstrated a differing prevalence to periodontitis19. Other researchers found higher levels of periodontal pathogenic bacteria comparing peri-implantitis patients with healthy stable implants20. These pathogens colonize the sub-gingival crevice soon after implant placement21,22, as the biofilm community becomes organized resulting in inflammation of the supporting bone and related tissue injury.

Current methods of treatment and prevention involve individual oral hygiene instructions and professional mechanical plaque (biofilm) removal along with behavioral interventions to decrease risk factors and augment periodontal prevention23. Problems are reported for methods using mechanical removal of plaque and biofilm components24. Mechanical treatments show a significant decrease in the initial number of biofilm members, but biofilms regrow to exceed pre-treatment levels within 2 to 7 days on natural and denture teeth25,26.

Complications exist for other treatments focusing on the control of infection on implants involve the detoxification of the implant surface and regeneration of the alveolar bone as a means to control the disease and host response27. Surgical treatment of peri-implantitis at six months showed most sites continued to have bleeding on probing and/or suppuration, leading the authors to recommend better long-term maintenance options28. Bacteremia occurs with mechanical interventions such as scaling and root planing and/or surgery through an increased incidence of bacteria, bacterial toxins or host inflammatory products becoming systemically dispersed 30,31. Systemic as well as local inflammatory problems exist with mechanical biofilm removal.

Mechanical intervention such as scaling and root planing (S&RP) leaves the same biofilm agents in the subgingival region following treatment that were there prior to S&RP29. It is only a matter of time before the bacteria regenerate as investigations have shown that mechanical debridement causes a three to four fold increase in biofilm reproduction30. Any increase in biofilm regeneration is detrimental to wound healing31. Homecare may not be able to reach subgingival biofilms around many implants32 and homecare can be a contributing factor to bacteremia33. The remaining bacteria regrow and research has shown the subgingival biofilm recolonization is extremely diverse34.

In attempting to manage the biofilm regeneration, adjunctive
peri-implant therapies, such as antibiotics, antisepsics, and ultrasonic and laser treatments, have been proposed to improve the treatment options of peri-implant mucositis and peri-implantitis. However, evidence suggests these methods may not be sufficient and results may be similar to conventional debridement\textsuperscript{38,39,40,41}. Comparing results of open flap debridement of peri-implantitis with and without adjunctive systemic antibiotics demonstrated there was no significant difference in benefits with using the antibiotics\textsuperscript{42}. The criteria for success in this study was also pocket probing depths of $<5\text{mm}$ which provides an environment where facultative and obligate anaerobes may become the predominant species\textsuperscript{43,44}. Reports of sub-mucosal debridement accomplished by utilizing either an ultrasonic device or carbon fiber curettes demonstrate these are not sufficient for the decontamination of the surfaces of implants with peri-implant pockets $\geq5\text{mm}$ and exposed implant threads\textsuperscript{45}. Application of topical antiseptics like $2\%$ Chlorhexidine has resulted in changes in the topical biofilm\textsuperscript{46} and Chlorhexidine may adversely affect the host inflammatory response. Chlorhexidine causes an increase in inflammatory chemokines and cytokines and inhibit gingival fibroblast activity\textsuperscript{37}. Chlorhexidine increases poor cellular morphology, increases the reactive oxygen species per unit area and greatly diminishes the number and vitality of osteoblasts in a concentration-dependent manner\textsuperscript{48}.

Research on the use of lasers shows the efficacy of Er: YAG laser appeared to be limited to a 6-month period and the treatment with Er:YAG laser may not be adequate for stable long-term therapeutic measures\textsuperscript{38}. Research of conventional nonsurgical therapy even with the use of adjunctive systemic and local antibiotic are minimally effective and surgical intervention failed to demonstrate re-osseous integration\textsuperscript{50}. Conventional treatments are not able to manage the biofilm cause of peri-implants in correction of defects around implants\textsuperscript{51}.

In light of these problems in treating periodontal disease, peri-implantitis and perimucositis infections, a direct medication delivery system (Perio Protect Method, St. Louis, MO) was used to evaluate the management of the causative agents and host responses around implants. The direct medication delivery system (Perio Protect Method) uses custom formed medical devices (Perio Tray) to deliver hydrogen peroxide gel (1.7\%) [Perio Gel], with or without doxycycline, to modify the micro-environment of the gingival sulcus and tissues around teeth resulting in decreased tissue inflammation, decreased pocket depth and diminished bleeding upon probing\textsuperscript{52}. Prior studies on natural teeth using medications delivered by this subgingival deliver method increased the oxygen saturation to 5.7 X which is comparable to hyperbaric oxygen and the medicaments are delivered up to 9mm subgingival and were maintained for over 15 minutes\textsuperscript{53}.

Research using a live/dead dye demonstrated that virtually 100\% of the surface biofilm bacteria were eradicated in 15 minutes. Other studies of this method demonstrated 98\% to 100\% of the biofilm micro-organisms were eradicated by using the hydrogen peroxide gel when applied and subsequently reapplied directly to the biofilm\textsuperscript{34}. The delivery, maintenance and ability to reapply medications enable better control of the etiology of infection.

The direct medicine delivery device (Perio Tray) through the formation of oxygen under pressure (hyperbaric oxygen) facilitates wound healing through a number of positive healing processes such as angiogenesis, fibroblast proliferation, leukocyte oxidative killing, toxin inhibition and antibiotic synergy\textsuperscript{55}. Hyperbaric oxygen increases fibroblastic proliferation and leads to increased neo-vascularization\textsuperscript{56}. Hyperbaric oxygen reverses vasoconstrictive hypoxia and reduces tissue edema and tissue swelling\textsuperscript{57}. Oxygen is vital for hydroxylation of lysine and proline as part of collagen synthesis for improved cross linking thus increasing the collagen strength required for strong wound healing\textsuperscript{58}. Wound healing with hyperbaric oxygen has demonstrated significant healing rates in 87\% of patients when dealing with non-traumatic wounds\textsuperscript{59} and hyperbaric oxygen is an instrumental aspect of non-healing wound care with the medical profession\textsuperscript{60,61}.

Delivery of hydrogen peroxide and doxycycline has been shown to inhibit osteoclasts through hyperbaric oxygen generation and doxycycline augments osteoblastic activity\textsuperscript{62}. This helps explain how direct medication delivery of hyperbaric oxygen and doxycycline to the periodontal pocket has resulted in decreased bone loss and increased bone apposition around natural teeth\textsuperscript{44}. Direct medication delivery was demonstrated to control the biofilm responsible for causing periodontal disease\textsuperscript{63}, helped to manage the biofilm\textsuperscript{64} and resulted in improved patient conditions\textsuperscript{65}. These den- tition based studies found changes from a community of predominant virulent microorganisms to a post-treatment community of a less virulent population and the number of bacteria decreased by a - log 2-4. Since there is a correlation between the etiology of periodontal disease and peri-implantitis / perimucositis, the method that was effective around natural teeth is used in this study to evaluate efficacy around implants.

**Method and Protocol:**

Direct medication delivery (Perio Protect Method) delivers hydrogen peroxide (Perio Gel 1.7\%) used in combination with doxycycline into the gingival sulcus or periodontal pocket and the frequency of treatment is determined by the patient’s conditions (pocket probing depth and bleeding indices). The severity of the patient’s disease at the onset of treatment determines the initial frequency of treatment. The direct medication delivery method advocates wearing the trays for 15 minutes 1-4 times / day so the medications (hydrogen peroxide, hyperbaric oxygen and Vibramycin [doxycycline [Pfizer] 50 mg/5ml]) can control or modify the biofilm etiology of disease. The treatment progress is determined by the patient pocket probing depth changes and changes in the bleeding indices as treatments are modified in accordance with improvements in the pocket probing depths and bleeding indices (Figure 1).
Direct medication delivery protocol

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;7</td>
<td>4 times / day @ 15 minutes</td>
<td></td>
</tr>
<tr>
<td>3-6</td>
<td>3 times / day @ 15 minutes</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>2 times / day @ 15 minutes</td>
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<tr>
<td>Maintenance</td>
<td>1-2 times / day @ 15 minutes</td>
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<tr>
<td>Patients with severe conditions (6mm or &gt;) = 2 / day</td>
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<td>Patients with 5mm or less = 1 / day</td>
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**Figure 1** The time and frequency of treatments with direct medication delivery are determined by the patient's conditions. The patient's initial pocket probing depths are recorded and the most severe conditions determine the frequency of treatment in accordance with the guidelines provided. The treatments are modified as healing occurs and patient's conditions improve. Long-term maintenance is advocated in accordance with the initial patient conditions to prevent reoccurrence of the disease and improved host response.

The Perio Tray serve to increase the oxygen saturation within the tray to 5.7 X atmospheres. The formation of oxygen under pressure (hyperbaric oxygen) facilitates wound healing through angiogenesis, fibroblast proliferation, leukocyte oxidative killing, toxin inhibition and antibiotic synergy. Hyperbaric oxygen increases neovascularization, reverses vasoconstrictive hypoxia and reduces tissue edema and tissue swelling and oxygen increases the collagen strength required for strong wound healing. Use of the Perio Tray prior to mechanical intervention facilitates biofilm management through decreasing the number and virulence of the bacteria decreasing the probability of bacteremia.

The action of hydrogen peroxide modifies the calculus, facilitating removal. Adjunctive treatments are part of the direct medication delivery method that may include scaling and root planing to remove subgingival calculus and tarter and laser or conventional surgery where conditions warrant, such as granulomatous tissue. The trays may be worn prior to invasive therapy to control the biofilm before mechanical interventions cause a local inflammatory response or systemic bacteremia. The trays are worn as part of the long-term maintenance after active treatment to provide a micro-environment that controls the pathogens, decreases reoccurrence and augments tissue recovery.

Three cases are used to illustrate the treatment efficacy, biofilm modifications, radiographic and tissue improvements. The first patient with advanced periodontal disease received conventional treatments. The doctor used treatments included scaling and root planing, antibiotic therapy, topical antiseptic rinses, laser and conventional surgery in an attempt to control the infection. The treatments were unsuccessful and three teeth in the patient's upper right quadrant were extracted and replaced with implants in 2007. Routine maintenance and homecare were implemented to assist the patient in controlling the oral conditions. By 2014 there were 4 to 7mm pockets around the implants with bleeding upon probing and moderate subgingival calculus. Conventional treatments including surgery were discussed, but the patient wanted to avoid more surgery, so other options were proposed. The patient chose to use the Perio Protect Method through direct medication delivery using prescription trays (Perio Tray). Impressions were completed and the custom medical devices were fabricated and treatments were implemented in accordance with the Perio Protect Protocol. (Figure 2)
Figure 2: The patient’s periodontal probing in 2014 followed conventional treatments including surgery are indicative of periodontal disease that is unabated by conventional periodontal specialty treatments. The recordings around the implants for teeth 2, 3 and 4 as well as the other greater than normal probing depths and bleeding around the teeth are evidence of an ongoing infection and this damage determines the frequency and duration of treatment with the Perio Protect Method. The initial treatment was four times a day for 15 minutes with just hydrogen peroxide (Perio Gel) 1.7%.

A salivary diagnostic test was completed (figure 3) prior to treatment to evaluate the bacteria present in the subgingival area. The DNA saliva analysis showed a presence of bacterial biofilm associated with advancing periodontal disease. This analysis was used to compare results with a post-treatment analysis to determine treatment efficacy. Perio Trays were placed in August 2014 in accordance with the pocket probing depth and the bleeding index. The tray usage was four times per day spread over the course of the day for a time of 15 minutes per application.

Figure 3: An analysis of the bacteria present in the patient’s saliva in 2014 was determined using the MyPerio Path® Test – Oral DNA labs. This system uses a salivary sample to help determine the presence or absence of 11 oral bacteria which are often associated with periodontal and systemic diseases. This sampling found 8 of the 11 bacteria were present and 7 of the 8 were found at concentrations that generally involved an increased risk for periodontal disease and bone loss.

The initial frequency of Perio Tray usage in August 2014 was 4 times a day as determined by the patient’s initial pocket probing depths. After a few weeks additional treatments also included four rounds of periodontal debridement, laser therapy and subgingival irrigations between September and November 2014. A re-evaluation visit on December 2014 (figure 4) demonstrated a significant decrease in bleeding upon probing and the pocket probing depths decreased where the deepest pocket measured 5mm. This patient continued to use the direct medication delivery system as a part of the Perio Protect maintenance regimen.

Figure 4: The pocket probing of 2015 followed the patient using the Perio Protect Method 4 times a day with four quadrants of scaling and root planing. Pocket depths decreased, demonstrating a change in both the pocket probing depth and the bleeding upon probing in response to the direct medication delivery. The frequency of usage was modified as healing occurred. The treatments were reduced to three times a day and finally twice a day. The patient then used the direct medication delivery method as a part of the long-term homecare and maintenance program to prevent reoccurrence.
Use of a direct medication delivery method (Perio Protect Method) showed significant improvements and disease management. Figure 5 shows an initial DNA analysis (Oral DNA) of bacteria present before direct medication delivery and after direct medication delivery. The bacteria comprising the predominant species before treatment are not the same bacteria found after direct medication delivery. Eight of the eleven bacterial species present before treatment were not discovered post-treatment. Three bacterial species remained, but only one of these was found at a clinically sufficient concentration. These changes demonstrate a change in the species present before and after treatment and also demonstrate a reduction in the number of bacteria related to the direct medication delivery. Use of the direct medication method prior to mechanical or invasive techniques may decrease the possibility of bacteremia from the mechanical treatments as fewer bacteria are evident.

The salivary DNA analysis demonstrated a significant change in the biofilm constituency. The change in the bacteria relate to the host improvements as pocket probing depth and bleeding upon probing decrease. Figure 6 demonstrates the before and after pocket probing depth and bleeding indices around the maxillary teeth and implants before and after direct medication usage as the cause of disease/infection is managed. The frequency of treatments is modified as the patient’s conditions improve until the direct medication delivery is part of the long-term maintenance program.

The second case evaluates radiographs taken at the time of implant placement, after the development of peri-implantitis and after treatments with direct medication delivery. The implant was placed in 2007 (figure 7). The implant placement was done without problems and tissues at this time were normal without any sign of infection. The top of the implant was positioned even with the alveolar crest so all of the threads of the implant engaged alveolar bone.

**Figure 7:** The post-implant placement radiograph demonstrated the conditions at the time the implant was placed. The implant and healing cap were placed so all of the implant threads engaged bone. All of the implant threads were surrounded by bone in this slide taken August 2007.

The healing cap was removed and the analog and crown were place in February 2008. The patient returned for a re-evaluation appointment due to swelling, bleeding and pain around the implant by April 2009. During the clinical examination a purulent exudate was discovered and a diagnosis of peri-implantitis was determined. Systemic antibiotics were administered as well as several office visits for mechanical debridement, laser surgery and local irrigation to cleanse the area around the implant. The tissues remained infected, tender and swollen and the bone support around the implant became compromised as four threads were exposed above the alveolar crest. (figure 8).

**Figure 8:** In April 2009 the patient was aware of an infection with swelling and pain and clinically there was a periodontal pocket and bleeding upon probing. During the clinical examination a purulent exudate was discovered. Systemic antibiotics were administered as well as several office visits to irrigate and cleanse the area around the implant. Mechanical treatments and laser therapy were used, but the infection and defect remained. The implant was now compromised by April 2009 as four threads of the implant are exposed.

Perio Trays were delivered June 16, 2009. The patient’s tissue conditions began to improve within a few days. There was no longer a purulent exudate and the pocket depth decreased as did the bleeding upon probing. After the treatment phase, the patient used the direct medication delivery as part of the long-term maintenance program using Perio Gel (1.7% hydrogen peroxide gel) and local delivery of Vibramycin syrup. The Vibramycin was placed in the Perio Tray and worn for the prescribed treatment time as per the doctor’s instructions.

Subsequent radiographs taken in May of 2012 (figure 9) indicate reformed bone where two of the four threads were covered by new bone and two of the four threads remain above the alveolar crest. This indicates there is a decreased bone loss and an augmentation of bone regeneration. Clinical evaluation in July 2013 demonstrated there was no peri-implantitis or perimucositis as the implant was stable for four years as the patient maintains the health of the tissue with direct medication delivery.
The direct medication delivery method is able to modify the biofilm components as determined by changes in the type and number of bacteria present in the biofilm. The third example involves pre-treatment DNA analysis before implant placement, following implant placement and following restoration of the implant. The initial DNA analysis was completed for tooth #14 prior to removal and replacement with an implant. Figure 10 shows the type and frequency of bacteria through a DNA analysis that were gathered by negative pressure around tooth #14. The DNA analysis showed the biofilm composition prior to treatment for any bacteria present at least 2% of the total number as well as the total number of bacteria per area of the samples (1.18 X 105).

Figure 10: The sample of the biofilm was collected with a negative pressure method from the sulcus around tooth #14. The tooth had internal resorption and was treated by direct medication delivery after bacterial DNA analysis and prior to tooth removal. Following tooth removal and prior to implant placement the sulcus and alveolar bone were allowed to heal for 6 months as the patient continued to wear the Perio Tray once a day. The implant was placed subgingival along with a sinus lift surgery which remained covered for another six months as the patient used the Perio Protect Method once a day. The bacteria present are those that comprise 2% of the population or more. The total number of the bacteria is 1.18 X 105 prior to direct medication delivery.

A custom formed tray was fabricated in accordance with the patient’s conditions and the wearing sequence was modified as healing occurred. The initial treatment was twice a day for 15 minutes. The medical device was used to control the biofilm prior to implant placement. The tooth was removed and the patient continued to wear a Perio Tray once a day during the healing process. After 6 months the implant was placed subgingival and remained in place for 6 months as the patient continued wearing the Perio Tray once a day. A healing cap was placed on the implant for three months. The Perio Tray was modified during these times for the implant and healing cap. After the placement of the healing cap the maxillary Perio Tray was worn using both Vibramycin and the Perio Gel (hydrogen peroxide 1.7%). Subsequent DNA cultures were taken by the negative pressure method as described (Keller and Buechel). There was a dramatic decrease in both the number and characteristics of the biofilm from the pre-treatment analysis. Figure 11 demonstrates there were not enough bacteria present in any of the three samples to register any bacteria. This demonstrates a significant reduction in both the type and the number of bacteria around the implant and healing cap following direct medication delivery.
Figure 11: DNA cultures were collected and submitted three times to determine the scope and magnitude of the biofilm around the implant and healing cap. All three cultures had insufficient bacteria for an adequate DNA analysis demonstrating a change in the biofilm. These results demonstrate a negative (-) log4-5 reduction in the number of bacteria around the implant following the direct medication delivery of hydrogen peroxide and Vibramycin to this region. There was an insufficient biofilm to determine predominant species.

An analog and crown were placed over the implant. A new Perio Tray was fabricated for the changed oral conditions. The seal around the implant directed the medications subgingival and interproximal and a culture was taken at two months for DNA bacterial analysis around the crown and implant. The numbers of bacteria around the implant were evaluated and there was a log 1-3 number of bacteria comprising the biofilm. This equates to an overall reduction from the initial culture of a –log 2-4 change in the number of bacteria. The predominant species before treatment was not the same predominant species found after treatment.

Figure 12: Following the placement of the analog and crown, the biofilm was re-evaluated and found at a log 101-3 order. The overall reduction in the number of bacteria was a - log -2-4 and the predominant species before treatment was not the same as the predominant species after treatment.

Results:
Direct medication delivery reduced pocket probing depths and bleeding upon probing around implants. Salivary analysis of the biofilm following direct medication delivery demonstrated a significant alteration in both the type and the number of bacteria in the biofilm. Radiographic evidence of peri-implantitis bone loss was first halted and then reversed with direct medication delivery of hydrogen peroxide and doxycycline as new bone was evident as threads once exposed were re-supported by newly formed bone. Tissue conditions appear to improve as the biofilm population is modified. Bacterial DNA analysis showed the type and number of bacteria are changed during direct medication treatment. The predominant species before therapy was not the same as the post-treatment predominant species. The sample present before treatment is more numerous and appears to be more virulent than the decreased number and type of post treatment species. This change in the biofilm appears to relate to the improved patient conditions of decreased pocket probing depth and bleeding upon probing. The only adverse side effect was the teeth were whitened by the hydrogen peroxide.

Conclusion:
Direct medication delivery guides medications to the source of periodontal disease, peri-implantitis and perimucositis. The medications cause a change in the subgingival biofilm. A DNA analysis of the biofilm demonstrated a significant population of bacteria prior to prescription tray usage (1.18 X 105). Following treatment with direct medication delivery there was a net reduction of a –log 2-4 in the number of bacteria. The before treatment predominant species was not the same as the after treatment species. Direct medication delivery results in reducing the presence of virulent bacteria which are replaced by less virulent bacteria. Direct medication delivery to teeth and implants provides benefits that assist conventional treatments like scaling and root planing, laser surgery and topical antimicrobial rinses. Direct medication delivery helps in wound debridement through disruption of the biofilm. Wound healing is improved by the medicinal effect of hydrogen peroxide and hyperbaric oxygen. The decreased number and type of bacteria may decrease the incidence of bacteremia as more virulent bacteria are replaced by less virulent bacteria. This also helps explain local healing as pocket depths and bleeding upon probing decrease around implant with direct medication delivery. Bone loss is halted and new bone is evident as threads that were once exposed are recovered by new bone around an implant with peri-implantitis. This is due to the osteogenic activity of the medications delivered into the periodontal pocket. Direct medication application is widely applicable due to the incidence of periodontal disease throughout the world. Combining direct medication delivery with conventional methods may help...
control the etiology of disease and reinfection through both a treatment program and maintenance and prevention program. This article demonstrates the effectiveness of direct medication delivery for implants and for natural teeth used in combination with conventional methods. There are no ethical concerns found with this method except the side effect of whitening teeth.

**Discussion:**

Periodontal disease, peri-implantitis and perimucositis are worldwide problems that may be helped by direct medication delivery using custom formed medical devices to deliver doctor selected medications subgingival and interproximal to control the etiology of disease. This article demonstrated that for three patients there was a positive response to direct medication delivery of hydrogen peroxide gel and doxycycline syrup to the periodontal pocket around teeth and implants. The custom formed trays hold the medications in place and the medications provide multiple therapeutic benefits, such as providing hyperbaric oxygen, enabling anti-inflammatory benefits and helping to control microorganisms. Managing the bacteria in periodontal pockets and around implants reduces the type and number of bacteria. Reducing the virulence and number of bacteria may provide positive results by decreasing bacteria present for systemic bacteremia. Direct medication delivery is an easy and simple means whereby the doctor can assist the patient in biofilm control. Direct medication delivery also provides distinct advantages when used with conventional mechanical treatments through managing the causes of the disease. This is exemplified by the decreased pocket depth, decreased bleeding upon probing and healing that occurred for the cases shown. Direct medication delivery provides materials like doxycycline to the periodontal pocket that assist in osteogenic control as illustrated by the bone regeneration in response to therapy. The bacteria as determined by DNA analysis showed changes in the biofilm constituency as the predominant species at the onset of treatment were not the same as the bacteria found at the end of treatment. Controlling the biofilm species and number of bacteria resulted in improvements in the host inflammatory conditions around infected implants and teeth and where pocket probing depth and bleeding upon probing were managed. Decreasing the bacterial population and virulence provides advantages in health for the patient. Direct medication delivery can be utilized both as a treatment method and long-term management and prevention technique.

This study has a limited population and opinions reached must take this limitation into consideration. A larger study over a greater period of time needs to be completed for additional proof of efficacy. This article demonstrates specifics of treatments that the individual health care provider will need to consider when determining the optimum ways to address a chronic wound like periodontal disease and peri-implantitis and perimucositis.

**Conflict of interest:**

Dr. Duane C Keller is CEO and President of Perio Protect and has a vested interest in the company.

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