Oral Biology and Dentistry
ISSN 2053-5775 | Volume 6 | Article 2

HOAJ
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Original Research Open Access

Chronic wound management of periodontal disease

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Abstract

Periodontal disease afflicts much of humankind, even when the patient seeks professional care and exercise homecare recommended by the dental profession. The accepted guidelines of the dental profession are scaling and root planing along with professional prophylaxis and sound home care. Patients suffer with periodontal disease even when they follow these guidelines. These guidelines are flawed because they are acute modality treatment guidelines, while periodontal disease is a chronic wound.

The etiology and stages that occur in acute wounds differ significantly from chronic wounds. Acute wound treatment modalities are not capable of successfully treating most chronic wounds. The American Medical Association (AMA) has established guidelines for chronic wound management. The steps in theAMA guidelines of chronic wound therapy are incorporated into direct medication delivery in the treatment of chronic periodontal disease.

The AMA guidelines recommend managing the etiology of disease using antimicrobials, oxygen and topical antiseptics before physical intervention. Once the cause is managed, wound debridement is an essential step along with long-term prevention of reoccurrence. Direct medication delivery has been shown to control the etiology of periodontal disease using a 1.7% hydrogen peroxide and a subclinical doxycycline dose to manage the biofilm. Long-term management and prevention of reoccurrence fulfill the guidelines of chronic wound management.

Keywords: Perio protect method, direct medication deliver, chronic wound management, biofilm control, anti-inflammatory, compression therapy, long-term maintenance, Perio Tray

Introduction

Periodontal disease remains a plaque on humankind as it has not been successfully managed, despite years of research and multiple methods of treatments. The primary reason this disease has not been successfully managed is the current methods of treatment follow acute disease modalities and chronic wounds like periodontal disease do not respond satisfactorily to acute disease treatments.

This article presents Guidelines for Chronic Wound Treatment as developed by the American Medical Association and successfully applies these chronic wound guidelines to the treatment of periodontal disease using a direct medication delivery method. The direct medication method follows the guidelines of chronic wound care by first fabricating a custom formed medical device to deliver doctor selected medications to the periodontal pocket to control the etiology of disease before wound debridement. Following etiology control and debriding the wound, the method manages the micro-environment of the periodontal pocket so only a decreased number of less-virulent bacteria predominate the gingival sulcus so the patient can remain disease free long-term and prevent the reoccurrence of infection.

Background

An acute wound is one where an injury occurs, and the body's expeditious responses allow complete resolution and healing, resulting in minimal loss of function. Chronic wounds differ as they fail to heal in a reasonable time, usually three months and have a polymicrobial etiology and a prolonged patient de-generating response with a generalized loss of tissue function. Significant differences exist between acute and chronic wound etiology such as an increase in inflammatory mediators, biofilm

 doi: 10.7243/2053-5775-6-2

characteristics like decreased oxygen concentration, and treatments must take these differences into consideration [1].

Acute wound healing involves a coordinated cellular and molecular response that begins within minutes on an injury and is directed to restoring homeostasis through the formation of a provisional wound matrix. The initial phase of acute wounds is an inflammatory phase that involves neutrophils recruitment in response to platelet and other cascading activating signals. This proceeds through a coagulation phase where monocyte transformation occurs with the concomitant formation of granulation tissue, which occurs through fibroblast activation in the proliferative phase with the restoration of vascular and neurologic components. Restoring the tissue integrity often involves the extracellular matrix undergoing-physiologic changes as a scar is formed [2].

Inflammation is an important part of wound healing, but chronic wounds usually get stalled in the inflammatory phase of healing with a generalized incomplete tissue resolution and a failure to restore homeostasis. Therefore, chronic wounds do not respond in the normal healing sequence and may exist without resolution. There is usually an extended inflammatory sequence where neutrophils and other cells differ from those found in an acute wound [3]. Neutrophil products may continue to be produced and become a part of a larger inflammatory problem.

Part of this difference between acute versus chronic wounds is the incidence and duration of matrix metalloproteinases (MMP's). MMPs are secreted by both inflammatory and stromal cells, such as keratinocytes, fibroblasts and endothelial cells in response to an infection or injury and these cells produce a wide range of cytokines and growth factors [4]. MMPs facilitate leucocyte recruitment, cytokine and chemokine processing, defensin activation and matrix remodeling. MMP's degrading the components of the extracellular matrix allows immune cells to migrate to the site of inflammation. MMP's modulate cytokines and chemokines which drives the inflammatory cell recruitment which further opens a pathway for neutrophil migration to the inflamed cells. MMPs activate defensins that kill bacteria by membrane disruption. There are multiple interactions between MMPs and chemokines, which produces a chemokine degradation negative feedback loop to dampen inflammatory cell influx and helps resolve the inflammation in acute wounds [5].

Excessive MMPs can also be part of an inflammatory problems that favors pathogen persistence and dissemination. Certain pathogens may induce increased MMP secretion through a lipopolysaccharide-associated activation, resulting in proteolytic enzyme injury to the host cells [6]. Tissue inhibitory metalloproteinases (TIMP) are mainly active in inhibiting MMP activity. TIMPs are produced by a variety of cells, including macrophages, platelets, and vascular smooth muscle cells. TIMPs normally occur in acute wounds around three to five days, but the level of TIMPs is lower in chronic wounds and this results in an increase in MMPs in chronic wounds [7]. Bacterial extracts from anaerobic bacteria found in periodontal disease (Prevotella intermedia, Fusobacterium nucleatum, Porphyromonas endodontalis and Porphyromonas gingivalis) inhibited TIMP production and accelerated MMP production [8]. Continued inflammation due to the presence of these bacteria found in periodontal disease helps explain the persistence of infection when mechanical treatments and adjunctive antimicrobial therapy fail to alter the microbiome.

Studies have shown that scaling and root planing leave all of the biofilm bacteria in the subgingival region where they can regrow when conditions warrant [9]. The biofilm is able to regenerate on natural teeth at a rapid rate [10] and mechanical debridement increased the biofilm redevelopment to a 3-4X level [11] Acute wound modalities like scaling and root planing reduce the periopathogens in the subgingival region, but the regrowth demonstrates an expansion in the pathogen-related components and a decrease in the non-pathogen related components six weeks after scaling and root planning [12].

In a 24-month study, patients treated with subgingival scaling with systemic amoxicillin, plus metronidazole and chlorhexidine irrigation were compared to a scaling and root planing only group. Both treatments failed to induce long-term changes in the microbiome [13]. A full-mouth ultrasonic debridement with the systemic administration of amoxicillin and metronidazole failed to improve the microbiologic or immunologic outcome [14]. Mechanical debridement, local irrigation and systemic antimicrobials are not able to alter the periodontal microbiome, but there is a difference in acute and chronic wound microorganisms.

The microbiome of the acute wound has a lower bacterial diversity and a higher incidence of gram positive aerobic microorganisms with a higher susceptibility to antibiotic therapy as compared to chronic wounds which were predominantly gram-negative microorganisms [15]. The chronic wound microorganisms live in a biofilm and there will be a greater number of microorganisms as well as a difference in the predominant species compared to acute wounds [16]. The distinctive subgingival microflora of periodontal disease is made up of gram-negative anaerobes including A actinomycetemcomitans, P gingivalis, P intermedia, B forsythus, C rectus, E nodatum, P micros, S intermedius and Treponema that greatly exceed healthy tissue concentrations [17].

The clarification of the etiologic / host response interaction has a definite bearing on the healing outcome. Chronic inflammation is a hallmark of the chronic wound and appears related to the presence of an excessive number of pathogens that modulate the healing process. The chronic wound inflammation persists in part due to the different nature of the chronic wound biofilm, when compared to an acute wound which is comprised of more gram positive aerobic bacteria. The nature of the chronic wound gram negative anaerobic biofilm is part of the cause of the immune response [18].

Control of the biofilm is key to chronic wound manage-

doi: 10.7243/2053-5775-6-2

ment and should include wound debridement and the use of topical antimicrobials rather than antibiotics. Wounds which were debrided healed 83% of the time compared to sporadic debridement, where only 25% of the wound healed. Periodontal wound debridement such as scaling and root planing and subgingival pocket lavage helped convert chronic wound into acute wound that can heal [19].

However, debridement procedures can place the patient at an increased infectious risk. Scaling and root planing and periodontal surgery have been shown to increase bacteremia. Well-conducted studies demonstrate the frequency of passage of periodontal microorganisms into the host bloodstream as a result of periodontal procedures [20]. Treatments to reduce the numbers of bacteria before invasive procedures decreased the incidence of bacteremia [21].

Multiple wound treatment options exist for managing chronic wounds like periodontal disease. Antiseptics are effective through many mechanisms of action, but the use of systemic antibiotics has resulted in an increased resistance of the microorganisms [22]. Paquette DW et al recommend a medical/mechanical model with locally delivered antimicrobials for the treatment of chronic periodontitis in combination with wound debridement, but their method recommends the use of antibiotics and does not provide long-term results [23]. Hyperbaric oxygen, wound compression, ultrasound and electromagnetic therapy and positive and negative pressure therapies [24] are options that are available for treating chronic wounds.

Steps in chronic wound management have been provided by the American Medical Association (AMA) Wound Healing Society [25]. These involve managing the etiologic agents, wound bed preparation including debridement and/or surgery, and prevention of reoccurrence [26]. These guidelines recommend the use of topical antimicrobials in place of antibiotics along with wound debridement, initiation of compression therapy and minimizing the level of bacteria in the wound. Using a direct medication delivery method enables usage of these steps in treating periodontal disease.

Direct medication delivery involves the fabrication of a custom formed medical device (Perio Tray™ Perio Protec LLC, St. Louis, Mo) that can deliver a topical antimicrobial and/or anti-inflammatory management medication to the source of the infection. The medications must be maintained for a sufficient time to enable biofilm matrix penetration and time for the medication to effectively complete the desired tasks. Subgingival delivery of oral debriding agents demonstrated that a 1.7% hydrogen peroxide gel (Perio Gel™ Perio Protect LLC St. Louis, MO) broke down the exopolysaccharide slime and cell wall of biofilm bacteria and began wound debridement within 10 minutes. Diffusion models showed the hydrogen peroxide gel penetrated up to 9mm pockets and the concentration in the pockets increased during the tray wearing as it reduced the subgingival bacterial load and enhanced wound healing [27]. The biofilm in chronic periodontal disease was modified by direct medication delivery through a reduction in the number of bacteria and an alteration in the type of bacteria in the chronic wound. The biofilm composition shifted from predominantly gram negative obligate anaerobes before to gram positive anaerobes, gram positive and negative facultative anaerobes and aerobic bacteria during treatment. There was a -log $^{2\text{-}4}$ reduction in the number of bacteria during treatment [28]. Fewer less virulent bacteria provided better treatment results through host responses to the improved subgingival conditions.

Direct medication delivery of hydrogen peroxide and Vibramycin helped modify the micro-environment of the periodontal pocket and this improved situation resulted in clinically less bleeding upon probing and decreasing periodontal pocket depth. Hydrogen peroxide penetrates the oral biofilm, breaks down to water and oxygen and serves to debride the periodontal wound. The modified biofilm constituency resulted in less host inflammation and improved healing [29].

Successful management of periodontal disease involves both biofilm control along with modifying the host inflammatory process. Wound compression helps reduce the tissue cytokine level, thus helping reduce inflammation [30]. Wound compression was found to significantly reduce MMP activity in chronic wounds and was associated with decreasing protease levels, thus helping in chronic wound healing [31]. Wound compression helped converted many chronic wounds to healing by decreasing MMP levels and the surface area of chronic wounds was found to decrease [32]. Wound compression increases vascular and tissue oxygen levels, reduces capillary filtration, thus increasing microcirculatory blood flow. Compression prevents neutrophil and monocyte adhesion to the capillary endothelium and helps reduce inflammation. Compression reduced pro-inflammatory cytokines and helps endothelial cells release anti-inflammatory and anti-thrombotic biochemical mediators [33].

Inflammation can be managed through the topical use of anti-inflammatory medications. Low dose doxycycline did not produce resistant bacteria strains but was effective in modulating lipopolysaccharide induced inflammation [34]. Tetracyclines have an array of therapeutic properties that related to chronic wound treatment. Doxycycline inhibits MMPs and suppresses hydrolases and scavenges reactive oxygen species, thus reducing tissue destruction. Tetracyclines suppresses cytokines involved in inflammation thus further decreasing tissue inflammation [35].

Traditionally, treatment of periodontal disease was focused on reducing the bacterial load by mechanical means. Periodontal treatment of a chronic wound requires more than just mechanical debridement, such as wound compression, biofilm management and inflammatory product control. All of these advantages can be incorporated into direct medication delivery mechanics.

Materials and method

Chronic wound management principles are applied to treat-

 doi: 10.7243/2053-5775-6-2

ing periodontal disease through the use of direct medication delivery with custom formed medical devices (Perio Tray™) and the use of wound debridement agents like hydrogen peroxide and medications like topically applied doxycycline that are able to help manage the host inflammatory response. AMA guidelines for chronic wound care involve first managing the cause of infection.

The predominant biofilm species in periodontal disease are gram negative obligate anaerobes [36]. Biofilm management with mechanical treatments like scaling and root planing, even with antibiotics and antimicrobial agents are not effective. One method that has been shown to successfully manage the periodontal biofilm uses a direct medication delivery system. This system uses a custom medical device (Perio Tray™, Perio Protect LLC St. Louis, Mo.). to direct topically applied hydrogen peroxide (1.7% hydrogen peroxide gel [Perio Gel™), into the periodontal pocket [37].

Direct medication delivery decreased the number of bacteria by a -log$^{2\text{-}4}$ and demonstrated the method altered the gram negative obligate anaerobic virulent population to a less numerous and less virulent population [38]. The delivery of hydrogen peroxide resulted in a 5.3X increased concentration of oxygen, which changed the pocket micro-environment from an anaerobic to aerobic condition that controlled the anaerobes. Decreasing the number of bacteria from 100,000 to 1,ooo to 10 and causing an alteration in the predominant species from a more virulent to a less virulent population meets the AMA standard for chronic wound infectious agent management (**Table 1** and **Figure 1**).

Table 1. Shows the before treatment composite numbers of all bacterial species determined by DNA analysis that are present following conventional mechanical treatment and homecare .

Composite	G- Anaer	G+ Anaer	G- F An	G+ F An	G- Aero	G+ Aero	G- Micro
Before	742	43	14	0	0	4	16
During	518	172	0	0	20	9	16
After	56	237	65	50	20	33	10

These numbers can be compared to during and after direct medication treatment. The number of gram negative obligate anaerobes was found to decrease as the number of gram positive anaerobes and all facultative and aerobic bacteria increased during treatment. The total numbers of bacteria decreased during the treatment and maintenance phase when compared to the before treatment numbers.

Another aspect of the AMA Guidelines for Chronic Wound Care involves controlling inflammation. Control of inflammation is possible where hydrogen peroxide has multiple anti-inflammatory effects. Hydrogen peroxide suppresses the action of IL-8 mRNA, resulting in a reduction of the pro-inflammatory cytokine IL-8. Hydrogen peroxide modulates dendrite cell phenotypic activation and decrease pro-inflammatory chemokine and cytokine release. Adding hydrogen peroxide

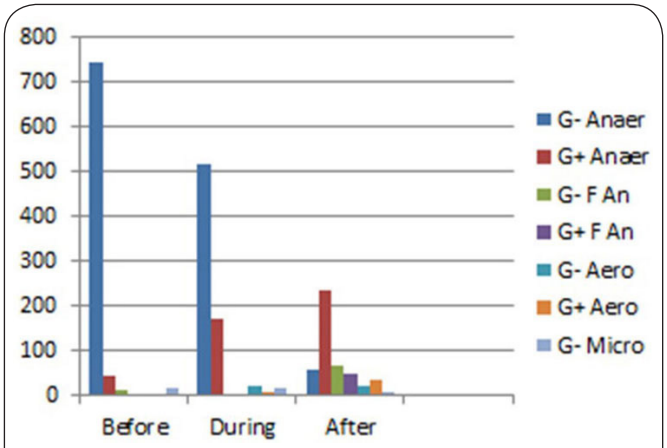

Figure 1. The graph (Before) demonstrates the number of bacterial species present six to twelve months following conventional mechanical treatment and routine homecare. Direct medication delivery is initiated with the use of hydrogen peroxide gel (Perio Gel) delivered with a Perio Tray in accordance with the Perio Protect Method protocol. The changes in specific category types are evident as the total number of bacterial species are found to decrease with treatment (During). This graph also demonstrates a significant decrease in gram negative obligate anaerobe found to be more virulent bacteria that are being replaced with a lesser number of bacteria associated with a more normal less virulent flora (After).

to the periodontal pocket increases the oxygen concentration to a level similar to hyperbaric oxygen [39].

The increased oxygen concentration in the periodontal pocket can affect pro-inflammatory cytokine production. Inflammatory cytokines were found to decrease in a higher oxygen tension as well as reduce prostaglandin production, resulting in a decreased inflammatory effect. Hyperbaric oxygen concentrations have been shown to improve tissue health, repair and healing [40].

Adding a subclinical dose of doxycycline to the Perio Tray delivers doxycycline as an antioxidant to help reduce gingival inflammation [41]. Doxycycline reduces macrophage inflammatory mediators, which provides proven clinical benefits on the inhibition of proinflammatory cytokine responses [42]. Doxycycline and tetracyclines block the lipopolysaccharide stimulated TNF-alpha secretion, therebyhelping prevent inflammatory tissue destruction [43].

Wound compression decreases inflammation. The use of a custom formed periodontal tray (Perio Tray) applies compression to the wound through the design of the medical device. Wound compression reduces tissue cytokine level, thus helping reduce inflammation [44]. Wound compression reduces MMP activity in chronic wounds and decreases protease levels, thus helping in chronic wound healing [45]. Decreasing MMP and protease levels and the surface area of a chronic wound help many chronic wounds heal [46]. Wound compression increases vascular and tissue oxygen levels,

doi: 10.7243/2053-5775-6-2

reduces capillary filtration, thus increasing microcirculatory blood flow. Compression prevents neutrophil and monocyte adhesion to the capillary endothelium and helps reduce inflammation. Compression reduced pro-inflammatory cytokines and helps endothelial cells release anti-inflammatory and anti-thrombotic biochemical mediators [47]. Case studies show treatment of chronic periodontal disease with a direct medication delivery method decreases bleeding upon probing and periodontal pocket depths were also decreased, indicative of a decreased host inflammation [23]. These results were shown to be maintained for up to 6 months [48].

Results

Acute wound management for chronic periodontal wounds is not successful. Acute treatment modalities such as scaling and root planing (with and without antibiotics) does not alter the periodontal biofilm. Scaling and root planing leaves all of the biofilm constituents after mechanical debridement, enabling them to regrow under favorable conditions. Mechanically disturbing the biofilm increases the reproductive capacity of the bacteria 3 to 4 X. Scaling and root planing initially decrease the number of pathogens, but the shift in the microbiota composition was characterized by the expansion of the pathogen-related components at the expense of the non-pathogen- related components.

Managing a chronic wound necessitates following guidelines for chronic wound management as proposed by the AMA. The infectious agents are addressed first, and published research on direct medication delivery of hydrogen peroxide and doxycycline using a custom formed medical device demonstrated a -log$^{2\text{-}4}$ reduction in the number of bacteria and a shift from more virulent to a decreased number of less pathologic bacteria. Research has shown that treating the bacteria prior to wound debridement reduces the likelihood of systemic bacteremia.

Wound debridement is completed when there is a verified reduction in the bacteria load with less virulent microorganisms. Modifying the biofilm decreases the possibility of local and systemic bacteremia along with a decreased in bleeding upon probing and a reduction of pocket probing depths.

Inflammation is addressed through wound compression and the delivery of anti-inflammatory medications to the source of the diseaseas MMPs and other inflammatory products are reduced. Hydrogen peroxide, oxygen and doxycycline have all been shown to have positive medicinal benefits on treating inflammation. Published research demonstrates that direct medication delivery used as a maintenance treatment prevents a reoccurrence of infection and is the final aspect of the AMA chronic wound care guidelines.

Discussion

A chronic wound like periodontal disease does not respond satisfactorily to acute wound treatment modalities. Acute wound debridement such as scaling and root planing, with and without antibiotic treatments, does not alter the initial biofilm, resulting in regeneration when conditions exist for the biofilm regrowth.

Acute treatments do not sufficiently alter the micro-environment of the infection to control the biofilm, or the myriad of inflammatory products that become part of the chronic wound. Failure to control the chronic wound etiology results in the regeneration of a virulent etiologic population and the chronic wound continues. Chronic wound guidelines established by the AMA manage demonstrate a means to the circumstances and conditions of a chronic wound.

These guidelines recommend management of the biofilm as the initial step. Direct medication delivery of hydrogen peroxide penetrates the subgingival biofilm. Hydrogen peroxide debrides the wound and begins controlling the source of the infection. Oxygen generated from the hydrogen peroxide alters the micro-environment from an anaerobic situation to an aerobic environment, which control the predominant obligate anaerobes. The number and virulence of the chronic wound biofilm is replaced by a decreased (-log$^{2\text{-}4}$) number of less virulent biofilm.

The delivery of anti-inflammatory agents (hydrogen peroxide, oxygen and a subclinical dose of doxycycline) address the host inflammatory chronic wound response. Wound compression therapy and mechanical debridement decrease the MMPs and other inflammatory products and foster the development of anti-inflammatory TIMP.

DNA analysis demonstrated the change in the biofilm where the virulent population was replaced by a less virulent population that remained altered for six months. Continued use of the direct medication delivery helped fulfill the final step in the AMA Chronic Wound Guidelines; prevention of disease reoccurrence.

Conclusions

Chronic wounds like periodontal disease do not respond to acute wound treatments. Chronic wound guidelines require that the biofilm that is the cause of disease must be addressed before mechanical debridement. Direct medication delivery of hydrogen peroxide and a subclinical dose of doxycycline reduced the number of bacteria in the biofilm by a -log$^{2\text{-}4}$ and the virulent gram-negative obligate anaerobes were replaced by less virulent bacteria.

Chronic wounds exist in an inflammatory phase which negates healing. Direct medication delivery of hydrogen peroxide (oxygen) and anti-inflammatory agents like subclinical doxycycline help manage the host inflammatory responses. Compression therapy by the custom formed medical device directly decreases inflammation and these combined benefits enable healing to occur.

Long-term use of the medical device and direct medication delivery allow the patient to maintain the healing, control the biofilm, and decrease the host inflammation so a reoccurrence of the disease does not occur. Long-term maintenance

provides an improved state of health with decreased pocket probing depths and bleeding upon probing.

Competing interests

The author is the President/CEO of Perio Protect.

Acknowledgements

The author wishes to thank Dr. Bill Costerton (deceased) and the Society of Wound Care and the Wound Healing Society for their work in microbiology and the management of chronic wounds.

Publication history

EIC: Thimios A. Mitsiadis, University of Zurich, Switzerland.
Received: 17-Aug-2018 Final Revised: 15-Sept-2018
Accepted: 22-Oct-2018 Published: 04-Nov-2018

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Citation:
Keller DC. **Chronic wound management of periodontal disease**. *Oral Biol Dent*. 2018; **6**:2.
http://dx.doi.org/10.7243/2053-5775-6-2