The Importance of Hemostasis in Chronic Wound Care: An Open-Label Controlled Clinical Study of OMNI-STAT (Chitosan) Versus Standard of Care in Post-Debridement Treatment of Patients with Chronic Wounds with or without Concomitant Use of Anticoagulants

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ABSTRACT

Chronic wounds are those that fail to heal despite optimum care. Ulcers associated with diabetes, venous stasis, and pressure are the most common. Estimates are that more than 6.5 million Americans suffer from chronic wounds with prevalence highest in patients with diabetes and obesity. Sharp debridement is often required to initiate healing, however, this procedure is frequently accompanied by significant bleeding — a risk elevated in patients with clotting dysfunction or are treated with anticoagulants such as warfarin, aspirin, or antiplatelet agents. Advanced therapies are available to speed hemostasis (i.e. minimize the blood loss in the presence of anticoagulants such as warfarin and heparin). These modalities may improve clinical outcomes over standard care (e.g. gauze and firm pressure), work faster, and exhibit less blood loss.

A recent study evaluated Omni-Stat Hemostatic Gauze as a treatment to ensure hemostasis of local bleeding after sharp debridement of wounds. In this study, Omni-Stat significantly reduced treatment time and peri-treatment pain, and demonstrated statistically significant improvement in visualized granulation tissue post-treatment, including for patients on anticoagulation therapy. These results could lead clinicians to treat wounds on anticoagulants more aggressively in an outpatient setting without fear of creating uncontrolled bleeding and rebleed post procedure.

Keywords: chitosan, chronic wounds, hemostasis, moist wound dressing, Omni-Stat

INTRODUCTION

Wounds that fail to heal in an orderly and timely manner despite optimum wound care are considered to be chronic wounds. While all wounds have the potential to become chronic, diabetes, venous stasis, and pressure ulcers commonly become chronic wounds. The presence of chronic wounds not only affects patient quality of life but also represents a major health burden and enormous drain on financial and human resources.[3]

Advanced therapies are available to speed up hemostasis (i.e. minimize the amount of blood loss especially in the presence of anticoagulants such as warfarin and heparin). These modalities may provide improved clinical outcomes over standard care (i.e. gauze and firm pressure), take less time to work, and exhibit less blood loss. This article compares hemostasis in an open-label controlled clinical investigation of freshly debrided chronic wounds of various etiologies using chitosan impregnated hemostatic gauze or standard of care, which included standard 4 x 4 gauze and manual pressure by the examiner with two forefingers or silver nitrate in the presence of anticoagulants.

EPIDEMIOLOGY OF CHRONIC WOUNDS

An estimated 6.5 million Americans suffer from chronic wounds. The prevalence of chronic wounds in the United States is approximately 2% of the total population — a prevalence similar to that of heart failure — and is projected to increase due to an aging population and a steep rise in the incidence of diabetes and obesity. Recent estimates indicate that the cost of caring for chronic wounds exceeds $20 billion per year.[6]

Chronic wounds result from multiple etiologies including surgical, pressure, diabetic, and vascular, and often occur in patients with multiple comorbidities.[7] An analysis of 7,099 chronic wounds examined during a 5-year period from 5,240 patients enrolled in the U.S. Wound Registry noted that the mean number of comorbid conditions per patient was 1.8, with the most common being diabetes (46.8%), obesity (71.3%), and vascular disease (51.3%).[7] Nonhealing surgical wounds represented the largest

category at 20.8% of the total, followed by pressure ulcers (19.2%), diabetic foot ulcers (13.7%), and traumatic wounds associated with diabetes or vascular disease (12.8%).[7] Two-thirds of the 7,099 wounds required an average time to heal of 15 weeks while 10% of wounds required 33 weeks or more to heal. The presence of diabetes, renal failure, immune deficiency, current smoking, and the need for systemic antibiotics were all associated with increased healing time and overall cost of care. Wound healing is also attenuated by diabetes, malnutrition, immunodeficiency, or use of certain medications. When patients had one or fewer comorbid conditions, the cost to heal the wound was significantly less than when two or more comorbidities were present.[7]

DEBRIDEMENT

Wound healing generally proceeds through a well-ordered and timely process that re-establishes anatomic and functional integrity of the affected area.[8] However, the presence of local infection, necrotic tissue, and/or foreign bodies in the wound may impair the healing process. Debridement involves removal of devitalized tissue and debris from the affected area and converts a chronic wound into an acute one.[9,10] In addition to allowing the clinician to more clearly observe and assess the wound and the condition of the surrounding tissue, removal of nonviable or infected tissue recruits neutrophils, macrophages, and related growth factors that promote wound healing.[10]

There are four methods of debridement: sharp or surgical, enzymatic, autolytic, and mechanical. Several factors influence the method of debridement including wound size, type, location, and moisture levels; available pain management and time to conduct the procedure; and the healthcare setting in which the debridement will be performed. It is also important to consider the patient's overall health condition and coagulation status when choosing the debridement method.[10] In some cases, the use of more than one debridement method may be appropriate. Sharp debridement with curette, scalpel, forceps, or scissors is considered the SOC for wounds presenting with significant necrosis, callus, advancing cellulitis or sepsis, or thick adherent eschar.[11] Repeated sharp debridement of chronic wounds has been demonstrated to reduce the need for antibiotics, minimize the risk of hospitalization and amputation, and decrease healing time.[12]

CHALLENGE ASSOCIATED WITH THE ANTICOAGULATED PATIENT

Sharp debridement removes necrotic tissue down to the level of well vascularized tissue.[7] However, vigorous sharp debridement can increase the risk of bleeding, a risk exacerbated by the extensive use of anticoagulants in our aging population.[13] Prophylactic anticoagulation using warfarin, antiplatelet agents, and/or aspirin plays a vital role in the prevention of stroke in the more than 2.3 million people who carry a diagnosis of atrial fibrillation,[14] and nearly 1 million at risk for venous thromboembolism.[15] Anticoagulation is also SOC during surgical procedures commonly performed in older individuals, including joint replacement, cardiothoracic and vascular surgery, and endovascular procedures. Long-term anticoagulation is also commonly utilized in patients undergoing kidney dialysis and in patients with mechanical heart valves and hypercoagulable conditions.[13]

With nearly 31 million prescriptions for anticoagulants filled in the United States each year,[16] there is a high probability that many chronic wound patients presenting for sharp debridement may be taking anticoagulants. However, the management of anticoagulation in these patients—both before and after debridement—can be challenging as the use of perioperative anticoagulation may increase the risk of bleeding and impede wound healing.[17] Currently, there are little randomized clinical trial data and no definitive guidelines to address the perioperative needs of chronic wound patients on anticoagulant therapy.[18] Clinical management of these patients involves assessing and balancing individual risks for thromboembolism and bleeding. Discontinuing anticoagulant therapy is often required for debridement of large or multiple wounds, though discontinuation may increase the risk of thrombotic events. In contrast, it appears that anticoagulation does not need to be interrupted for debridement of smaller wounds.[18]

TOPICAL HEMOSTATIC AGENTS

Management of hemostasis is of fundamental importance in any surgical procedure because before a wound can heal, it must stop bleeding. Post-operative bleeding is also associated with unscheduled office visits, emergency room visits, hematoma, necrosis, and infection. In many cases, hemostasis can be accomplished using mechanical interventions such as local pressure, limb elevation, ligatures, stitches, clips, silver nitrate, and electrical cauterization. However, when

mechanical interventions are inadequate or not feasible, hemostasis becomes challenging. The use of silver nitrate and electrical cauterization may also damage healthy tissue and induce pain. Topical hemostatic agents—many of which were originally developed for military applications—promote hemostasis in a wide variety of surgical procedures where the control of bleeding may be particularly difficult.[19] Most topical agents physically block the outflow of blood in the wound and, working in concert with inherent clotting activities, provide a matrix for increased platelet interactions and accelerate clotting reactions. These actions result in faster and stronger fibrin clot formation that can bind to and seal vascular injuries. Therefore, the effectiveness of these agents depends heavily on the competent coagulation function of patients.[19]

Although the usefulness of topical hemostats is clear, the relative efficacy of the agents is difficult to understand. Despite a large body of literature on the use of topical hemostatic agents in numerous applications, there are few robust, randomized trials directly comparing available agents.[20] Thus, when selecting a topical hemostatic agent, the size and configuration of the wound, bleeding severity, and the agent's efficacy, possible adverse effects, method of application, ease of use, timing requirements, and storage specifications should all be considered.[21]

THE IDEAL TOPICAL HEMOSTATIC AGENT

Although there has been significant improvement in topical hemostats during the last decade, there is still a need for the ideal topical hemostatic agent. According to Pusateri et al. and Acheson et al., in two prospective studies in swine (one of severe arterial hemorrhage and one of severe hepatic injury), an ideal hemostatic dressing should stop bleeding from any source within minutes even when applied to actively bleeding vessels or in a pool of blood, be without toxicities and adverse side effects, work independently of host coagulation function, stop bleeding in patients with clotting dysfunction or those treated with anticoagulants, be easily stored and ready to use at room temperature without premixing, require minimal training to use, be easily administered, and be relatively inexpensive.[22,23]

STUDY DESIGN

MATERIALS AND METHODS

This study evaluated the utility of Omni-Stat Hemostatic Gauze (Medtrade Products, Ltd., Electra House, Crewe Business Park, Crewe, Cheshire, CW1 6GL) as a treatment to ensure hemostasis of local bleeding after sharp debridement of a range of wounds. An open-label, controlled clinical investigation of chitosan impregnated hemostatic gauze versus standard of care (SOC) in open wounds of various etiologies post-debridement was conducted at a single site among 40 patients.

Topical anesthesia was applied, and then the wound was debrided with a 15 blade or curette; debridement tools were left to the discretion of the investigator. After debridement, excess blood was wiped away, and the wound was then treated with chitosan impregnated hemostatic gauze or gauze control followed by pressure for two minutes. If bleeding continued, two additional minutes of pressure were applied. The chitosan impregnated hemostatic gauze was then covered with gauze bandage, and control patients were dressed with moist wound care dressings. Both treatment and control bandages were kept on for seven days and removed at a follow-up visit after being saturated with saline for five minutes. Follow-up was a single visit at one week to evaluate wound appearance, pain at dressing removal as measured by Mean Wilcoxon Rank-sum Test Score, and safety.

The hemostatic agent studied consists of the chitosan hemostatic granules bonded to a 4-by-4 inch absorbent gauze pad dressing. The hemostatic granules studied are composed of chitosan, a natural polysaccharide of glucosamine and N-acetyl glucosamine. Chitosan (granules) has been proven in preclinical trials to stop major arterial bleeding within three minutes and reduce blood loss.[24]

The primary endpoint in this study was the time required to achieve hemostasis. One secondary endpoint was patient's assessment of pain levels as recorded at the time of treatment, on a scale of zero (no pain) to 10 (severe). The same method was used to record pain levels at the time of dressing removal at follow-up visit. Another secondary endpoint was a visual assessment of the wound made by the investigator at follow-up visit to record the appearance of the wound bed and note improvement or deterioration.

ETHICAL CONSIDERATIONS

The chitosan impregnated hemostatic gauze study protocol was pre-approved by the Snyder Research Institute. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All patients signed consent forms prior to their participation, and all patient information was kept in a password-protected file.

STATISTICS

Investigators selected 20 patients with wounds of various etiologies for treatment with chitosan impregnated hemostatic gauze and an additional 20 control patients. ***Table 1*** shows an analysis of the demographics of the treatment and control groups. Both groups included a large proportion of patients on anticoagulant therapy (15/20 treatment, 16/20 control). The most common anticoagulant used was acetylsalicylic acid (ASA–aspirin). Other anticoagulants included warfarin (Coumadin) and clopidogrel (Plavix). A small number of patients were taking moloxican (Mobic), which was recorded as an NSAID (non-steroidal anti-inflammatory drug).

Table 1: Patient Demographics

Patient Data	Treatment (n=20)	Control (n=20)
Anticoagulant Therapy	15/20 (75%)	16/20 (80%)
ASA	10/20 (50%)	11/20 (55%)
Other (Coumadin, Warfarin, Plavix)	5/20 (25%)	5/20 (25%)
None	5/20 (25%)	4/20 (20%)
Ulcer Type		
Diabetic Foot Ulcer (DFU)	6/20 (30%)	10/20 (50%)
Venous Leg Ulcer (VLU)	10/20 (50%)	7/20 (35%)
Other	4/20 (20%)	3/20 (15%)
Ulcer Location		
Knee and Leg	12/20 (60%)	8/20 (40%)
Ankle	2/20 (10%)	2/20 (10%)
Foot and Toe	6/20 (30%)	10/20 (50%)

RESULTS

TRIAL ENDPOINTS

The primary trial endpoint was time to hemostasis immediately following debridement. Secondary endpoints included improvement in quality of granulation tissue as visualized at the follow-up visit, and patient-reported level of pain measured during application and removal of dressings measured by Mean Wilcoxon Rank-sum Test Score (***Table 2***). Rebleeding after hemostat removal and/or dressing change at the follow-up visit was not measured, however, none of the patients in either the control or the treatment group re-bled.

Table 2: Trial Endpoints

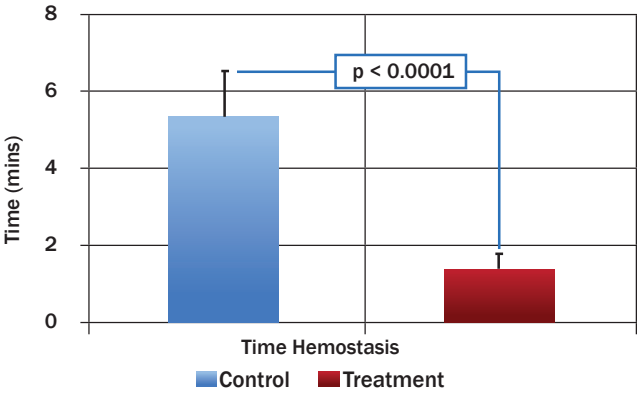
Endpoint	Treatment (n=20)	Control (n=20)
Time to Hemostasis in Minutes (Std Dev)	1.19 (0.47)*	5.19 (1.25)
Quality of Granulation Tissue Upon Removal		
Improved - n (%)	16/20 (90%) †	0/20 (0%)
Unchanged - n (%)	2/20 (10%)	16/20 (80%)
Deteriorated - n (%)	0/20 (0%)	4/20 (20%)
Pain During Hemostasis (Mean Wilcoxon Rank-sum Test Score)	0.2 †	1.5

* Statistically significant from control, p<.0001
† Statistically significant from control, p<.05

TIME TO HEMOSTASIS

Both the treatment and control groups showed a fit to a normal distribution. The mean time to hemostasis for cases treated with chitosan impregnated hemostatic gauze was 1 minute, 19 seconds, and for control subjects it was 5 minutes and 19 seconds (***Figure 1***). The difference was statistically significant (p<0.0001) using the T-test. The chitosan impregnated hemostatic gauze treated group reduced time to hemostasis by 4 minutes. The chitosan impregnated hemostatic gauze dressing was equally effective for different types of anticoagulant therapy.

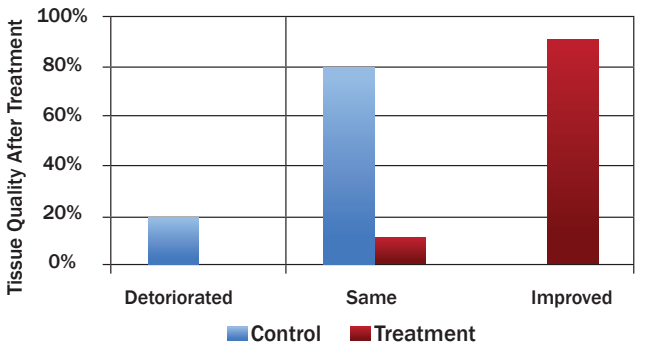
Figure 1: Time to Hemostasis (minutes)



SECONDARY ENDPOINTS

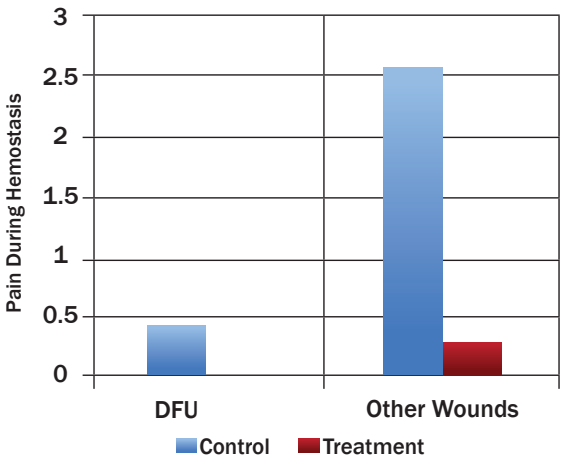
The quality of granulation tissue of the wound was assessed visually at the follow-up visit, after one week (***Figure 2***). The difference between chitosan impregnated hemostatic gauze (18/20 improved, none deteriorated) and SOC (none improved, 4/20 deteriorated) was significant when compared using the Chi-squared test.

Figure 2:
Tissue Quality After One Week Dressing



Analysis of pain scores in the control group showed a difference between the diabetic foot ulcers (DFUs) compared to other wound types (mean pain score of 0.4 on application for DFU, compared to 2.6 for other wounds.) This is consistent with the neuropathy associated with many DFU patients. Following this observation, the pain scores between the treatment and control groups were compared for DFU and for all other wounds separately. For wounds other than DFUs, pain in the treatment group averaged 0.3, compared to 2.6 in the control group during application. For DFUs, pain in the treatment group was 0 (no pain) during application (***Figure 3***). On removal, the pain in all chitosan impregnated gauze patients was 0 (no pain) compared to a mean of 1.3 in the control group (***Figure 4***) for all wound types other than DFU.

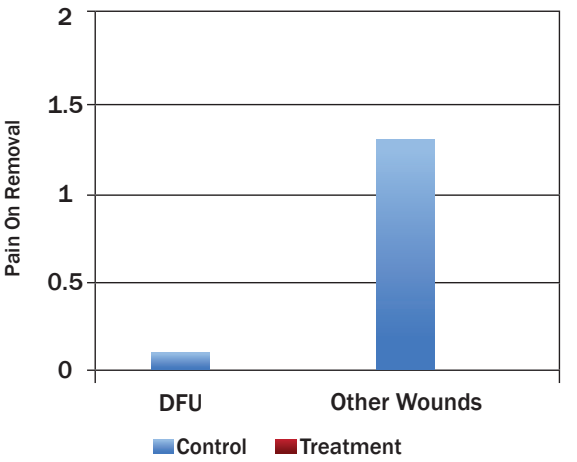
Figure 3: Pain Score During Hemostasis



DISCUSSION

The need to control bleeding before the patient leaves the clinic may lead to significant delay while the clinician applies gauze and pressure or styptic such as silver nitrate. This delay can disrupt clinic schedules and defer treatment for other patients. During this time, there can be discomfort for the patient caused by efforts to control

Figure 4:
Pain Score on Dressing Removal After One Week



the bleeding (pressure, elevated leg position, burning due to styptic application), or distress due to the continuing bleeding. In this study, chitosan impregnated hemostatic gauze statistically significantly reduced treatment time. The study and control groups are comparable, with similar proportions on anticoagulant therapy. Different anticoagulants have different mechanisms of action, including antiplatelet (aspirin), but the hemostasis was equally effective on patients taking ASA (aspirin), warfarin (Coumadin), clopidogrel (Plavix), NSAIDs, and combinations of anticoagulant therapies. The treatment group had more patients with leg ulcers, which may influence the results, but observing the results for subgroups (venous leg ulcer and diabetic foot ulcer) a similar pattern of treatment time compared to control time can be seen in each group. The study showed a statistically significant result. Chitosan impregnated hemostatic gauze provided a moist wound environment for the one week period between treatments. The finding that quality of granulation tissue appeared to improve with chitosan impregnated gauze treatment compared to control is interesting. The use of the chitosan impregnated hemostatic gauze allows the clinician to use the same dressing to gain hemostasis and be kept in place as a dressing providing a moist wound environment until the next dressing change, in seven days. The chitosan granules and the high-density gauze fabric used are both absorbent (more absorbent than generic gauze) and may contribute to maintaining the moisture balance at the wound bed.

There are many studies of chitosan and its use in the body, in a range of applications. Tissue response to chitosan can vary with the degree of deacetylation,[25] molecular

weight,[25] combination with other materials,[26] material structure,[27] and other factors not fully identified.[28] Recently, a great deal of wound research has focused on the role of proteolytic enzymes and elastase. In work performed by the sponsor, chitosan dressings were found to absorb matrix metalloproteases MMP-2 and MMP-9 into the structure of the dressing,[29] and binding of excess protoeolytic enzymes in the dressing may contribute to the improved quality of the granulation tissue. Further study is recommended to confirm this finding.

IMPLICATIONS OF FINDINGS

The pain score results support that the treatment provides a comfortable method of achieving hemostasis, with very low pain scores on application and no pain on removal. As an observation, the investigators felt that they did not need to apply as much firm pressure as when using gauze and obtaining hemostasis by tamponade. It could also be that the reduced time with the leg elevated was more comfortable. Reducing the time for which pressure is held and the general level of discomfort for the patient can be expected to lead to improved patient compliance to ongoing treatment.

The study gives confidence that chitosan impregnated hemostatic gauze does help with controlling bleeding after debridement. In some situations where the patient's time is restricted or there is a high risk of uncontrolled bleeding, debridement might be delayed and possibly moved to the operating room with additional cost implications. Chitosan impregnated hemostatic gauze may allow the clinician to conduct debridement thoroughly in the clinic with fewer concerns for possible complications to the patient visit.

The consequences of unhealed wounds can lead to amputation and death. Nearly half of all unhealed neuropathic foot ulcers result in death within five years.[30] There are one million amputations globally, which means one every 20 seconds.[31] Studies support that post-op mortality rates for diabetic amputees are between 39–80% after five years.[32] These results are a reminder of the critical need to properly care for these wounds, which includes aggressive surgical debridement and offloading to remove necrotic and devitalized tissue. Without appropriate debridement, chronic wounds are left with dead tissue that is unreceptive to growth factors and any bioactive treatment. However, once a wound is adequately debrided growth factors are stimulated, and micro-healing can begin.[33] Although aggressive debridement is necessary often times in clinical settings, the choice to aggressively debride depends on the ability of the patient to clot. Many patients taking anticoagulant therapies to prevent life threatening comorbities like pulmonary embolisms, deep vein thrombosis (DVT), atrial fibrillation, and angina are at greater risk for bleeding uncontrollably. As the population continues to age, the use of anticoagulant medications will continue to increase. The evidence suggests that these patients often do not receive proper care in the clinical setting due to concern of the increased potential for bleeding complications at the time of debridement and occurrence of rebleed post procedure. The threat of uncontrolled bleeding may increase the propensity to undertreat patients undergoing anticoagulant therapies. The risk of undertreating chronic wounds in this specific patient population may lead to a greater incidence of amputations and death. The ability to treat patients effectively without the need to alter their anticoagulant therapies while quickly stabilizing active bleeding would be very beneficial. The findings from this study suggest that chitosan impregnated hemostatic gauze could potentially alter the paradigm for the way clinicians treat this patient population in allowing for rapid control of bleeding despite the prevalence of anticoagulants. However, due to the small number of patients in this study, the results are not necessarily generalizable. In the future, further investigation may be needed.

CONCLUSIONS

The prevalence of chronic wounds among Americans continues to increase. Chronic wounds often require debridement to facilitate healing, however vigorous debridement is often accompanied by significant bleeding. In many cases, hemostasis can be challenging, especially when patients are on prophylactic anticoagulation therapy for cardiovascular comorbidities. Chitosan impregnated hemostatic gauze provides a safe and effective method of controlling bleeding after sharp debridement of wounds and a suitable environment for moist wound healing conditions. It significantly reduces the time taken to gain control of bleeding in a mixed group of patients, including patients on various anticoagulant therapies. Patients find the treatment more comfortable than traditional methods of gaining control of bleeding after hemostasis. The gauze can be used as a wound dressing after gaining hemostasis and provides an environment for wound healing to progress, with improved granulation tissue after treatment.

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Dr. Snyder has published several book chapters, more than 125 papers on wound care in peer-reviewed and trade journals, and has been a principal investigator on more than 30 randomized controlled trials. He is the medical director for Systagenix and chairman of its Medical Advisory Board.

Dr. Brian D. Sigal

Dr. Brian D. Sigal has been a podiatrist for 20 years, during which time he has developed an expertise in the practice of wound management and limb salvage.

Dr. Sigal is a diplomat of the American Board of Podiatric Surgery and is certified in foot surgery. Additionally, he holds diplomat status in the American Board of Wound Management and is a certified wound specialist. He is also co-medical director of the Broward Health Coral Springs Center for Wound Care & Hyperbaric Medicine. In addition, Dr. Sigal is currently involved, as sub-investigator, in numerous research studies concerning many innovative wound healing modalities and products.

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