CASE STUDY

Use of Topical Small Molecule Technology to Improve Patient Outcomes in the Diabetic Wound Care Setting

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Abstract Patients were chosen at random by primary investigator based upon initial presentation with dry, cracked, and/or reddened skin, with underlying complications from compromised microvasculature. Intervention was conducted by using topical products designed to utilize small molecule technologies, with a molecular weight of fewer than 500 Da, to deliver, via topical diffusion, nutrients and antioxidants through the skin layers to address issues stemming from inadequate blood flow to the dermis. An “all-in-one” moisturizing cleansing lotion was applied to the affected areas and washed gently with a warm damp cloth. After cleansing, the skin was treated with a moisturizing skin cream or a chlorhexidine-containing skin shield on areas with redness or advanced breakdown. All products contain dimethicone as an active ingredient and are classified as OTC skin protectants per approved FDA monographs. Patients were evaluated by the primary investigator for noticeable resolution or improvements in dryness, scaling, skin cracks, and erythema.

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Introduction

Skin is the largest organ of the body, and hygiene and hydration is often neglected or rendered in suboptimal ways, both in the out-patient and in-patient care setting. Frequently, these practices place the patient at increased risk for further tissue breakdown and can be compounded by the deleterious effects of co-morbidities such as diabetes, peripheral neuropathy, peripheral arterial disease, micro-vascular disease, and/or venous insufficiency. Health care costs for people with diabetes are 2.3 times higher than the non-diabetic population with otherwise

similar health profiles.¹ The economic costs of health care associated with diabetes is \$245 billion annually including \$176 billion in direct costs and \$69 billion in direct costs including loss of income due to disability and premature mortality.¹

Diabetes is among the diseases that continue to grow in the number of patients that are currently diagnosed, or are estimated to be in a pre-diabetic state. The prevalence of patients diagnosed with diabetes in the United States increased by 128% from 1988 to 2008.² In the population of patients 20 years of age and older, there are 5205 newly diagnosed cases a day.³

The majority of patients with lower-limb problems that place them at risk of amputation have diabetes. More than 60% of non-traumatic lower-limb amputations occur in people with diabetes. Each year about 65,700 non-traumatic lower-limb amputations are performed in people with diabetes representing 180 patients a day.⁴

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Problems that are associated with diabetes include heart disease, kidney disease, diabetic retinopathy, and blindness. In the wound-care setting, the most complicated problems are associated with neuropathy, vascular disease and poor rates of wound healing. Blood flow compromise to the lower legs and feet results in increased serious skin issues and risk for infection.

Problem

While the field of wound medicine has advanced and today we have many more tools at our disposal that allow us to either avoid amputation or reduce the aggressiveness of amputation, we are still, more often than not, left with few good choices.

Healing rates of patients with diabetes are nearly double that of patients without diabetes,⁵ 49 h versus 26 h, when studied in a traditional laboratory diabetic wound model.⁶ This places the health care provider at a significant disadvantage. Couple this with neuropathy and vascular disease, the rate of amputations continues to grow and this is a statistic that we all must work to reverse using new technologies.

Methodology

In order to determine if a new type of treatment can be effective on the diabetic patient population, at risk for either an amputation or a greater level of amputation, two high risk patients were selected for treatment using topically diffused small molecules with a molecular weight of under 500 Da.

A new line of advanced skin and wound care products containing Viniferamine™ was selected for the study. Viniferamine™ products contain potent antioxidants with molecular weights that easily penetrate the stratum corneum by passive diffusion and have been proven to improve viability of endothelial cells by 50%.⁷ Endothelial cells are the cells that line the vital capillaries that are required to deliver nourishment to the dermal-epidermal junction. The small molecules in Viniferamine™ include trans-resveratrol from grapes, Oleuropein from olives and Epigallocatechin gallate (EGCG) from green tea.

The initial evaluation was done on two high-risk patients with diabetes presenting with skin problems that had remained unresolved using traditional standard of care including regular foot exams and the use of moisturizers except between the toes. Based upon the favorable results of the first two patients, 6 additional patients have been enrolled in the study.

Case 1

Well developed and groomed 42 year old Caucasian male with personal medical history of, Type II Diabetes-insulin

treated, Peripheral Neuropathy, Hypertension, Coronary Artery Disease, Hyper-cholesterolemia, Peripheral Arterial Disease and micro-vascular disease, Venous disease of lower extremities, and foot ulcerations with cellulitis and amputations (Fig. 1).

Social History

Patient has a prior history of tobacco use, with mild consumption of alcohol. He does not exercise and is fully intact in all forms of dimension and memory.

Allergies

Patient is allergic to Heparin, Lovenox, Tetanus, Norvasc, Vancomycin, Enoxaparin and Tazobactam.

Medications

Ambien 5 mg at bedtime, Cardura XL 8 mg ER daily, Losartan 100 mg daily, Tramadol 50 mg every 4–6 h for pain, Lantus 30 units/ml twice daily, Effient 10 mg daily, Aspirin 81 mg daily, Victoza 1 mg/ml daily, Lisinopril 20 mg daily, Clonidine 0.1 mg twice daily. Antibiotic usage history includes Keflex, Ciprofloxacin, Levaquin, and Augmentin.

Past Surgical History

Knee Arthroscopy, Orchiectomy Left, Amputation 1st toe Left followed by 2nd toe Left, followed by trans-metatarsal amputation Left, Amputation Partial 1st Ray Right followed by Revision 1st ray resection. Cardiac Catheterization, Stent-Descending Coronary Artery, Percutaneous Transluminal Angioplasty Lower Extremity, Atherectomy and Percutaneous Transluminal Angioplasty of Right Peroneal Artery, Selective Right Lower Extremity Angiography with runoff.

Case 1 Details

Patient had chronic ulceration to plantar right foot, complicated by diabetes, vascular and neuropathic compromise, as well as, mechanical deforming forces increasing the risk of a sustained ulceration. Prior partial amputation of the first ray and a subsequent revisionary surgery, due to secondary osseous changes to area, had been performed. This condition was further complicated by a series of surgeries to the contra-lateral foot, resulting in a final trans-metatarsal amputation. This trans-metatarsal amputated foot had remained stable, closed and healed. Patient maintained moderate control of fasting blood sugars over treatment course in the range of 94–190 mg/dl. Standard offloading and local advanced wound care principles were used to care for ulcer. Complications of cardiac disease also resulted in catheterization and stent placement. Endovascular

Figure 1 (A, B) 42 year old Caucasian male with Type II Diabetes-insulin treated, Peripheral Neuropathy, Hypertension, Coronary Artery Disease, Hyper-cholesterolemia, Peripheral Arterial Disease and micro-vascular disease, Venous disease of lower extremities, and foot ulcerations with cellulitis and amputations. Treated with a twice a day regimen of Viniferamine™ small molecule technology. This patient was followed for a period of 5 weeks.

intervention was rendered to increase perfusion to the lower extremities. Percutaneous Transluminal Angioplasty of Lower Extremity resulted in no significant residual stenosis in Right Peroneal artery with adequate flow into distal collateral; which demonstrated 100% stenosis prior to procedure. The Dorsalis Pedis artery was patent after removing 99% stenosis at mid vessel. There was an overall improvement to the perfusion of the foot. The ulcer condition improved after application of amniotic allograft, however, the skin condition of the foot and peri-wound had continued to decline over the course of treatment. Patient suffered with increased dryness, cracking and excoriated peeling skin. The patient's skin care regiment included cleansing with an over the counter, high pH, anti-microbial soap and use of a petrolatum based ointment. This was done inconsistently by patient. Additionally, the skin of the foot suffered from benign neglect due to constant covering with external cotton containing gauze bandages and elastic containing wraps. Skin hygiene and hydration was only rendered every few days to these areas. Despite sustained adequate perfusion to the lower extremity following cardiovascular intervention treatments, the skin sustained a dehydrated, cracking and excoriated state. A twice a day regimen of cleansing with Viniferamine™ Skin Cleansing Lotion, and treating the affected areas with Viniferamine™ Skin Renewal Cream, and the chlorhexidine-containing Viniferamine™ Skin Shield to wounded and reddened, or areas of new breakdown, was introduced. This was followed for a period of 5 weeks.

Case 2

Well developed and groomed 84 year old Caucasian female with personal medical history of Type II Diabetes-insulin treated, Peripheral Neuropathy, Hypertension, Hypo-thyroidism, History of Methicillin Resistant Staph Aureus, Arteriosclerotic Disease/Peripheral Arterial Disease and micro-vascular disease, and ulceration with gangrene 1st toe (Fig. 2).

Social History

Patient has been exposed to second hand tobacco smoke, and is a non-user of nicotine products or alcohol. She does not exercise and is fully intact in all forms of dimension and memory.

Allergies

Patient has no known food or drug allergies.

Medications

Prednisone 5 mg daily, Lisinopril 10 mg daily, NovoLog 100 units/ml daily, Clopidogrel 75 mg daily, Levothyroxine 0.075 mg daily, Caduet 5/20 mg daily, Hydrochlorothiazide 12.5 mg daily, Klor-Con 10 meq three times a day,

Figure 2 (A–D) 84 year old Caucasian female with Type II Diabetes-insulin treated, Peripheral Neuropathy, Arteriosclerotic Disease/Peripheral Arterial Disease and micro-vascular disease, and ulceration with gangrene, Hypertension, and Hypo-thyroidism. Treated with a twice a day regimen of Viniferamine™ small molecule technology. This patient was followed for a period of 8 weeks.

Metformin 1000 mg daily, Januvia 100 mg daily. Antibiotic history includes Levaquin, Vancomycin intravenous, Keflex, Doxycycline Hyclate, and Avelox.

Past Surgical History

Hysterectomy, Right Hip replacement, Bilateral Knee replacement, Percutaneous Transluminal Angioplasty Lower Extremity, Percutaneous Transluminal Angioplasty – Superficial Femoral artery, and Percutaneous Transluminal Angioplasty of Right Anterior Tibial artery, Selective Right Lower Extremity Angiography with runoff.

Case 2 Details

Patient's initial presentation was with an ulcerated great toe which developed gangrene. Patient maintained moderate control of fasting blood sugars over treatment course in the range of 102–150 mg/dl. Standard offloading and local advanced wound care principles were used to treat ulceration. Endovascular intervention to increase perfusion to lower extremities preceded distal hallux amputation. Percutaneous Transluminal Angioplasty of Lower Extremity resulted in a minimal residual stenosis (10–20% compared to 100% stenosis prior to procedure) to popliteal and anterior tibial arteries with brisk retrograde flow to the foot. Short term, full closure was disrupted after traumatizing the healed surgical digit by normal unprotected walking. Skin condition of the foot had continued to decline over the course of treatment with increased dryness, cracking and erythematous excoriated skin. The patient's

prior skin care regimen included cleansing with an over the counter, high pH, anti-microbial soap and use of a low concentration urea based moisturizing cream after bathing once a day. Overall, the skin of the foot was benignly neglected due to constant covering with external cotton based gauze bandages and wraps. Skin hygiene and hydration was only rendered every few days to these areas. Despite sustained adequate perfusion to the lower extremity following cardiovascular intervention treatments, the skin sustained a dehydrated, cracking and erythematous/red, excoriated state. A twice a day regimen of cleansing with Viniferamine™ Skin Cleansing Lotion, and treating the affected areas with Viniferamine™ Skin Renewal Cream and the chlorhexidine-containing Viniferamine™ Skin Shield applied to areas of redness or acute breakdown was introduced. This patient was followed for a period of 8 weeks.

Discussion

Skin hygiene and hydration for our wound patient often is neglected or rendered in a suboptimal way. Subjects in this series had responded to the treatment protocol with observable signs of improvement to skin condition within 1 week of application of advanced small molecule products. Improved response had continued throughout follow up during case series and excellent skin hydration health with decreased redness and cracking was maintained.

Implementing small molecule science treatment protocols into practice serves to reverse cell death. This is

accomplished by topical diffusion of molecules, under 500 Da, into the skin's cells to stop or reverse free radical damage. Oleuropein and Hydroxytyrosol eliminate 1 million free radical molecules per cell, per second. These small molecules move into the cells that are damaged and repair them; making them viable enough to restore tissue with minimal intervention.

Oleuropein and Hydroxytyrosol are important phenolic compounds derived from olives and olive leaves that possess a variety of beneficial qualities including antioxidant, anti-inflammatory, anti-microbial, and wound healing activities.^{6,8,9} In addition, Hydroxytyrosol, a potent antioxidant that results from the hydrolysis of Oleuropein, was found to increase the activity of the oxidative defense enzyme, manganese superoxide dismutase (MnSOD), three-fold in studies where Hydroxytyrosol also extended the chronological lifespan of skin cells.¹⁰ In a model of wound healing that included glucose impaired wound healing, similar to diabetic conditions, Hydroxytyrosol and Oleuropein were shown to increase endothelial cell migration and decrease wound healing times by 50%.⁶

ViniferamineTM products represent a new advanced-standard of care that combines advanced technologies in easy-to use products. These topical products contain small molecules, which enter the skin and then the cells to repair and restore. By offering patients this new technology, which is effective to initiate the healing process by utilizing microscopic tools that are under 500 Da in size; so small that one cannot see them can significantly facilitate the body's ability to heal. Surprisingly, these simple and low cost products are available today that deliver small molecules that are scientifically proven to reduce healing times and repair damaged cells. This all leads to superior outcomes and very happy patients.

Patients and staff alike noticed improvement within days of starting the study. Patient compliance was made easy due to the patient's ability to see improvement. The price of ViniferamineTM products is another advantage. The products are well within the price range of most patients and they have agreed to continue using the products beyond the study period.

Conclusion

The use of small molecules, passively diffused, found in the ViniferamineTM products substantially improved skin quality issues that had not resolved over extended periods of time using standard of care. The products were easy for the patients to use at home and the attitude of the patients toward their care was a marked improvement. Thus, use of advanced small molecule products, delivered in simple creams and lotions, can serve to promote faster healing and potentially save more patient limbs while reducing the cost of care.

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