



Treatment of Early Diabetic Foot Ulcers with Curaderm HP Cream

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Abstract

Between 5-10 percent of all diabetics will, at some time in their life have an ulceration of their lower extremities (33 – 35). In those who develop gangrene of the ulcerated lower extremity, the operative mortality can be as high as 25 percent with a significant number of the survivors dying within the first post-operative year (36 – 40). If there was only a 3 percent reduction in the number of amputations through successful medical therapy, approximately 300 lives could be saved. In addition, over 27 million dollars would be saved per 1,000 amputations not performed (33). The indirect health care cost saved would be at least 2 to 3 times this amount. Development of a simple, cost effective therapy that could be utilized by the patient at home could significantly impact on the incidence and progression of lower extremity ulcers in diabetics and, as a result, lower overall medical treatment costs.

Previously, we had demonstrated that use of a specific skin cream (Curaderm hp, PhytaTek Laboratories, Inc.) resulted in a rapid resolution of pressure ulcers in a debilitated, elderly population (41). We postulated that a similar healing rate may be seen in a diabetic population with lower extremity ulcers. The healing of chronic, therapy resistant lower extremity diabetic ulcers was accelerated during a 30 day therapy interval. Greater than 50% of patients demonstrated complete resolution of their ulcers. The remaining patients demonstrated between 85 – 90% reduction in ulcer area.

Introduction

The diabetic foot is profoundly susceptible to a multitude of insults that may result in disease. This susceptibility is secondary to an impaired vascular and neurologic state. This state of impairment can affect any component of the foot. The clinical findings of the diabetic foot include nail deformities, callus formation, skin lesions, foot ulcers and ultimately, the involvement of bone (1). The diabetic with neuropathy frequently has sensory deficits that result in a decreased ability to detect trauma. In the compromised foot, even trivial trauma can ultimately result in significant pathology. For example, an unimpressive initial ulceration may lead to infection and irrevocably to an amputation. It has been estimated that 20% of all diabetes-related admissions to the hospital are secondary to foot ulcerations (2). The average stay is about four weeks and the cost in 1989 most likely will exceed 500 million dollars per year (3, 4). This cost does not include the morbidity of amputation procedures nor the strain on the mental well-being of these patients.

Diabetic foot ulcers are defined by several specific criteria based upon their severity. These are graded from 0 to 5. In general, ulcers that are grade 0 – 3 are related primarily to a neuropathic process, whereas grades 4 and 5 are primarily vascular. Later stage ulcers usually began as incidental trauma and over time progress. The following are common definitions for the early grade diabetic ulcers:

- Grade 0: No obvious ulcer, but thick callus with or without bony deformities
- Grade 1: Superficial ulcer, but not clinically infected
- Grade 2: Deeper ulcer than Grade 1, and clinically infected but without bone involvement
- Grade 3: Deep ulcer with bone involvement and abscess formation
- Grade 4: Localized gangrene
- Grade 5: Gangrene of the entire foot

The ultimate outcome of most diabetic foot ulcers is amputation. Traditionally, this is associated with significant morbidity and mortality. The survival rate of the diabetic amputee is not impressive. There has not been a significant improvement in the mortality rate for the past 35 years. Even today the mortality rate associated with lower extremity amputation is between 1.5 – 10% (5). This data does not, however, differentiate between below the knee and above the knee amputation. Above the knee amputation is twice as lethal as below the knee amputation (6). The post amputation statistics still demonstrate only a 65% survival rate at three years and a 40% survival rate at 5 years. On the average, greater than 50% of amputation survivors will have the opposite leg amputated within 5 years (7, 8, 9, 10). These statistics may be improved by decreasing the incidence of pressure sores in the “at risk” diabetic population. The first step is to make the skin less susceptible to minimum trauma.

Diabetic neuropathy is the major reason for the development of the diabetic foot ulcer. This condition is also the principle explanation for successive hospitalizations in this population. In one study there were three times more hospital admissions for painless foot trauma when compared to painful ischemia (vascular insufficiency) (11). The two most common neurological deficits are the loss of both temperature perception and tactile sensation. With the loss of touch and temperature, trauma is common. This may be related to mechanical irritation from either shoes or callus. It may also be secondary to chemical/thermal irritation, eg. hot baths. If untreated, ulcerations develop, followed by infection. This initiates a cascade of events whose ultimate outgrowth may be amputation of the affected limb. Neuropathy also affects bone reformation. One common type of reformation is termed Charot foot. The changes in the bone result in an altered gait. New pressure points are created. The new pressure points promote the formation of new callus. This buildup of new callus results in local pressure ischemia and that may progress to ulceration (12).

Diabetes also affects the autonomic nervous system. This defect plays a significant part in the formation of foot ulcers. The dysfunction of the autonomic nervous system results in a significant decrease in the production of moisture. The skin becomes dry, scaly, and eventually becomes fissured and cracked. This promotes ulceration. The ulcerations are a natural portal for bacteria, allowing access to the deeper layers of the skin. In this manner, autonomic dysfunction may be the most important in the production of the diabetic foot ulcer (13, 14, 15). Conversely, the prevention of skin changes may be the single major factor in the prevention of pressure ulcers of the diabetic foot. Interestingly, in these patients, there is an increased blood flow to the foot secondary to arteriovenous shunting. The shunting results in a decrease in blood flow to the capillary beds. The impaired perfusion results in a decrease in oxygen and nutrient delivery, thus enhancing ulcer formation. The progression or regression of the early stage ulcer can be followed by measuring the temperature of the skin (16, 17, 18).

The skin of the diabetic lower extremity is at increased risk for breakdown because it is vascularly compromised. The vascular disease that is associated with diabetes involves both the large and small sized vessels (19). This disease is initiated by the deposition of atheromatous plaques. These are similar to those seen in the non-diabetic, but are found in larger animals. They also appear earlier in the diabetic. This may reflect accelerated endothelial damage secondary to an aberrant glycosylation process (20). Interestingly, the most severely involved vessels are below the knee (19). The subsequent degree of vascular compromise is directly related to the incidence of disease in the lower extremity. Bell (14) demonstrated that gangrene occurred about 60 times more frequently in diabetic patients than the general population. Interestingly, a fifty-year old diabetic has greater than 150 times the incidence of gangrene when compare to age-matched controls (14).

The mechanism appears to be related to the accelerated formation of thrombus in the vessels (21). Other risk factors that play an important role in the formation of atherosclerotic plaques and thrombus include smoking, hypertension, hypercholesterolemia, hyperglycemia, and increased age (22, 23, 24).

Reversal of the neurologic and atherosclerotic changes would be the ideal treatment for the diabetic foot ulcer. However, at this time, this is not possible. Therefore, decreasing the risk factors may be the best strategy for the prevention and treatment of the diabetic ulcer. Treatment of the ulcer disease should begin with timely evaluation of the feet. One study has demonstrated that the early evaluation and treatment of diabetic foot ulcers occurred in only 12% of patients presenting to the doctors office (25). Careful evaluation of the skin is needed. This allows for early intervention in the patient at risk. The need to keep the skin intact and supple should not be underestimated. Ulcers form where the skin has broken down for whatever reason. A reduction of callus will decrease local pressure and may aid in increased nutritional delivery to compromised tissues. Special foot ware may be needed. However, even with the best fitting footwear, the formation of the diabetic foot ulcer may not be prevented if the skin is already cracked and fissured.

Improving circulation is effective in a select subpopulation of diabetics with foot-ulcer disease, eg. those with large vessel occlusive disease. This is accomplished by vascular bypass procedures. The overall outcome in patients with small vessel disease, however, is not significantly affected by such bypass procedures. The reduction of additional risk factors for atherosclerosis include stopping smoking, lowering the blood pressure, and correcting hypercholesterolemia.

Most ulcers are caused by moderate pressure over a relatively short period of time in a specific area of the foot. Studies have shown that moderate, repetitive pressure will result in damage to the foot. This was demonstrated by an increase in hyperemia, edema and skin temperature of the foot pads of rodents subjected to a specific, repetitive stress over a period of time (25, 26, 27). After about one week, full thickness ulcers formed. In these studies, the changes in skin temperature were a sensitive indicator of early damage. The progression or regression of the ulcers correlated directly with skin temperature. Skin temperature was measured either by thermography or a thermometer with a thermocouple. Another factor evaluated in one study was the ability of normal and damaged skin to withstand the sheer forces of walking. Normal, moist, supple skin was able to withstand the sheer forces well since these forces were locally absorbed (19). In the compromised foot, the sheer forces were not adequately absorbed. These sheer forces are distributed over a greater area in non-compliant skin. This leads to local micro-hematoma formation (28, 29). This has been postulated to increase the local ischemia of the diabetic foot. Other studies have demonstrated that as tissue becomes stiffer, eg. Calloused, less force is required to achieve a set degree of blood vessel compression. Although callus is a protective mechanism for areas of prolonged stress, it can concentrate stresses produced by skin on bone, trapping the thin layer of soft, compliant tissue. After sufficient damage has occurred, the ultimate consequence is ulcer formation.

Pressure reduction in diabetic feet involves the use of the proper footwear, foam insoles and the maintenance of soft, supple skin. Numerous oil-based moisturizers have been recommended for the softening of skin in these patients (28). However, there is no objective evidence that the moisturizers affect the progression of a diabetic foot ulcer. This simple procedure, if able to make diabetic skin more supple, may significantly decrease the risk of ulcer formation in the at-risk population. Any decrease in the relative risk must impact on the overall morbidity and mortality of the diabetic foot ulcer.

One over-the-counter moisturizer, Curaderm hp (PhytaTek Laboratories, Santee, CA) has been shown to have efficacy in the treatment of many dry skin conditions. It is an herbal formulation that also contains several vitamins. This formulation is clinically used as adjunctive treatment for early stage decubitus ulcers. The results have been favorable (30). In addition, anecdotal clinical trials with early stage diabetic foot ulcers using the Curaderm hp cream have been promising (31). Skin that was dry, scaly and heavily calloused became supple within a three week period. In addition, this formulation was also shown to be efficacious in the treatment of eczema (32) suggesting anti-inflammatory as well as moisturizing properties. This preliminary data suggests that Curaderm hp may be efficacious in the treatment of the early stage diabetic foot ulcer.

Methods

This protocol was approved by the Human Investigation Committee of Rush-Presbyterian St. Luke's Medical Center.

Eighteen insulin-dependent diabetics were enrolled into the study. The admission requirements were the following: insulin-dependent diabetes and a stage I ulceration of the lower extremity for at least four months that was not responding to several different medical therapies. Patients were excluded from the study if the ulcers showed signs of infection (warm, painful erythema, pus drainage, etc.). Participants were asked to apply the Curaderm hp cream (PhytaTek Laboratories, Inc.) to the ulcer site three times a day for one month. The composition of Curaderm hp cream has been described previously (9). The amount of cream applied varied according to the ulcer size. Participants were instructed to apply enough cream to cover the ulcer. The cream was to be applied after cleaning of the ulcer and/or bathing. Participants were evaluated on day one, approximately day fifteen and after approximately one month. One participant was lost to follow up after 14 days.

The size of the ulcer was evaluated by photograph and by measuring the area of the ulcer at the initiation and termination of the study. The area of the ulcer was calculated from the product of the longest diameter and 90 degrees to that axis. The percent resolution of the ulcer was calculated as follows: $(1 - (\text{final ulcer area}/\text{initial ulcer area})) \times 100\%$. Initial blood chemistries and cell blood count were performed.

Discussion

The participants in the study were chosen on the basis of long standing diabetes and an ulceration of the lower extremity that was resistant to medical therapy. The only change in the participants daily lives was the application of Curaderm hp cream to the ulcers three times a day. They were instructed to gently apply the cream and not to rub it in. For any other medical problems, the participants were followed by their private medical physicians.

The ulcers treated in this clinical trial were unresponsive to other therapy and therefore a more difficult ulcer to treat. In the elderly, these ulcers often become infected and result in sepsis and even gangrene of the extremity (1, 5). Amputation is often required in the more severe cases (7, 8). The morbidity and mortality of an amputation is very high and the medical costs for this treatment can run into hundreds of millions of dollars (1, 2). Effective treatment and prevention of progression of diabetic ulcers may be extrapolated to a saving of life and the quality of life. In addition, if

amputations and prolonged hospitalizations are able to be avoided, the overall cost of treatment of diabetic ulcers could decrease by tens of millions of dollars.

The results demonstrate a rapid resolution of the stage I ulcers after a 30-day application of the Curaderm hp cream (TABLE 2 and PICTURES 1 - 17). This is consistent with other data demonstrating the efficacy of Curaderm hp cream for the resolution of early stage pressure ulcers (9). Resolution of the pressure ulcers was not due to only a decrease in sheer forces (10, 11), but to other components in the Curaderm hp cream. The mechanism by which Curaderm hp influences healing is not known.

This data suggests that a skin cream, Curaderm hp, may be efficacious in the treatment of diabetic ulcers. The number of patients in this clinical trial is small and the measurements of the ulcers not blinded. However, the response rate of ulcer resolution is impressive. While all patients had greater than an 85% healing of their ulcers as defined as decrease in the total area of the ulcer, greater than half had total resolution of their ulcers. Some of those ulcers had not healed in over a year (TABLE 2). A larger clinical trial may more completely define the efficacy of Curaderm hp as a primary medical therapy for the treatment of diabetic ulcers.

Results

The patient population was comprised of male and female insulin-dependent diabetics with lower extremity ulcerations for at least three months (TABLE 1). Most of the patients were elderly and had slight to moderate elevations in their blood glucose levels. The ulcers were not infected but had failed other medical therapies (METHODS). All patients were able to apply the cream to their ulcers three times a day except for patient #13. The cream was applied by the nursing staff three times a day.

The location of the ulcers varied between the anterior leg, foot and toe. Patient #013 had an ulceration on the elbow. Greater than 80% of the patients had 90 – 100% resolution of the ulcers. 54% of the patients had total resolution of their ulcers. All patients demonstrated at least 85% resolution of the ulcers (TABLE 2). Patient #013 died before the completion of the study. However, the ulcer was rapidly resolving after two weeks of therapy. Leg ulcers appeared to heal faster (all leg ulcers completely healed), whereas foot, ankle and toe ulcer resolution varied between 88 and 100%.

The photographs of the ulcers before and after treatment with the Curaderm hp cream demonstrate the range of healing from complete to greater than 85% healed.

TABLE 1

Patient Demographics				
Patient #	Age	Sex	Duration of Ulceration (years)	Hemoglobin/Glucose (mg/% / mg/%)
001	72	M	0.5	10.1/ 225
002	63	M	0.75	9.8/207
003	56	F	1.83	10.2/112
004	65	M	2.5	12.4/119
005	72	F	0.58	9.9/200
006	66	F	0.46	9.2/221
007	34	M	0.42	14.5/175
008	47	F	2.0	14.4/207
009	50	M	0.3	14.7/225
010	67	M	2.0	10.0/195
011	77	M	0.25	11.4/135
012	75	M	1.25	10.3/256
013	63	F	0.25	8.9/408
014	34	M	1.2	12.1/225
015	56	F	2.2	11.1/285
016	61	M	1.5	10.1/254
017	56	F	0.2	11.1/254

TABLE 2

Diabetic Ulcer Size, Location and % Resolution				
Patient #	Location	Area (cm ²)		% Area Healed
		Initial	Final	
001	Leg	1.35	0.0	100
002	Leg	2.0	0.0	100
003	Leg	7.2	0.0	100
004	Foot	1.75	0.08	95
005	Ankle	3.24	0.4	88
006	Foot	4.0	0.4	90
007	Foot	0.45	0.0	100
008	Foot	6.25	1.2	92
009	Toe	2.78	0.2	93
010	Leg	18.2	0.0	100
011	Foot	0.7	0.0	100
012	Leg	13.8	0.0	100
013	Elbow	9.8	1.5	85 (*)
014	Toe	9.0	0.0	100
015	Tibia	18.0	0.0	100
016	Toe	1.1	0.0	100
017	Tibia	5.0	0.0	100

(*) Patient died before completion of the study

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