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RESEARCH PAPER

Effects of Hypochlorous Acid Solutions on Venous Leg Ulcers (VLU): Experience With 1249 VLUs in 897 Patients

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Abstract In order to assess the impact of comorbidities and identify factors that accelerate the healing rate of venous leg ulcers we performed an extensive, retrospective analysis of our experience in a diverse population. From June, 2006 to June, 2014, 897 patients with 1249 venous leg ulcers were treated at Lake Wound Clinics. Treatment protocols utilized the standard regimen of wound cleaning, debridement and compression bandaging. Wound cleaning, autolytic debridement, packing and dressing of venous leg ulcers utilized aqueous solutions of hypochlorous acid (HCA) rather than the standard normal saline. This protocol caused all ulcers to close completely. Comorbidities that delayed healing included uncontrolled or poorly controlled diabetes mellitus, advanced peripheral artery occlusive disease (PAD), active smoking, use of steroid medications and/or street drugs, large initial ulcer size and significant depth. Other factors, including advanced age, recurrent venous ulceration, stasis dermatitis, lipodermatosclerosis, morbid obesity and infection with one or more multidrug resistant organisms did not delay closure. From this experience we conclude that venous leg ulcer care protocols that clean, debride, pack and dress with hypochlorous acid solutions can reduce the effects of some comorbidities while accelerating healing times. Additional benefits are described.

Introduction

"Chronic venous insufficiency" manifests as a cornucopia of clinical problems. The mildest of these is dependent edema that is readily relieved by elevation. The most severe is venous ulceration. Venous insufficiency is progressive and worsens over time. In the United States, it is estimated that 1% of the adult population, i.e., approximately 3.2 million people, have late stage venous insufficiency and either have, or are at risk for development of, venous leg ulcers.[1] Although there are multiple factors that produce venous valvular incompetence in the superficial, deep and perforating veins, the end result is the same. Venous congestion and pooling cause increased

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capillary pressure and permeability. In turn, water, serum protein and formed blood elements leak into the interstitial space and cause fibrin deposition. These pericapillary fibrin deposits limit diffusion within tissues and the leaked leukocytes stimulate the release of inflammatory mediators.[2] Ultimately, the persistent inflammatory state induces tissue necrosis and the venous leg ulcer forms. VLUs most commonly occur at the malleolar level and can become very large.[3] Current standard treatment regimens are based on the provision of extramural, mechanical compression and limb elevation.[4]

There is no longer any debate as to the severity of the socioeconomic impact caused by chronic venous insufficiency and VLUs. Today, the annual cost of treating VLUs is over two billion US dollars, with actual, direct treatment costs of approximately $10,000 per person per ulcer[5] and the average time to heal venous ulcers is 190 days.

These figures are exclusive of the economic losses resulting from life style alterations, time lost from work and frequent hospitalizations.

Development of an effective plan of care for patients with venous leg ulcers must address multiple issues including healing the active ulcer and recurrence prevention. In order to achieve these obvious goals, adequate treatment and management of comorbidities is essential. Furthermore, ulcer-associated infection must be identified and cleared before granulation and epithelial repair can occur. Despite many advances in the development of adjunctive wound care therapies, the average time to heal venous ulcers remains at approximately 190 days.[6]

In 2006 we reported our experience with a cohort of 231 venous leg ulcer patients and our treatment measures that resulted in an average time to heal of 29 days.[7] In this communication we report our retrospective experience with 897 additional patients and their 1249 venous leg ulcers. The evolution of our treatment protocols has maintained our average healing times but has significantly reduced VLU treatment costs. This economic improvement is the result of the addition of HCA[a] to our treatment regimens.

Costs and time to heal recurrent venous ulcers were no greater than those associated with initial venous ulcers. Those comorbidities which extended healing times included active smoking, uncontrolled diabetes, use of steroid medications, use of street drugs, the presence of significant peripheral artery occlusive disease and very large initial size.

Patients and Methods

From June, 2006 to June 2014, 936 patients presented to Lake Wound Clinics for treatment of 1311 venous leg ulcers. Of these, 39 patients with 62 venous ulcers were lost to follow up before healing was complete. All venous leg ulcer care protocols were based on standards of care and were approved by institutional review boards and medical directors. Details of this patient cohort, including comorbidities, are summarized in Table 1. Significant comorbidities included diabetes mellitus, peripheral arterial occlusive disease (PAD) with ABI < 0.80, smoking, morbid obesity (BMI > 45) and the presence of one or more multidrug resistant organisms, most notably methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *S. aureus* (VRSA), *Pseudomonas aeruginosa, Escheriscia coli*, *Acinetobacter baumanii* and *Clostridium difficile*. All ulcers were cultured and, whenever appropriate, patients were referred back to their primary care providers for systemic antibiotic treatment. Ulcer characteristics, including volume, color and type of exudate, presence of odor, ulcer location, duration, surface area (cm^2) and maximum depth (cm) were recorded.

Initial treatment of all venous leg ulcers involved cleaning and debriding foreign matter, debris and necrotic material via application of copious HCA, under pressure if necessary. Where needed, this was accompanied by abrasion using sterile gauze wet with HCA. In all cases requiring sharp debridement, this was performed in an appropriate surgical facility and within 10 days of presentation.

Following initial treatment, all ulcers were dressed and/or loosely packed with sterile gauze soaked with HCA. An appropriately compressive, multilayered, overlying bandage system, utilizing short-stretch or nonstretch materials, was constructed such that greatest compression was at the ankle level. At no time did compression pressures exceed arterial perfusion pressure in the extremity. Those patients whose leg ulcers were complicated by the presence of severe stasis dermatitis, 3−4+ pitting edema, lipodermatosclerosis, lymphedema and/or serous fluid transudation, underwent placement of a paste bandage Unna's Boot[b] applied over the ulcer dressing and extending from the metatarsal heads to the knee. This bandage was reinforced with sterile cotton gauze and overlying short-stretch materials. In all cases requiring paste boot bandaging, the dressing/bandage system was changed at two and four days following initial application, then weekly thereafter until the edema was resolved and healing was determined to be advancing via monitoring of wound size reduction. At every treatment occasion, digital photographs of the wound were obtained and subjected to precise area measurement through the application of planimetry software.[c]

[a] Puracyn and Puracyn Plus Wound & Skin Care Solutions with Preservatives Innovacyn, Inc. 3546 North Riverside Avenue, Rialto, CA 92377, USA. www.puracyn.com.

[b] Unna's Boot Dressing. Patient Technology Inc., Atlanta, GA 30360, USA.

[c] Pictzar-CDM Photo Digital Planimetry Software. Bio-visual Technologies, LLC. 271 B Market Street, Elmwood Park, NJ 07407, USA.

Table 1 Patient characteristics (n = 897 patients).

Age (years)	63 ± 32[a]		
Gender, *n* (%)	Men 323 (36%)		Women 574 (64%)
#VLUs on admission	1	2	>2
n (%)	522 (58%)	289 (32%)	86 (9%)
Comorbidities			
Diabetes mellitus	NIDDM 401 (44%)		IDDM 263 (29%)
Active smoking	624 (69%)		
Diabetes + smoking	222 (24%)		
Morbid obesity (BMI >45)	683 (76%)		
Varicose veins	530 (59%)		
Stasis dermatitis	671 (74%)		
Lipodermatosclerosis	313 (34%)		
CHF	196 (22%)		
Recurrent VLU	216 (24%)		
Duration of VLUs	36 ± 22 months (range 1–120 months)		
PAD (ABI < 0.80)	601 (67%)		

n: # of patients; %: percent of cohort; VLUs: venous leg ulcers; PAD: peripheral arterial disease; ABI: ankle/brachial systolic pressure index; IDDM: insulin-dependent diabetes mellitus; NIDDM: non-insulin dependent diabetes mellitus; BMI: body mass index; CHF: congestive heart failure.
[a]Mean ± 1SD.

The degree of bandage compression achieved was controlled by continuous monitoring of digital artery pressure pulse waveforms whenever possible.[d] In the absence of detectable waveforms, a handheld 8 mHz continuous wave Doppler instrument was used to insonate digital or pedal arteries before, during and at completion of bandaging. In all cases, developed bandage compression pressures did not meet or exceed distal artery perfusion pressure.

Except as described above, the frequency of dressing/bandage system changes was dictated by the ulcer exudate volume and bioburden mass. Heavily exudative wounds initially required daily treatment with the hypochlorous acid solution and concomitant compression bandage system change. This schedule was quickly revised to provide fewer clinic visits and wound treatments as healing progressed. Once the VLUs were healed, and whenever possible, patients were encouraged to wear appropriate compression garments and to seek interventionalist consultation for possible vein ablation to prevent ulcer recurrence.

Nutritional deficiencies common to venous ulcer patients have been described.[7] Whenever appropriate, patients were directed to increase their consumption of high quality dietary protein and to use a vitamin/mineral supplement. In diabetic patients, close monitoring and consistent control of serum glucose levels to <120 mg/dL is essential to the healing process.

Venous leg ulcers that were infected with one or more multidrug resistant organisms required extremely aggressive treatment structured to reduce the bioburden mass and inhibit further growth.[8] When use of systemic antibiotics was contraindicated, we found that frequent, i.e., more than three times per day, wound lavage with copious volumes of HCA would achieve infection clearance with 2–5 days. It is important to note that, regardless of infection status, all wound care was performed using contact isolation protocols.

Microcirculatory integrity was assessed by measuring tissue oxygen concentration ($tcpO_2$)[e] in the immediate, periwound tissue.[9,10] Measurements were obtained at the time of initial presentation and 15–30 s following exposure of wound tissues to HCA. Measurements were repeated at 72 h after initial exposure to HCA then as necessary.

Results

It is well known that venous ulcer size alone is directly proportional to healing times[7] and, as seen in Table 2, this was not different in our experience. However, the extent of healing time increase appeared to be more directly related to maximum wound depth rather than to surface area alone. Very large VLUs, i.e., those with surface areas >40 cm^2, usually exhibited variable depths within the wound. These could reach depths >10 cm in morbidly obese patients or those with extreme edema. Wound tunneling and/or undermining did not affect healing times.

Healing times were extended in all VLU patients, regardless of initial wound size, when more than one significant comorbidity was present. These results are

[d] Vicorder. Physicians Resource Network, Inc. 218 Shove Street, Fall River, MA 02724. www.prnvascular.com.

[e] Radiometer Copenhagen TCM 4 Series MKII. Radiometer Medical ApS, DK-2700 Bronshoj. www.radiometer.com.

Table 2 Effect of initial VLU size on healing times.

# of patients	VLU dimensions maximum area (cm^2)/depth (cm)	# days to healed
26	<5/<1	2–5
131	6/<1	2–7
122	7–20/1–3	9–27
454	21–30/2–4	9–31
101	21–40/5–10	14–40
63	>40/1–10	21–180

illustrated in Table 3. Extended healing times occurred when VLUs were complicated by the presence of diabetes, smoking, use of steroid medications, use of street drugs, peripheral artery disease and morbid obesity (BMI > 45). Healing times were not extended, however, for recurrent VLUs *per se* nor did the presence of congestive heart failure retard healing. Patients with varicose veins, stasis dermatitis, lipodermatosclerosis, multidrug resistant infections and immunocompromise (HIV) did not experience significant extensions of VLU healing times. Microcirculatory integrity, assessed via measurement of $tcpO_2$ in periwound tissues, was most compromised in diabetic patients who were also smokers or who were positive for significant PAD (Table 4). Following 15–30 s of exposure to HCA, all patient categories exhibited increased $tcpO_2$ except for those with significant PAD and/or smoking. At 72 h, those patients who exhibited increased $tcpO_2$ in response to initial wound bed exposure to HCA also demonstrated persistent elevation of $tcpO_2$ above baseline. Diabetic patients and diabetics who smoke and/or who had significant macrovascular PAD had trivial increases in periwound $tcpO_2$ that were not sustained for 72 h. Similarly, nondiabetic patients who smoke also failed to exhibit residual increases in $tcpO_2$ at 72 h.

Table 3 Effect of comorbidities on healing times.

# of patients	Comorbidities present	Days to heal
101	IDDM	17–34
393	NIDDM	6–41
42	IDDM + active smoking	36–117
34	IDDM + active smoking + BMI > 35	44–186
26	NIDDM + PAD + active smoking	48–180
21	NIDDM + CHF	18–36
136	MDRI + NIDDM	16–39
211	IDDM + active smoking + MDRI	35–114
280	MDRI only	5–13
16	MDRI + age > 95 years	9–29

NIDDM: Noninsulin Dependent Diabetes Mellitus; IDDM: Insulin Dependent Diabetes Mellitus; PAD: Peripheral Artery Disease (Ankle/brachial systolic pressure index < 0.80); BMI: Body Mass Index; CHF: Congestive Heart Failure; MDRI: Multi-drug Resistant Infection.

Of concern in the treatment of VLUs is the development of biofilm within the wound. Biofilm is a structural community of microorganisms encased in a self-produced extracellular matrix that is variably adherent to the wound surface.[8] The biofilm itself is avascular, resists the host immune system and is not readily penetrated by antimicrobial agents. Biofilms in wounds cause substantial healing delays. In this study, biofilm presence within a wound was determined via Flow-through Gram Stain.[9] This method reveals the presence of microcolonies within the matrix structure and distinguishes a true biofilm formation from visually similar appearances of exudate accumulation, slough and mucoid debris.

Defeating biofilms and preventing their recurrence required mechanical disruption of the biofilm with immediate exposure to antimicrobial agents. We find that light abrasion utilizing sterile cotton gauze soaked with HCA, followed immediately by flushing the wound with more of the solution, effectively destroys the extant biofilm *in situ* and, with several repetitions over several days, prevents biofilm from being reestablished. However, we have found that the treatment episodes must be performed no more than 36 h apart to completely remove the biofilm. With incomplete removal, recurrent biofilm will retard all healing stages.

Discussion

All 1249 venous leg ulcers reported in this data set were healed completely. The shortest healing times (2–5 days) occurred in patients who were nonsmokers and who were not diabetic. Patient age did not significantly affect healing time. Extended healing times (>4 weeks) were found in patients with larger initial ulcer size, greater ulcer depth and with two or more comorbidities. Comorbidity combinations of special note include diabetes accompanied by significant peripheral artery disease (ABI < 0.8) and diabetes accompanied by persistent smoking. The longest healing times were encountered by patients for whom compression therapy was contraindicated,[10] e.g., diabetic patients with severe arterial occlusive disease (ABI < 0.6). Regardless, aggressive management with HCA resulted in complete closure within 180 days in this very difficult patient cohort.

Monitoring digital artery pressure pulse waveforms and/or Doppler signals is a reliable method of controlling the level of compression achieved during compression bandaging. Additionally, effective compression bandaging begins the wrapping at the level of the distal metatarsal heads and terminates at the knee. Compression bandage composition varied in response to wound and patient conditions. Materials included paste wraps (Unna's boot), non-stretch or short-stretch materials. All compression

Table 4 Effect of comorbidities on microcirculatory response of periwound tissue to HCA exposure.

# patients	Comorbidities	$tcpO_2$ (mm Hg)		
		Initial	$_{+}$HCA@30s mean ± 1 SD	$_{+}$HCA@72 h mean ± 1 SD
101	IDDM	89 ± 8	148 ± 23	122 ± 15
393	NIDDM	111 ± 11	179 ± 14	146 ± 25
42	IDDM + active smoking	38 ± 10	78 ± 19	34 + - 13
34	IDDM + active smoking + BMI > 35	33 ± 11	75 ± 20	29 ± 9
26	NIDDM + PAD + active smoking	26 ± 11	31 ± 11	<25
280	MDRI only	139 ± 17	211 ± 22	158 ± 11
16	MDRI + age > 95 years	96 ± 18	194 ± 28	133 ± 30

HCA: Superoxidized Solution stabilized with hypochlorous acid; $tcpO_2$: tissue oxygen concentration; @30s: 30 s following exposure to HCA; @72 h: 72 h following exposure to HCA; Mean ± 1: Standard Deviation; IDDM: Insulin Dependent Diabetes Mellitus; NIDDM: Noninsulin Dependent Diabetes Mellitus; BMI: Body Mass Index; PAD: Peripheral Artery Disease (Ankle/Brachial systolic pressure index < 0.80); MDRI: Multi-drug Resistant Infection.

bandages were comprised of 2–4 layers and all materials were a minimum of 4 inches wide to prevent development of constricting bands.

All venous leg ulcers were cultured and antibiotic sensitivities to all identified flora were obtained. When appropriate, the patient was referred to his primary provider for antibiotic therapy. We found that most patients with large VLUs had undergone unsuccessful care attempts at other facilities. Subsequently, infecting agents were often iatrogenic and were multidrug resistant.[11] When such infections occur in the diabetic VLU patient, rapid identification of the responsible organisms is key to developing effective strategies to eliminate the infection.

Perhaps the greatest advance in VLU care is the addition of HCA to the treatment armamentarium. These aqueous solutions of hypochlorous acid, even in trace amounts, will kill most pathogens within 30 s of exposure. Additional actions of HCA include reduction of mast cell degranulation[12] and active capillary dilation.[13–15] The latter effect is of great importance in the diabetic VLU patient since one of the paradoxes in diabetes is the reduction of capillary perfusion via arteriovenous shunting at the microcirculatory level.[13] The capillary dilation in turn elevates the $tcpO_2$ within the wound. We have observed that this improvement in periwound tissue oxygen concentration and perfusion can be persistent to 72 h following exposure to the HCA. Comorbidity combinations of diabetes, smoking and PAD precluded significant increases in tcpO2 with no demonstrable residual increase at 72 h following exposure to HCA. In nonsmokers, accelerated angiogenesis, granulation formation and epithelialization occur. Similar results are obtained in nondiabetic VLU patients.

Additional factors in acceleration of healing of VLUs includes management of diabetes mellitus to reach and maintain target serum glucose levels of 80–120 mg/dL and smoking cessation. Patients are strongly encouraged to maintain normal physical activity and to ambulate freely while undergoing VLU treatment. Frequent calf muscle and venous foot pump action[16] and the increased limb perfusion that accompanies exercise can only improve the ulcer environment and promote healing action and the increased limb perfusion that accompanies exercise can only improve the ulcer environment and promote healing.

It is well known that there are three factors that contribute to failure of wounds to heal in a timely manner: compromised perfusion resulting in diminished tissue oxygen levels; invading flora and host immunological impairment. We have found that the use of HCA in our VLU care regimen successfully addresses the first two factors and can favorably influence the third.

From this experience we conclude that aggressive management of VLUs results in accelerated healing of these wounds. The addition of HCA to our treatment protocols has provided significant mircocirculatory amendment of the damage caused by the presence of comorbidities. Considerable bioburden reductions, via direct antimicrobial effects, as well as prevention of biofilm recurrence, quickly improve tissue conditions within the wounds. Treatment cost reductions are facilitated by the shortened healing times and the reduced need for expensive wound care materials and modalities.

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