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ORIGINAL ARTICLE

Treatment of Non-Healing Diabetic Foot Wounds with Vaporous Hyperoxia Therapy in Conjunction with Standard Wound Care

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Vaporous Hyperoxia Therapy (VHT™), a patented FDA-510 (k) cleared technology, is an adjunct therapy used in conjunction with standard wound care (SWC). VHT is said to improve the health of wounded tissue by administering a low-frequency, non-contact, non-

Online Early
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thermal ionic anti-microbial hydrating mist alternating with concentrated topical oxygen therapy (TOT). VHT was used to treat 36 subjects with chronic diabetic foot ulcers (DFUs) that were previously treated unsuccessfully with SWC. The average age of DFU in the study was 11 months old and the average size was over 3 cm². Wounds were either Wagner Grade 2 or 3 and most commonly on the plantar surface around the midfoot. Treatment consisted of twice weekly applications of VHT and wound debridement. Subjects were followed to wound closure, 20 weeks, or 40 treatments, whichever came first. The combination of SWC and VHT in the group that met and maintained compliance throughout the study period achieved an 83% DFU closure rate within a 20-week time period. The average time for DFU closure in this study was 9.4 weeks. Historical analysis of SWC shows a 30.9% healing rate of all wounds, not differentiating chronic wounds. Accordingly, SWC/VHT increases chronic diabetic foot ulcer healing rates by 2.85 times compared with SWC alone. The purpose of this study was two-fold: first, to observe the effect of VHT on healing rates and time to healing in previously nonhealing DFUs and second, to compare VHT with SWC, TOT and hyperbaric oxygen therapy (HBOT) and ultrasound therapies.

DFUs are a significant burden, both medically to patients and financially to the United States health care system and SWC historically heals DFUs only 30% of the time. Approximately, $9-13 billion dollars are spent on diabetic foot disease by public and

Online Early
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private payers.[1] This is in addition to the general cost of diabetic care in America which, in 2012, exceeded $245 billion dollars.[2] Diabetes is the seventh leading cause of death in America, and due to the increasing population of diabetic patients, could rise even higher on that list.[3] Roughly 85% of amputations in diabetic patients originate from DFUs and worsen through chronicity and eventual gas gangrene or osteomyelitis.[4]

The cost of managing non-healing DFUs is higher than the costs of the top five cancer treatments combined.[5] Therefore, many different treatments have been created to combat acute and chronic DFUs to avoid amputation and lower emotional distress, financial burden, and other stressors to the patient. SWC therapy (sharp debridement, cleansing of the wound and offloading) has an average healing rate of only 30.9%, based on a meta-analysis of randomized control trials.[6]

HBOT for nonhealing DFUs has been popularized. In addition to its anti-edemic and anti-bacterial effects, HBOT also neovascularizes wounds. Literature shows varying results with regards to wound healing rates compared to standard therapy, but ranges from 50-66%.[7-9] Negative pressure wound therapy (NPWT) is another modality which can be used for difficult to heal DFUs. The goal of NPWT is similar to HBOT by promoting neovascularization but uses negative pressure, creating a moist environment and drainage to promote wound healing. One randomized control trial that did not specify wound age, showed that NPWT had a 43.2% healing rate versus alginate dressing therapy and

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standard wound care (28.9%).[10] Both HBOT and NPWT therapies can be efficacious but also problematic for the patient. Positioning the NPWT device on the bottom of the foot while keeping a vacuum seal, combined with frequent dressing changes and aggressive offloading requirements can be difficult on the patient. HBOT benefits are accompanied by possible risks including oxygen toxicity, ear/eye/lung damage, and possible explosion. It is expensive, time consuming, and can have difficult parameters for insurance approval as it is only indicated for Wagner grade 3 DFUs that involve osteomyelitis and have failed an adequate course of standard wound care.

To circumvent some of these problems, newer therapies have been developed to aid in healing of chronic DFUs. TOT has been shown to be efficacious and avoids the drawbacks of HBOT with good results. In multiple studies, TOT increases Vascular Endothelial Growth Factor (VEGF) concentration around wounds and subsequently increases angiogenesis.[11,12] These factors are integral for the neovascularization process, inflammatory stage in wound healing, and subsequent healing of wounds. In one randomized, double-blinded study, healing rates were 41.7% in the TOT group versus 13.5% in a sham therapy group in chronic wounds that were at least 4 weeks old.[13] In another retrospective study of over 4,000 patients, there was a healing rate of 27.5% and 60% of the study population had a decrease in chronic wound size. However, these wounds were from many different etiologies and locations.[14] This therapy is not without downsides. In some studies, the

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highly concentrated oxygen pressure can cause ischemia to the tissues not in the therapy area.[15,16]

Ultrasound therapy has been established as another modality for wound healing. It has been shown in increase activity of chemotactic factors which aid in wound healing and decrease matrix metalloproteinase activity. A meta-analysis study calculated a 41.7% healing rate with noncontact low-frequency ultrasound therapy (NLFU), an 80% volume decrease and an 79% pain reduction among patient's chronic wounds at 12 weeks.[18]

VHT combines low-frequency, non-contact, non-thermal ultrasonic antimicrobial mist with concentrated topical oxygen to optimize the therapeutic benefits of both treatments. The medley of delivering the anti-microbial mist with topical oxygen allows for chronic DFUs to receive a stimulus, which increases angiogenesis and fibroblast formation, to ideally heal completely.

Materials and Methods

After IRB approval was received, patients were screened during an office visit to determine eligibility for the study. We prospectively enrolled thirty-six consecutive patients from three private practice podiatry offices with three wound care providers (Authors DK, KM, JC). Enrollment continued until twenty-nine wounds met inclusion and exclusion criteria.

Online Early
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Consent was obtained from the patients to attempt DFU healing via VHT therapy. Patients agreed to a minimum of two sessions per week to be enrolled. SWC (cleansing and excisional debridement) was performed once per week in addition to the 2 weekly VHT treatments.

Inclusion criteria to this study were: DFU with a Wagner Classification between 1-3 which had resisted healing with SWC for at least 6 weeks, ages 18-75 years old, no systemic symptoms of sepsis or Systemic Inflammatory Response System (SIRS) criteria, able to maintain reasonable nutrition and hydration, able to maintain adequate home care between treatment visits, and able to understand and follow basic wound care instructions (or has caregiver who can assist). Wagner 3 wounds were included if there was bone exposed but no radiographic evidence of infection nor abnormally elevated serological markers. Exclusion criteria were as follows: Skin wounds with neoplastic etiology, wounds involving possible osteomyelitis or tendon involvement, methicillin-resistant *Staphylococcus aureus* by wound swab, acute skin conditions, surgery within 30 days of enrollment, wounds where ends cannot be probed, participation in another clinical trial within 120 days prior to study onset, noncompliant patients (missed debridement or VHT sessions), pregnancy, presence of abscess/infection elsewhere, and presence of co-morbid conditions that would lead physician to exclude patient in study. If these criteria were met, the patient was enrolled in the VHT study according to the protocol.

Demographic and independent variables were obtained for each patient enrolled in the study which included: gender, age, ethnicity, employment status, Wagner Grade, wound location, adequate perfusion (palpable pulses or an ABI greater than 0.6), wound characteristics (exudate, edema or necrosis), HbA1c (%), blood glucose, age of wound at initial intake (months), volume of wound at intake (cm^3), area of wound at intake (cm^2).

All debridement and treatment sessions were performed by senior authors (DK, KM, JC), explicitly controlling the standard of care each patient was provided as constant and unvaried from non-healing to healing within the study period. The senior authors assessed, measured and photographed the DFUs at every treatment session to determine the size of the studied wounds. DFUs were measured to determine accurate volume of the wound via the longest dimensions in length, width and depth via a standardized metric ruler.

Each treatment included visual inspection of the DFU, with measurements and photograph performed. Wound volume was calculated after debridement and before VHT treatment. The affected foot was placed in the treatment basin and the VHT-100 ran for a one-hour session alternating four cycles of a proprietary antimicrobial ultrasonic mist for 10 minutes followed by five minutes of TOT (Figure 1). The DFUs were then offloaded and dressed as deemed appropriate by the study doctors. Offloading protocol for all senior authors was a standard felt to foam, or total contact cast based on the practitioner's discretion. Offloading was required after each VHT therapy session in this study.

Online Early
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Treatment visits occurred twice weekly until the wound was healed or conclusion of 20 weeks. Wound healing was defined as complete epithelialization and granulation of the surface of the wound. The primary endpoints of the study were: if the wounds were healing prior to 20 weeks, 40 treatments, or if the patient did not heal the wound by the 20-week cut off (Figure 2-4). Seven patients were excluded due to missed treatments, infection, death, surgical treatment of the wound or relocation to another state. Patients had the right to self-withdraw at any point of the study. Serious adverse events (SAE) were also evaluated. These included: death, events that are life threatening, inpatient hospitalization, persistent or significant disability, incapacity or further surgical amputation.

Statistical analysis was performed by Technomics Research based out of Minneapolis, MN. Time-to-closure was estimated by Kaplan-Meier time-to-event analysis, a standard type of analysis for events that occur over time, such as death, infections, wound closures, and other endpoints in this study as described previously.

Additionally, demographic and wound-characteristic variables were assessed individually for their ability to affect time-to-closure using univariate Cox's survival analysis with regression covariates. Those significantly associated with time-to-closure were included in a multivariate Cox's regression and the ones that remained significant were chosen with a stepwise procedure. The percent of DFUs closed at 12 and 20 weeks (or 40 treatments) were reported from the final model using the covariate values of subjects in the dataset. In univariate analyses, the level considered statistically significant was the

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standard 5% (p=0.05). This was also the significance level used to enter variables into the multivariate model; 10% was required for removal once in the model.

Results

VHT improved the health of wounded tissue by administering a low-frequency, non-contact, non-thermal ionic anti-microbial mist in the hydrating treatment mixture in conjunction with concentrated TOT and is a viable treatment option to heal chronic, nonhealing DFUs that were otherwise stalled. The combination of SWC and VHT in the group that met and maintained compliance throughout the study period achieved an 83% DFU closure rate within a 20-week time period. The average time for DFU closure in this study was 9.4 weeks. Historical analysis of SWC shows a 30.9% heal rate of all wounds, not differentiating chronic wounds [6]. It would be reasonable to expect that the SWC/VHT combination therapy would heal 88.3% of a population of DFUs. Accordingly, the SWC/VHT combination therapy increased the overall healing rate by 2.85 times compared to SWC alone.

There were 29 patients who met inclusion and exclusion criteria and completed the 20-week treatment period or healed prior to this time. Seven patients did not meet the criteria due to death, abscess at location away from DFU, poor compliance to protocol, moving away from area, or surgical intervention. Demographics of the study population

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(Table 1) showed that 75.9% of patients were male and 69% of patients were 65 and older. Thirteen patients (44.8%) had Wagner grade 2 wounds, whereas sixteen (55.2%) had Wagner grade 3 DFUs. Of the 29 DFUs, 22 (75.9%) were on the plantar foot and 17 (58.6%) were located in the midfoot. Subjects were overwhelmingly male (75%), 65 or older (>66%), and white (>85%). Typically, their diabetes was under reasonable control, as the average HbA1c was 7.5%, but one subject had an HbA1c of 14.1%. Excluding this outlier, the average HbA1c were 7.2. At initial intake, the average age of the wounds were 11.7 months, with one subject had a wound age of 110.4 months. Excluding this outlier, the average wound age was 7.2 months old and the average area size was 3.32 cm^2.

In the study population, healing rates were measured on a weekly basis. At 6 weeks, 31% of the study population's wounds had closed. At 12 and 20 weeks, 56% and 83% of wounds were healed, respectively (Table 2). Among the 24 subjects whose wounds closed within 20 weeks, the average time to healing was 9.4 weeks (minimum: 3, maximum: 18). The average healing rate per week (in area of tissue created) was .26 cm^2 (minimum: -.085, maximum: 1.5). Larger wounds had a slightly increased healing rate over smaller ones: the healing rate averaged .05 times the wound area in cm^2 (regression analysis $p<0.001$ for area at study start). Among those whose wounds healed within 20 weeks, the mean healing rate was .31 cm^2 (minimum: .01, maximum: 1.5). Figure 5 illustrates the percentage

Online Early
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closed at 20 weeks using a Kaplan-Meier time-to-event analysis, showing an 83% healing rate in the study population.

Predictors of wound closure were measured using a univariate time-to-closure Cox regression analysis with Age (< 65 vs ≥ 65), HbA1c, and employment status. In the study population, the hazard ratio for age was 3.3 and 0.69 for HbA1c. Therefore, people 65 and older are 3.3 times as likely to achieve wound healing as those under age 65, and for each 1% increase in HbA1c, the "risk" of wound healing decreases by 31%.

Discussion

The purpose of this study was to evaluate the healing rates of DFUs, which failed SWC, with the innovative, FDA cleared VHT medical device. Chronic wounds, such as the DFUs in this study, have decreased oxygen tension compared to healthy tissue or more acute ulcerations.[19] This factor makes chronic DFUs increasingly difficult to heal. As a result, oxygenation of the tissues has been proven to increase wound healing rates due to the upregulation of VEGF at wound edges and increasing angiogenesis to the tissues. [14,20,21] Due to long-standing diabetes, microvascular disease prevents proper angiogenesis of small vessels and thus decreases tissue turnover and inhibits wound healing. VHT improves the health of wounded tissue by administering a low-frequency, non-contact, non-thermal anti-microbial mist in the hydrating treatment mixture with concentrated oxygen. This study

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shows it improves healing rates and time to healing in previously nonhealing DFUs in a small patient population. The mist penetrates the stride microcapillaries and allows circulation to resume without applying any positive or negative pressures to the wound site. This in turn restores the natural blood flow to the tissues. In addition, the treatment does not cause edema that can result from artificial perfusion as observed by the study doctors.

In poorly controlled diabetics with microvascular disease, there are decreased numbers of endothelial progenitor cells (EPCs), at wound sites.[25] EPCs normally travel to the sites of injury and are essential for both the formation of new blood vessels and wound healing. Hyperoxia enhanced the mobilization of EPCs from the bone marrow to the peripheral blood circulation.[25] The increased presence of EPCs at the wound site correlated with accelerated wound healing. This provides a causal explanation for the results produced by VHT.

SWC, which includes offloading and debridement, is the typical first line treatment for diabetic foot ulceration treatment. In a systematic review, Margolis et al. reviewed healing rates with standard wound care therapy. They reviewed ten studies which met their inclusion criteria, four had a 12-week treatment cut off and six had a 20-week cut off. There was a 24.2% healing rate in the 12-week cut off studies and a 30.9% healing rate in the 20-week studies.[6] Our study group healed 83% of wounds at 20 weeks and 56% at 12

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weeks. Compared to the majority of wound healing studies performed on DFUs, VHT had over two-fold better healing rate in comparison to historical data.

HBOT can be a useful adjunct in treatment of nonhealing DFUs, however, there are numerous drawbacks to the therapy which include: oxygen toxicity, barotrauma, pneumothorax, risk of fire and explosion, cost, insurance approval limitations, and inconvenience of accessing a clinic equipped with a chamber.[14] Healing rates for HBOT vary from 50-66%.[7-9] Löndahl et al. performed a randomized, double blinded, placebo-controlled trial which compared patients who received HBOT versus hyperbaric air. At one year, there was a 52% healing rate with HBOT and a 29% in the placebo group. These results were statistically significantly better, however, clinically about half of the patients could not heal their wounds. In Löndahl's study, the time per session was 85 minutes for five days per week. In our study, VHT is used twice weekly for two hours of treatment total.[9] Therefore, VHT has increased efficiency and healing rates in relation to the result of previous studies of HBOT.

TOT is a similar treatment modality to VHT, which increases angiogenesis in the wound bed to improve healing outcomes.[11,12] Frykberg et al., in their double-blinded prospective study, had healing rates of 41.7% in the TOT group versus 13.5% in their sham therapy group.[13] These results insinuate that TOT is roughly three times better in healing than their sham therapy group. However, their healing rate is still less than 50% and close to standard wound care therapy rates. In Copeland and Purvis's retrospective study of over

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4,000 patients, they found a 27.5% healing rate and 60% wound size reduction rate.[14] Therefore, it is difficult to determine the rate of healing in patients treated with topical oxygen therapy due to the confounding results.

A number of new treatment options, including VHT, have been FDA cleared for treatment for DFUs. A handheld, non-contact ultrasound therapy device (HNUD) has gained popularity for wound healing. This device, in theory, allows for microbubble formation within the tissues to increase shearing and microstreaming of the tissues to increase cellular turnover and ideally tissue regeneration.[22] A multitude of studies have been performed on this device, however, many of them do not have wound healing as primary end points. In a large meta-analysis, Driver et al., noted a 41.7% wound healing rate and an 85.2% wound area reduction rate in 463 wounds. However, these wounds had many different etiologies and differed in chronicity of wound age.[18] Ennis et al., in a randomized double-blinded, multi-center study, showed the HNUD had a 40.7% wound healing rate compared to the 14.3% sham group. In contrast, VHT had an 83% healing rate, defined by complete wound closure. Out of the wounds that did heal using the HNUD, the ultrasound group healed roughly 2.6 weeks quicker than the sham group,-[23,] , however in comparing this VHT study to the HNUD meta-analysis wound healing, the HNUD results are 14.3% worse at 12 weeks and 37.3% worse at 20 weeks.

In addition to ultrasound type therapies, there are also newer topical oxygen modalities for chronic diabetic foot ulcerations. Frykberg et al. performed a multinational,

Online Early
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multicentered, randomized placebo double-blinded, placebo-controlled study. Of 220 total patients who completed the 12-week study, 41.7% of patients in the topical oxygen group healed their wounds, compared to the sham group who healed 13.5% of their wounds.[13] These numbers are very similar to the study performed by Ennis et al. and markedly lower than our results using VHT. Niederaurer et al. showed similar results with a similar method of TOT, but a different product in their randomized double-blinded, placebo-controlled study. Their results indicated the topical oxygen group healed 46% of their wounds, whereas the sham group healed 22% of their wounds.[24]

Due to the nature of scientific investigation, there are shortcomings with many studies. In our study, we had a number of limitations. First, our study had a small number of participants. The results, however, demonstrated VHT to be a promising treatment for DFUs in our study population. Second, we only evaluated DFUs. Many other studies have a mixed wound population and therefore can extrapolate healing rates with many wound etiologies. Third, our study was not randomized. Larger studies using VHT need to be conducted to properly evaluate our healing rates with other products on the market. Fourth, we did not compare our product head to head with similar products on the market, therefore, conditions could have been different, and our results are potentially subjected to bias. However, our clinical results have value in dictating a benchmark for healing rates using VHT in future studies.

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VHT is a new treatment modality which shows promise in healing chronic diabetic foot ulcerations. Our study of twenty-nine patients showed an 83% wound healing rate at 20 weeks, a clinically significant positive outcome for this treatment modality comparatively to similar products on the market. Among patients whose wounds were closed at twenty weeks, the average time to closure was 9.4 weeks with VHT. It is interesting to note in our univariate time to closure Cox regression analysis showed patients who were older than 65 years old were 3.3 times more likely to heal their wounds thank patients younger than 65. This could be due to the fact younger patients are more active and therefore not offloading similarly to their older study counterparts, compared to the retired older population. To further evaluate VHT as a treatment modality in all wound etiologies, further studies are needed to be conducted. Comparison studies with similar products would be ideal to determine the optimal treatment for patients suffering from chronic diabetic foot ulcerations. In conclusion, vaporous hyperoxia therapy shows preliminary success in healing of chronic diabetic foot ulcerations at 83% with 20 weeks of treatment, twice weekly. Utilizing basic wound care principles, such as debridement and offloading, and adding ancillary treatments like VHT, improves wound healing and ideally the patient's quality of life and therefore lower mortality.

Online Early
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Conflict of Interest:

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Online Early
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Figure 1 Depiction of vaporous hyperoxia therapy machine in use.

Online Early
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Figure 2 Initial intake of patient's wound after excision debridement before VHT therapy

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Online Early
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Figure 3 Patient's wound at 35 days of treatment protocol

Online Early
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Figure 4 Patient's wound healed at 57 days

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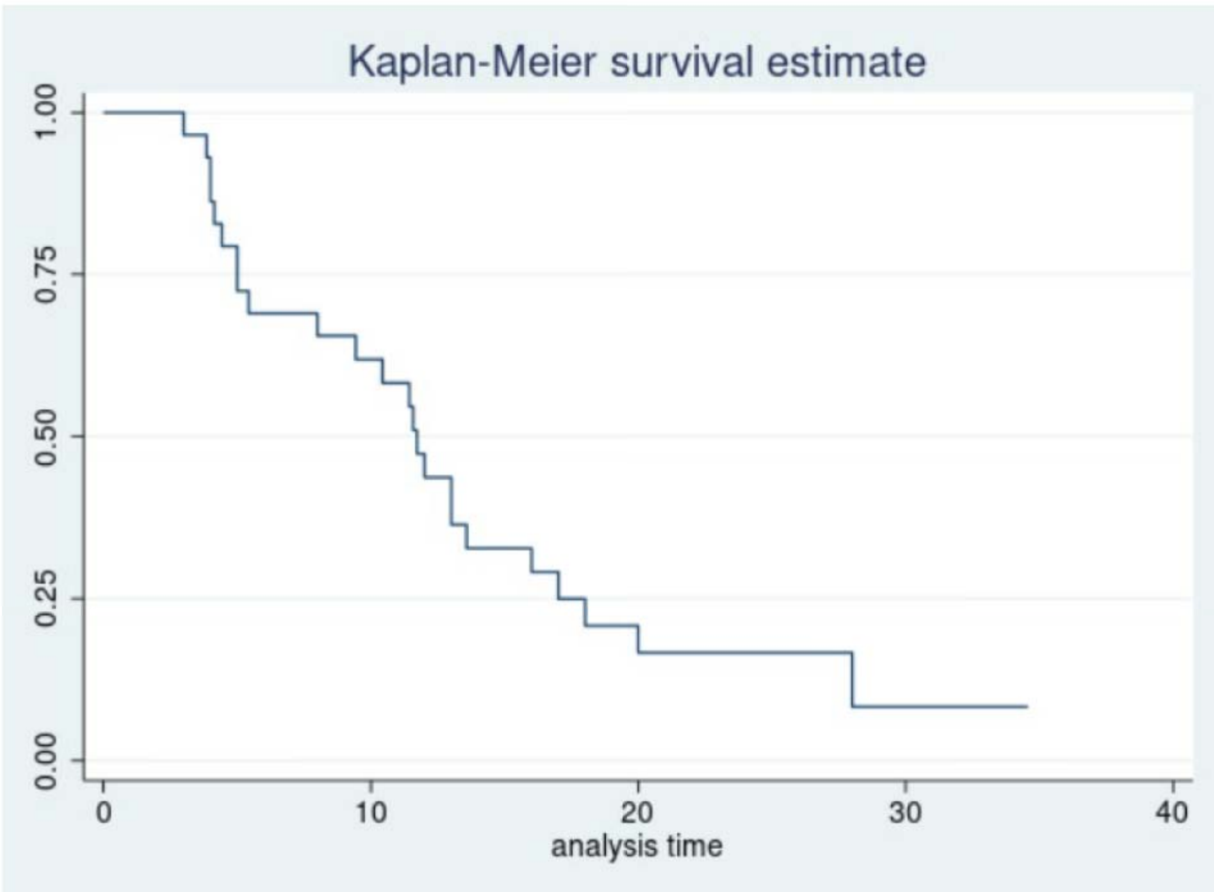

Figure 5 Kaplan-Meier Survival estimate of wounds healing during the study period

Online Early
DOI: 10.7547/20-259

Table 1: Demographics of study population

Demographics	**Patient population (N=29 wounds in 29 patients) N (%) Or Mean (N) SD [95% CI]**
Male sex	22 (75.9%)
Age ≥ 65	20 (69.0%)[a]
Caucasian	25 (86.2%)
Employed during study	21 (72.4%)[a]
Wagner Grade 2	13 (44.8%)
Wagner Grade 3	16 (55.2%)
Plantar Wound	22 (75.9%)
Midfoot Wound	17 (58.6%)
Adequate perfusion	23 (79.3%)
Exudate present	18 (62.1%)
Edema present	17 (58.6%)
Necrosis present	17 (58.6%)
HbA1c (%)3	7.54 (29) 2.05 [6.76-8.32][a,b]
Average Blood Glucose (mg/dL)	136 (12) 22.5 [122-150]
Age of wound at intake	10.8 (29) 19.9 [3.24-18.4]
Volume of wound at intake (cm^3)	1.05 (29) 1.68 [0.414-1.69]
Area of wound at intake (cm^2)	3.17 (29) 4.50 [1.45-4.88]

[a] Variables that were significant predictors of time-to-closure in univariate Cox's regressions.

[b] Variables that were significant predictors of time-to-closure in multivariate Cox's regression.

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Table 2: Time to wound closure

Week	Number of patients closed (%) [95% CI]
0	0 (0%)
2	0 (0%)
4	2 (14%) [5.4%-33%]
6	8 (31%) [18% - 51%]
8	9 (34%) [20%-55%]
10	11 (38%) [23%-58%]
12	16 (56%) [39%-75%]
14	19 (67%) [50%-83%]
16	20 (71%) [54%-86%]
18	23 (79%) [62% - 92%]
20	24 (83%) [67%-95%]