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Original article

Negative-pressure wound therapy versus standard wound dressing in the treatment of diabetic foot amputation. A randomised controlled trial☆

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ABSTRACT

Introduction: Foot amputation wounds in patients with diabetes are complex and treatment is often difficult. At the moment negative pressure wound therapy (NPWT) is widely used for the treatment of several types of wounds. Nevertheless, the clinical evidence to support the application of this dressing in foot amputation wounds in patients with diabetes is scarce. The aim of this study was to evaluate the efficacy of NPWT compared with standard wound dressing to treat diabetic foot amputation wounds.

Patients and method: Randomised controlled trial. Diabetic patients aged 18 years or older with a foot amputation wound were assigned to treatment with NPWT (A group) or standard wound dressing (B group). Primary efficacy end point was time in reaching 90% of wound granulation. A size of sample of 11 patients per group was used. NPWT was prepared with a polyurethane ether foam dressing, a Nelaton catheter, a transparent adhesive drape and continuous negative pressure of 100 mm Hg. The wound was treated every 48–72 hours and evaluated weekly. Descriptive and analytical statistics were used.

Results: There were 24 patients, with a mean age of 61.8 (9) years (79% men), 12 in each group. The average time to reach 90% of granulation was lower in A group (18.8 [6] days vs 32.3 [13.7] days), a statistically significant difference (P=.007).

Conclusion: NPWT reduces the granulation time of diabetic foot amputation wounds by 40%, compared with the standard wound dressing.

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Curación asistida por presión negativa comparada con curación convencional en el tratamiento del pie diabético amputado. Ensayo clínico aleatorio

Palabras clave:
Pie diabético
Tratamiento de la herida por presión negativa
Tratamiento por presión negativa tópica
Cierre asistido por presión
Curación por presión negativa

R E S U M E N

Introducción: Las heridas del pie diabético secundarias a amputación son complejas y de difícil tratamiento. Actualmente, la curación asistida por presión negativa (CAPNE) es ampliamente utilizada para el tratamiento de diversos tipos de heridas. Sin embargo, en la literatura médica hay escasas pruebas científicas sólidas sobre la aplicación de este tipo de curación en heridas del pie diabético amputado. El objetivo de este estudio es comparar la efectividad de la CAPNE con la de la curación convencional en heridas del pie diabético secundarias a amputación.

Pacientes y método: Ensayo clínico aleatorio. Sujetos mayores de 18 años, diabéticos de tipo II, con herida por amputación del pie, asignados a curación con CAPNE (grupo A) o a curación convencional (grupo B). La variable respuesta fue el tiempo en alcanzar el 90% de granulación. Se estimó un tamaño de muestra de 11 pacientes por grupo. La CAPNE se preparó con una espuma de éster de poliuretano, sonda Nelaton n.º 16, apósito transparente adhesivo y aspiración central a 100 mmHg. La herida se curó cada 48 a 72 h y se evaluó semanalmente. Se utilizó estadística descriptiva y analítica.

Resultados: Veinticuatro sujetos con un promedio de edad de 61,8 ± 9,0 años (79% varones), 12 sujetos en cada grupo. El tiempo promedio para alcanzar el 90% de granulación fue significativamente menor en el grupo A (18,8 ± 6 días frente a 32,3 ± 14 días), p = 0,007.

Conclusión: La CAPNE reduce en un 40% el tiempo de granulación de la herida en el pie diabético amputado comparado con el de la curación convencional.

Introduction

It is estimated that diabetes mellitus will affect close to 366 million people by the year 2030.[1-3] Twelve percent to 25% of diabetics will develop a foot ulcer during their lives[4,6-8]; this is one of the complications that causes more incapacity in these patients.[4,5] Its prevalence is 12%[9] and they are frequently accompanied by infections of varying magnitudes. They present a fast evolution and the final outcome in 7% of the cases is amputation.[10] The injuries from these amputations are large, deep[11,12] and they require intensive local care, with slow scarring and prolonged incapacity.[13] Furthermore, the delay in the closing of the injuries of the diabetic foot is related with infections in the bone tissue or in the soft parts, which complicates the prognosis and treatment of the lesion.[14]

As a consequence, curing techniques have been developed and perfected (gel hydrocolloids, topical ointments with growth factors and enzymatic debridement compounds, hyperbaric chambers, skin substitute cultures, etc), but many of these treatments are associated with greater economic costs and in some situations they are being used without confirmed scientific proof.[15] Within these new treatments, the use of negative pressure on the wound[16] has begun to be used, that is a non-invasive curative method that consists of placing a sponge with large pores in the wound or cavity, with a localized and controlled sub-atmospheric pressure to promote curing. At present, negative pressure wound therapy (NPWT) is accepted and used worldwide to care for and cure all types of wounds.[17-25] However, there are few solid tests in existing medical literature about the use of this type of wound therapy in amputated diabetic foot wounds.[26] The goal of this study is to compare the effectiveness of the NPWT with that of conventional wound therapy regarding granulation time in partially open amputation wounds in the feet of diabetics.

Patients and method

Clinical trial conducted in the Vascular Surgery Department of the Hospital Dipreca in Santiago, Chile (from August 2006 to July 2007). This study complies with the principles of the Helsinki declaration and it has been approved by the Ethics Committee of this hospital. All patients were informed verbally and in writing about the wound therapy techniques that were going to be used, their benefits and their possible complications.

Definitions

a) Adequate perfusion of the foot. Presence of one or more of the following criteria: adequate metatarsal pulse volume recording (MPVR)[27-29] (height of pulse wave greater than or equal to 5 mm, systolic pressure greater than or equal to 50 mm Hg and ankle/brachial index greater than or equal to 0.5), pedal pulse or posterior tibia pulse present or previous successful revascularization.[30]

b) Granulation time. Time in days until the wound reached 90% granulation, without necrotic tissues, bone or tendon exposure and without local signs of infection. If the wound did not reach 90% granulation, the time it took to completely close by second intention was measured.

c) Adverse effects. Pain, bleeding, and infection were evaluated.
   - Pain. Measured using a Visual Analogue Scale.[31,32] It was considered as secondary to treatment with a value greater than 5, within the first 6 hours of applying treatment and that did not disappear with the administration of traditional analgesics.
   - Bleeding. Need for haemostasis with a ligature or revision in surgery.
   - Infection. Determined according to international standards.[33]

d) Saturated bandage. The saturation of a bandage refers to the capacity of the bandage to absorb the exudation of a wound. The saturation was evaluated macroscopically and the secondary bandage was checked for spotting or wetness greater or lesser than 50%.

e) Depth of the wounds. The University of Texas Diabetic Wound Classification System[34] was used to characterize the wounds.

Selection criteria

Subjects older than 18 years old, type II diabetics, with a transmetatarsal amputation wound of 2 or more contiguous toes or the first toe (Figure 1a) from resolved infectious or vascular causes, with adequate perfusion of the affected member and that would accept to participate in the study. Subjects with active Charcot feet were excluded from the study as well as those with uncontrolled hyperglucaemia (glycated haemoglobin [HbA_{1C}] greater than 12%), being treated with steroids, immunosuppressive drugs or chemotherapy, with severe malnutrition (albumin lower than 2.1 mg/dL).[7,35-38] and being treated with growth factors or with hyperbaric oxygen in the last 30 days.

To calculate the sample size, a previous pilot study was needed (subjects that underwent the NPWT compared with conventional treatment) due to the fact that the existing information on wounds secondary to amputations in the diabetic foot only refer to the proportion of closed wounds in a determined period of time as a result variable[26] and not to the average of days in reaching 90% granulation, as established in this study. By using a confidence interval (α) of 95%, a power of 80% and a difference between the groups of 14 days in the average time needed to reach 90% granulation, the sample size required was 11 patients per group.

The subjects were assigned randomly to treatment with NPWT (group A) or to conventional treatment (group B) between the third and fifth day after surgery (so that the wound would not be bleeding or actively infected). The vascular surgeons of this Department performed all of the amputations to ensure the use of a standard surgical technique. The random sequence was elaborated using a computer programme. Closed envelopes were created with an arbitrary identification number and inside the previously determined treatment assignment was found, which was hidden until the end of the study.

A nurse that was trained and had experience in each type of treatment carried out the treatments. Given the physical differences between the treatments, it was impossible to hide the random assignment from the patient or the treatment team.

The patients assigned to group A received a treatment that consisted of covering the wound with a polyurethane ester sponge with large pores (400-600 µm) and a fenestrated drainage tube (Nelaton No. 16), inserted between the sponge and a transparent impermeable adhesive bandage placed as a seal over the entire system (Figure 1b). The system was connected to a central suction system and it was kept at a continuous sub-atmospheric pressure of 100 mm Hg until the next treatment.[39]

The patients of group B received treatment according to the saturation of the secondary bandage. If the bandage presented a rate of saturation lower than 50%, the wound was covered with a gel hydrocolloid, tulle (woven gauze impregnated with a petrolatum emulsion), and a bandage. If on the contrary it presented saturation greater than 50%, the wound was covered with alginate and a bandage. The patients of both groups received treatment before being assigned,

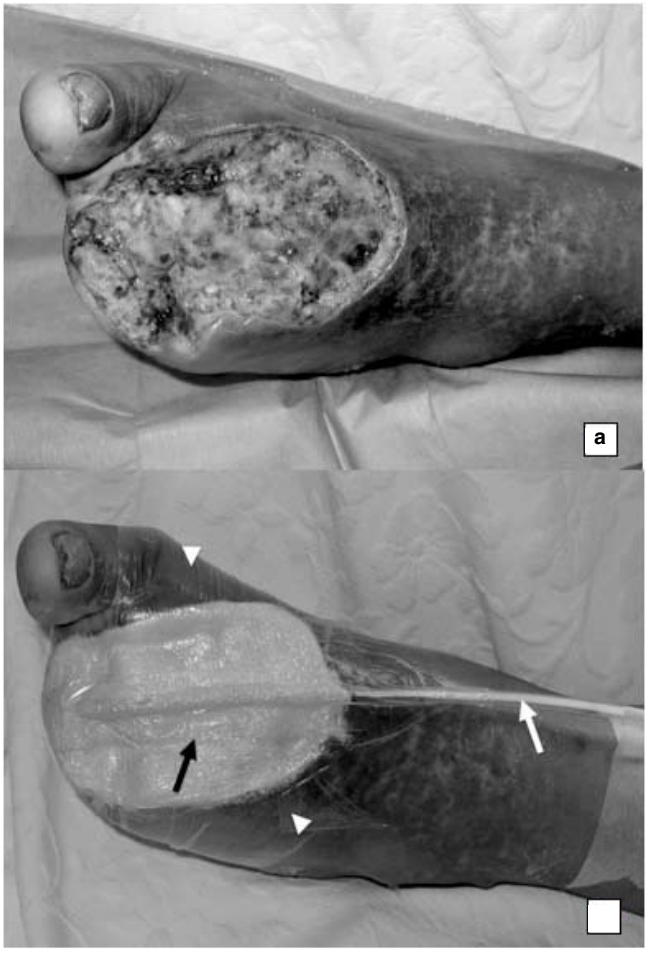

Figure 1 – a) Foot with partial amputation. b) Diagram of the wound treatment system assisted by negative pressure in a foot with partial amputation. Black arrow: sponge. White arrow: Nelaton no. 16 tube. Point of white arrow: impermeable transparent adhesive bandage.

according to the clinical guides of the Chilean Health Ministry (shower-therapy, saline solution, and debridement).[40]

The wound was treated every 48 to 72 hours and evaluated weekly with digital photography. The photography was crosshatched and analyzed square by square to determine the fraction of granulated tissue in each square. The total percentage of granulation of the wound came from the average of all of the fractions of all of the squares of the image. An independent group of the research team masked from the assigned treatment, conducted the evaluation of the percentage of granulation.

Statistical analysis

The statistical analysis was performed with the intention to treat and mask the assigned treatment. SPSS software, version 13.0, was used for the statistical analysis. Aside from the descriptive statistics, such as frequency distributions, measurements of the mode and dispersion, analytical statistics were also used. The normality of the variables was confirmed using the Shapiro-Wilks test, the Student *t* test was used for independent samples and the χ^2 test was used depending on the type of variable. The Kruskal-Wallis non-parametric test was used for independent samples if there was no normality. Accumulated probability curves were used to compare the treatment rates of each group (Kaplan-Meier method) and later, the log-rank test. The multiple lineal regression was used for the principle response variable and the logistic regression for the proportion of amputations and asepsis.

Results

Twenty-four subjects were selected (12 per group). The average global age was 61.8 (9) years (42-85 year-old). Nineteen patients (79%) were male. The average weight was 78.1 (12) kg. The average size and body mass index of the sample were 169.2 (8) cm and 27.3 (4) respectively. Thirteen subjects (54%) were classified as never having consumed tobacco, 14 subjects (58%) presented a normal lipid profile, and 11 subjects (46%) presented high blood pressure controlled with only one drug. Two subjects had a history of terminal renal failure and were in haemodialysis (one in each group) and none were taking oral anticoagulant treatment. The average creatinine level was 1.9 (3) mg/dL. The average albumin level and HbA_{1C} level were 3.36 (0.4) mg/dL and of 9.6 (2%) respectively.

In the MPVR, the average systolic pressure was 140.6 (73) mm Hg, the ankle/brachial index was 1.10 (0.6) and the height of the pulse wave was 14.1 (5) mm. Twenty three subjects (96%) were classified as grade II for depth according to the Texas classification, and one subject was classified as grade III. Revascularization of the affected member was performed in 5 subjects (21%) before the random assignment. A transmetatarsal amputation of a foot was performed in 50% of the patients. There were no statistically significant differences between the biodemographic variables and the clinical variables of the groups (Table 1).

During the follow-up period, 23 subjects (96%) reached a rate of granulation around 90%. Only 1 case from group B did not reach 90% granulation and the complete closure time of the wound was considered. There were no losses or interruptions of treatment in either group (Figure 2). The average time of global granulation was 25.6 (12) days. When comparing both groups of the study, the average granulation time was lower in group A (18.8 [6] days compared with 32.3 [14] days), a statistically significant difference (P=.007). The accumulated probability curves for the granulation times according to the group (Figure 3) presented statistically significant differences (log-rank test = 0.002).

Only 1 subject from group A presented bleeding, while in group B there was one subject that presented pain

Table 1 – Clinical and bio-demographical characteristics of the study population

	Group A (n=12)	Group B (n=12)	*P*
Age,[a] mean (SD), y	61.5 (10)	62.1 (8)	.878[b]
Sex, n (%)			1.000[c]
Female	2 (16.7)	3 (25.0)	
Male	10 (83.3)	9 (75.0)	
Weight,[a] kg	80.8 (9)	75.5 (14)	.298[b]
Size,[a] cm	168.0 (8)	169.6 (6)	.774[b]
BMI[a]	28.1 (4)	26.6 (4)	.113[b]
Smoker, n (%)			.688[b]
Never	7 (58.3)	6 (50.0)	
Stopped >1 year	2 (16.7)	3 (25.0)	
Stopped <1 year	1 (8.3)	0 (0.0)	
Active	2 (16.7)	3 (25.0)	
Dyslipidaemia, n (%)			.574[b]
Normal profile	7 (58.3)	7 (58.3)	
Control with diet	0 (0.0)	1 (8.3)	
Needing drugs	5 (41.7)	4 (33.4)	
Arterial hypertension, n (%)			.662[b]
Diastolic <90 mm Hg	4 (33.3)	6 (50.0)	
Control with 1 drug	6 (50.0)	5 (41.7)	
Control with 2 or more drugs	2 (16.7)	1 (8.3)	
Creatinine, mg/dL	2.1 (3)	1.6 (2)	.639[b]
Albumin,a gr/dL	3.36 (0.5)	3.57 (0.5)	.784[b]
HbA_{1C},[a] %	9.5 (2)	9.7 (2)	.535[b]
Pulse volume recordinga			
Transmetatarsal, mm Hg	126.9 (81)	154.3 (66)	.502[b]
Ankle/brachial index	1.05 (0.5)	1.16 (0.6)	.735[b]
Wave height, mm	15.9 (6)	12.4 (4)	.231[b]
Revascularization,[c] n (%)	3 (25.0)	2 (16.7)	1.000[c]
Type of amputation,[c] n (%)			1.000[c]
Only first toe	3 (25.0)	3 (25.0)	
Two or more toes	3 (25.0)	3 (25.0)	
TMT of the foot	6 (50.0)	6 (50.0)	
Side of amputation, n (%)			1.000[c]
Left	5 (41.7)	4 (33.3)	
Right	7 (58.3)	8 (66.7)	

BMI indicates body mass index; HbA_{1C}, glycated haemoglobin; TMT, tarsometatarsal.
[a]Average (standard deviation).
[b]χ^2 test.
[c]Fisher exact test.

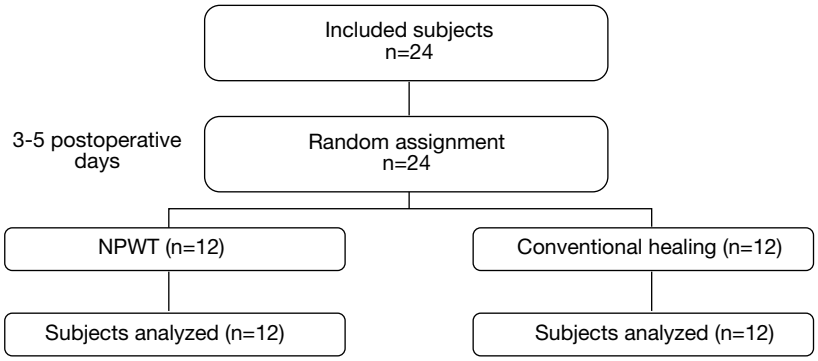

Figure 2 – Flow diagram of the participants.

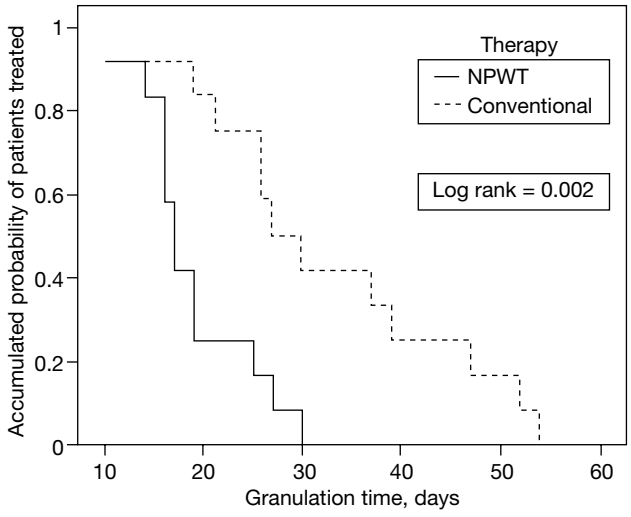

Figure 3 – Accumulated probability curves for the granulation times according to the group.

and another that presented an infection. There were no re-amputations, asepsis or mortality in this series.

Discussion

The present study measures as a result variable the time in reaching 90% granulation of partially open amputation wounds of the foot in diabetic subjects. The results show that the NPWT is more effective than conventional treatment in the treatment of these wounds due to the fact that it significantly reduces the granulation time up to 40%. However, the NPWT seems to be as safe as the conventional treatments regarding adverse effects, re-amputations, and surgical asepsis.

At present, the concept of keeping a humid environment to favour the closure of wounds is widely known and accepted.[31,32,41] But it seems, keeping the wound humid is not enough, other elements are required that intervene and favour the curing process, and thus various more complex active pharmacological agents[2] have appeared as well as other treatment to treat wounds,[42] but many of these are associated with greater economic costs and to applications with uncertain scientific proof.[15] The NPWT is included within these treatments and emerging technologies as a response to the need to treat chronic wounds and those that present closure difficulties.[16] Unlike other treatments, the NPWT has been accepted worldwide and is being used more and more frequently in the care and treatment of all types of wounds.[17-25]

The explanation of the success of the use of the NPWT is found in the work of Argenta and Morykwas,[18] that postulated that this new treatment technique removes excess interstitial liquid, increases angiogenesis, decreases bacterial colonization, and increases the formation of granulated tissues as a response to the stimulus of the mechanical forces created by the negative pressure transmitted through the sponge. Other authors have confirmed these concepts.[43,44] In addition to this, it has been postulated since long ago that if the excess of liquid is not removed adequately from the wound after an operation, its components can act like physical and chemical impediments to the closure of the wound.[43]

One of the limits of this project concerns the treatment of patients that are hospitalized, as this device obtains its negative pressure from the central suctioning system. This may prolong the hospital stay. However, unlike other projects that use an industrially manufactured device to provide the negative suction system,[15,17,26,43] in this project, elements are used that are found at hand in any community hospital and that comply with the functioning standards and requirements.[45] Although a study on the costs has not been carried out, the elements used in this study are clearly of a lower price than that of using an industrial device. It is also known that there are studies of the cost-effectiveness relationship in favour of the suctioning system[46,47] it seems attractive to use the NPWT in this type of patients.

The only project comparable with this project is that done by Armstrong and Lavery[26] which, although it presents a greater number of patients, has certain shortages in its methodology, such as not presenting a clearly defined research question nor justifying the calculation of the sample size of clarifying if the randomization sequence was kept hidden until the end of the study. However, the project of Armstrong and Lavery

establishes the result variable as a proportion of closed wounds in a determined period of time. Using the time in reaching 90% granulation as a response variable, aside from shortening the study time, it makes it possible to offer other wound closure methods to the patients. There is data that demonstrates that the NPWT can be used as an alternative treatment for the primary closure by second intention or for the secondary closure with other techniques by preparing an adequate granulated wound bed.[26] In this study, almost all of the patients with transmetatarsal amputation of a foot were grafted that received NPWT, which shortened the wound closure time. This opens an alternative for treatment in selected patients.

To summarize, these results demonstrate that the NPWT is an effective and safe treatment to treat wounds of partial foot amputations in diabetic subjects. The treatment with NPWT makes it possible to reach 90% granulation of a wound in a shorter time and with few complications when compared with conventional treatments. Future projects should include studies on the cost-effective relationship as well as on the quality of life.

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