

Use of Vacuum Assisted Closure Therapy in the Treatment of Diabetic Foot Wounds

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Abstract:

Diabetic foot disease is a major health problem, which affects up to 15% of the more than 200 million patients with diabetes worldwide and is associated with an increased risk of amputation. Vacuum-Assisted Closure (V.A.C.®) Therapy has been shown to be effective in the treatment of diabetic foot wounds. In two parallel randomized controlled trials we have evaluated the effectiveness of VAC Therapy in enhancing skin-graft take of diabetic foot wounds (study I) and the effectiveness in treatment of infected open minor amputations (study II). In study I, 70 patients were randomly assigned to either VAC Therapy (V1 group) or coverage of the grafts with non adherent gauze (C1 group). In study II, 130 diabetic subjects were randomized to either surgical debridement and VAC Therapy (V2 group) or surgical debridement and semi-occlusive silver dressing (C2 group). In study I the take rate was 80% in the V1 group versus 68% in the C1 group ($p = 0.05$). In study II a more rapid development of granulation tissue covering the exposed bone was shown in the V2 group when compared to the C2 group (41 ± 8 vs 59 ± 18 days, $p = 0.03$). Also a better and more rapid control of the infections (10 ± 8 days in V2 group vs 19 ± 13 days in C2 group; $p = 0.05$) and reduced time to complete closure of the wound was found with VAC Therapy (65 ± 16 days in V2 group vs 98 ± 45 days in C2 group, $p = 0.005$). Total time required for surgical procedures was reduced in the VAC group (2.5 hours versus 6 hours in the control group, $p = 0.02$). In conclusion, this study demonstrates that treating diabetic wounds with VAC Therapy can result in a faster wound bed preparation, a faster closure, and in a better graft take rate when compared to standard wound care.

Key words: Amputation; Diabetic Foot Ulcer; Limb Salvage; Negative Pressure Wound Therapy; Wound Healing.

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Introduction

Chronic wounds are a tremendous burden to the healthcare system, accounting for about \$20 billion in healthcare costs per year world wide.^{1,2} Foot ulceration is the precursor to approximately 85% of all diabetic amputations, with an estimated 14% to 20% of patients with foot ulcers undergoing an amputation.²⁻¹⁶ Infection of the ulcer further increases the risk of amputation. It has been estimated that if such patients were initially treated by a multidisciplinary team, major amputations could be prevented in 80–90% of those with limb-threatening ischemia¹⁷⁻²² and in 95% of patients with infection.²³⁻²⁷ This is significant considering that amputations are related to high morbidity / mortality rates and to a financial burden of up to \$60,000 per patient.

The treatment of diabetic foot wounds requires a multidisciplinary approach. Treatment of peripheral vascular disease (PVD), infection and pathological plantar pressure play a significant role in the overall management of these lesions. Topical treatment of wounds using advanced wound dressings has, unfortunately, not yet produced entirely consistent results. Recently, more promising outcomes have been obtained in the treatment of neuropathic wounds due to the introduction of bioengineered tissue in clinical practice³¹⁻³⁴ and to the availability of Vacuum-Assisted Closure Therapy (V.A.C.[®], Kinetic Concepts Inc., San Antonio USA).

The V.A.C. Therapy system consists of an inert, reticulated open cell foam that is modeled to fit into the wound. The foam is subsequently covered and sealed with a semi-occlusive film. Tubing is attached to a small aperture that is cut on the dressing's surface, while the other end of the tubing system is attached to the V.A.C. Unit. This device and configuration delivers negative pressure to the wound that can be administered in a continuous or intermittent mode.

V.A.C. Therapy has been shown to help wound healing in various ways. Early tests on animals have demonstrated that V.A.C. decreases bacterial burden in wounds, changing them from infected wounds to colonized wounds within 4 to 5 days of treatment.⁴¹ Other postulated mechanisms of action that might affect wound healing are the induction of an increased local wound perfusion^{35,42}, the induction of micro-deformations at the wound surface^{35,36} and the removal of exudate including inhibitory factors contained therein.³⁶ These mechanisms might explain how V.A.C. stimulates granulation tissue formation in comparison with wet-to-moist dressings.⁴²

V.A.C. Therapy has been shown to be an effective treatment of both complicated and non-complicated ulcerated wounds³⁵⁻⁴⁹, however high level of evidence is still marginally available.

Until the end of 2005 only two randomized controlled trials (RCT) that evaluated clinical effectiveness of V.A.C. Therapy in the treatment of diabetic foot wounds were found in the literature.^{38,40} McCallon included only 10 patients but found faster healing and greater wound surface reduction when V.A.C. Therapy was compared to gauze dressings.³⁸

Armstrong et al have published a large multi-centre randomized controlled study, in which V.A.C. Therapy was applied to open amputations. The control group was treated with advanced moist wound dressings according to standard guidelines of the participating centers. Treatment with V.A.C. Therapy resulted in a statistically significant reduction in healing time, a higher percentage of healed wounds and a potential reduction in the number of re-amputations.⁴⁰ However, less than 50% of the patients reached complete healing during the 112 day-follow-up period.

Furthermore, it has been shown that V.A.C. Therapy is effective in improving the qualitative and quantitative take-rate of skin grafts in venous leg ulcers⁵⁰ and several other wound types, but not in diabetic foot ulcers.^{51,52}

Aim of the study

The goals of our studies were to evaluate:

1. The effectiveness of the V.A.C. in diabetic patients selected to undergo skin graft procedures on ankle and foot ulcers. The primary end point was to quantitatively evaluate the skin graft take when compared to a standard dressing in patients with diabetic wounds.
2. The effectiveness of the V.A.C. on infected ulcers, open amputations and surgical dehiscence after foot surgery. The primary end point was to evaluate the effect of V.A.C. therapy on the healing

time when compared to standard of care in our hospital. Secondary end points were duration until wounds were free of infection, the mean time for bone coverage by granulation tissue, the percentage of new amputations, and the total time spent for surgical procedures.

Patients and Methods

This prospective, randomized clinical trial with a follow up period per patient of 6 months was conducted between July 2007 and July 2008. After local Ethics Committee approval, written informed consent was obtained from all participants before inclusion. The study was performed in accordance with guidelines as defined by the Declaration of Helsinki.

Two different groups of diabetic patients with ulcerations below the ankle were enrolled. In the first group (Study I), 70 subjects affected by diabetes mellitus, hospitalized and selected for receiving meshed skin graft for coverage of wounds were enrolled. The primary endpoint was the evaluation of the skin graft take rate. Inclusion criteria were presence of wounds of level I-A according to the University of Texas Classification (U.T.C.), with dimensions equal or greater than 4 cm². The exclusion criteria for study I were critical limb ischemia, presence of infection, and osteomyelitis. To appraise the presence of neuropathy we have used the Semmes-Weinstein 10g-monofilament test, sensibility to vibrations through a 128 Hz tuning fork, and the absence of tendo-Achilles reflexes. Vascular assessment with non invasive techniques was performed in all patients by clinical evaluation of the pulse, arterial examination by duplex scanning and transcutaneous oxygen tension (TcPO₂) measured on the dorsum of the foot. The clinical and instrumental diagnostic parameters, as featured in **Figure 1**, led to decisions of necessity for revascularization.¹⁷ Patients were randomly assigned using a computerized randomization procedure to either the V.A.C.

Therapy group or the control group. Thirty-five subjects were assigned to the V.A.C. therapy (V1 group). This group received V.A.C. therapy immediately after the skin graft application in the operating theatre. The other 35 patients were randomized to the control group (C1) in which the graft dressing was covered with non-adherent gauze. A photographic documentation was accomplished at enrollment in the study, during the intermediate phase and at the end of the therapy. All patients that developed signs of infection during therapy were treated with antibiotic therapy after microbiological examination. For the diagnosis of infection clinical criteria as previously described were used.²⁶ Infected Group 1 patients were treated with antibiotics until the wound was in a clinically diagnosed non-infected condition. Only then were subjects scheduled for a skin graft procedure.

A second group of 130 patients (**Study II**) were studied to compare the effectiveness of V.A.C. Therapy in the treatment of open amputations, or surgical dehiscence of minor amputations with standard modern wound dressings. The goal was to evaluate the effectiveness of V.A.C. therapy in controlling infection using clinical parameters. Endpoints were: time needed for complete coverage of exposed bone with granulation tissue, healing time and number of surgical procedures (hours of operating theatre activity).

The study included patients presenting with open amputations or surgical dehiscence of minor amputations of level II-III A-B according to the U.T. classification. The study excluded patients with bleeding wounds or untreated osteomyelitis. In those cases of recent debridement of the wound a minimum 24 hour period was awaited before applying a V.A.C. dressing. Diagnosis of bone infection was done before study enrollment. This diagnosis was done based on clinical and radiological findings. When in doubt, MRI diagnosis was taken in consideration as well. Clinical assessment was used to determine adequate control of acute infection.

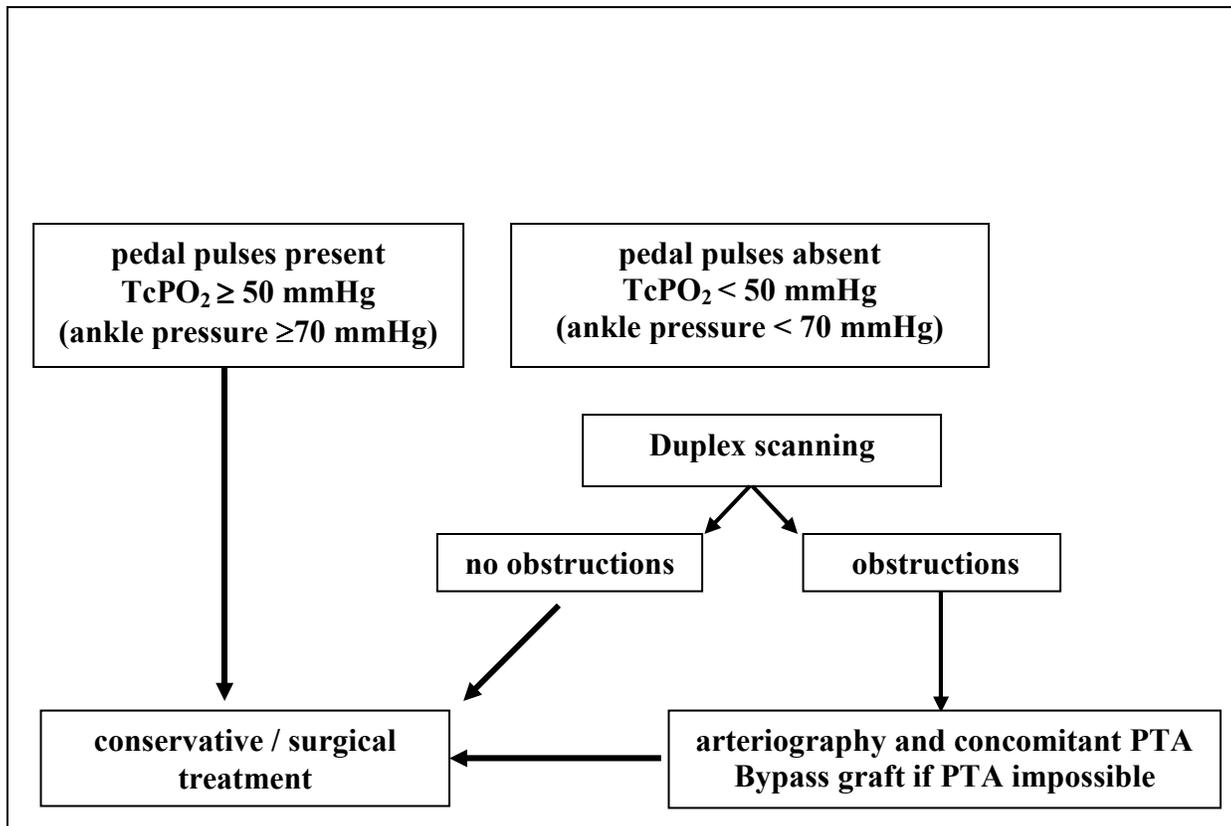


Figure 1: Flow chart of diagnostic-therapeutic protocol in PVD

Definitions: Critical Limb Ischemia (CLI): TcPO₂ < 30 mm Hg; peripheral Vascular Disease (PVD): TcPO₂ > 30 to 40 mm Hg; No PVD: TcPO₂ > 40 mm Hg

As complete wound healing was the most important aspect of these studies, wound size and duration of wound existence were not measured at study start and for this reason was not evaluated.

A population of 130 diabetic subjects was randomly assigned to receive either V.A.C. therapy (V2) or a variety of advanced dressings (control group, C2) following surgical debridement. Again randomization was performed using a computerized randomization procedure. Duration of therapy depended on the functional parameters of the wound area. All patients underwent vascular assessment, through duplex scanning of the lower limbs and transcutaneous oxygen pressure (TcPO₂) measured on the dorsum of the foot.

Before study participation it was known from all patients if they had non-ischemic wounds or if they had been effectively revascularized.

V.A.C. therapy was applied according to the manufacturer's instructions. Non occlusive wound dressings were used as protection for exposed tendons or vessels. Dressings were changed three times per week and during every dressing change the wound bed was inspected. The treatment of the control group consisted of advanced dressings such as alginate, hydrofiber, silver-dressing, or polyurethanes. The choice of dressing mostly depended on the amount of exudate and presence of infection.

In both the V.A.C. group and the control group, an adequate off-loading was achieved via fiberglass casts or orthopaedic footwear (half shoe, walker, pneumatic walker) dependent on the type and the location of the wound treated. A photographic documentation was carried out upon enrollment in the study, during the intermediate phase and at the end of the therapy. End of therapy was defined as complete coverage of the wound with epithelial tissue. A planimetry of superficial wounds was done to evaluate the dimensions of ulcerated wounds. Clinicians (non-blinded, participating in the study) evaluated the wound bed and made a subjective estimation of the depth of the wound and of the quality of the wound bed. Presence and quantity of granulation tissue was also documented and microbiological examinations (after wound debridement, based on wound biopsies) were repeated. All patients with clinical signs of infection, after microbiological examination, were treated with targeted antibiotic therapy.

In both studies, all results were compared between the two treatment groups (V.A.C. group or Control Group). The statistical analyses were always performed with the standard Student's t-test ($\alpha=0.05$) and confidence intervals were set at 95%.

Results

The clinical and demographic characteristics at baseline of patients in study I are listed in Table 1. Although the number of patients receiving oral diabetes therapy is different between the groups, no statistical differences were observed in other clinical and demographic characteristics that might influence the outcome of treatment.

In patients undergoing skin grafting and subsequent V.A.C. therapy, the percentage of patients with a complete graft take rate was significantly better than in patients treated with control therapy (80% versus 68% respectively, $p=0.05$ (Figure 2).

Demographics and clinical characteristics of patients in study II are shown in Table 2. A more rapid development of compact, well vascularized granulation tissue that covered exposed bone was found in V2 group than in C2 group (41 ± 8 vs 59 ± 18 days, $p = 0.03$) (Figure 3)

In addition, infection control was better and faster in the V.A.C. group than in the control group (10 ± 8 vs 19 ± 13 days $p = 0.05$) (Figure 4). Infection control was measured based on clinical evaluation, including extent of granulation tissue, reduction in exudate production and visual aspect of the wound. Only when necessary, wound biopsies were taken for microbiological control.

In cases where the wound was infected with MRSA, systemic treatment started with parenteral therapy with vancomycin, linezolid, or teicoplanin. MRSA infections were equally distributed in both groups; in V2, 40% of the infections involved MRSA and in C2, 42% of infections involved MRSA. Intravenous therapy was followed by oral continuation when needed.

In both study II groups healing was achieved by surgical closure or by secondary intention. All patients with grade III lesions were treated with surgery (skin graft) for closure of the wounds. Patients with grade II lesions were treated with skin grafts in all cases except for 2 patients in the V2 group and 3 patients in the C2 group that healed via secondary intention. In patients treated with V.A.C. the complete closure of the wound was reached in a statistically shorter time (65 ± 16 days V2 group vs. 98 ± 45 days C2 group, $p = 0,005$) (Figure 5).

Patients treated with V.A.C. did not have major amputations during the follow up period. Three major amputations have been carried out after this period in V2 group and in all three cases due to relapse of ischemia. In C2 group five cases of major amputation were carried out. In addition, in the V2 group a significantly lower number of surgical treatments were required (measured in hours of operating theatre activity) when compared to the C2 group ($p = 0.02$). (Figure 6).

Treatment	V1 group	C1 group	P-value
	(n = 35)*	(n = 35)*	
Male	24 (69)	23 (66)	NS.
Female (Male)	11 (31)	12 (34)	NS
Age (years)	64±12,4	60,6±14	NS.
BMI	29±2,6	29,1±1,2	NS
Smoking	10	8	NS.
Diabetes duration (years)	16±3,2	15±4,5	NS.
HbA1c (%)	7,4±1,5	7,1±2,1	NS
Insulin therapy (n)	26 (74)	31 (89)	NS
Oral diabetes therapy	9 (26)	4 (11)	0.05
PVD (n)	23 (66)	21 (60)	NS.
TcPO ₂ after revascularization (mm Hg)	42.0±8.5	43.0±10.1	NS
Neuropathy (n)	34 (97)	33 (94)	NS
Wound level U.T.C.			
I	35 (100)	35 (100)	NS.

Table 1. Study I - Demographics and clinical characteristics.

PVD: Peripheral Vascular Disease

*Data are mean ± S.D. or number and (%) unless otherwise specified.

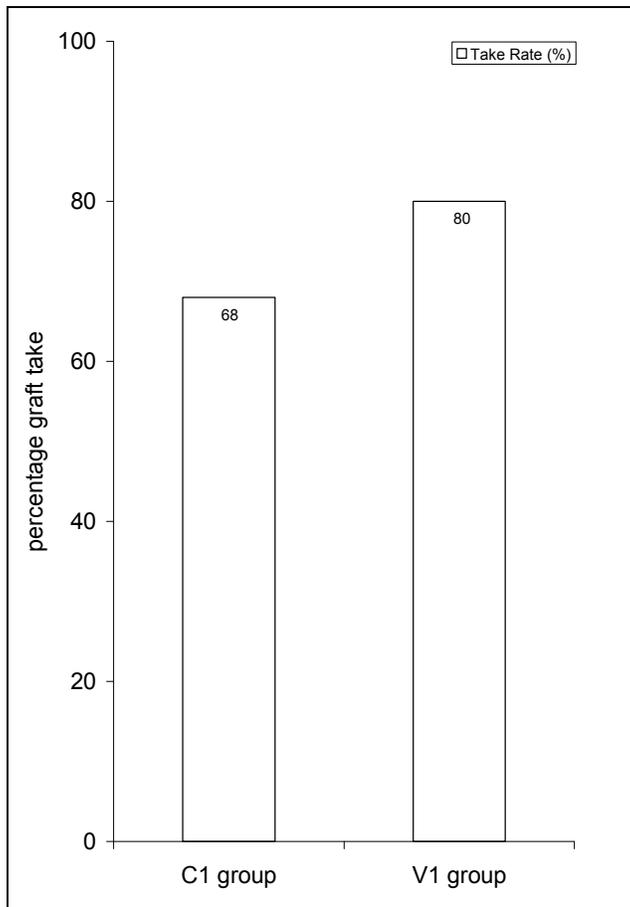
Discussion

Skin-graft, where indicated, represents an effective approach for the treatment of skin ulcers. Before making the choice to use this surgical technique, it is important to evaluate the chance of success. A sufficiently vascularized and non infected wound bed is an essential factor to obtain a good outcome.

Several studies have demonstrated the effectiveness of V.A.C. in promoting the graft take rate. Improvement of the surgical outcomes might be explained by the reduction of hematomas or exudations below the mesh graft,

by the reduction of dead space, by fixation of the graft to the wound surface, and by the increased perfusion induced by V.A.C. therapy.⁴⁶⁻⁴⁸

These same results are confirmed by other studies, also in more critical areas for skin-grafting where good results are often difficult to obtain; mobile areas such as the nuchal area and maxillary area.⁴⁹ Other studies also provide evidence of a reduction in repeat skin grafting in patients treated with V.A.C. compared to those treated with conventional therapy.⁴⁷

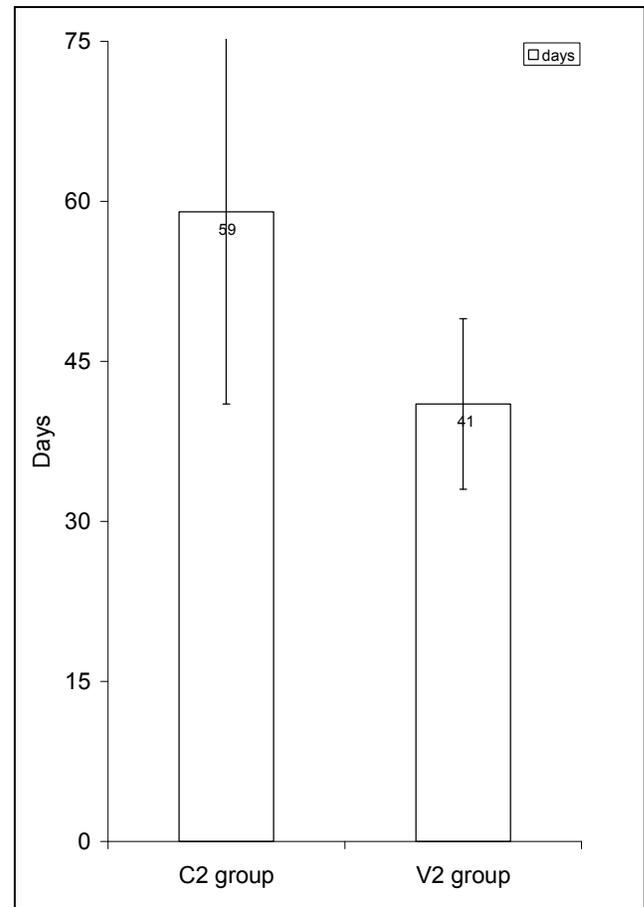


(p = 0.05)

Figure 2. Percentage of skin graft take in V.A.C. and Control group.

There are many studies which have focused the attention on the efficacy of this type of therapy concerning the take rate of skin-grafts, but none of these have placed attention on a diabetes population.

Our study took into consideration patients affected by diabetes mellitus who were undergoing skin-grafting at the lower limb level. Our data confirm the importance of V.A.C. in promoting the “taking” of the skin graft.



(p = 0.03)

Figure 3. Time until bone is covered with granulation tissue.

In this population which presented with deep wounds from dehiscence of minor amputations or open amputations with exposure of both bones and tendons, the use of V.A.C. reduced healing time by promoting good granulation tissue, a more rapid control over infections and a reduction in surgical re-interventions.

In a controlled randomized multicenter trial, Armstrong et al. have demonstrated the superiority of V.A.C. in treating outcomes of surgical wounds from minor amputations compared to local standard therapy.⁴⁰

Treatment	Treatment		P- value
	V2 group (n = 65)*	C2 group (n = 65)*	
F/M	55 (85)	53 (82)	NS
Female (Male)	10 (15)	12 (18)	
Age (years)	65±11,5	64,5±5,0	NS
BMI	27±3,1	28,1±2,1	NS
Smoking	7	9	NS
Diabetes duration (years)	18±6,3	14,8±7,8	NS
HbA1c (%)	7,4±1,5	7,1±2,1	NS
Insulin therapy (n)	58 (89)	60 (92)	NS
Oral hypoglycemics (n)	18 (28)	15 (23)	NS
PVD (n)	53 (82)	58 (89)	NS
TcPO ₂ after revascularization (mm Hg)	45.3±6.8	44.9±9.8	NS
Neuropathy (n)	61 (94)	58 (89)	NS
Wound level U.T.C.			
II	20 (31)	22 (34)	NS
III	45 (69)	43 (66)	NS

Table 2. Study II - Demographics and clinical characteristics.

PVD: Peripheral Vascular Disease

*Data are mean ± S.D. or number and (%) unless otherwise specified.

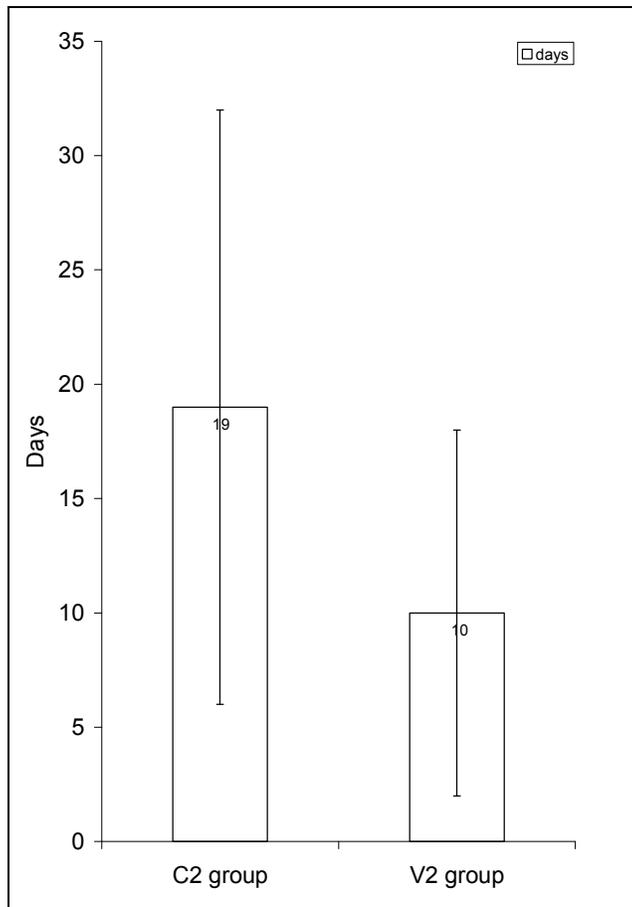
On contemplating open surgical wounds with exposure of bone structures and tendons, we must keep in mind the need for frequent repeated surgical procedures and revisions before obtaining the final result. Obviously, this determines an extension in healing time but we firmly believe that it is an acceptable condition if the final result is salvage of the limb.

In the recent past amputation was performed at a more proximal level in order to achieve closure by primary intention, thereby not salvaging limbs which otherwise might have been saved.

The use of V.A.C. in this field is of fundamental importance. Before the availability of this therapy, keeping a surgical wound open and trying to close it by second intention involved a very high risk of infection.

This type of complication is now significantly reduced, as our study has demonstrated. Therefore this has allowed us to work in a way that is more conservative compared to the past.

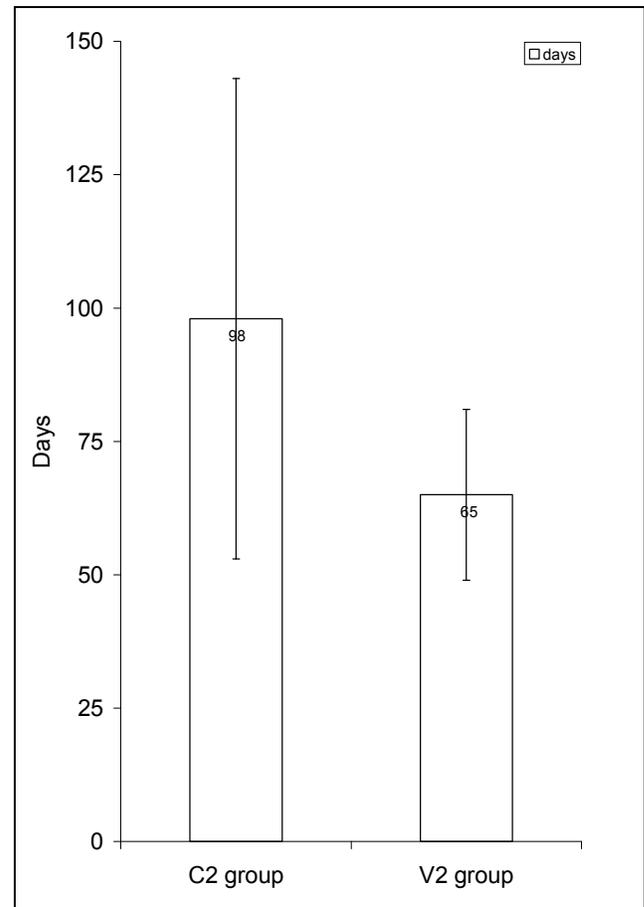
While our study confirms that V.A.C. stimulates the proliferation of granulation tissue, our data regarding this aspect is unfortunately only subjectively and qualitatively based.



(p = 0.05)

Figure 4. Infection control in days.

Nonetheless, we have shown that after only several days of treatment with V.A.C., the presence of a well cleansed and granulated tissue were achieved, even in those patients that at enrollment had little to absent granulation tissue. It is the presence of granulation tissue that is critical to determining further changes in the therapeutic approach and the clinical decision to promote closure of the wound by first or second intention, skin graft, or bioengineered autologous / heterologous tissues.



(p=0.005)

Figure 5. Average healing time in Study II patients.

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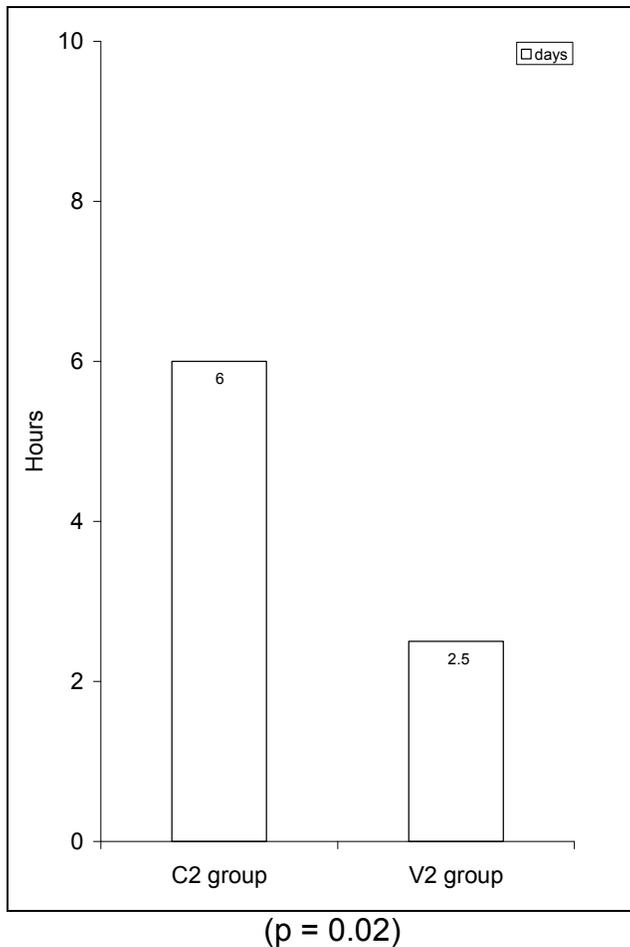


Figure 6. Time used in operating theatre activity.

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