



Prospective, Randomised Trial of Vacuum Assisted Closure in Patients With Chronic Non Healing Leg Ulcers in Type-2 Diabetes Mellitus

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ABSTRACT

Objective: Ensuing study was aimed to evaluate the efficacy of VAC (Vacuum Assisted Closure) therapy compared with normal saline dressing in chronic leg ulcer in type 2 diabetes mellitus.

Design: Randomized placebo controlled study.

Methods: Patients were randomly assigned to either VAC therapy once weekly or conventional dressing once daily and received standard treatment for good glycaemic control by insulin and control of infection by appropriate antibiotics and debridement, if needed. Dressing was removed on the 8th day of application and its effect was observed every week to see the response up to a maximum of 12 weeks.

Participants: 100 patients (M:F; 74:26) suffering from chronic leg ulcers of type 2 Diabetes were included, each group consisted of 50 patients.

Main outcome measures: Primary endpoint was healing of ulcers which was measured by reduction in the ulcer area of the two longest perpendicular diameters from baseline and defined as complete, partial, non-complete and non-responder.

Results: - On comparing control and study group for effect of VAC therapy, improving trend was observed in study group. After 6 weeks complete healing was achieved in 30% while in control group it was only in 8%. After 12 weeks, in control group 10 (20%) cases had complete healing while partial healing was found in 19 (38%), non complete healing was found in 16 (32%) while 5 (10%) cases were non responder/drop out from the study. In study group after 12 weeks, 27 (54%) had complete healing while 15(30%) had partial healing, 4 (8%) had non healing while 4 (8%) were non responder/drop out from study. When parameters were compared between both groups (i.e. study v/s control) the difference was statistically highly significant ($X^2=15.593$; $p<0.001$).

Conclusion: With good glycaemic control early application of VAC therapy appears to be more efficacious than conventional dressing for treatment of diabetic foot ulcer. By using VAC therapy, the risk of amputation of foot can be reduced.

KEYWORDS

Vacuum Assisted Closure, Leg Ulcer, Type 2 Diabetes

INTRODUCTION

Non healing ulcers of the leg and foot are among the most common complications of diabetes. Poor wound healing results from a combination of neuropathy, ischaemia and prolonged hyperglycemia. Hyperglycemia is directly related to increased susceptibility to infection.

The care of chronic foot ulcers in diabetes has become a major health problem. Foot ulceration precedes majority of amputations in diabetes and these ulcers are responsible for more than 50% of major limbs amputations.¹

Diabetes accounts for up to 50% of non-traumatic leg amputations and 1% of diabetic people have undergone amputation which is about 15 times the rate prevalent in the general population.² Prevention and early treatment of foot ulcers require multidisciplinary team work from nurses, podiatrists and doctors, preferably at the primary care level, supported by hospital foot clinics. Currently foot problems are an important cause of morbidity in diabetes.

In recent years, several new treatment strategies have been developed to stimulate wound healing in diabetic foot ulcers. These are topical growth factors, extra cellular matrix products, bioengineered human skin, and hyper-

baric oxygen therapy and granulocyte macrophage colony stimulating factors (GM-CSF).³

The surgical treatment of the diabetic wounds with loss of soft tissue continuity usually consists of closure using a split-thickness skin graft of transportation flap. However, immediate surgical closure often fails because surgical closure is not always appropriate considering the general condition of the patient and the wound. Therefore, initial treatment begins with open wound care.

The Negative Pressure Wound Therapy (NPWT) developed by Argenta and Morykwas, assists in healing open wounds. In clinical and experimental studies, the effects of NPWT that accelerate wound healing are reported as increased local blood flow, formation of granulation tissue, and decreased bacterial colonization. NPWT also showed successful results with faster wound healing in another study.⁴

Hence it was planned to conduct a prospective randomized trial of VAC therapy in patients with chronic non healing leg ulcers in type 2 diabetes mellitus.

MATERIAL AND METHODS

SELECTION OF PATIENTS:

A total of 100 patients suffering from chronic leg ulcers in type 2 diabetes mellitus were selected randomly for the study. After explaining the procedure and motto of the study informed written consent was taken prior to enrolment in the study. Institutional ethical committee approval was also taken before hand.

These patients were divided into two groups after meeting the inclusion and exclusion criteria. The inclusion criteria constituted a) Adult patients (30 years and above) of any sex, b) Clinical diagnosis of chronic leg ulcers of more than 3 months' duration and ulcer Wagner grade <3. c) Patients having glycaemic control (HbA_{1c} <9). The individuals excluded from the study comprised of osteomyelitis (untreated), malignancy, chronic leg ulcer Wagner grade ≥ 3, fistulas to organs or body cavities, necrotic tissue in eschar, immunosuppressive treatment in the last 3 months and any serious pre-existing cardiovascular, pulmonary or immunological disease. The method employed for randomization was computer generated, which resulted into study and control group. The study group (n=50) received the VAC therapy. The control group (n=50) constituted the patients who had been treated with normal saline dressing.

Additional background data of each patient were also collected. FBS, BMI, WHR, HbA_{1c}, ABPI were measured in every patient. Diabetic leg ulcer was assessed by detailed clinical examination and Wagner's classification was followed to classify individual patient.⁵ Each eligible patient underwent thorough clinical and biochemical examination. The fundamentals of caring for diabetic leg ulcers like off-loading, frequent dressing and smoking were not allowed during the study period.

PROCEDURE

Vacuum assisted closure (also called vacuum therapy, vacuum sealing or topical negative pressure therapy) is a sophisticated development of a standard surgical procedure that uses vacuum assisted drainage to remove blood or serous fluid from a wound or operation site.

In essence, the technique is very simple. A piece of foam with an open-cell structure is introduced into the wound and a wound drain with lateral perforations is laid on top of it. The entire area is then covered with a transparent adhesive membrane, which is firmly secured to the healthy skin around the wound margin. When the exposed end of the drain tube is connected to a vacuum source, fluid is drawn from the wound through the foam into a reservoir for subsequent disposal.

The plastic membrane prevents the ingress of air and allows a partial vacuum to form within the wound, reducing its volume and facilitating the removal of fluid. The foam ensures that the entire surface area of the wound is uniformly exposed to this negative pressure effect and prevents occlusion of the perforations in the drain by contact with the base or edges of the wound. It also eliminates the theoretical possibility of localised areas of high pressure and resultant tissue necrosis. Dressing was removed on the 8th day of application of dressing and effect of which was observed every week to see the response up to a maximum of 12 weeks, according to response new dressings were done.

RESPONSE TO TREATMENT

- Complete healing of leg ulcer (complete responder)
- 50% or greater reduction in the product of the two longest perpendicular diameters from baseline (Partial Responder)
- Less than 50% reduction in the product of the two longest perpendicular diameters from baseline (Non complete responder)
- No reduction in ulcer area or increase in ulcer area over baseline (Non responder)

TREATMENT DURATION

Treatment was given once a week for twelve consecutive weeks or until ulcer healing, whichever occurred first.

EVALUATION OF RESPONSE

The two longest perpendicular dimensions of the ulcers were recorded at baseline at each subsequent follow up visit. Patients were followed for a total of 12 weeks with regular visits at weekly interval or until complete healing of ulcer, whichever occurred earlier. Complete healing is defined as 100 percent wound closure with epithelialization or scab with no wound drainage present and no dressing required.

STATISTICAL ANALYSIS

In this randomized placebo controlled study, data are presented as mean ± SD. Comparison has been carried out between baseline characteristics by student 't' test and for categorical variables the chi square test has been applied. At p value <0.05, differences were considered statistically significant.

OBSERVATIONS

Table 1 shows baseline characteristics of the patients enrolled in the study. When these parameters were compared between study and control group, no statistically significant difference was found in all the parameters i.e. age, duration of diabetes, HbA_{1c}, BMI, WHR, TC, HDL, LDL, VLDL, TG, FBS, ABPI, systolic and diastolic blood pressure, which signifies that the base line values are equally distributed among cases and control.

The distribution of study and control participants in relation to unfavorable independent variables is depicted in table 2. Number of complete responders observed in the diabetic study group were 17 (45.94%) as compared to 4 in controls (10.25%).

It is evident from table 3 that the mean size of ulcer was almost same at the start of study

yielding the mean values for study (55.14±7.67) and control group (53.02±5.5) (p>0.05, t=1.59). Subsequently after the successive weeks, it is observed that the mean size has reduced in both the groups. It was further analyzed that the mean size of ulcer among study group has significant reduction in size during first week in comparison to control. (p<0.001). Same significant association was observed in the subsequent weeks.

An attempt was made to study the healing response among study and control group at sixth and twelfth week. (table 4). The findings at sixth week revealed that complete healing accounted at 15 (30%) among study group in comparison to controls 4 (8%) with statistically significant association (χ² 6.49, df 1, p<0.01). It was also observed that more number of study group participants 26 (52%) had partial healing response compared to controls 21 (42%). The overall statistical analyses at sixth week revealed that the study group population was significantly associated with the healing response (p<0=0.003). The relationship at twelfth week for completed healing response among study group 27 (54%) in comparison to control 10 (20%) revealed a highly significant association (χ² 10.98, df 1, p=0.0009). At this week, the study group population was significantly associated with the healing response (p<0=0.001).

DISCUSSION

Foot ulceration is a serious problem for people with diabetes, which also results in huge economic costs.⁶ Diabetic neuropathy has been identified to be an important risk factor for foot ulceration and amputation.

The spectrum of diabetic complications is very wide, and to some extent unpredictable, as it can not explain presence or absence of complications of diabetes, despite good glycaemic control.

Of the many complications of diabetes, those involving the foot lead not only to pain and suffering, but take months to heal. It leads to loss of working hours, hospitalization and great expense both to the patients and the community.

Different modalities of treatment have been used from time to time to treat the diabetic leg ulcers such as debridement, different anti-infective wound dressing, antibiotics according to culture sensitivity, skin grafting etc.

Even after taking different modes of treatment, treatment failure rate is very high. Hence use of Vacuum Assisted Closure Therapy (VAC) was planned for the treatment of diabetic leg ulcer. VAC therapy is a noninvasive system that creates localized controlled sub-atmospheric (Negative) pressure environment. VAC therapy promotes wound healing by delayed primary or secondary infection through creating moist wound environment, removal of excess interstitial fluid and exudates, an increase in vascularity and associated decrease of bacterial colonization, stimulation of granulation tissue formation through the responses of wound tissue to the mechanical forces exerted by application of negative pressure through the foam dressing.⁷

Fleischmann et al enrolled 25 patients with compartment syndrome of the lower limb and 313 patients with acute and chronic infections of various types.^{8,9} It was reported that majority were closed by secondary suturing (65.5%) and the remainder by spontaneous epithelization (17.2%), skin grafting (12.3%) or flap transfer (2%). These differences from our present study are probably due to the fact that patients enrolled in Fleischmann et al study were non diabetic and duration of ulcer both acute and chronic were taken into study, along with secondary suturing. Skin grafting and flap transfer techniques were taken for complete healing of the wound. But in our present study all patients are type 2 diabetes mellitus and duration of ulcer was ≥ 3 months, so results of present study was encouraging for non healing diabetic leg ulcer patients.

Mullner et al enrolled 45 patients with soft tissue injuries including sacral pressure ulcer, acute traumatic soft tissue defects and infected soft tissue defects following rigid stabilization of lower extremity fractures.¹⁰ They reported that in 38/45 patients (84%) the use of vacuum sealing technique following irrigation and debridement decreased the dimension of the initial wound, thus facilitating healing time and eradication of any pre-existing infection. When the results of Mullner et al study were compared with that of the present study, it showed that the ulcer healing rate was equal in both studies (84%) despite patients in present study were diabetic with chronic non healing ulcer. Mullner et al did not mention how much time was taken for ulcer healing, how much dressing was done and whether other methods of ulcer healing like secondary suturing or grafting were undertaken.

Argenta and Morykwas described the clinical use of the commercial VAC in 300 wounds of varying etiology.⁴ These were treated until completely closed or could be covered with a split thickness skin graft or were suitable for surgical reconstruction by rotating a flap on to the healthy granulating wound bed. Overall 296 wounds responded favourably to treatment for treating chronic and difficult to heal wound. Argenta et al did not mention the grading of wound, diabetic v/s non diabetic, duration taken for healing and number of VAC dressing.

Smith et al in a retrospective review described the use of VAC over a four year period in 93 patients who required open abdomen management for a variety of conditions.¹¹ A total of 171 dressings were applied to the wounds of 38 surgical patients and 55 patients with traumatic injuries. Smith et al concluded that with careful subsequent management good patient outcomes could be achieved and recommended vacuum assisted closure as the treatment method of choice for open abdomen management and temporary abdominal closure.

Blackburn et al has used VAC therapy in the treatment of donor sites, particularly in areas that are difficult to manage using conventional technique such as those on the radial forearm.¹²

In studies carried out by Scheider et al and Pfau et al, vacuum assisted closure has also been used in conjunction with split thickness skin grafting in the treatment of burns and is claimed to be particularly useful for body sites with irregular or deep contours such as the perineum, hand or axilla.^{13,14} In all these situations the vacuum helps to hold the graft securely onto the wound bed thus preventing pooling of tissue fluids which would otherwise make the graft unstable.

VAC study by Blume et al showed that in VAC group complete ulcer closure was achieved in 43.2% compared to conventional dressing group (28.9%) after 16 weeks of treatment.¹⁵ These results are lower than present study probably because mean BMI of Blume study group was 32.4 v/s 25.36 and grade of ulcer was II and III V/s grade II in present study.

Nather et al concluded that VAC therapy, useful in treatment of diabetic foot infections and ulcer, after debridement may present exposed tendon, fascia, bone.¹⁶ Results showed that healing was achieved in all wounds. In average 23.3 days these results are better than present study because Nather et al used ulcer closure by split skin grafting, by secondary closure along with mean chronicity of ulcer which was 34.7 v/s 201 days.

Moretti et al in their study showed that after 20 weeks of treatment 53.33% of the external shock wave therapy treated patients had complete wound closure compared with 33.33% of control patients.¹⁷ The results of this study is comparable to present study but the duration of ulcer healing is more than present study (20 v/s 12 weeks).

Agrawal et al in their study with GM-CSF injections in patients with chronic leg ulcer in type 2 diabetes mellitus" showed that after 12 weeks of GM-CSF treatment, 87.5% patients achieved complete healing.¹⁸ The results are better but high cost and side effect profile of GM-CSF is not known.

CONCLUSION

The following conclusions were drawn

1. A significantly greater number of patients achieved complete ulcer closure and granulation tissue formation by VAC therapy than conventional dressing group.
2. Significant reduction in median time was needed to heal diabetic leg ulcer in VAC therapy.
3. Good glycaemic control and early application of VAC therapy had better results.

Table 1
Baseline characteristics of the patients enrolled in the study

Characteristics	Control Group		Study Group		t	p
	Mean	SD	Mean	SD		
Age (yrs)	56.50	10.45	55.88	8.00	-0.333	0.740
Male	38/50		36/50			
Female	12/50		14/50			
Duration of Diabetes (yrs)	10.58	6.40	10.06	5.01	0.452	0.652
BMI (kg/m ²)	26.40	3.22	25.36	2.61	-1.790	0.076
WHR	1.01	0.102	1.04	0.15	1.098	0.275
Total Cholesterol (mg/dl)	224.76	38.51	211.70	28.95	1.917	0.058
HDL (mg/dl)	38.26	7.11	37.90	5.45	0.284	0.777

LDL (mg/dl)	141.54	21.53	151.40	30.33	1.874	0.064
VLDL (mg/dl)	36.22	11.31	37.18	12.45	-0.404	0.687
Triglyceride (mg/dl)	167.60	14.80	160.54	21.34	-1.923	0.057
Systolic BP (mmHg)	146.60	10.51	147.76	10.45	-0.554	0.581
Diastolic BP (mmHg)	91.40	8.34	91.76	6.44	-0.242	0.810
FBS (mg/dl)	178.12	73.73	164.86	49.15	1.058	0.293
HbA _{1c} (%)	8.58	0.81	8.37	0.90	1.193	0.236
ABPI	0.93	0.14	0.91	0.14	-0.712	0.478

Table 2
Distribution of participants in accordance to dependent (healing response) and independent variables.

Variables	CR	PR	NCR	NR
FBS >126				
Study group	17 (45.94%)	12 (32.43%)	4 (10.81)	4 (10.81)
Control group	4 (10.25%)	18 (46.15%)	14 (35.89%)	3 (7.69%)
BMI ≥ 25				
Study group	19 (59.37%)	8 (25%)	2 (6.25%)	3 (9.37)
Control group	6 (22.22%)	10 (37%)	9 (3.33%)	2 (7.41)
ABPI < 0.95				
Study group	8 (33.33%)	10 (41.66%)	3 (12.50%)	3 (12.5)
Control group	0	4 (23.52%)	12 (70.58%)	1 (5.88)
HbA _{1c} >8				
Study group	14 (40%)	13 (37.14%)	4 (11.42%)	4 (11.42)
Control group	1 (2.77)	15 (41.66%)	15 (41.66%)	5 (13.88)
Ulcer Duration >4				
Study group	1 (5.88%)	9 (52.94%)	4 (23.53%)	4 (23.53%)
Control group	1 (5.55%)	6 (33.33)	8 (44.44%)	3 (16.66%)

* CR= Complete Responder, PR= Partial Responder, NCR= Non-Complete Responder, NR= Non Responder (Drop Out)

Table 3
Size of ulcer in response to VAC therapy (study group) and conventional dressing (control group)

Week	Study group	Control group	t	P
	Mean ± SD	Mean ± SD		
Start	55.14±7.67	53.02±5.50	1.59	>0.05
First Week	30.32±7.28	36.04±8.16	3.37	0.001
Second Week	16.42±3.14	29.08±8.14	16.6	<0.001
Third Week	9.14±2.50	23.36±6.79	12.1	<0.001

Fifth Week	3.94±1.14	17.04±6.42	14.6	<0.001
Twelfth Week	1.22±0.42	13.76±6.20	14.3	<0.001

Table 4
Healing response in study & control group at sixth and twelfth week

Healing Response	Study Group		Control Group		x ²	p
	No.	%	No.	%		
After sixth week						
Complete	15	30	4	8	14.99	0.003
Partial	26	52	21	42		
Non Complete	7	14	22	44		
Non Responders	1	2	1	2		
Drop out	1	2	2	4		
Total	50	100	50	100		
After twelfth weeks						
Complete	27	54	10	20	15.593	=0.001
Partial	15	30	19	38		
Non Complete	4	8	16	32		
Non Responders	2	4	2	4		
drop out	2	4	3	6		
Total	50	100	50	100		

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