Comparison of Negative Pressure Wound Therapy v/s Conventional Dressings in the Management of Chronic Diabetic Foot Ulcers in a Tertiary Care Hospital in North India

Dr Biplav Singh[1], Dr Dhruv Sharma[2], Prof. K S Jaswal[3]

[1]Resident, Department of General Surgery, Indira Gandhi Medical College and Hospital, Shimla, India
[2]Associate Professor, Department of General Surgery, Indira Gandhi Medical College and Hospital, Shimla, India
[3]Professor and Head, Department of General Surgery, Indira Gandhi Medical College and Hospital, Shimla, India

Abstract: ***Introduction**: Foot Ulcers 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 Chronic Diabetic Foot Ulcers is scarce. The aim of this study was to evaluate the efficacy of NPWT compared with standard wound dressing to treat chronic diabetic foot ulcers. **Patients and method**: Prospective time bound comparative study. Diabetic patients aged 18 years or older with a foot ulcer were assigned to treatment with NPWT (Study group) or standard wound dressing (Control group). Primary efficacy end point was time in reaching complete ulcer closure. A size of sample of 15 patients per group was used. NPWT was prepared with a polyurethane foam dressing, a Silicone catheter, a transparent adhesive drape and continuous negative pressure of 125 mm Hg. The wound was treated for cycles of 5 days and evaluated at every dressing change. Descriptive and analytical statistics were used. **Results**: There were 30 patients, with a mean age of 54.4 years (73.3% men), 15 in each group. The average time to complete ulcer closure was lower in Study group (41.2 [8.5] days vs 58.9 [14.5] days), a statistically significant difference (P=.003). **Conclusion**: NPWT reduces the time to complete ulcer healing of diabetic foot by 30%, compared with conventional wound dressing.*

Keywords: Negative Pressure Wound Therapy, VAC, NPWT, Diabetic Foot Ulcers, Conventional Dressing, DFUs

1. Introduction

It is estimated that in 2005 around 150 million people worldwide affiliated by diabetes mellitus lived in the developing countries. The lifetime risk for foot ulcers in people with diabetes has been estimated to be 15 % with a 3% risk of lower limb amputations during their lifetime [1]. Globally, diabetic foot infections are the most common skeletal and soft-tissue infections in patients with diabetes. The overall risk of amputation is increased by 15 folds in diabetics than non-diabetic population. It is well accepted that a macrovascular disease, neuropathy, abnormal pressure loading, and susceptibility to infection constitute major factors in pathogenesis of diabetic foot.

A multidisciplinary team, particularly in specific diabetic foot clinics, is very successful in avoiding and treating foot complications. This strategy has been shown to reduce both the incidence of major leg amputation (by 40% or more), and the duration of in-patient admissions for the treatment of diabetic foot ulceration[2].

Diabetes remains the major cause of non traumatic lower extremity amputations (LEAs) in up to 85% of all cases, which is 15 times more than the general population [3]. It is also the most common cause of Charcot's neuroarthropathy which too is preventable [4]. It has cannot be over emphasized that prevention is the primary step to managing Diabetic Foot Ulcers (DFUs) as an ankle is lost to diabetes somewhere in the world every 30 seconds.

Wounds and their management are fundamental to the practice of surgery. Dressings are applications for wounds, burns, ulcers & other skin lesions to provide the ideal environment for wound healing. Standard wound management consists of initial surgical debridement, a rapid and effective technique to remove devitalised tissue. Then either wet to moist gauze dressing or occlusive dressings, which needs to be changed frequently to cover the wound. These dressings are relatively inexpensive, readily available and easy to apply. However there are some disadvantages, non-selective debridement with dressing removal, possible wound dessication, pain, and the need for frequent dressing changes. Other approaches include topical enzymes, bio-surgical therapy and topical antimicrobial agents.

Negative Pressure Wound Therapy (NPWT) or Vacuum Assisted Closure (VAC) provides a new paradigm for diabetic wound dressing. Vacuum assisted wound closure is a wound management technique that exposes wound bed to negative pressure by way of closed system[5]. The vacuum assisted closure device was pioneered by Dr Louis Argenta and Dr Michael J Morykwas in 1993. It is a development from standard surgical procedure, which uses negative pressure assisted drainage to remove blood or serous fluid from an operation site to provide a drier surgical field and control blood flow. Other names include Vacuum Assisted Closure (VAC), topical negative pressure, sealed surface wound suction, vacuum sealing, and foam suction dressing. The system is powered by a microprocessor-controlled vacuum unit that is capable of providing continuous or intermittent sub-atmospheric pressure ranging from 25 to 250 mmHg. The application of NPWT to a wound provides a moist wound healing environment which is the standard of care for wound healing[6].

NPWT provides negative pressure through medical grade polyurethane (PU), polyvinyl alcohol or collagen base foam dressing that is fitted at the bedside to the appropriate size for each wound. The dressing is then covered with an adhesive PU drape to create an airtight seal. An evacuation tube embedded in the foam is connected to a fluid collection canister contained within a portable vacuum machine. The machine creates negative pressure at the wound interface surface. NPWT provides optimal fluid level, tissue tension, and capillary flow to enhance vascular perfusion. The negative pressure, due to the foam, is equally distributed across the open wound and evacuates stagnant fluid from the wound and also helps to remove infectious material from the wound. It is simple to use with quick and dramatic results.

Very limited data is available on the role of Negative pressure wound therapy in the management of chronic diabetic foot ulcers, hence this study aims to establish the efficacy of Negative Pressure Wound Therapy in the healing of Chronic Diabetic Wounds in regards to the time to complete ulcer healing, time to appearance of healthy granulation tissue, duration of hospital stay, and a reduction in complications, including amputations.

2. Methods

2.1 Study Population

Patients admitted in the Deptt. of General Surgery,IGMC, Shimla between July, 2015 and June, 2016 with chronic diabetic foot ulcers. Inclusion criteria were wounds involving the diabetic foot. Exclusion criteria included ulcers associated with malignancy, Collagen Vascular Diseases, Extensive Osteomyelitis or Charcots Arthropathy, Pregnancy, and medications like corticosteroids, immunosuppressive, chemotherapy.

2.2 Study Design and Conduct

The study was a prospective time bound comparative study conducted over a period of 1 year (July,2015 to June,2016). All patients were admitted under the department of General Surgery, IGMC. History, relevant investigations and local examination of wound was done in all patients. Patients were then randomly assigned to a "Study" group and "Control" group. This was followed by thorough initial wound irrigation and debridement of the diabetic foot in all patients. NPWT dressing was then applied to the patients under "Study" group and conventional saline and povidone iodine based dressing was done in patients assigned under "Control" group. The NPWT dressing was changed every 5 days and repeated debridements done as and when required. The patients under "Control" underwent saline based dressings daily with repeated debridements as and when required. Data was recorded in Study group at every NPWT dressing change, while in the control group; wound characteristics were recorded weekly to ensure homogeneity of data recording in both groups. Patients were treated in both arms until complete ulcer closure by either direct closure / secondary closure / SSG / Flap. The NPWT system included a sterile non adherent nanocrystalline silver gauze, gauze foam, transparent polyurethane adhesive dressing, paper tape, silicon drain with connecting tube, 500 ml canister with absorbent polymer, and negative pressure generating unit. Negative pressures of between -125 mmHg and -150 mmHg was maintained for all patients. All wounds were graded based on the Wagner Grading System. The costs were borne by the government under the Rashtriya Swasthiya Bima Yojana (RSBY) Health scheme and patients not covered by the scheme were provided assistance in funding by the hospital. The study was approved by the Ethics Committee of the Institution.

2.3 Follow up and efficacy assessment

Patients were examined weekly until wound closure. The primary efficacy end point was complete wound closure rate. Complete wound closure was defined as skin closure (100% reepithelization of wound) without drainage or dressing requirements. Secondary end points included time to appearance of granulation tissue, reduction of ulcer size, overall duration of hospital stay.

2.4 Sample size

A total of 30 patients were included, randomized in two groups of 15 each and weekly assessment of wound was recorded.

3. Results

Thirty subjects were selected. The average global age was 54.4 years (37-74 year-old). Twenty two patients (73.3%) were male. Eight subjects (26.7%) were smokers, 9 subjects (30.0%) presented with deranged lipid profile, and seven subjects (23.3%) presented high blood pressure controlled with only one drug (Table 1).

The average HbA1C level was 8.75 (SD = 1.73%). Eight subjects (26.7%) were classified as grade III according to the Wagner classification, and twenty two subjects (73.3 %) were classified as grade II. Twenty four patients (80.0%) had arterial insufficiency on USG Doppler study. Most common organism isolated on wound cultures was E. coli (12 patients, 40.0%) (Table 1).

No foot amputations were performed in any of the thirty subjects. There were no statistically significant differences between the biodemographic variables and the clinical variables of the groups.

`All subjects attained complete ulcer closure and 4 cases (13.3%) required split skin grafting for wound closure while 7 patients (23.3%) attained wound closure by secondary healing. There were no losses or interruptions of treatment in study subjects. The average time of complete wound healing was 41.2 (SD = 8.5) days in the study group vs 58.9 (SD = 14.5) days in control group (p value = 0.0003).

None of the subjects presented with bleeding, while there was one subject that presented pain. There were no re-amputations, asepsis or mortality in this series.

Picture 1: Wound at presentation

Picture 2: Wound after 5 cycles of NPWT.

Picture 3: Wound after Split Skin Grafting

Picture 4: Wound at 3 months follow up

Table 1

Clinical and bio - demographical characteristics of study population (n=30)		
Age	Mean = 54.4 years	SD=8.97
Sex	Male = 22 subjects Female = 8 subjects	73.3% 26.6%
Smokers	8 subjects	26.7%
Arterial Hypertension	7 subjects	23.3%
Merritt Wagner Grade	Wagner II = 22 patients Wagner III = 8 patients	73.3% 26.7%
Glycated Hb (HbA_{1c})	Mean = 8.75	SD = 1.73
Dyslipidemia	5 subjects	33.33%
Pus Cultures	E. coli = 12 patients	40.0%

	Pseudomonas = 1 patients Proteus = 4 patients Klebsiella = 2 patients Staph aureus = 7 patients Non fermenter Group of organisms=1 patient MRSA = 1 patient Coagulase negative Streptococci = 1 patient Citrobacter = 1 patient	3.3% 13.3% 6.6% 23.3% 6.6% 3.3% 3.3% 3.3%
Antibiotic Sensitivity	Imipenem = 17 Ciprofloxacin = 2 Doxycycline = 4 Clindamycin = 15 Amoxiclav = 1 Linezolid = 8 Gentamicin = 5 Levofloxacin = 4 Tetracycline =1 Ceftazidime = 2 Tobramycin = 3 Piperacillin Tazobactam = 2	56.6% 6.6% 13.3% 50% 3.3% 26.6% 16.6% 13.3% 3.3% 6.6% 10% 6.6%
Arterial Insufficiency on USG Doppler	22 subjects	80%
Osteomyelitis on MRI scans	8 subjects	26.7%
Time to appearance of granulation tissue	Cases (Mean) = 15.1 days Controls (Mean) =21.5 days	SD = 5.4 SD = 4.9 P value = 0.002
Time to appearance of 100% granulation tissue	Cases (Mean) = 25.1 days Controls (Mean) =41.1 days	SD = 8.4 SD = 12.5 P value = 0.0003
Time to complete wound closure (days)	Cases (Mean) = 41.2 days Controls (Mean) =58.9 days	SD = 8.5 SD = 14.5 P value = 0.0003
Skin Closure by Split Skin Graft Secondary Healing Direct closure	4 subjects 7 subjects 19 subjects	13.3% 23.3% 63.3%
Complications	Pain = 1, Bleeding = none, Infection = none, allergy = none	6.6% 0%

4. Discussion

The present study measures as a result variable the time in reaching complete wound closure in chronic diabetic foot ulcers with the use of Vacuum Assisted Closure vs Conventional saline povidone iodine based dressings. This study shows that first appearance of granulation, time to appearance of 100% granulation tissue and time to complete ulcer healing, all were attained much faster in patients under the NPWT "Study" arm compared to the control arm (15.1, 25.1, 41.2 days v/s 21.5, 41.1,58.9 days) with a statistically significant difference (p value = 0.0003).

Time to complete ulcer healing by conventional dressings according to multiple RCTs and prospective studies range between 59 to 133 days[7,8,9].

NPWT is an effective treatment modality in chronic diabetic ulcers as shown in our study with reduction in duration of complete ulcer healing by almost 30%.

This study is in agreement with multiple other studies that state that NPWT is superior to conventional dressings for the management of Chronic diabetic foot ulcers[10,11,12,16].

The explanation of the success of the use of the NPWT is found in the work of Argenta and Morykwas, 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. It is also a proven fact that excess liquid acts as a physical and chemical deterrent to wound healing and the NPWT is an effective method for wound drainage[6].

5. Mechanism of Action of NPWT

1) **Macrodeformation**
Macrodeformation[13,14] refers to the effects exerted by the NPWT system on a macroscopic level which leads to wound shrinkage and a significant decrease in overall wound size due to the centripetal forces exerted on the wound foam interface by the dressing. Due to the variable tension in dermis and attachment of underlying structures, different wounds show variable degrees of contraction.
2) **Microdeformation**
Microdeformation[14] refers to the effects that take place on a micron to millimetre level. The foam diameter is commonly between 400-600 µm, and the negative pressure is equally distributed to the individual cells of the wound via the extra cellular matrix. The cells are subjected to various mechanical forces including shear,

stretch and compressional forces along with gravity. Cell shape has been a proven determinant of cellular function with healthy cells showing adaptation and proliferation when exposed to such mechanical stresses while unhealthy cells eventually dying out due to apoptosis.

3) **Reduction of Edema**
Chronic wounds and edema often go hand in hand and fluid buildup is an accepted deterrent to wound healing[15]. It has compressive effect on local tissue and microvasculature thereby decreasing perfusion and delaying wound healing. NPWT exposes the wound to subatmospheric pressure with an effective resultant drainage of edema fluid which leads to improved tissue perfusion and oxygenation and eventual faster rates of wound healing.

4) **Maintenance of the wound environment**
The Polyurethane (PU) drape is semiocclusive and is integral in maintaining the required negative pressures at the wound dressing interface. This dressing is impermeable to micro organsims and proteins hence reducing the risk of contamination while it is semi permeable to water vapour and gases thus helping ensure a warm and moist wound environment ideal to healing.

5) **Modulation of inflammation and cellular responses**
NPWT has multiple effects on wound healing by modulating inflammation and augmenting cellular responses to healing. It removes infiltrating leukocytes while simultaneously inducing inflammation[15].The cellular deformations induced by NPWT leads to altered function in cellular proliferation, migration, and differentiation[17]. Cell shape is a known determinant of cell function and as the cell is exposed to the shear, stretch and hydrostatic pressures of NPWT, healthy cells show proliferation with release of multiple growth factors and chemical activators while unhealthy cells undergo spherization and ultimately cell death by apoptosis leading to robust granulation tissue formation, increased angiogenesis, enhanced perfusion and faster wound healing rates.

6) **Angiogenesis**
The negative pressure generated at wound dressing interface results in local hypoxia with resultant vascular endothelial growth factor (VEGF) gradient that drives blood vessel growth[18]. This is mitigated through various pathways like the hypoxia inducible factor-1α–VEGF pathway, removal of anti-angiogenic factors, dilatation of microvasculature, induction of angiogenesis promoting factors which all eventually result in improved angiogenesis in the wound bed.

7) **Stimulation of Granulation tissue formation**
NPWT induces fibrogenesis and endothelial cells with microvascular ingrowth, tissue proliferation and reultant robust granulation tissue formation[19].

8) **Peripheral nerve response**
Younan and colleagues demonstrated that NPWT also activates the neurocutaneous system[20], thereby stimulating neural growth and neuropeptide expression which act as homeostatic factors in the skin. These include substance P, calcitonin gene–related peptide, and neurotrophin nerve growth factor.

9) **Alterations in bioburden**
The influence of NPWT on bacterial load remains controversial[21,22,23]. Some studies have shown a decrease in bioburden with treatment while others have shown comparable levels between cases and controls. This remains an area that requires further studies for definitive answers

The limitations of this study include a smaller sample size and the lack of randomisation in the two groups, due to financial and ethical constraints, as most government hospitals in India usually cater to the lower to middle class demography. Further randomised controlled trials are needed to confirm the results of this study.

6. Conclusion

This study shows that Negative Pressure Wound Therapy (NPWT) is a more effective method of treatment of Chronic Diabetic Foot Ulcers as compared to Conventional Dressing with 30% faster healing rates, reduced overall complication rates and better patient acceptance.

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