A COMPARATIVE STUDY OF COST-EFFECTIVE VACUUM ASSISTED CLOSURE (VAC) THERAPY AND CONVENTIONAL DRESSING ON WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCER

A DISSERTATION SUBMITTED TO THE TAMILNADU
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This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF COST-EFFECTIVE VACUUM ASSISTED CLOSURE (VAC) THERAPY AND CONVENTIONAL DRESSING ON WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCER"** submitted by **Dr.G.NAVANEETHA KRISHNA PANDIAN** to Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement of the award of MS Degree Branch - I (General Surgery) is a bonafide research work carried out by him under direct supervision and guidance from August 2018 to August 2019 in the Department of General Surgery, Madurai Medical College.

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I, **Dr.G.NAVANEETHA KRISHNA PANDIAN** hereby declare that this dissertation entitled "**A COMPARATIVE STUDY OF COST-EFFECTIVE VACUUM ASSISTED CLOSURE (VAC) THERAPY AND CONVENTIONAL DRESSING ON WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCER**" is a bonafide and genuine research work carried out by me in the Department of General Surgery, Madurai Medical College during the period of AUGUST 2018 TO AUGUST 2019. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad. This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of regulations for the award of M.S. degree (Branch I) General Surgery course.

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INTRODUCTION

INTRODUCTION

Diabetic foot ulcers constitute one of the most important complications of diabetes mellitus, with a staggering 25% lifetime risk[1,2]. The morbidity and prolonged need for hospital stay greatly affects the quality of life of those affected by it. The importance to these becomes even more significant considering that India houses the largest number of diabetics in the world[3]. If not treated promptly, progression of infection and sepsis may necessitate a limb amputation to prevent mortality[4].

Treating diabetic foot is a challenging task since it requires multimodal approach including control of infection by appropriate antibiotics, serial and aggressive debridement, strict blood sugar control and effective pressure off-loading. Healing of the diabetic foot ulcers takes significantly longer duration even with strict glycaemic control and effective treatment for infection due to the larger raw area which requires considerable time for the granulation tissue coverage. Numerous studies have shown Negative Pressure Wound Therapy (NPWT) to be efficacious in wound healing of different types of wounds which include chronic wounds, bums wounds, diabetic foot ulcers, venous ulcers, orthopaedic trauma, flaps and grafts, open abdominal wounds and sternal wounds[5,11]. The efficacy and safety of NPWT in the management of DFU has been witnessed in numerous prospective and multi-centred randomised control

trials[12]. These studies report faster time to complete wound closure, increased rates of granulation tissue formation, decrease in number of subsequent amputations, decreased bacterial load, improved patient satisfaction and safety with NPWT[1,13-16]. Though the International Diabetes Federation (IDF) in its 'Clinical Practice Recommendation on the Diabetic Foot -2017' states Negative Pressure Wound Therapy (NPWT) as 'revolutionary' in the management of DFU[17], it states NPWT as an 'adjunctive' therapy and recommends its use, if 4 weeks of standard wound therapy fails to produce any improvement[17]. Majority of the studies have been performed in Western populations. Though these studies have significant implication on the use of NPWT in DFUs; the Indian population differs from the western population in various aspects. The age of onset of the complications of diabetes one of which is DFUs; are comparatively much earlier in Indians due to the differences in genetics, lifestyle, culture, socio-economic status and health education. Also, general factors as BMI and albumin, and wound characteristics as size of DFU, bacteriology etc which affect wound healing are comparatively different in an Indian population. Hence this study was carried out to compare the efficacy, safety and complications of VAC therapy in DFU compared to the conventional dressings in Indian population.

AIMS AND OBJECTIVES

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Aim

To compare the efficacy and safety of Cost-Effective VAC therapy and conventional dressing in patients with diabetic foot ulcers.

Primary objective

To compare the time taken for complete wound healing following VAC therapy and conventional dressing in patients with diabetic foot ulcers.

Secondary objectives

1. To compare granulation tissue formation between VAC therapy and conventional dressing among patients with diabetic foot ulcer using visual score.
2. To assess the complications of VAC therapy and conventional dressing in patients with diabetic foot ulcer patients: Bleeding, Pain and Infection.

REVIEW OF LITERATURE

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Epidemiology and burden of Diabetes and Diabetic Foot Ulcers

The word ‘diabetes’ echoes in health sector globally and has come up as a global epidemic with its prevalence and incidence ever increasing. Estimates by the World Health Organisation (WHO) suggest that 3% of the world’s population has diabetes mellitus (excluding Gestational Diabetes Mellitus), portraying the gravity of the condition. Further the WHO’s estimates that of these affected with diabetes mellitus, 70% belonged to ‘developing’ countries; which makes it a great concern, knowing the health scenario in these countries . India now popularly entitled as “diabetes capital of the world” has over 62 million persons diagnosed with diabetes mellitus[22]. Actual figures can only be expected to be higher understanding the health status across the different states throughout the country. Studying the trends of prevalence of the disease over the course of years; longer life-expectancy, sedentary lifestyle and changing dietary patterns, it is adumbrated that the prevalence of diabetes mellitus will double to 366 million globally by 2030; with the maximum rise in India[23]. Preliminary results of a large community-based study conducted by the Indian Council of Medical Research (ICMR) reveals that the ubiquity of diabetes mellitus is less in the northern states of India when compared to its southern counterparts[24]. An even tenor was noted by the National Urban Survey conducted across various Indian metropolises[22]. Possible explanations for

this difference in prevalence could be that north Indians are migrant Asian populations while south Indians are host populations ; this though has to be corroborated through further research. The prevalence of diabetes mellitus in rural India is estimated to be one- fourth of that in urban India[24], this however might not be true considering poverty, illiteracy and lack of reliable screening methods in the rural areas.

Diabetes mellitus causes an enumerable list of complications many of which are morbid and can cause mortality; of these, a diabetic foot ulcer is one which frequently presents to a surgeon and has now taken over hyperglycaemic coma as the major cause of mortality in diabetic patients[26]. Understanding the importance of diabetic foot disease, the International Diabetes Federation had called 2005 as the 'year of the diabetic foot'[27]. With estimated lifetime risk of 25% of developing foot infections in diabetic patients one can clearly foresee the odds of its prevalence. In a study by Boyko *et al*[29] it was shown that over a period of three years, 17% of diabetic patients developed a foot ulcer. The need to prevent and treat diabetic foot ulcers is of paramount importance knowing that a leg is lost every 30 seconds due to diabetes[30]; and that the 5-year mortality rates are just next to lung cancer following lower limb amputations[31]. Eight of ten non-traumatic amputation are accounted for by diabetes of which 85% are due to diabetic foot ulcers. Limb amputation is up to 10-30 times more common in diabetics than in the non-diabetic population[32].

Sharad Pendsey in the 'Epidemiological aspects of Diabetic foot' states that the prevalence of diabetic foot ulcers is 3.61%; mean age of presentation is 53.55 years; and mean age at amputation is 61.25 years in an Indian population as against values of 3%, 68 years and 75 years respectively in a western population[33]. These could be attributed to socio-cultural practices as barefoot walking, poverty, illiteracy, lack of knowledge regarding foot care and poor health services[34]. In another study by Viswanathan *et al,* prevalence of foot infection was 6-11% and of amputation was 3% in type 2 diabetes mellitus patients. They also showed that the prevalence of peripheral neuropathy was higher in south Indian population (15%) compared to the north Indian counterparts (9%)[35].

A retrospective study by Vijay *et al* showed that the recurrence of foot infections was common in South Indian type 2 diabetes mellitus patients and related to the presence of peripheral vascular disease (PVD) and neuropathy[3].

Pathophysiology of Diabetic Foot Ulcers

The cause of diabetic foot ulcers is multifactorial which act in an amalgated manner continuously. These include peripheral neuropathy, peripheral vascular disease, trauma, foot deformities and impaired resistance to infection[36].

Morbach *et al* in a prospective study among 613 diabetic patients from Tanzania, Germany and India showed that while the neuropathy was

a common risk factor in all the three centres, the prevalence of peripheral vascular disease was more in Germany (48%) as compared to Tanzania (12%) and India (13%).This could possibly be explained by the relatively younger population (Tanzania-51 years; India- 56 years) in the latter two centres as compared to that of the population in Germany (71 years)[37].

Neuropathy

Neuropathy is one of the major factors which result in diabetic foot ulcers[38]. Patients with diabetes mellitus have peripheral neuropathy in the lower limbs as high as 66%[39]. Diabetic peripheral neuropathy affects all types of fibres (i.e. sensory, motor and autonomic). Loss of perception of pain, pressure, temperature and proprioception are the results of sensory neuropathy and this results in traumatic stimuli to be perceived either minimally or not at all. But it is not sensory neuropathy alone which cause a diabetic foot ulcer. Motor neuropathy causes atrophy and weakness of lower limb muscles which amount to abnormal walking pattern and pressure loading of the foot - causing foot deformities; which add up to the effect of sensory neuropathy. Also, the effects of autonomic neuropathy as dry skin due to decreased sweating further add up to the problem and increase the risk of a diabetic foot ulcer[40]. Different mechanisms have been proposed to explain why neuropathy happens; the prime ones include elevated levels of intracellular production of advanced glycated end

precursors, activation of protein kinase C, increased hexosamine pathway activity and increased flux through the polyol pathway[41].

Peripheral Vascular Disease

Peripheral artery occlusive disease, commonly referred to as peripheral arterial disease (PAD) or peripheral vascular disease (PVD), refers to the obstruction or deterioration of arteries other than those supplying the heart and within the brain; and atherosclerosis is the most important pathological change associated with peripheral vascular disease. In diabetic patients, PVD occurs at an earlier age, more progressive, more diffuse and extensive when compared to non-diabetics[42]. Neuro-ischaemic ulcers account for 15-20% of diabetic foot ulcers and another 15-20% is accounted for by ischaemic ulcers[43]. PVD usually acts alongside neuropathy to bring about foot ulcers in diabetic patients. Inadequate limb perfusion in PAD impairs wound healing, leads to gangrene and amputation further adding to the problem[36].

Infection

Infection is seldom the direct cause of a diabetic foot ulcer and is rather a consequence of it. But once an infection is established in a diabetic foot ulcer there is exponentiation of the problem and is limb threatening[36]. Infection can be superficial or deep; and the cataclysmic results of deep infections in a diabetic foot is due to distinct anatomical peculiarities, such

as; several inter-communicating compartments which facilitate infection to flame through from one into the other. Soft tissue in the foot as plantar aponeurosis, fascia, tendons and muscle sheath are not very resistant to infection; this combined with neuropathy, ischaemia and hyperglycaemia make way for infections, easy[44].

Limited Joint Mobility and Plantar Pressure

Limited joint mobility of the foot occurs in diabetes mellitus due to the glycosylation of collagen in tendons and ligaments. This limitation of joint mobility makes it difficult for the foot to maintain its shock absorbing mechanisms and thus increase in plantar foot pressures which increases the chance of one developing a diabetic foot ulcer[45].

Microbiology of Diabetic Foot Infection

The polymicrobial nature of diabetic foot infections makes their management challenging[46]. Superficial infections and those previously untreated are usually monomicrobial and caused by gram-positive cocci while deep and chronic wounds are polymicrobial and often show gram-negative and anaerobic growth. A study by Rastogi *et al* suggest that diabetic foot ulcers previously treated with antibiotics manifest with monomicrobial infections rather than polymicrobial. Shanmugam *et al*[49] reported single bacterial isolates in 50% of the patients included in the study. Over the past three decades numerous studies have been done on the

bacteriology of diabetic foot infections and their results have been varied. Overall organisms frequently encountered included *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli*[49]. In a study conducted on 440 patients with diabetic foot infections, Khalifa *et al*[50] showed that 75% of the diabetic foot infections showed polymicrobial growth; Gram-negative microbes (51.2%) constituted more than both Gram-positive pathogens (32.3%)and anaerobes (15.3%) of the organisms isolated; and *Staphylococcus aureus* was the most common single pathogen (18.5% of the total). Shanmugam *et* a/[49] states Gram negative bacilli was the commoner organism (65.1%) and that *Pseudomonas spp* (16%) was the most frequent isolated organism. A comparison of different Indian studies suggest *Pseudononas aeruginosa* as the common isolated organism followed by *Escherichia coli* and *Staphylococcus aureus*[32].

Definition of Diabetic Foot Ulcer and Infection

The World Health Organization and the International Working Group on the Diabetic Foot, defines diabetic foot as the foot of diabetic patients with ulceration, infection and/or destruction of the deep tissues, associated with neurological abnonnalities and various degrees of peripheral vascular disease in the lower limb[51,52]. According to the International Consensus on the Diabetic Foot, a diabetic foot ulcer is defined in the current research system as a full thickness wound below the

ankle in a diabetic patient, irrespective of duration. ‘Full thickness’ implies that the wound is penetrating through the dermis; lesions as blisters or skin mycosis are not included. The current research system also includes gangrene and skin necrosis as ulcers[44].

As per the Infection Disease Society of America (IDSA), a diabetic foot ulcer is said to be infected if there is an obvious purulent discharge and/or the presence of two or more classic signs of inflammation which include erythema, warmth, pain, tenderness and induration[53].

Over 10 different classification systems for diabetic foot ulcers have come up. These classifications facilitate communication between health-care providers, helps in deciding appropriate management, predict the outcome and enables follow up and progress of a diabetic foot ulcer during the treatment period[53].

On the basis of etio-pathogenesis

Diabetic foot ulcers can be divided into neuropathic, ischemic and neuro-ischemic ulcers[52]. The proportion of these ulcers are 54%, 34% and 10%, respectively[54]. Neuropathic ulcers are painless, and are more often encountered on the plantar surface of the foot and over areas overlying a bony prominence or deformity. Ischemic and neuro-ischemic ulcers are painful and frequently encountered at the tips of the toes and lateral border of the foot[52].

Wagner-Meggit classification

Formulated for a dysvascular foot, the Wagner-Meggit classification is in use for the past 25 years and is one of the most popular and widely used classification for diabetic foot ulcer[55]. It classifies diabetic foot ulcers into six grades based on the depth of the ulcer, the presence of gangrene and amount of necrosis. However, this system of classification does not take into account important clinical parameters as infection, ischaemia and comorbid variables[36].

Table 1

Wagner-Meggit Classification System

Grade	Foot lesion
0	No open lesions or cellulitis
1	Superficial ulcer
2	Deep ulcer up to tendons and joint tissue
3	Deep ulcer with abscess, osteomyelitis and joint
4	Local gangrene forefoot or heel
5	Gangrene of entire foot

Depth Ischaemic Classification

A modification of the Wagner-Meggit classification, this system classifies diabetic foot ulcers on the basis of depth of the wound and degree of ischaemia. It also clears up the difficulty in differentiating grade 2 from grade 3 diabetic foot ulcers in the Wagner-Meggit system[36].

Table 2

Depth-Ischaemic Classification System

Depth Grade	Definition	Ischaemia Grade	Definition
0	At risk, foot with ulcer that may cause new ulcer	A	No ischaemia
1	Superficial non-infected ulcer	B	Ischaemia no gangrene
2	Deep ulcer with tendon or joint exposed(+/-infection)	C	Partial forefoot gangrene
3	Extensive ulcer with bone exposed or deep abscess	D	Total foot gangrene

University of Texas classification

The University of Texas Antonio classification system (UTSA) classifies diabetic foot ulcers into four grades (0-3) on the basis of the depth; and into four stages (A-D) based on the ischemia and wound bioburden of the ulcer. The higher the grade and stage; the more likely the diabetic foot ulcer needs a vascular repair or amputation for healing. This system of classification has the drawback in that it doesn't go into specifying the causative organism or antibiotic selection[36].

Table 3

University of Texas classification system

Stages	Grades 0	1	2	3
A	Healed pre or post ulcerative lesion, completely epithelized	Superficial wound not involving bone tendon or capsule	Wound penetrating tendon and capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

International working group classification

The International Working Group on the Diabetic Foot (IWGDF) classifies patients with diabetes into different risk groups for developing diabetic foot complications[35]

Table 4

International working group on the diabetic foot

Risk group 0	No neuropathy, No PVD
Risk group 1	Neuropathy, no-deformity/PVD
Risk group 2	Neuropathy and Deformity and or PVD
Risk group 3	History pathology

SINBAD classification

The SINBAD classification and scoring of diabetic foot ulcers is a simple scoring system which helps in predicting ulcer outcome. It classifies diabetic foot ulcers on the basis of site, ischaemia, neuropathy, bacterial infection, area and depth. Ince *et al* in their study noted that patients with scores of ≥3 (max 6) a step-up in the number of days to healing was noted[47].

Table 5

SINBAD system of classification and scoring

Category	Definition	SINBAD Score
Site	Forefoot	0
	Midfoot & Hindfoot	1
Ischaemia	Present pedal blood flow with at least	0
	one pulse palpable	
	Clinically reduced pedal blood flow	1
Neuropathy	Sensation +	0
	Sensation -	1
Bacterial infection	Absent	0
	Present	1
Area	< 1cm^2	0
	> 1cm^2	1
Depth	Involving skin and subcutaneous tissue	0
	Involving muscle, tendon or deeper	1
	Total possible score	6

PEDIS system of classification by the IWGDF

The International Working Group of the Diabetic Foot (IWGDF) has devised a system of classification, primarily for research purpose. This system classifies diabetic foot ulcers into five categories which include perfusion, extent/size, depth/tissue loss, infection and sensation; hence the term 'PEDIS'. This system was especially developed to ease

communication in the area of research. The system classifies diabetic foot ulcer considering all the major factors affecting pathogenesis, management and outcome for patient with diabetic foot ulcers, using strict criteria to prevent misclassifications of patients[53]. To facilitate the classification in clinical use, a score is give as mentioned in table 6, the score from the five different variables are added up which adds up to a maximum of 12[55]. Chuan *et al*[55] concluded that this classification system has a sterling capability in predicting outcome of diabetic foot ulcers, and that its usefulness could be applied to the clinical field as well. It is shown to have superiority in diagnostic accuracy when compared to well accepted classification like the Wagner-Meggit and SINBAD classifications[55].

Table 6

PEDIS Classification system and scoring

Grade	Perfusion	Extent	Depth	Infection	Sensation	Score
1	No PAD*	Skin Intact	Skin Intact	None	No loss	0
2	PAD, No LI**	<lcm^2	Superficial	Surface	Loss	1
3	CLI	1-3 cm^2	Fascial, muscle and tendon	Absces, fasciitis, septic arthritis		2
4		>3 cm^2	Bone or joint	SIRS		3

*PAD- Peripheral Arterial Disease, **CLI- Critical Limb Ischemia

Classification of Diabetic Foot Infection

Many studies classify diabetic foot ulcers and several of them include the variable-'infection' with it being either just present or absent. However only the Infectious Disease Society of America (IDSA) and the International Working Group on Diabetic Foot (IWGDF) classify ulcers defining the severity of infection[36].

Table 7

Classification of diabetic foot infection as per the IWGDF/IDSA

Clinical classification of infection with definitions	IWGDF grade (IPSA classification)
Un-infected - No systemic or local symptoms or signs of infection	1 (uninfected)

Infected-

- At least 2 of the following are present: local swelling or induration, erythema >0.5cm around the ulcer, local tenderness or pain, local warmth, purulent discharge
- Other causes of inflammatory response of the skin are excluded

Infection involving the skin or subcutaneous tissue Erythema extending <2 cm around the wound No evidence of systemic inflammatory response syndrome (SIRS)	2 (mild infection)
Infection involving deeper structures to skin and subcutaneous tissue No evidence of SIRS	3 (moderate infection)
Any infection with the presence of SIRS	4 (severe infection)

Management of diabetic foot ulcers

Management of diabetic foot ulcers requires a multi-disciplinary approach. As per the International Diabetes Federation's (IDF) Position Statement 2005: The Diabetic Foot, this multi-disciplinary team should ideally consist of a surgeon, a podiatrist, a physician, a nurse, a specialist educator, an orthotist and an administrator; all of which should closely involve and work with the patient and the patient's family caregivers[57]. The aim during managing a diabetic foot ulcer is towards rapid wound closure. However wound closure may not be possible always especially with wounds with large surface areas. These can be managed with skin grafts, flaps and bioengineered tissue.

Treatment is step wise and the first paramount step is to recognise an infection and treat it. This consist of first classifying the diabetic foot infection, in order that the decision will be made as to what antibiotic to be empirically started if at all its needed and if the patient needs hospitalization[17]. Hospitalization is needed for all patients with severe infections and for patients with moderate infection who aren't compliant (with treatment as antibiotic dose and duration and off-loading of the ulcer) and unsure to be involved with wound care. Excluding these others can be cautiously managed on an out-patient basis with specific instruction to report immediately if infection worsens or doesn't improve[56].

Surgical management includes debridement, drainage and amputation as per the nature of the wound and an early surgical intervention is associated with better outcomes. Debridement aims to remove all unhealthy and unviable tissue and done till bleeding tissue is visualized. In a south Indian study, debridement was the most common procedure in 65.8% hospitalized patients for diabetic foot infection. Major amputation is considered when the limb is non-viable or affected by life threatening conditions as gas gangrene[32,56].

With no evidence that antibiotic accentuate wound healing or prevent infections, antibiotic therapy is not indicated for uninfected diabetic foot ulcers; especially taking into consideration the adverse effects, development of resistance and financial constraints associated with their use. Generally, mild to moderate infections are treated for 1-2 weeks, and severe infections are treated for 2-4 weeks; and once infection subside they are discontinued. Intra-venous antibiotics are given to moderate and severe infections and switched onto oral antibiotics once patient is stabilized and the infection responds[31,54].

Very few studies are present to recommend topical antibiotic therapy though theoretically it allows high level of the drug into the wound without its system side effects[56,58]. Lipsky *et al*[59] in a randomized, controlled, double-blinded, multi-centre trial showed that treatment with topical antibiotic peptide is as efficacious as with oral fluoroquinolones. At

first, an empiric antibiotic regimen is started which should cover the common pathogens at least against staphylococci and streptococci. The choice for an empirical antibiotic therapy is guided by the severity of infection -relatively narrow spectrum for minor and broad spectrum for severe infections; Gram-stain; characteristics of the wound; previous anti-biotic therapy. The antibiotics therapy is then subsequently changed as per culture and sensitivity. It must be remembered that antibiotics are used to cure the wound of infection and not aid in wound healing[56].

Off-loading, regular debridement, paring of hyperkeratotic rim and creation of a moist environment comprise the basics of wound care in a patient with diabetic foot ulcer; and of these offloading of pressure forms the mainstay of therapy[17]. Offloading of pressure is achieved with bed rest, wheel chair, crutches, walkers, total contact casts(TCC), instant total contact cast (iTCC)- removable cast walker rendered irremovable, foam padding, wedged shoes, Mandakini off-loading device, zimmer frames[17,52,60]. Off-loading can also be achieved by surgical procedures as Achilles tendon lengthening and a first metatarsophalangeal joint arthroplasty. When clinically limb oedema is present off-loading is combined with limb elevation'. Negative pressure wound therapy (NPWT) has proved to be rewarding by faster healing and better granulation[17]. In large ulcers where primary wound closure is not possible or time consuming, once the wound bed is filled with healthy granulation tissue;

modalities as bio-engineered tissue, skin expansion, flaps and grafts can be considered to quicken closure of wound[17].

A wound ensconced in a warm moist environment from external contamination favours wound healing. This can be provided by saline dressing and other special dressing as semipermeable films, hydrocolloids, foams and calcium alginate swabs[61]. Saline dressing wet-dry are more effective than most others[56,6,264]. IDF recommends adjunctive therapy if four weeks of standard wound therapy doesn't demonstrate an improvement which is defined as >50% wound area reduction[17]. Adjunctive therapies include NPWT; biologies as PDGF- egbecaplermin, living cellular therapy, extracellular products, amniotic membrane products, recombinant granulocyte colony stimulating factor(G-CSF), Apligraft (bioengineered skin) and Dermagraft (human dermis); systemic hyperbaric oxygen (HBO) and larval (maggot) therapy[17,56,61]. A randomized control trial done by Londahl *et al* show that HBO facilitates healing in selected patients diabetic foot ulcers[65].

As wound healing is determined to a large extended by the vascularity of the wound and as PAD forms one of the important cause of etiopathogenesis for diabetic foot ulcers, arterial insufficiency is addressed when present and extreme distal arterial reconstructive procedures are considered whenever possible. Also, it is important to address dyslipidaemia and hypertension which is commonly associated with

PAD[17,52,56,61]. Most of the patients with diabetic foot ulcers present with uncontrolled diabetes, the control of which is crucial to wound healing as is treatment of malnutrition, oedema and other comorbidities[52].

Vacuum Assisted Closure (VAC) / Negative Pressure Wound Therapy (NPWT)

VAC or NPWT is one of the adjunctive methods used in the management of diabetic foot ulcers[17]. In this system, a porous material (gauze-based system or polyurethane foam) is placed on the wound bed and then made airtight using polyurethane films; this is then connected to a mechanical pump (vacuum source) via tubing to provide negative pressure. The negative pressure is either maintained continuously or intermittently between 80-125mm Hg[66,67].

Components of a NPWT system

Wound filler

Polyurethane foam, polyvinyl alcohol foam and saline moistened gauze is what are commonly used as wound fillers.

Conventionally the polyurethane(PU) foam (black foam) is what is used in VAC. PU foams are hydrophobic and using this dressing conform to the wound bed forming a foam-tissue interface, it results in rapid and thick granulation formation and hence used in wounds with large defects.

The polyvinyl (white) foam is hydrophilic and in view of their tensile strength and low adherence these are indicated in tunnels and shallow undermining ulcers. Saline soaked gauzes offer easy application on irregular wounds. These along the white foams are ideal for use in wounds with exposed tendons and bone[4]. Malmsjo et al showed that wound healing rates are not found to be different with gauze or foams.

Dressing, Tube, Negative pressure source and Canister

Negative pressure is achieved sealing the wound by using adhesive dressing which is usually polyurethane which is cut to the size and shape of the wound. The use of idophore-alcohol adhesive dressings is also described which is believed to be a better adhesive and also has

anti-bacterial property preventing bacterial colonisation. The sealed dressing is connected to the negative pressure source which may or may not be portable using external power or batteries respectively. The canisters serve to collect the exudate drawn in by the vacuum from the wound[5].

Pressure settings & Continuous, Intermittent and Variable NPWT

VAC pressure is usually set at around -125mm Hg. Studies have shown that NPWT produces its best effects at this pressure with increase in blood flow by four times[5,69].

Vacuum in NPWT therapy can be applied either continuously, intermittently or as variable NPWT. As the name suggest in continuous mode a constant negative pressure is set; in intermittent pressure therapy (IPT) the vacuum is created on and off while in variable pressure therapy(VPT) there is a smooth transition between two set values of negative pressure, thus a negative pressure is maintained in continuum[70].

The beneficial effect of intermittent NPWT rather than continuous vacuum has been demonstrated by increased angiogenesis and proliferation has been demonstrated in studies by Morykwas *et at*[69] and Wackenfors et al[71]. Malmsjo *et al* in a comparison between effects of continuous, intermittent and variable negative pressure therapy found that wound contraction and

granulation tissue formation was better in IPT and VPT compared to continuous NPWT. Intermittent NPWT is given with cycles of negative pressure of 125mm Hg for five minutes with subsequent 2 minutes at Omm Hg[69,70]. Kremers et al[72] found that with intermittent NPWT there was increase in p38 protein kinase and appended transcription factor which aid in cellular proliferation.

Different pressure regimes (either continuous or intermittent, target negative pressure and frequency of dressing change) has been devised for different types of wounds, but these are not definitive[5].

Though NPWT has its current form developed in the early 1990's, its roots can be traced to the earliest civilizations. During the times of the Roman empire, 'sucking healers' who were thought to heal poisonous wounds by giving suction with their mouth; were indispensable[73]. The use of so called 'Cupping Therapy'; of which NPWT is considered its modem form; dates back practices to as early as 1000 B.C by the Chinese with the thought to promote wound healing by increasing blood flow[74,75].

Dr Louis Argenta and Dr Michael Morykwas of the Wake Forest University School of Medicine, North Carolina, USA; pioneered the modem NPWT system with the use of polyurethane foam and a mechanical pump[66]. With over a thousand reviewed publications, the efficacy of NPWT is well established[76]. Numerous NPWT devices are have been developed. Currently VAC devices commonly use polyurethane

foam for packing the wound bed[66]. However recently gauze-based systems are being increasing being used and their efficacy was proved by a retrospective analysis published by Campbell *et al*[66,77]. Further to decrease the duration of hospital stay and improve the quality of life; portable NPWT devices have come up. The single use PICO system (Single Use Negative Pressure Wound Therapy Device) is one such system and is superior to others as the Acti VAC Therapy system the latter being bulky, noisy and requiring maintainence. Besides providing the benefits of NPWT, these systems allow the wounds to be managed on an outpatient basis[76]. Another recently developed system is the Smart Negative Pressure(SNaP) wound care systems which uses springs to deliver NPWT having the advantage in that it doesn't depend on electricity. How these portable systems are difficult for use in wounds with large surface area which produces significant exudate[4]. Modifications of NPWT such as NPWT with instillation (NPWTi) have been described which combines conventional NPWT with instillation of different fluids. Studies suggest decreased hospital stay, accelerated wound healing and bacterial load (bio-burden) with NPWTi using saline[78,79].

Mechanism of Action

NPWT brings about its beneficial effects on wound healing by four primary effects which include macrodeformation (contraction of wound); stabilization of wound environment; removal of extra-cellular fluid and

microdeformation at the foam wound interface. Macrodeformation-NPWT draws the wound edges close leading to early contraction of the wound[5]. The effect of macrodeformation depends on the amount of deformable tissue present at the site of application of VAC; e.g. an incisional wound will nearly approximate while a scalp wound will show minimal contraction[80]. NPWT stabilizes the wound environment by providing a moist environment (which is ideal for wound healing) protected from the external environment. It is theorized that the osmotic and oncotic pressure gradients at wound surface is made stable by NPWT by evacuating both fluid with electrolytes and proteins[80]. Oedema impedes wound healing by increasing tissue pressure hence compromising tissue perfusion and hence cell death. It also causes a decreased proliferative response of cells by causing compression of cells which decreases their intrinsic tension. Thus, evacuation of oedema by NPWT causes decrease interstitial pressure and when this falls below capillary pressure, the capillaries open and vascularity is enhanced facilitating wound healing[5,80,81]. In burns wounds the zone of stasis (which can either revert to zone of hyperaemia (tissue recovers) or worsen to the zone of coagulation (irreversible tissue loss)) worsens with oedema and hypoperfusion, thus decreasing oedema will have its beneficial effects; and this has been shown by Morykwas *et al* that there is significant decrease in bum depth with NPWT[80,82,83]. Microdeformation (tissue reactions at microscopic level)

induces a proliferative and angiogenic response[80]. NPWT causes mechanical stress by shearing strain at the wound dressing interface, fluid removal and tension and compression of tissue. This in turn deforms the cytoskeleton which activates cascades which bring about cellular proliferation and angiogenesis[84]. Studies show increase in fibroblast proliferation, fibroblastic growth factor, transforming growth factor beta(TGFβ) and α-smooth muscle actin[85]. NPWT brings about neovascularization by its mechanical forces on existing blood vessels and elevating levels of interleukin 8 and vascular endothelial growth factor (VEGF)[85,86]. Reduction in bacterial load, increased blood flow and angiogenesis, cellular procreation and propagation, enhanced granulation and decreased inflammation comprise the other secondary effects of NPWT .

Indication Contraindication and Complications of NPWT

NPWT has been widely described for use in acute and chronic wounds, diabetic foot ulcers, venous ulcers, orthopaedic trauma, composite tissue flaps, bums wounds, split-thickness skin grafts, open abdominal wounds, pressure ulcers, sternal wounds and high risk incisions[5-11].

Contraindications to use of NPWT include wounds with exposed blood vessels, nerves, anastomotic sites and organs; infection; bleeding;

malignancy; coagulopathies; ischaemic wounds allergies to foam used in VAC devices[5]. Jones et al in a retrospective study of NPWT in infected wounds showed a mean reduction of 29% in wound surface area with p value of <0.05[87]. Ischaemic wounds are not ideal for NPWT as it may worsen ischaemia. NPWT is contraindicated in deeps infections as osteomyelitis application of a VAC device over such a wound may enclose the infection thereby forming an abscess[4]. Studies have shown relative hypo-perfusion in the immediate proximity of wound edges and even intact skin[6]. NPWT is not used in the setting of malignancy as its proliferative effect is unwanted and also malignant tissue is more likely to bleed[5].

Complications of NPWT reported include bleeding, infection, pain, rupture of heart, anxiety, loss of protein & malnutrition, overgrowth of granulation tissue onto the foam, desiccation of wound if not well sealed, blocked tubing and kinking, fistula formation and toxic shock syndrome[81,88,89]. Pain occurs can occur due to the suction of vacuum per se; and the granulation tissue which grows into the pores of the foams used, which get disrupted during dressing change. Saline gauze based NPWT systems were found to be comparatively less painful[88]. Bleeding is the major and occasionally worrisome complication of NPWT. This happens due to the foam being directly being placed over an exposed vessel, wound bed fragments which migrate and cause injury and when the foam used sticks adherently to the tissue bed which bleeds on change of dressing[88].

Life threatening bleeding following NPWT has been reported from its use in sternal wounds following cardio-thoracic surgeries. This is usually due to bleeding from a major vessel such as aorta or from the right ventricle. This occurs due to infective erosion of a vessel or the right ventricle being drawn to the sternum causing its injury[88]. The use of rigid barriers has been described to prevent bleeding and these have not show to influence mechanics of NPWT[90,91].

NPWT and Diabetic Foot Ulcers – outline of previous studies

In a recent systematic review and meta-analysis conducted by Liu *et al,* it was seen that rates of complete healing, healing time, reduction in surface area of ulcer and reductions in ulcer depths were overwhelming in patients with diabetic foot ulcer treated with NPWT as compared to standard dressing and these were all statistically significant[12]. Annstrong *et al* in a 16-week multi-centre randomised controlled trial (RCT) involving 162 patients showed that more wounds healed in the control group (56% vs 33%), faster time to wound closure and rates of granulation tissue formation[13]. A RCT conducted by Ravari *et al* showed that the depth of ulcer reduced significantly in diabetic foot ulcer (DFU) patients after two weeks of therapy with NPWT. Statistically positive results were noted in terms of patient satisfaction and the size of the ulcer before and after two weeks of NPWT[14]. Nather *et al*[15] in a prospective study showed that the average reduction in wound surface area was 32.8%. The study also

showed that at the end of the study none of the wound swabs sent showed any growth. Singh *et al*[16] in a study conducted in a tertiary centre in north India showed that time to complete healing was reduced by about 30% in patients treated with VAC.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study; designed as a prospective parallel randomized controlled trial was carried out in the Department of General Surgery, Govt Rajaji Hospital Madurai between August 2018 and August 2019 after being approved by the Institute Ethical Committee (IEC).

With a power of 80%, a error of 5%, and expected difference of 20 days in the time taken for complete granulation cover[18], the sample size was calculated to be 54 with 27 in each group. With the expected drop out rate of 10%, the sample size of 30 in each group was taken for the trial.

Patients

Inclusion Criteria

All diabetic patients >18 years of age admitted in Rajaji Hospital General Surgery wards with a diabetic foot ulcer (DFU).

Exclusion Criteria

1. Coagulopathy
2. Venous disease
3. DFU patients with underlying osteomyelitis
4. DFU patients with Charcot's joint
5. DFU classified under Wagner-Meggit classification as grade III, IV and V
6. Peripheral Vascular Disease
7. DFU involving both feet

Randomization of patients

Stratified Block randomization was carried out with randomly selected block sizes of 4 and 6. Further after randomization of patients in two groups, the patients in the respective groups were stratified into two groups of ulcer size <10 cm in and of ulcer size >10cm in the longest dimension, considering size of ulcer as a known confounding variable.

Study Procedure

All patients with a DFU in Rajaji Hospital General Surgery wards were enrolled into the study after fulfilling exclusion criteria and after informed written consent. The nature, methodology and risks involved in the study were explained to the patient and informed consent was obtained. All the information collected was kept confidential and patient was given full freedom to withdraw at any point during the study. All provisions of the Declaration of Helsinki were followed in this study.

Initial treatment including necessary surgical debridement of the wound, appropriate antibiotic based on culture sensitivity and glycemic control was done. The wound was defined fit to be included in the study when the DFU was deemed “clean” by the treating surgeon and the wound culture shown no growth or skin flora, all patients were also checked for strict glycemic control defined as having AC (ante-cibum) and PC

(post-cibum) values of less than 120mg/dL and 180 mg/dL respectively before including in the trail. After satisfying the said criteria, the enrolled patients were then randomized into two groups to receive either conventional dressings or Vacuum Assisted Closure (VAC) therapy. The patients in the study group received VAC therapy while those in the control group received conventional dressing. Further patients in the two groups were stratified in to groups of patients with DFUs of <10cm and >10cm in the longest dimension. Wagner's grade of the DFU, duration of diabetes (in years), whether the patient was on Insulin/OHAs/both prior to study, HbAlc, baseline albumin, hemoglobin, BMI and comorbidities were recorded in both the groups before starting the intervention. Assessment of nutrition was done by monitoring albumin and hemoglobin levels every week. Culture sensitivity was sent at the start of the study and then every week.

In the study group, the wound bed was filled with a saline soaked gauze piece after it was thoroughly cleaned. VAC was applied by placing sterile pads in two layers with a 16Fr Ryle's tube placed between the two layers and then the wound was sealed by a sterile transparent polyurethane sheet. The tube was connected to a wall mounted suction device and the pressure was set at -125mm Fig. Mode of Negative Pressure Wound Therapy (NPWT) was continuous. This dressing was changed every 48

hrs. At any point of time during the study if the treating surgeon notices any adverse wound parameters, the VAC therapy was immediately discontinued.

In the control group conventional dressing was given. This consisted of placing a saline soaked gauze piece over the wound bed after cleaning the wound. Two layers of sterile gauze piece was placed on the dressing and secured with roller bandages. The dressing was changed daily and assessment of the wound was done every 48 hours by the treating surgeon for improvement or any adverse wound parameters. The outcome parameters were recorded in a specified proforma. Photographic documentation was also done at the start of the study and then followed weekly. Patients were assessed till satisfactory wound healing was achieved which is defined when the wound is completely filled with granulation tissue and is fit for split-skin grafting (SSG).

Primary Outcome measure

The time needed for satisfactory wound healing was calculated by the number of days from the start of the study till the wound was fit for grafting.

Secondary Outcome measures

1. Granulation tissue formation: This was assessed using a visual score[19] as mentioned in Table 8. Granulation tissue score was noted every week and the mean value was taken for statistical analysis.

Table 8.

Definition	Score
No granulation present	1
<25% of wound covered by granulation tissue	2
25-74% of wound covered by granulation tissue	3
75-100% of wound covered by granulation tissue	4

2. Parameters of pain, bleeding and wound culture sensitivity was compared between the two groups.

Pain was assessed using a Visual Analog Score. Assessment was done every 48 hourly and a mean value was calculated for each week and taken for analysis. Bleeding was assessed by the number of times the wound dressing had to be changed (excluding the one which was done every 48 hourly) due to soakage of blood. Total number of dressings changed due to soakage of blood was noted every week and taken for analysis

Wound culture sensitivity was sent every week and organisms grown were noted for analysis on a weekly basis

Other Parameters

1. Wound surface area calculated by the ruler method, was done at the start and end of the study; and the difference between the two was taken for analysis as the decrease in wound surface area.

2. Rate of granulation tissue formation was calculated by dividing the wound surface area at the start of study by the number of days required for wound healing.

3. Total number of minor amputations and debridement (excluding the debridement done prior to start of study) done during period of study was compared between the two groups

The primary and secondary outcome measures, decrease in wound surface area and rate of granulation tissue formation were compared between the study and control groups. Besides complications (i.e. pain, bleeding, bacteriology, amputation and debridement); these were also compared in the stratified subgroup to assess the impact of wound size on the intervention.

Analysis was done consulting an expert in the field of statistics using 'stata' version 12.0 software. Categorical variables as gender was

calculated using Pearson Chi^2 test. Unpaired t-test was used for variables which were continuous and normally distributed. Mann Whitney test was used for ordinal variables and for variables which were continuous but abnormally distributed.

RESULTS

RESULTS

This study was a single-centre, prospective, parallel arm randomized control trial conducted in the Department of General Surgery, Govt Rajaji Hospital, Madurai, India between August 2018 and August 2019. 128 patients were assessed for eligibility to include in the study. 28 patients were having Wagner's grade of III or more and hence were excluded from the study. 14 patients were having associated peripheral vascular disease and three patients had osteomyelitis of the foot. Three patients had bilateral diabetic foot infection and 20 patients declined participation in the study. Following the assessment for eligibility,60 patients satisfying inclusion and exclusion criteria we enrolled into the study and randomized into two groups each with 30 patients each. Study group received VAC therapy while the control group received conventional dressing. In none of the patients in the control group, VAC therapy had to be discontinued. Three patients in conventional group and two patients in the VAC group withdrew consent from the study within the first week of therapy. One patient in the VAC group absconded during the second week of treatment and hence was excluded from the study, leaving 27 patients in each group for analysis at the end of the study.

CONSORT FLOW CHART

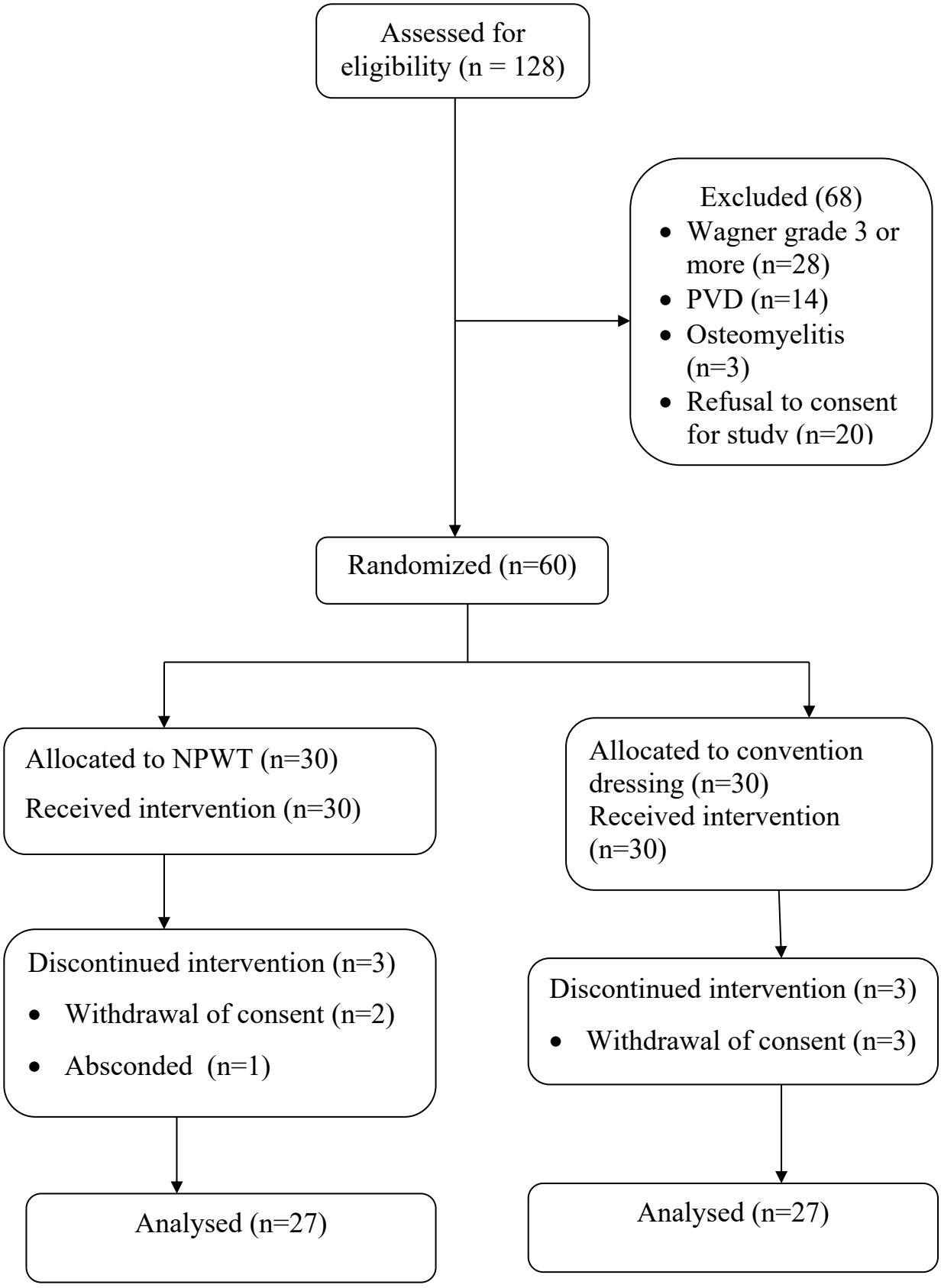

Table 9 *Demographic characteristics of the study population*

Baseline Characteristics		Group A	Group B	P -value
Age in years (Mean)		55.85(35-95)	52.89(28-70)	0.3596[3]
Gender	Male	16 (59.26%)	15 (55.56%)	0.783[b]
	Female	11 (40.74%)	12 (44.44%)	
Diagnosis	Right DFU	16(59.26%)	13(48.15%)	0.413[b]
	Left DFU	11(40.74%)	14(51.85%)	
Duration of DM		7.29 years	6.24 years	0.462[3]
Treatment of DM before study	New onset	1(3.7%)	0(0%)	0.779[b]
	On OHA	20(74%)	20(74%)	
	On insulin	5(18.52%)	6(22.22%)	
	On insulin &OHA	1(3.7%)	1(3.7%)	
Co-morbidities	None	22(81.48%)	20(74.07%)	0.067[b]
	CAD	0 (0%)	2(7.41%)	
	HTN	5(18.52%)	1(3.7%)	
	HTN& CAD	0 (0%)	3(11.11%)	
	BA	0(0%)	1(3.7%)	
BMI (kg/m^2)		22.99	23.26	0.7780[3]
Haemoglobin (g/dL)		10.28	10.18	0.8163[a]
Albumin (g/dL)		2.77	2.72	0.5287[3]
HbAlC		8.74	8.54	0.6525[3]
Wagner-Meggit Grade	Grade 1	8(29.63%)	2(7.41%)	0.036[b]
	Grade 2	19(70.37%)	25(92.59%)	
Number of patients with ulcer size	>10cm	11(40.74%)	10(37.04%)	0.780[b]
	<10cm	16(59.26%)	17(62.96%)	
Ulcer area (cm)		70.97	80.44	0.5675[3]

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; DM- Diabetes Mellitus; DFU-Diabetic Foot Ulcer; OHA-Oral Hypoglycaemic Agents; HTN- Hypertension; CAD-Coronary Artery Disease; BA-Bronchial Asthma; BMI- Body Mass Index; Unpaired t-test[a]; Pearson Chi^2 test[b].

As a whole, demographic characteristics and factors which affect wound healing was comparable between the two groups

The age distribution was noted to be normal in both the study and control groups with One Sample Kolmogorov-Smimov (KS) test showing a p-value of 0.125 and 0.150 respectively. The mean age in the patients who received VAC therapy was 55.85 years while those among patients who received conventional dressing was 52.89 years. The age between the two groups was compared using unpaired t-test, which showed no difference between the two groups with a p value of 0.359. Most of the patients were noted be in the ages between 40-60 years (55.6% and 77.8% in the study and control group respectively).

Out of the 54 patients, 31 were male and 23 were female. Of these 16 males and 11 females received VAC therapy, while 15 males and 12 female received conventional dressing. The gender distribution was uniform between the two groups with Pearson Chi test giving as p value of 0.783.

Duration of diabetes in the two groups was also assessed and mean duration was found to be 7.29 years in the study group and 6.24 years in the control group. Overall the duration of diabetes in patients in the two groups was comparable with a p value of 0.462 by unpaired t test.

Of the 54 patients included in the study, one patient had new onset diabetes mellitus and hence was not on any treatment for sugar control prior to hospitalization. 40 patients (74.1%) were on OHA, 11 were on insulin (20.4) and 2 were on both OHA and insulin (3.7%). In the study group, 1 patient was_newly diagnosed of diabetes, 20 patients were on OHAs, 5 on insulin and 1 on both OHA & insulin; in the control group 20 were on OHAs, 6 on insulin and 1 patient was on both OHA and insulin. This was comparable between the two groups with Pearson Chi^2 test showing a p value of 0.779.

Assessing comorbidities in the patients, 42 (77.8%) patients had no other comorbidities, 6 (11.1%) had HTN alone,2 (3.7%) had CAD alone, 3(5.6%) had both HTN & CAD and 1 (1.8%) patient had BA. Comorbidities were comparable in the two groups with a p value of 0.067. The mean BMI, haemoglobin, albumin and HbAlc in the study group was 22.99, 10.28, 2.77 and 8.74 respectively while in the control group it was 23.26, 10.18, 2.72 and 8.54 respectively. These parameters were uniform in the two groups with p values of 0.7780, 0.8163, 0.5287 and 0.6525 respectively.

Distribution of Wagner grade 1 & 2 DFUs was unequal in the two groups; eight grade 1 DFUs were in conventional dressing group while only two grade 1 DFUs were in the NPWT group. However, the possibility

that this distribution favour results in the NPWT group was unlikely as both these grades were superficial. Also, when the primary objective in the two groups was compared by stratifying on the basis of grade, results were in favour for NPWT for both Wagner grade 1 and 2 DFUs.

Considering that size of the ulcer could affect the time to wound healing the patients in the groups were stratified as those having ulcers <10cm in longest dimension and those with ulcer >10cm in the longest dimension. A total of 21 of the 54 patients had ulcers >10cm, of these 11 were in the study group and 10 in the control group. Of the 33 patients with ulcer size <10cm; 16 were in the study group and 17 were in the control group. These numbers were comparable between the two groups with a p value of 0.780 as given by Pearson Chi^2 test.

Ulcer surface area calculated at the start of the study was normally distributed in both the patients receiving VAC therapy and conventional dressing. The mean surface areas were 70.97 cm^2 and 80.44 cm^2 in the study and control groups respectively; and comparable between the two groups with a p value of 0.5675.

Table 10 Time to wound healing

Time to wound healing			Group A	Group B	P -value
Time to wound healing in days	Mean		22.52	33.85	<0.0001[c]
	Median		21	34	
	Min		13	18	
	Max		36	55	
Time to wound healing in days	>10cm size ulcers	Mean	29.36	38.5	0.0042[c]
		Median	30	39.5	
		Min	19	27	
		Max	36	50	
	<10cm size ulcers	Mean	17.81	31.11	<0.0001[c]
		Median	17.5	30	
		Min	13	18	
		Max	25	55	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Mann Whitney test[c]

Table 11. Time to healing (days) with respect to Wagner grade

Wagner Grade		Group A	Group B	P value
1	Mean	15.75	30	0.0361°
	Median	15.5	30	
	Min	13	21	
	Max	19	39	
2	Mean	25.37	34.16	0.0012°
	Median	27	34	
	Min	15	18	
	Max	36	55	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Mann Whitney test[c]

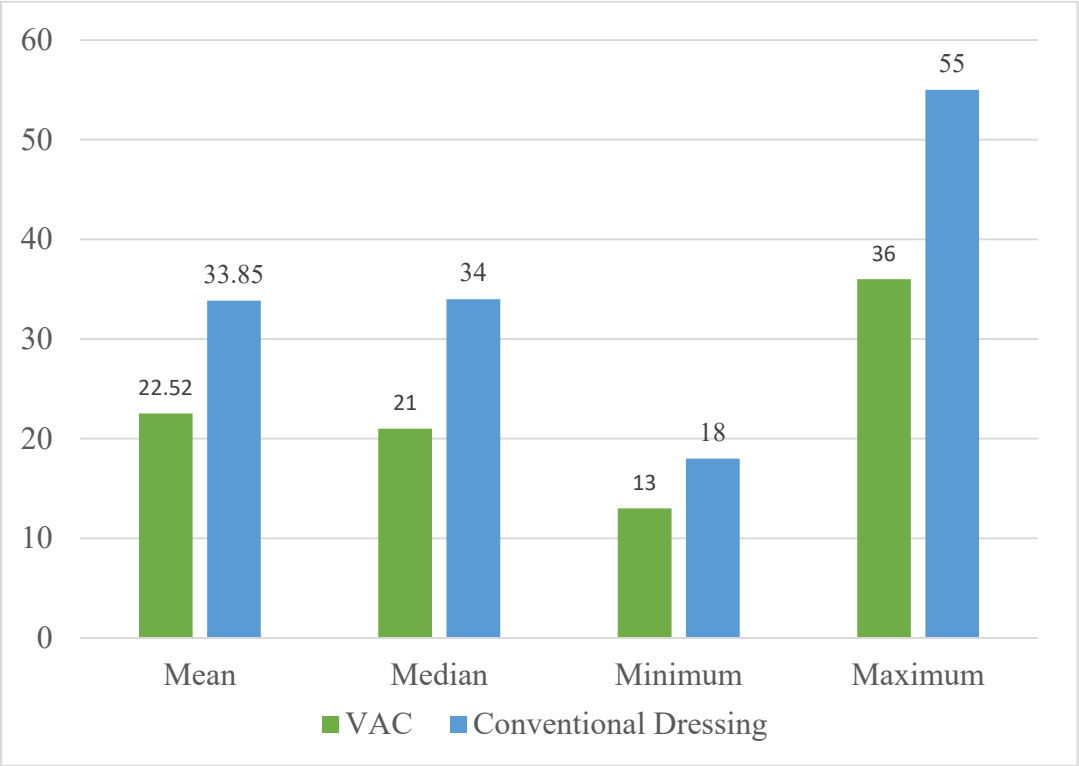

Figure 1. Time taken (in days) for healing of diabetic foot ulcers

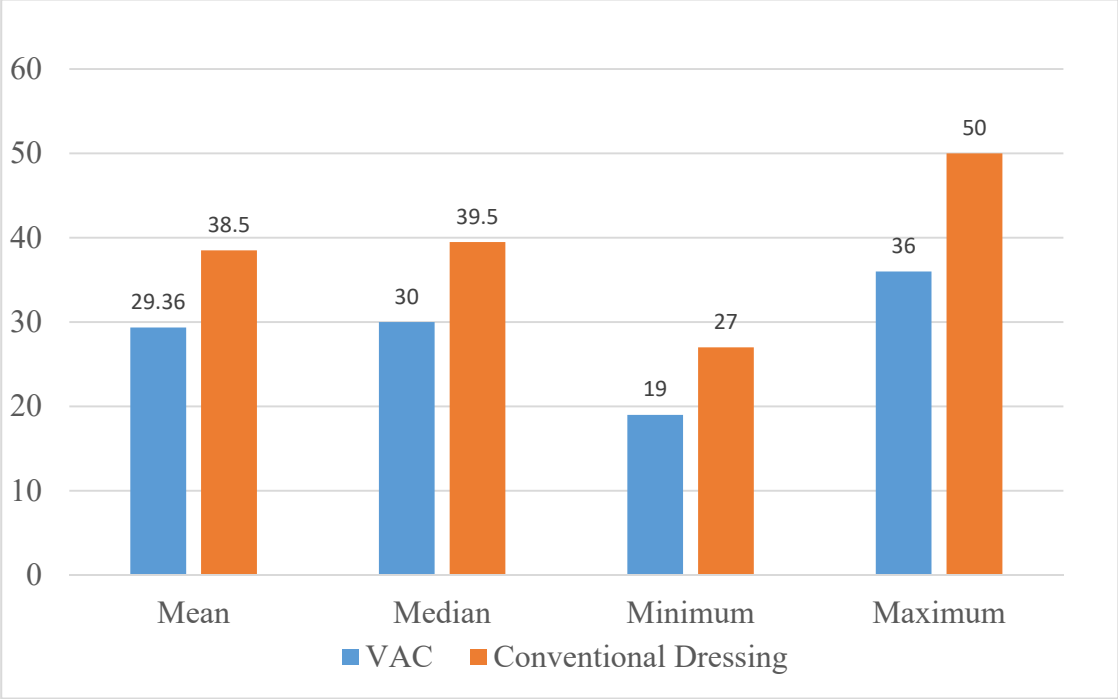

Figure 2. Time taken (in days) for healing of diabetic foot ulcers ≥10 cm in the longest dimension

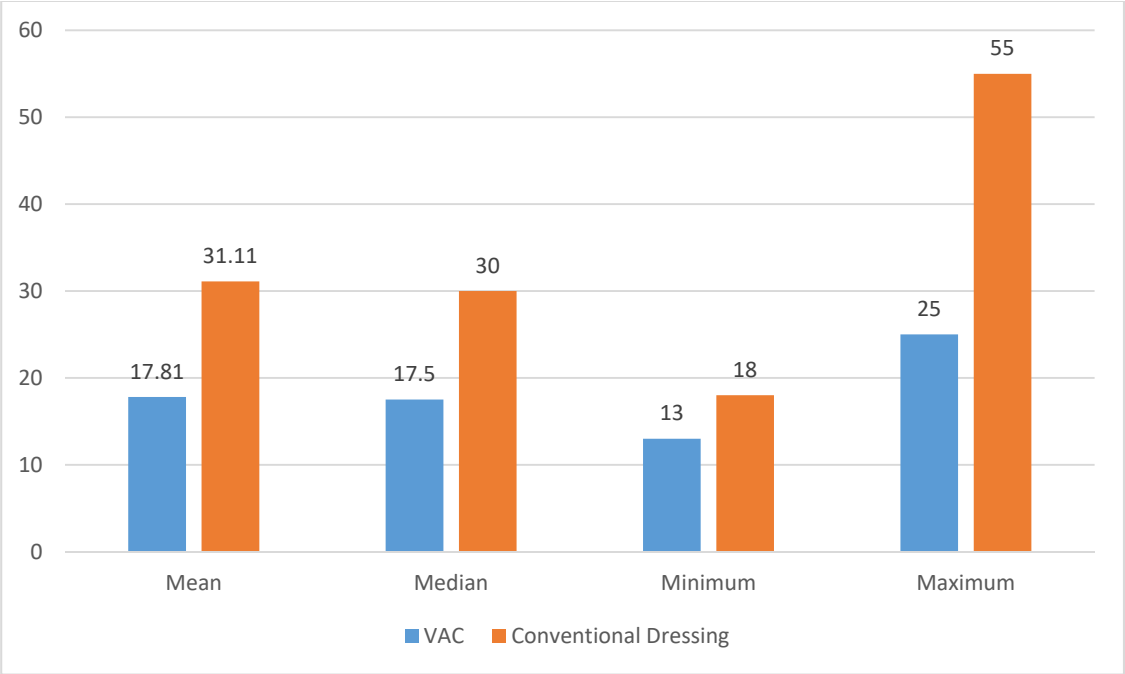

Figure 3. Time taken (in days) for healing of diabetic foot ulcers <10 cm in the longest dimension

The primary objective of the study i.e. time to healing, was found to be significantly better in the study group with a p value of <0.0001. The mean and median time to healing were 22.52 days and 21 days respectively in the study group while these were 33.85 days and 34 days respectively in the control group. The maximum time to heal was 36 days and 55 days in the study and control groups respectively.

The time to healing when compared between ulcers with sizes <10cm and >10cm between the study and control groups were also found to be significant. This was more pronounced in patients with ulcers <10cm where p value was found to be <0.0001 while in patients with ulcer size >10cm this was found to be <0.0042.

The primary objective was also compared between the study and control groups with respect to grade. For Wagner grade 1 DFUs, the mean and median time to healing was 15.75 days and 15.5 days respectively in the NPWT group; while for the conventional dressing group these were both 30 days; and this was statistically significant (p=0.0361). Time to healing was even better for Wagner grade 2 DFUs in the NPWT group with mean and median values of 25.37 days and 27 days respectively, while these were 34.16 days and 36 days respectively in the conventional dressing group.

Table 12. Reduction is ulcer area (cm^2)

Reduction in ulcer area (cm^2)			Group A	Group B	P value
Reduction in ulcer area (cm^2)	Mean		14.29	4.78	<0.000 1[c]
	Median		10.34	3.5	
	Min		0.28	0.00	
	Max		36.85	25	
Reduction in ulcer area (cm^2) based on ulcer size	>10cm size ulcers	Mean	23.93	7.04	0.0005[c]
		Median	25	6.845	
		Min	10	0	
		Max	36.85	25	
	<10cm size ulcers	Mean	7.66	3.46	0.0018[c]
		Median	7.73	3	
		Min	0.28	0	
		Max	13.25	16.7	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Mann Whitney test[c]

As noted from table 3 the area of the ulcers reduced significantly in the patients who received VAC therapy when compared to those who received conventional dressing. The mean and median reduction in surface area of ulcers was 14.29 cm^2 and 10.34 cm^2 in the study group while in the control group it was 4.78 cm^2 and 3.5 cm respectively. The p value calculated by Mann Whitney test was found to be very significant with a p value of <0.0001. Reduction in surface area of ulcer was significant when this was compared separately for patients with ulcer sizes <10cm and

>10cm between the study and control groups. This was found to be better in those with ulcer size >10cm where the p value was 0.0005, while this in the other group was 0.0018.

Table 13. Mean time taken (in days) for granulation tissue cover of Visual score 3 and 4.

Visual Score	Group A	Group B	P value
3	14.52 days	15.04 days	0.561 l[a]
4	23.33 days	32.15 days	<0.0001[a]

Group A-Negative Pressure Wound Therapy group; Group B-Conventional Dressing group; Unpaired t-test[a]

The time taken to achieve granulation cover of >75% (Visual Score - 4) was significantly better in the patients who received VAC therapy with a p value of <0.0001. However this was not so to achieve a visual score of 3 where in the p value was found to be 0.5611. The mean time to achieve score of 3 was 14.52 days and 15.04 days in the study and control group respectively, while to achieve a score of 4 this was 23.33 days and 32.15 days respectively.

Table 14. Rate of granulation tissue formation (cm^2 /day)

Rate of granulation tissue formation (cm^2 /day)			Group A	Group B	P value
Rate of granulation tissue formation cm^2 /day			2.91	2.16	0.0306[c]
Rate of granulation tissue formation cm^2/day based on ulcer size	Size of ulcer <10cm	Mean	2.12	1.50	0.035 l[c]
		Median	2.025	1.43	
		Min	0.79	0.77	
		Max	5.2	3.89	
	Size of ulcer >10cm	Mean	4.05	3.29	0.3598[c]
		Median	4.2	2.766	
		Min	2.37	1.54	
		Max	7.29	5.5	

Group A-Negative Pressure Wound Therapy group; Group B-Conventional Dressing group; Mann Whitney test[c]

The rate of granulation tissue which was calculated by dividing the ulcer surface area by the number of days to healing. The mean and median value was found to be 2.91 cm^2/day & 2.4 cm^2 /day and 2.16 cm^2 /day & 1.7 cm^2 /day in the study and control group respectively with a p value of 0.0306. The rate of granulation tissue was also compared separately for ulcers <10cm and >10cm between the study and control groups, during which this was found to be significant (p value- 0.0351) for those with ulcers <10cm while it was not significant (p value-0.3598) for those with ulcers >10cm.

Table 15. Assessment of Pain: Visual Analog Score (VAS)

Time		Visual Analog Score		P value
		Group A	Group B	
Week 1	Mean	8.22	8.46	0.271[c]
	Median	8.5	8.5	
	Min	7	7	
	Max	9	10	
Week 3	Mean	3.18	4.42	0.004[c]
	Median	3	4	
	Min	2	2	
	Max	6	7	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Mann Whitney test[c]

As observed in table 6, in week Ion the mean VAS was 8.22 and 8.46 in the study and control groups respectively; and wasn't significant (p value 0.271). In week 3, the mean score was 3.18 and 4.42 in the study and control groups respectively, with a p value of 0.004. Noting the fact that 26 patients were compared in the study group in week 3, hence the significance is only expected to increase. Comparison of VAS was done in week 3, as the mean time to healing and time to achieve granulation visual score of 4 in the study group was 22.52 days and 23.33 days (~3 weeks).

Assessment of Bleeding

Table 16 a

Time	Number of change in dressings due to bleeding	Number of patients		P value
		Group A	Group B	
Week 1	0	13	11	0.656[c]
	1	8	10	
	2	6	5	
	3	0	1	
Week 3	0	25	25	0.579[c]
	1	1	2	
	2	-	-	
	3	-	-	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Mann Whitney test[c]

Table 16 b

Bleeding causing soakage	Number of patients		P value
	Group A	Group B	
Yes	14	16	0.584[b]
No	13	11	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Pearson Chi^2 test[b]

Table 7b shows that's 14 patients in the study group and 16 patients in the control group had change in dressing due to soakage caused by bleeding. In week 1, a total of 12 patients had to undergo change in dressing due to bleeding; while in week 3, none had to change dressing due

to bleeding more than once. The number of patients who had different number of change in dressing in week 1 and week 3, is described in table 7a and this did not show any significance (week l, p value=0.656; week 3, p value=0.579).

Bacteriology

Table 17 a

Organism	Number of patients		Total number of patients (% of 54)
	Group A	Group B	
No Growth	12	11	23(42.6%)
CONS	5	4	9(16.7%)
Staphylococcus aureus	16	19	35(64.8%)
Streptococcus spp	6	5	11(20.4%)
Pseudomonas aeruginosa	5	6	11(20.4%)
Escherichia coli	1	13	14(25.9%)
Klebsiella spp	1	2	3(5.6%)7%
Proteus mirabilis	2	5	7(12.9%)
Acinetobacter baumannii	2	5	7(12.9%)
MRSA	1	1	2(3.7%)
Morganella morgagnii	1	1	2(3.7%)
Enterococcus faecalis	2	4	6(11.1%)
Citrobacter spp	1	1	2(3.7%)
Bacteroides spp	1	0	1

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; CONS- Coagulase Negative Staphylococcus; MRSA- Methicillin Resistant *Staphylococcus aureus*

Table 17b

Nature of growth	Number of patients		P Value
	Group A	Group B	
Polymicrobial	8	22	<0.00 1[b]
Monomicrobial	19	5	
No Growth	12	11	0.783[b]
CONS	5	4	0.715[b]
No Growth/CONS	16	12	0.276[b]
Escherichia coli	1	13	<0.0001[b]
Gram +	22	21	0.735[b]
Gram -	10	23	0.0003[b]
Aerobes	5	6	0.735[b]
Facultative Anaerobes	26	27	0.315[b]
Anaerobes	1	0	0.315[b]

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; CONS- Coagulase Negative Staphylococcus; Pearson Chi^2 test[b].

The commonest organism associated with diabetic foot ulcer was *Staphylococcus aureus*, which was cultivated in the cultures of 35 patients. The other common organisms were *Streptococcus spp, Pseudomonas aeruginosa* and *Escherichia coli.* A total of 28 patients had either no growth or CONS during their hospital stay of which 16 belonged to the study group and 12 belonged to the control group; however, this was not significant. 22 patients in the control group demonstrated polymicrobial growth, while this was so in only 8 patients

in the patients receiving VAC therapy (p = <0.001). *Escherichia coli* growth was significantly less in the study group; with just 1 patient demonstrating growth in the study population while this was found in 13 patients in the control group (p=<0.0001). Gram negative bacterial growth was significantly less in the NPWT group(p=0.0003). Most of the patient in both groups demonstrated growth of Gram positive and facultative bacteria.

Table 18a & 18b Minor Amputations

Table 18a

Number of Amputations	Number of patients		P value
	Group A	Group B	
0	24	22	0.541[b]
1	3	4	
3	0	1	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Pearson Chi^2 test[b]

Table 18b

Amputations	Number of patients		P value
	Group A	Group B	
Yes	24	22	0.444[b]
No	3	5	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Pearson Chi^2 test[b]

The number of patients who had to under minor amputations was 3 and 5 in the study and control groups respectively; while 24 patients in the study group and 22 patients in the control group did not undergo any amputation. However, this wasn't significant, the p value being 0.444. Most of the patients who underwent an amputation, had so just once. Only one patient had three toes amputated and this patient was in the group who received conventional dressing. Table 7a shows the number of patients who underwent different number of amputations and this also was not significant (p = 0.541).

Table 19a & 19b. Debridement

Table 19a

Number of debridement	Number of patients		P Value
	Group A	Group B	
0	5	3	0.147[c]
1	5	6	
2	11	7	
3	6	4	
4	0	5	
5	0	2	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Mann Whitney test[0']

Table 19b

Debridement (Pearson Chi^2)	Number of patients		P value
	Group A	Group B	
No	5	3	**0.444**[b]
Yes	**22**	**24**	

Group A- Negative Pressure Wound Therapy group; Group B- Conventional Dressing group; Pearson Chi^2 test[b].

The number of patients who underwent debridement was 22 in study group and 24 in the control group and this was not significant (p=0.444). In the NPWT group none had to undergo more than 3 debridement, while 7 patients in the control group had to be debrided more than 3 times. However, the number of patients undergoing different number of debridement was comparable between the two groups (p=0.147).

Figure 4. Materials used for NPWT in the study

Figure 5. Wall-mount based VAC device with pressure set at 126 mm Hg

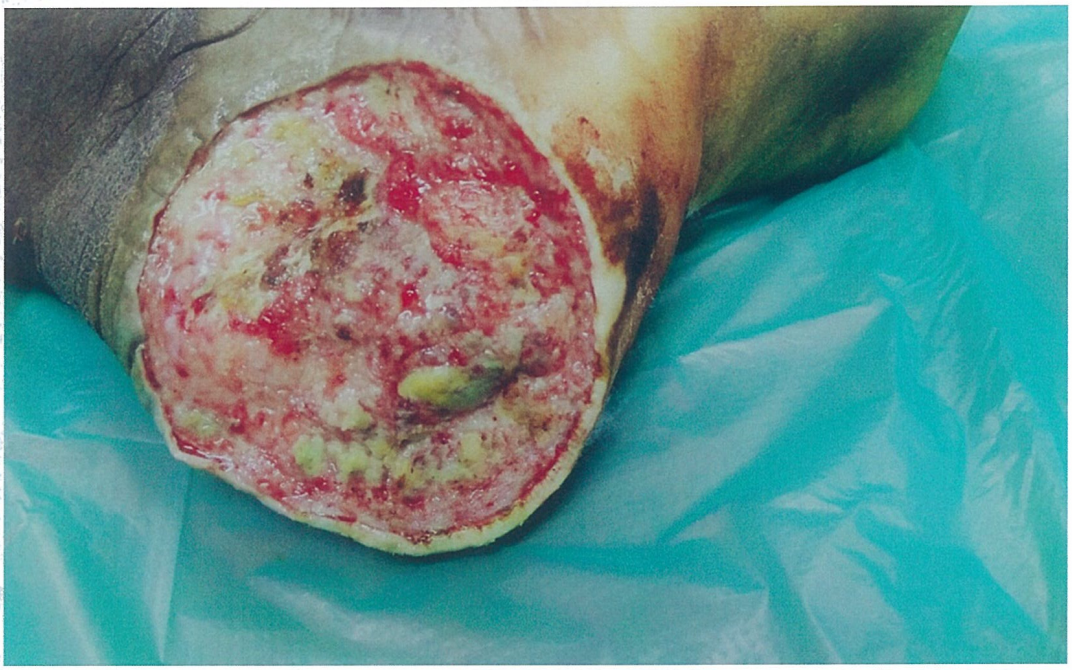

Figure 6. Diabetic foot ulcer at the start of NPWT

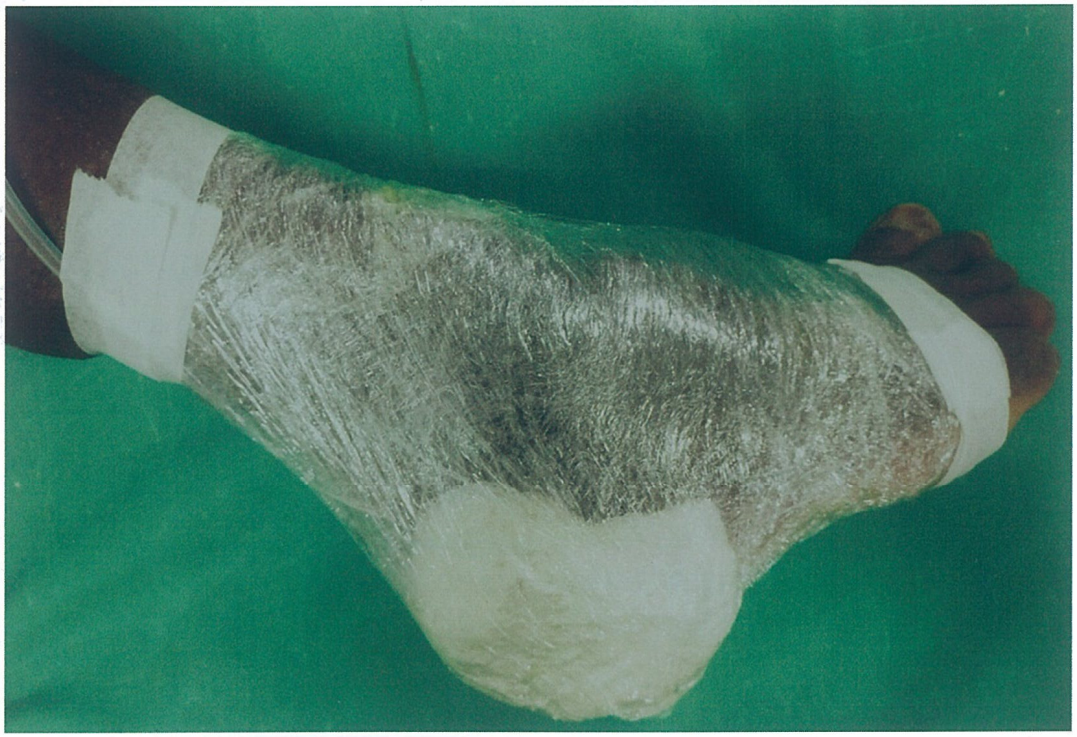

Figure 7. VAC therapy for the DFU in fig. 6

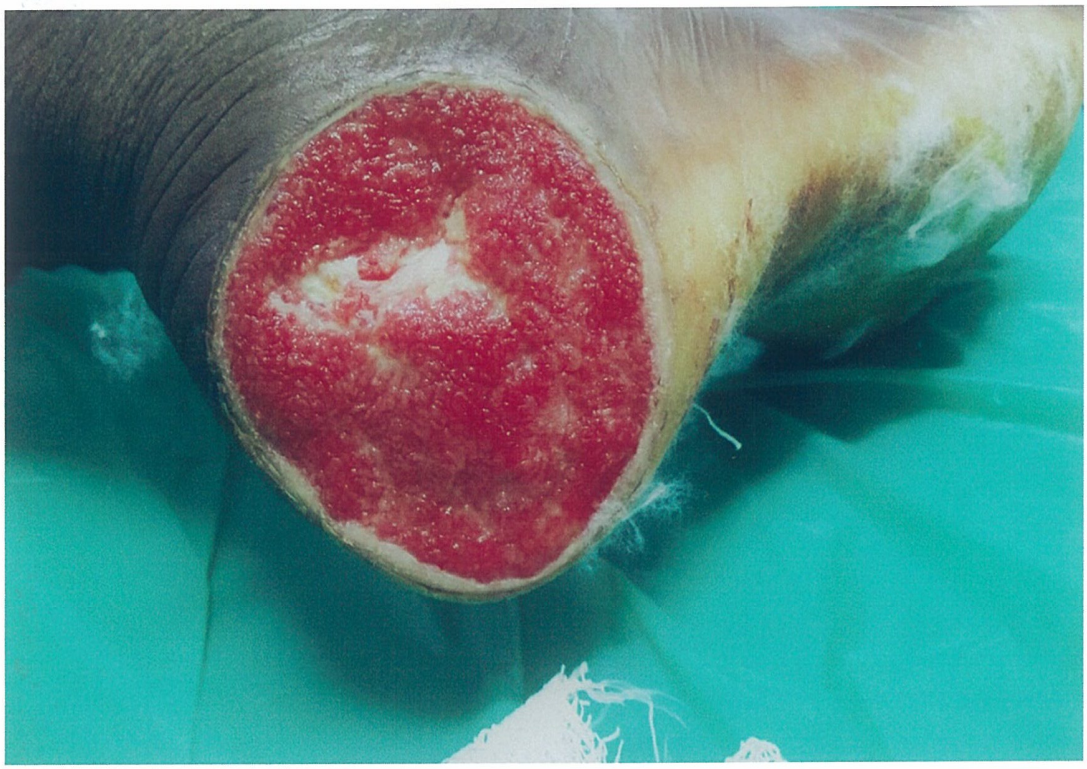

Figure 8. Wound after 15 days of NPWT of the diabetic foot ulcer in fig. 6

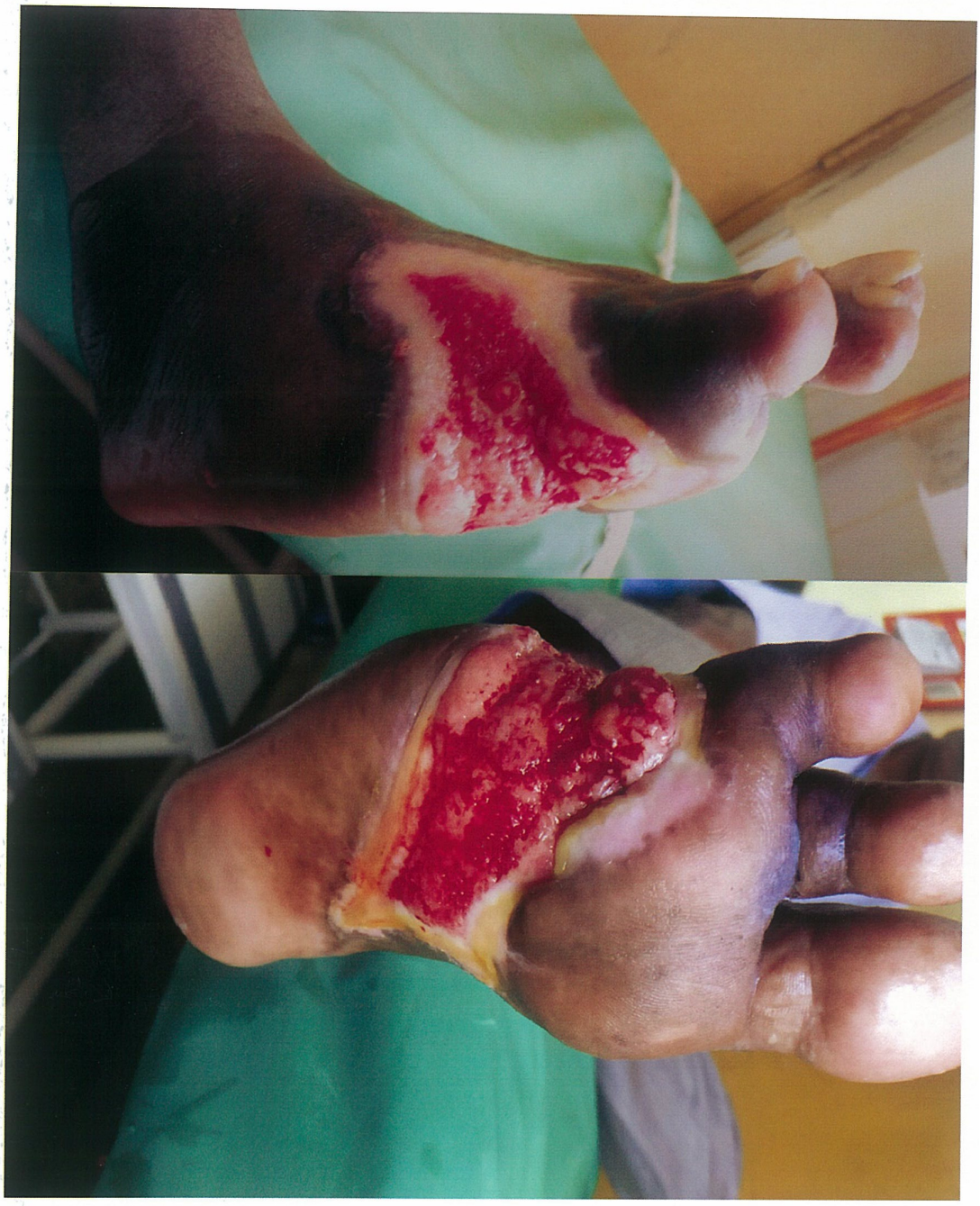

Figure 9. Diabetic foot ulcer wound after 28 days of NPWT

DISCUSSION

DISCUSSION

Considerable proportion of patients with diabetes mellitus develops diabetic foot ulcers (DFU). Incidence of DFU ranges from 1% in the West to as high as 11% in African populations[17]. DFU comprise the most common cause of non-traumatic amputation preceding as high as 85% of the cases[92]. Mortality rate among DFU patients is almost twice than in diabetics without DFU. Five-year mortality rates after new onset DFUs have been reported between 43%-55%, and; 74% mortality has been reported in DFU patients with major amputation. Another major concern is the cost in treating DFUs. In 2007, 33% of the total cost in treating diabetes and its related complication was linked to DFUs. It was found that the cost of care in patients with DFUs was over five times higher in the first year than in diabetics without foot ulcers[94]. This is mainly due to the long duration of hospital stay needed in DFU patients. The magnitude of problems is of more significance in India; owing to poor level of health education, inadequate health care system and as majority of the DFU patients belong to the lower socio-economic strata. NPWT has emerged as one of the most effective methods of wound care for DFUs and has shown to enhance and fasten healing.

This study was done to demonstrate the efficacy and safety of NPWT in the treatment of DFU as compared to conventional saline

dressings, essentially comparing the time to healing (defined as the time taken to make the wound fit for grafting), granulation cover and complications attributed to NPWT. Analysis was done for a total of 54 patients with 27 patients in the study group where in patients received NPWT therapy; and 27 patients in the control group, where conventional dressing was given.

Analysis of baseline characteristics

Mean age of patients in the study was 54.37 years. Distribution was comparable in both groups with mean age of 55.85 years and 52.89 years in the study and control groups respectively, reported studies from India by Vaidhya et al[93], Singh et al[16] and Lone et al[1] showed similar mean age of 56.5, 54.4 and 54.18 years respectively. Studies from Western population by Armstrong et al[13] and Etoz et al[96] showed slight more mean age of 58.6 and 65.45 years respectively. Genetic predisposition, unhealthy lifestyle, inadequate health education, poor glycaemic control are factors which contribute to early development of diabetic complications in Indians as compared to Western population[22].

The study also showed equal gender distribution in both the groups. Males comprised the majority in both the study and control groups (male to female ratio of 1.3:1). This was noted in previous studies[13,14,16,96] as well. This suggest that men are more at risk of developing DFUs than women.

Dinh et al[97] demonstrated that women have lower foot pressures, less severe neuropathy and increased joint mobility as compared to men. Diversity in lifestyle, behaviour and work environment between men and women are also important reasons why DFUs are more common in men.

Mean BMI in our study was 23.125 while Armstrong et al[13] showed a mean BMI of 31.1. This is possibly due to the differences in dietary habits, lifestyle and physical built between Indians and people in Western countries.

As larger wounds would understandably take longer time to heal hence to prevent size of the ulcer as a confounding variable, patients in the two groups were further stratified into ulcer size of <10cm or >10cm. Most of the DFUs in the study were <10 cm, as the ulcers of > 10 cm generally falls in to Wagner's grade III or IV and would require more debridement due to high infective load and slough hence are not candidate for NPWT. Also, significant proportion of patients with > 10 cm ulcer would require amputation. The mean length of DFUs in a study by Eginton et al was <10cm[98].

The size of the DFU in terms of area was comparable in both the study and control groups. Ravari et al[14] and Nather et al[99] showed mean ulcer area of 38.2 cm^2 and 54.6 cm respectively. In our study the mean ulcer area was 75.7 cm which was larger than the previously mentioned

studies. The large ulcer areas in our study population could be attributed to the delayed presentation of DFUs, requirement of extensive debridement as majority of DFUs were infected at presentation leading to larger ulcer surface areas.

Few of the studies have also included Wagner grade 3 in addition to grade 1 and 2 for comparing the efficacy of VAC therapy with conventional dressing on DFUs.[1,14,16,99,100] Application of VAC to Wagner grade 3 ulcers which include deep ulcers with abscess, osteomyelitis and joint sepsis; could enclose the wound infection and may form an abscess[4,36]. Further, significant number of patients with Wagner grade 3 DFUs presents with sepsis and non-functioning ankle joints and often ends up with amputation. Flence in our study we included patients with DFUs of no more than Wagner grades 1 and 2. The distribution of Wagner grade in our study population was found to be unequal, probably due to the relatively smaller sample size. However, considering the fact that both the grades includes only non infected wounds, it is less likely to have a considerable impact on the time to complete wound healing, taking into account that the size of ulcers were equally distributed. Further, when stratified analysis was done to assess the effect of Wagner grade on time to compete healing, the results were still in favour of VAC therapy. The median time to healing for grade 1 DFUs in NPWT group was 15.5 days

while this was 30 days in the control group with p value of 0.0361. Similar results were noted for grade 2 DFUs with median time to healing of 27 days and 34 days in the study and control groups respectively with p value of 0.0012.

Analysis of outcome variables

Time to wound healing

The time to wound healing was significantly better in the VAC therapy group as compared to conventional dressing. Similar results were obtained when comparison was done between the two groups stratifying the patients based on ulcer size (i.e. <10 cm and >10cm). while the time to complete healing in VAC group was significantly better in both DFU of <10 cm and >10cm compared to the conventional dressing group, its efficacy was more evident in the DFUs <10cm ($p < 0.0001$), than the DFUs >10cm ($p = 0.0042$). This can be attributed to the fact that time to healing is directly proportional to the size of the ulcer.

In a study by Annstrong et al[13] median time to complete closure was 56 days in VAC therapy group against 77 days in the conventional saline dressing group. Blume et al[100] demonstrated that a greater proportion of DFUs who received VAC therapy, achieved complete skin closure or 100% reepithelization. Singh et al[16] showed mean time to complete wound

closure of 41.2 days and 58.9 days in VAC therapy group and conventional group respectively. Vaidhya et al[95] in a similar Indian study of 60 patients with DFU showed a time to healing (defined when wound was fit for grafting or secondary suturing) of 17.2 days in VAC therapy group as compared to 34.9 days in conventional dressing group.

Faster healing in NPWT is attributed to macro-deformation including wound environment stabilization, decrease in oedema, wound contraction and microdeformation which include decrease bacterial load, providing suitable environment for healing, and increased cellular proliferation and angiogenesis; all which lead to enhanced granulation cover. When comparing with the results[16] of Armstrong et al and Singh et al; our time to healing was achieved in lesser number of days in both the study and control groups. This is because the end points in the latter studies was defined by spontaneous complete closure i.e. 100% reepithelization. The disadvantage of having complete closure as an end point is that this may not be achieved in all wounds, as the wound size differs considerably between patients; also, majority of the DFUs are wider and longer than deeper unlike the post-operative wounds which takes prolonged period for complete spontaneous closure. In none of the latter studies did all patients reached spontaneous closure. Further waiting for a wound to fully epithelize requires prolonged hospital stay which adds on to the cost of treatment.

Reduction in ulcer area

Reduction in ulcer area in our study was significantly better in the study group with a mean reduction of 10.34cm^2 (20.1% reduction) as compared to 3.5cm^2 (5.9% reduction) (p value <0.0001). Reduction in ulcer area was found to be more significant in ulcers >10cm compared to those <10cm (p value 0.005 vs 0.0018). NPWT enhances wound contraction by macro-deformation due to the centripetal forces acting at the wound-foam interface[16]. The extent of macro-deformation is dependent on the deformability of the wound tissue[80]. Thus in-our study too, wound contraction was more significant for ulcers >10cm which were more deep and hence responded better to the macro-deformation effect of NPWT. Liu et al[12] in a recent systematic review and meta-analysis on the effect of NPWT in DFUs, showed that NPWT significantly reduces DFUs compared to standard dressing. McCallon et al, Eginton et al and Sajid et al in their studies showed a reduction by 28.4%, 16.4% and 23.6% in DFUs who received NPWT[12]. An Indian study by Nain et al[11] showed similar results as ours with mean reduction in ulcer area by 16.14 cm" and 5.98 cm in DFUs treated with NPWT and conventional dressing respectively.

Granulation tissue formation

NPWT causes mechanical strain at the wound-foam interface, which deforms (micro-deformation) the cytoskeleton activating cascades

bringing about cellular proliferation and angiogenesis[84]. Increased levels of FGF, TGF(3, fibroblast proliferation, a-smooth muscle actin, IL-8 and VEGF are implicated in the enhancement of granulation tissue formation in NPWT[85,86]. VAC therapy also creates a suitable environment by decreasing oedema and bacterial load which would otherwise impede granulation. In our study granulation formation in the two groups was analysed by comparing the time to achieve Visual Score of 3 and 4; and the rate of granulation tissue formation. Though the time to achieve scores of 3 and 4 were comparatively less in VAC, this was significant only for Visual score 4 (23.33 days vs 32.15 days, p <0.0001). The possible reason as to why values were not significant in terms of Visual score 3 could be the wide range of 25-75% granulation used in score of 3. Armstrong et al[13] showed that the median time to achieve 76-100% granulation was almost twice as faster using NPWT than conventional dressing (median time of 42 days vs 84 days). Singh et al[16] showed the mean time to-appearance to 100% granulation tissue as 15.1 days in the NPWT group while it was 21.5 days in those who received conventional dressing. In a Spanish study by Sepulveda et al[101] showed the mean time to achieve 90% granulation was 18.8 days and 32.3 days in the NPWT group and conventional dressing group. In the present study, we also found that the mean rate of granulation tissue formation was 2.91cm and 2.16cm in the study and control groups respectively and this was found to be statistically significant (p of 0.0306).

Minor amputations and secondary debridement

Our study also compared the two groups with respect to minor amputations (digital amputations). Of the 54 patients, only 8 patients underwent a digital amputation of which 3 were in the VAC group and 5 were in the conventional dressing group, which was of no statistical significance (0.444). Of the 8 patients, 7 underwent one digital amputation and 1 underwent three digital amputations and the latter belonged to the control group. Armstrong et al[13] in its multicentre RCT showed that 2 patients in NPWT group and 9 patients in control group underwent a second amputation. Further in their study none of the patients in NPWT group needed a major amputation as compared to the control group where 5 patients underwent major amputations. Though these figures favoured NPWT over conventional dressing, it was not significant (p value in both cases 0.060). Blume et al[100] in a large RCT showed 7 of 169 patients in NPWT group, and 17 of 166 patients in AMWT group underwent amputations, majority of which were minor; and these numbers were found to be significant (p = 0.035). Singh et al[16] and Sepulveda et al[101] reported no secondary amputations in either group. Lone et al[1] in a similar study showed no difference in the incidence of amputations (p=0.299). With the available literature evidence, no definite consensus can be made on the effect of NPWT on secondary infections. Though few studies[14,100] have

shown NPWT to reduce the need of re-amputations, there is no explainable direct co-relation of re-amputations with NPWT. In our study all the wounds were well debrided at initial presentation and hence most of them did not require further secondary amputations.

Besides amputations, we also compared number of debridement in each group. None of the patients in the VAC group underwent a debridement more than thrice while this number was seven in the control group. However statistical significance was not found neither in respect with the number of patients who needed debridement nor with the number of debridement required.

Pain

Pain is one of the most common complications implicated due to NPWT. Pain in NPWT is thought to occur due to negative suction and during change of dressing and when granulation tissue which grow into the foam's pores, gets disrupted. In our study pain was assessed by Visual Analogue Score (VAS) and analysis done by comparing the scores in week 1 and week 3 of the study. Week 3 was chosen because the average time to healing was 22.52 days and 33.85 days in the study and control group respectively, which approximated to about 3 weeks. Pain was comparable with no difference in the two groups in the first week ($p=0.271$); with mean scores of 8.22 and 8.46 in the study and control groups. However, in week

3, the mean score was 3.18 and 4.42 in the study and control groups respectively and this was significant (p=0.004). At first presentation, all wounds would be extensively infected and covered with slough and necrotic tissue which require extensive debridement leading to more pain. With time, as the wounds fill up with granulation, pain is expected to come down. Hence, in our study pain scores were better in the NPWT group than the control group in week 3.

Only few studies were compared pain between NPWT and conventional dressing in DFUs. Sepulveda et al[101] found that one patient presented with pain (defined as score of >5 in VAS within first 6 hours of dressing not responding to analgesics) in the control group. Vaidhya et al[93] found NPWT less painful compared to conventional dressing in the treatment of DFUs.

Though pain is a well know complication of NPWT, pain was significantly less in the NPWT group in our study. This could be possibly due to less number of dressings required in the VAC group. NPWT group patients required half the number of dressing as compared to those in the control group as dressing was done once in two days in NPWT group. This was stated as the cause of less pain in NPWT by Nather et al[99]. Other reason for lesser pain could be the use of gauze based NPWT in the present study. Foam is more adhesive and poriferous, hence granulation tissue

grows into it, and thus at the time of dressing change, wound bed gets disrupted. Use of gauze based NPWT has been shown to produce less pain by Fraccalvieri et al[102] and Dorafshar et al[103]. Faster growth of granulation tissue in NPWT group cover raw wound bed faster and hence hasty reduction in the size of raw area also contributes to lesser pain than in the control group.

Bleeding

Bleeding was another common complication attributed to NPWT, which was compared between the two groups. Bleeding was said to be present when there was blood stained soakage necessitating change in dressing after the application of first dressing. 14 patients in NPWT group and 16 patients in conventional dressing group had bleeding. In week 1, 30 patients had bleeding; 18 patients had bleeding once of which 8 belonged to the study group and 10 belonged to the control group. Of the 12 patients who bled more than once in week 1, 6 belonged to the study group and 6 belonged to the control group. In week 3, only 3 patients had bleeding once of which 1 belonged to study group and 2 to control group. No patient reported bleeding more than once in either group in week 3. Though these results were figuratively in favour of NPWT, these were not statistically significant. The increased bleeding in week 1 in both groups was possibly due to aggressive debridement which the patients underwent.

Haemorrhage is one the most feared complications of NPWT and been responsible for 12 deaths since 2007[12]. However, such life-threatening bleeding has been reported only when NPWT was applied for sternal wounds. Major bleeding in NPWT on DFUs is mostly due to improper haemostasis following debridement, exposed large blood vessels and high set negative pressure all of which are avoidable causes. In our study where NPWT was done by the trained surgery residents, there was no significant bleeding reported.

Infection/Bacteriology

Staphylococcus was the most common organism grown and this was demonstrated in the cultures sent for 35 patients (16 and 19 patients in study and control group respectively). E coli grew in only one patient in the study group and 13 patients in the control group and this was statistically significant (p=<0.0001). The three most common organisms in the NPWT group were Staphylococcus aureus-16, streptococcus-6 and pseudomonas-5; and in the conventional dressing this was Staphylococcus aureus-19, Escherichia coli-13 and Pseudomonas aureginosa-6 (number indicate the number of patients). In a RCT by Ali M Lone[1], the most common organism grown were Pseudomonas aeruginosa and Acinetobacter baumannii in NPWT group while in the control grout it was P aeruginosa and Klebsiella.

Monomicrobial growth was significantly more in the NPWT group (19 vs 5, p=<0.001). When comparison was done between the two groups based on gram stain, growth of Gram negative organism was significant less in the NPWT group (10 vs 23, p=0.0003). Several other studies have shown that NPWT reduces Gram negative non-fermentative bacterial growth[104,105]. Gram positive organisms were equally distributed in both groups (22 and 21 in study and control group respectively, p=0.7355). Anaerobic growth was demonstrated in only one patient who belonged to the study group. Singh et al[16] in a similar study showed that Staphylococcus aureus was the common organism grown (23.3%). Nather et al[15] in a prospective study showed that Staphylococcus aureus was cultured from wounds of all five patients. Though different Indian studies report Pseudomonas as the most common organism, staphylococcus was the most common in our study. Most DFUs in the developing countries present late and thus are deep infections; often polymicrobial, mostly showing Gram negative and anaerobic growth[56]. On the other hand, our study included only superficial DFUs (Wagner Grade 1 & 2), and it is widely known superficial infections are common attributed to Gram positive cocci as Staphylococcus and Streptococcus which commonly inhabits normal skin. There is no definite consensus as to whether infection is a complication of NPWT. While there are studies[15,69,99] showing NPWT to decrease bacterial load and infection, there are studies like Armstrong et

a1[1j] which have reported infection as an adverse event. Also, studies like Stannard et al[106], Blume et al[100] showed no difference between NPWT and conventional dressing in respect with infections or bacterial load. Inadequate debridement, retention of foam, air leak, sealing of any underlying infection and bleeding due to NPWT serves as a culture medium are attributed to cause or worsen infection in NPWT. Though studies including ours show beneficial effect of NPWT on wound microbiology, NPWT should not be considered a substitute to control infection[106].

Limitations of the study

The present study was not without any limitations. Though sample size was calculated by statistical method, the number of patients analysed was relatively small. A larger sample could have avoided the unequal distribution of Wagner's grade between the two groups. Though stratified analysis of the primary outcome variable based on grade showed significant positive outcome, this analysis could have been avoided had both grade 1 and 2 DFUs been equally distributed by stratification in the study and control groups. Another limitation was that though bleeding was assessed, the methodology could not be made objective due to logistic reasons. Other important aspects which could have made the study more meaningful could be comparison of cost, quality of life and patient satisfaction.

SUMMARY

SUMMARY

This study was a prospective parallel randomised control trial, conducted in the Department of General Surgery, Govt Rajaji Hospital Madurai between August 2018 to August 2019; to compare the efficacy and safety of Cost-Effective Vacuum Assisted Closure therapy versus conventional dressing in diabetic foot ulcer patients.

A total of 128 patients with DFUs were assessed for eligibility, of which 60 patients fulfilled inclusion and exclusion criteria and gave consent. These 60 patients were randomized into two groups, 30 in each group; one received VAC therapy and one received conventional dressing for wound management. During intervention 5 patients withdrew consent, two in study group and three in the control group; one patient absconded, hence intervention was not continued in these patients and analysis was done for 27 patients in each group. The primary objective of the study was to compare the time to healing which was defined as the time taken for the wound to be fit for grafting. The other variables compared were reduction in surface are, granulation tissue formation, incidence of minor amputations & debridement and complications commonly attributed to VAC therapy as pain, bleeding and infection. All factors which affect wound healing were comparable between the two groups. Though Wagner grade 1 and 2 DFUs were not equally distributed in the two groups, their

effect as a confounding factor was minimal considering few differences between the two groups and this was confirmed by comparing the primary objective between the two groups based on the Wagner grade.

Time to healing was significantly less in the study group as compared to the control group (mean time to healing of 22.52 days vs 33.85 days respectively, p=<0.0001). When comparison between the two groups was Hone on the basis of Wagner's grade, this was also significantly less in the VAC therapy group with respect to both groups. For Wagner grade 1 DFUs, the mean time to healing was 15.75 days and 30 days (p=0.0361) in the study and control group respectively. For Wagner grade 2 DFUs this was 25.37 days and 34.16 days (0.0012) respectively. The reduction in ulcer area was significantly more in the VAC therapy groups with a mean reduction of 14.29 cm^2 vs 4.78cm^2 compared to the control group (p=<0.0001). Granulation tissue formation was analysed in terms of the rate of granulation tissue formation and the mean time to achieve Visual score of 3 and 4. Though the mean time to reach Visual score of 3 and 4 were less in the VAC therapy group, this was significant only significant for Visual score of 4 (23.33 days vs 32.15 days, p= <0.0001).

The median rate of granulation tissue fonnation was 2.4cm^2/day and 1.7cm^2/day in the study and control group respectively (p=0.0306). Though the median rates when compared separately for ulcer sizes <10 cm

and >10cm was more in the VAC therapy, this was significant only for ulcers <10cm (<10cm: 2.025cm^2/day vs 1.50cm^2/day, p=0.0351; >10cm: 4.2 cm^2/day vs 2.766 cm^2/day, p=0.3598). The number of patients who underwent secondary debridement was 22 and 24 in the study and control group respectively (p=0.444), while this was 3 and 5 for minor digital amputations (p=0.444). Thus, no difference was noted with respect to the number of patients who underwent secondary minor amputations or debridement in the VAC therapy group or conventional dressing group.

Pain between the two groups using Visual Analog Score (VAS) was found to be significantly less in the VAC therapy group in week 3 (median VAS of 3 and 4 respectively, p=0.004). Bleeding which is one of the most common and feared complication was comparable between the two groups with the number of patient who had bleeding were 14 and 16 in the VAC therapy group and conventional dressing group respectively (p=0.584). *Staphylococcus aureus* was the most common organism group in the both groups. Other major organisms were *Streptococcus spp, Pseudomonas aeruginosa* and *Escherichia coli.* The number of patients with no growth (12 vs 11) and CONS (5 vs 4) was comparable between the two groups (p=0.783, 0.715 respectively). VAC therapy group demonstrated significantly less Gram-negative growth (10 vs 23, p=0.0003) and polymicrobial growth (8 vs 22, p=<.001).

Thus, the results of the studied shows that VAC therapy is an efficacious and safe method of managing diabetic foot ulcers.

CONCLUSION

CONCLUSION

The present study showed that VAC therapy significantly decreases the time to complete wound healing when compared to conventional dressing. It was found that VAC therapy significantly improves total granulation cover over the wound and the study also showed significantly high rate of granulation tissue formation with VAC therapy. We found that pain score was significantly better at week 3 with VAC group compared to conventional dressing group and the study did not find any significant increase in the bleeding and infection in the VAC therapy group. The study showed significant reduction in the ulcer size in the VAC group compared to the conventional dressing group and the reduction was more pronounced in the ulcer DFU of >10cm size. We did not find any significant difference in the number of amputations or the number of debridement required between the two groups.

The present randomized controlled trial comparing VAC therapy with conventional dressing for DFU shows that VAC therapy is effective in reducing the time to complete wound healing and improving granulation cover with no increase in the complications such as bleeding and infection. Further RCTs with a larger number of patients is recommended to extrapolate the results of the present study.

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DATA COLLECTION PROFORMA

Name: Age/Gender:

Hospital No.: Surgery Unit:

Intervention Group (VAC/Conventional Dressing):

Date of Admission in hospital: Date of start of Study: Date of end of Study:

Co-morbidities besides DM (HTN/Bronchial Asthma /TB /CAD/Any other):

Biochemical Parameters:

Date:											
Hb											
HbAlC											
Albumin											

X-Ray of involved foot:

Number of debridements done during study period:

If Yes, Any Minor Amputations-

Ulcer Characteristics

Date																	
Ulcer surface area (cm^2)																	
Granulation tissue formation (Visual Score)																	
Pain (VAS)																	
Bleeding (Yes/No)																	

Date				
Bacterial C/S				

Time needed for satisfactory wound healing:

CONSENT FORM

Title of the project: Comparison of Cost-Effective Vacuum Assisted Closure (VAC) therapy and conventional dressing on wound healing in patients with Diabetic Foot Ulcer

Participant's name : Address :

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant : _____ Date : _____

Signature of the witness : _____ Date : _____

Name and address of the witness :

Signature of the investigator:_____Date : _____

KEYS TO MASTER CHART

COLUMN	KEY
Serial No.	-
Age (in years)	-
Gender	0- Male 1- Female
Intervention Group	1- (Vacuum Assisted Closure) VAC therapy 2- Conventional Dressing
Duration on Diabetes (in years)	-
Treatment for DM (prior to	0- Newly diagnosed DM
hospitalization)	1- Oral Hypoglycemic Agents (OHAs) 2- Insulin 3- Both OHAs and Insulin
Co-morbidities	HTN- Hypertension CAD- Coronary Artery Disease BA- Bronchial Asthma
Wagner Grade of DFU	-
DFU size >10cm	0- No 1- Yes
Dimensions of DFU (cm **X** cm)	-
DFU area (cm^2)	-
Body Mass Index (kg/m^2)	-
Haemoglobin (g/dL)	-
Albumin (g/dL)	-

HbAlc	-
Time to wound healing (in days)	-
DFU area at the end of study (cm ′	-
Reduction in DFU area	-
Visual Score Week 1-8	-
Rate of granulation tissue formation (cm^2/day)	-
Number of Debridement	-
Number of Minor Amputation	-
Culture Week 1-8	NG: No growth CONS: Coagulase-negative ***Staphylococcus aureus*** sa: ***Staphylococcus aureus*** bs: Beta-hemolytic Streptococcus pa: ***Pseudomonas aeruginosa*** ec: ***Escherichia coli*** kb: Klebsiella spp. pm: ***Proteus mirabillis*** ab: ***Acinetobacter baumannii*** MRSA: Methicillin-resistant ***Staphylococcus aureus*** mm: ***Morganella morganii*** ef: Enterococcus faecalis ct: Citrobacter spp. be: Bacteroides spp.
VAS Week 1-8	-
Bleeding episodes week 1-8	-

MASTER CHART

MASTER CHART

Serial No.	Age	Gender	Investigation Group	Duration of Diabetes	Treatment for DM	Co-morbidities	Wagner Grade of DFU	DFU size ≥10cm	Dimensions of DFU	DFU area cm2	Body Mass Index	Hemoglobin	Albumin	HbA1c	Time of wound	DFU area at the end of study	Reduction in DFU area	Visual score week 1	Visual score week 2	Visual score week 3	Visual score week 4	Visual score week 5	Visual score week 6	Visual score week 7	Visual score week 8	Rate of granulation tissue formation	Number of	Number of minor	Culture week 1	Culture week 2	Culture week 3	Culture week 4	Culture week 5	Culture week 6	Culture week 7	Culture week 8	VAS Week 1	VAS Week 2	VAS Week 3	VAS Week 4	VAS Week 5	VAS Week 6	VAS Week 7	VAS Week 8	Bleeiding episodes	Bleeiding episodes	Bleeiding episodes	Bleeiding episodes	Bleeiding episodes	Bleeiding episodes	Bleeiding episodes	Bleeiding episodes
1	56	0	1	4.5	1	None	1	0	5x6	30	25	8.1	2.8	7.4	15	20	10	2	3	4						2	2	0	sa	sa	NG						7	5	2						0	0	0							
2	70	0	2	2	2	HTN	2	1	10x15	150	20	9.6	2.5	8	31	150	0	2	3	3	4	4				4.8	4	1	sa,bs	bs,sa	sa	sa,bs	sa,bs				8	7	5	2	2				2	0	0	0	0			
3	65	0	1	15	2	None	2	1	18x10	80	27	9.3	2.4	8.9	19	55	25	2	3	4						4.2	1	0	sa	sa,pa	pa						7	5	2						0	0	0							
4	55	0	2	10	2	None	2	1	20x12.5	250	27	8.7	2.2	7.5	45	225	25	2	2	2	3	3	4	4		5.5	5	0	sa,ec	sa,ec,pa	sa,ec,pa	sa,ec,pa	sa	sa	NG		8	6	4	4	3	1	1		2	0	1	0	0	0	0	
5	55	0	1	8	1	None	1	0	3x6	18	30	11	2.8	9	19	15	3	2	3	4						0.9	2	1	pa,kb	pa,kb	NG						8	5	2						0	0	0							
6	47	0	2	6	2	HTN&CAD	2	0	7x6	42	20	9.8	2.7	8.4	27	42	0	2	3	4	4					1.5	3	0	ec,pa	ec,pa	sa	pa					7.5	6	4	2					0	0	0	0						
7	95	0	1	31	2	None	2	1	13x5	65	19	10	2.5	7.7	27	55	10	2	3	3	4					2.4	2	0	bs	bs	NG	NG					8	5	3	1					1	0	0	0						
8	50	0	2	5	2	None	2	0	3.5x6.5	22.8	24	14	2.5	8	18	20	2.8	2	3	4						1.26	1	0	sa	sa,bs		sa,bs					10	7	4.5						0	0	0							
9	67	0	1	8	1	None	1	0	8x9	72	21	8.7	2.9	14	14	66	6	2	4							5.2	3	0	pm	pm							8.5	5							1	0	0							
10	42	0	2	11	2	None	2	0	4x7	28	24	9.5	3	9.8	24	25	3	2	3	3	4					1.16	2	0	ab	ab	ab						7	5	2	1					0	0	0	0						
11	74	0	1	12	2	None	2	0	2.5x5	12.5	26	8.2	2.7	11	15	11	1.5	2	4	4						0.83	0	0	sa	sa	NG						8	6	3						0	0	0							
12	45	0	2	2	2	None	2	1	12x4	48	20	9.8	2.8	8.5	27	46	2	2	3	4	4					1.7	2	0	mm	sa,mm	sa,mm	NG					8.5	5	2	2					0	0	0	0						
13	45	0	1	5.5	2	None	2	1	15x8.7	131	18	8.5	2.4	9	30	99.5	31	2	3	3	4	4				4.35	3	0	sa,bs	sa,bs	sa	sa	sa				9	5	3	1	1				2	0	1	0	0			
14	66	0	2	11	2	None	2	1	13.9x7	97.3	23	9.6	2.6	7.9	40	90	7.3	2	2	3	3	4	4			2.43	2	0	sa,ec,ab	sa,ec,ab	sa,ec	sa,ec	sa				8	5	3	2	2	1			2	0	0	0	0	0		
15	70	0	1	17	1	None	1	0	5x6.8	34	20	8.2	2.5	6.9	14	25	9	2	4							2.4	0	0	sa	sa							7.5	5							1	0	0							
16	60	0	2	9	2	None	2	0	3.4x6.7	22.8	21	9.1	2.8	7.4	21	20	2.8	2	3	4						1.089	3	0	pa	pa	pa						8	5	3.5						1	0	0							
17	45	0	1	0	2	None	2	1	10x12.9	129	25	12	2.9	7.4	31	96	33	2	2	3	3	4				4.16	2	0	pa,ec	pa,ec	pa,ec	sa	NG				8	7	2	2.5	1				2	0	0	0	0			
18	55	0	2	6.5	2	CAD	2	1	11x7	77	20	12	2.4	8.9	50	69	8	2	2	3	3	3	3	4	4	1.54	4	3	ab	ab,sa	ab,sa	NG	NG	sa	NG	NG	9.5	5	6	2	1		1	1	1	0	0	1	0	0	0	0
19	45	0	1	5	2	HTN	2	0	5x5.5	27.5	24	11	2.9	8.4	20	20	7.5	2	3	4						1.37	2	0	bs	bs	bs						8	5	2						1	0	0							
20	39	0	2	3	2	None	2	0	4.5x4.5	20.3	25	8.5	2.4	8.2	26	18.5	1.8	2	3	3	4					0.77	0	0	ab	ab	sa	NG					8.5	5	2	2					0	0	0	0						
21	55	0	1	8	2	None	2	1	10x8.5	85	19	8.2	2.6	7.1	31	72	13	2	3	3	4	4				2.74	2	0	sa	sa	MRSA	MRSA	MRSA				8	6	3.5	2	1				0	0	0	0	0			
22	55	0	2	5	2	None	2	0	6.5x8	52	25	10	2.9	12	34	48	4	2	3	3	4	4				1.52	3	0	sa	sa,ef	sa,ef	ec,MRSA	MRSA				9	5	4	2.5	2				1	1	0	0	0			
23	75	0	1	9	2	HTN	2	0	7.5x6.5	48.8	18	12	2.4	8.9	21	36	13	2	3	4						2.32	2	0	ct	ct	NG						8.5	5	2						0	0	0							
24	48	0	2	7	2	None	2	1	11x8.5	93.5	31	14	2.8	11	39	90	3.5	2	2	3	3	3	4	4		2.39	4	0	sa,ec	sa,ec	sa,ec	sa					8	5	3	2.5	2	1			1	0	0	0	0	0		

25	40	0	1	4	2	None	2	0	4.7x3.2	15	26	13	2.6	7.9	19	10	5	2	3	4						0.79	1	0	sa	sa,bc	sa,bc						8	6	2						0	0	0					
26	64	0	2	2	2	None	2	0	5x6	30	23	11	2.5	6.8	34	28	2	2	2	3	3	3	4			0.8	1	1	bs	bs	ec,bs	bs,ec	bs				8.5	5	3.5	2.5	2.5				1	0	0	0	0			
27	35	0	1	4	2	None	2	0	5.7x6.2	35.3	27	9.6	2.5	7	23	25	10	2	3	4	4					1.53	1	0	sa	kb	kb						9	7	4						0	0	0	0				
28	50	0	2	6	2	None	2	0	9x23.8	214	33	9.4	2.8	8	55	198	17	2	2	3	3	3	3	4	4	3.89	3	0	sa,pm	sa,pm	sa,pm	sa,pm,ef	ef	NG	sa	NG	10	8.5	6.5	5	2.5	2	1	1	2	0	1	0	0	0	0	0
29	70	0	1	5	1	None	1	0	7.7x4.8	37	29	8.6	2.7	9.7	18	29	8	2	3	4						2.05	2	0	ab	sa	sa						8.5	5	2						0	0	0					
30	57	0	2	10	2	HTN&CAD	2	1	10x23.5	235	25	10	2.5	8.9	44	228	7	2	2	3	3	3	4	4		5.34	5	0	sa,pm	sa,pm	ec	ec	NG	sa	sa		8	7	5	4.5	3	2	2		3	1	0	0	0	0	0	
31	42	0	1	12	2	None	2	1	15x8	120	24	14	2.9	7.9	28	90	30	2	3	3	4					4.2	3	1	pa	pa	pa	NG					8.5	7	4	2					2	1	0	0				
32	55	1	2	2	2	None	2	0	5x4.7	23.5	20	12	3	7.8	27	20	3.5	2	3	3	4					0.87	0	0	pa,MRSA	pa,MRSA	MRSA	MRSA					8.5	6	3.5	2					0	0	0	0				
33	73	1	1	1	1	None	1	0	3.8x5.6	21.3	25	14	2.8	10	13	21	0.3	3	4							1.63	0	0	sa	sa							8.5	3.5							0	0						
34	55	1	2	1.5	2	BA	2	0	9x8.5	76.5	24	11	3.2	12	39	72	4.5	2	3	3	3	4	4			1.96	2	1	sa,bs	bs	CONS	bs	CONS	NG			8	6.5	4	2	2	2			0	0	0	0	0	0		
35	48	1	1	2	2	None	2	0	6x4.7	28.2	23	12	3	13	15	21	7.2	3	4	4						1.88	1	0	pm	pm	NG						8.5	3.5							0	0	0					
36	50	1	2	7	2	None	2	1	13.7x7.7	105	20	8.9	2.9	9.8	34	98.8	6.7	2	3	3	3	4				3.102	4	1	ab	sa,ab	sa,ab	sa	sa				9	7.5	5	3.5	2.5				2	1	0	0	0			
37	45	1	1	1	2	None	2	1	5.5x12.5	68.8	20	9.4	2.8	7.8	29	56	13	2	3	3	3	4				2.37	2	0	CONS	pa	pa	CONS	NG				8.5	6	5	3.5	2				1	1	0	0	0			
38	64	1	2	9	2	None	2	0	9x6.5	58.5	21	11	3.1	7.5	33	55	3.5	2	3	3	3	4				1.77	1	0	ec,pa	ec,pa	ec						8.5	6.5	5	2	2				0	0	0	0	0			
39	40	1	1	11	2	HTN	2	1	12.5x17.5	219	26	11	3.4	8	30	187	32	2	3	3	3	4				7.29	3	1	sa	sa,bs	sa,ef	sa	NG				9	7	6	2.5	1				1	2	0	0	0			
40	50	1	2	12	2	None	2	0	5x6.8	34	24	11	2.8	8.2	35	27	7	2	3	3	3	4				0.9	1	0	kb	kb	sa,kb	sa,kb	kb				9	7	7	3.5	2				1	0	0	0	0			
41	51	1	1	5	2	None	2	0	8.8x7.2	63.4	26	12	2.5	7.4	25	56	7.4	2	3	4	4					2.53	2	0	CONS	bc	bc						8	7	4	2					2	0	0	0				
42	28	1	2	5	2	None	2	0	7x4.7	32.9	27	8.7	2.4	7.5	29	29	3.9	2	3	3	4	4				1.13	1	0	bs	sa,bs	sa,bs	bs,ec					8.5	7	4	3.5	1				0	0	0	0	0			
43	60	1	1	7	2	None	2	0	6.5x8.8	57.2	21	9.8	2.9	7.1	21	48	9.2	2	3	4						2.72	0	0	sa	CONS	CONS						8	4	2.5						0	0	0					
44	57	1	2	1	2	None	2	0	5.5x7.9	43.5	28	9.7	2.5	7.5	30	40	3.5	2	3	3	4	4				1.44	2	0	ec,pm	ec,pm	ec	NG	NG	NG			8.5	7	5.5	3.5	2				1	0	0	0	0			
45	54	1	1	3	1	None	1	0	8.5x6.5	55.3	20	9.2	2.7	12	16	42	13	2	3	4						3.63	1	0	sa	sa	CONS						8.5	4							1	0	0					
46	50	1	2	3.5	2	CAD	2	1	13.9x12.6	175	23	10	2.8	7.8	41	168	7.1	2	3	3	3	4	4			4.26	4	0	ec,pm	pm,ef	pa	pa	NG				8.5	6.5	7	3.5	2	2			1	1	0	0	0	0		
47	40	1	1	4	2	None	2	1	14.5x6.8	98.6	17	11	2.9	6.7	29	81	18	2	3	3	3	4				3.4	3	0	ab	sa	sa	sa	NG				8.5	6	3.5	1					2	0	0	0	0			
48	55	1	2	8	2	None	2	1	5.8x11	63.8	21	8.4	2.8	8.1	34	60	3.8	2	3	3	3	4				1.87	2	0	ct	sa	CONS	sa	NG				8	6	7	3.5	2				0	0	0	0	0			
49	60	1	1	10	2	None	2	1	13.5x13.5	182	28	8.9	2.5	9.8	36	160	22	2	3	3	3	4	4			5.05	2	0	bs	bs,ef	bs,ef	bs	ef				8.5	7	5	2	2	1			1	1	0	0	0	0		
50	60	1	2	15	2	HTN&CAD	2	0	7.8x6.8	53	22	9.1	2.7	11	37	53	0	2	3	3	3	4	4			1.43	2	0	sa	sa	ef	cons	NG	NG			8	6.5	5	2	2.5	1			1	0	0	0	0	0		
51	48	1	1	3	2	HTN	2	1	8.9x16.5	147	19	9.4	3.4	9	33	110	37	2	3	3	3	4				4.42	3	0	bs	mm,bs	mm,bs	ng	NG				8	7	5	2	2				2	1	0	0	0			
52	55	1	2	4	1	None	1	0	5.5x7.5	41.3	21	11	3.2	8.4	21	41.3	0	2	3	4						1.95	0	0	ec,kb	ec,kb	ec						8.5	5.5	3.5						0	0	0					
53	55	1	1	2	1	None	1	0	4.9x7.4	36.3	22	12	3.5	8	17	24	12	2	3	4						2.11	0	0	sa	CONS	sa						8.5	6	2.5						0	0	0					
54	46	1	2	5	1	None	1	0	8.6x9.5	81.7	25	9.7	2.8	7	39	81.7	0	2	3	3	3	4	4			2.09	1	0	ec	ec	pm	sa,pm	sa	CONS			9	7.5	5	4	3.5	1			1	0	0					

ETHICAL COMMITTEE CERTIFICATE

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.G.Navaneetha Krishna Pandian
Designation	:	PG in MS., General Surgery
Course of Study	:	2017- 2020
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A comparative study of cost effective vacuum assisted closure (VAC) therapy and conventional dressing on wound healing in patients with diabetic foot ulcer
Ethical Committee as on	:	25.04.2019

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

DEAN
Madurai Medical College
Madurai-20

02 MAY 2019

PLAGIARISM VERIFICATION CERTIFICATE

URKUND

Urkund Analysis Result

Analysed Document: Dr Navaneetha krishna pandian - A Comparative Study of Cost-Effective Vacuum Assisted Closure (VAC) Therapy and Conventional Dressing on Wound Healing in patients with Diabetic Foot Ulcer (wecompress.com.docx (D57277383)
Submitted: 19/10/2019 11:16:00
Submitted By: navaneethgnanasekar@gmail.com
Significance: 7 %

Sources included in the report:

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https://www.dovepress.com/evaluation-of-negative-pressure-wound-therapy-for-patients-with-diabet-peer-reviewed-fulltext-article-TCRM
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Instances where selected sources appear:

CERTIFICATE II

This is to certify that this dissertation work titled, entitled "**A COMPARATIVE STUDY OF COST-EFFECTIVE VACUUM ASSISTED CLOSURE (VAC) THERAPY AND CONVENTIONAL DRESSING ON WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCER**" submitted by **Dr.G.NAVANEETHA KRISHNA PANDIAN** with registration number 221711118 for the award of MASTER DEGREE in the branch of GENERAL SURGERY has been personally verified by me in urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **7** percentage of plagiarism in the dissertation.

Guide and supervisor sign with seal