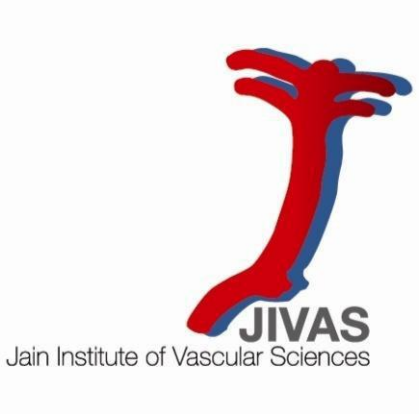
ANALYSIS OF FACTORS DELAYING HEALING OF ISCHAEMIC FOOT WOUNDS IN PATIENTS WHO UNDERGO LOWER LIMB REVASCULARIZATION.

Dissertation submitted to the National Board of Examinations, New Delhi, in partial fulfillment of the requirements for the award of the Diplomate of National Board in the super specialty of Peripheral Vascular Surgery



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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled “Analysis of factors delaying healing of ischaemic foot wounds in patients who undergo lower limb revascularization” is a bonafide and genuine research work carried out by me under the guidance and supervision of Dr. Vivekanand**,** Vascular surgeon, Jain Institute of Vascular Sciences (JIVAS), Bhagwan Mahaveer Jain Hospital, Bengaluru, in partial fulfillment of the requirement of National Board of Examinations regulation for the award of the Degree of DNB in Peripheral Vascular Surgery.

This has not formed the basis for the award of any degree or diploma to me before and I have not submitted this to any other university or board previously.

Date : **Dr. Roshan Rodney.S**

Place : Bengaluru

CERTIFICATE

This is to certify that the dissertation titled **"**Analysis of factors delaying healing of ischaemic foot wounds in patients who undergo lower limb revascularization." is a bonafide research work done by **Dr. Roshan Rodney.S, MBBS, MS(Gen surg)** under my guidance at Jain Institute of Vascular Sciences (JIVAS), a unit of Bhagwan Mahaveer Jain Hospital, Bangalore in partial fulfillment of the requirement of National Board of Examinations regulation for the award of the degree of DNB in super specialty of ***Peripheral Vascular Surgery.***

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Place : Bengaluru

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LIST OF ABBREVATIONS:

CLI	Critical Limb ischemia
EVT	Endovascular therapy
TASC	Trans Atlantic InterSociety Consensus
DM	Diabetes Mellitus
HTN	Hypertension
IHD	Ischaemic heart Disease
CKD	Chronic Kidney Disease
N/C	Non Compressible
ABI	Ankle Brachial Index
TBI	Toe Brachial Index
PVR	Pulse Volume Recording
TcPO2	Transcutaneous Oximetry
WIfI	Wound, Ischemia, foot Infection
ESRD	End Stage Renal Disease
QOL	Quality of life
PAD	Peripheral arterial disease
DFS	Diabetic foot syndrome
AHA	American Heart Association
CLTI	Chronic limb threatening ischaemia
CLI	Critical limb ischaemia
BMI	Body Mass Index
UT	University of Texas
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the Leg
DR	Direct Revascularization
IR	Indirect revascularization
DSA	Digital Subtraction Angiography
TOF	Time of flight
CTA	Computed tomography angiography
MRA	Magnetic Resonance Angiography
eGFR	Estimated Glomerular Filtration rate
MDRD	Modification of Diet in Renal Disease
WBC	White blood cell
LDL	Low density Lipoprotein
GRBS	General Random blood sugar
ESR	Erythrocyte sedimentation rate
CRP	C – reactive protein
AGP	Ambulatory Glucose Profile
SVS	Society of Vascular Surgery
HR	Hazard ratio
CI	Confidence interval

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Introduction

Introduction

Complete ulcer healing is one of the most important goals of treatment for critical limb ischemia[1]. Among the many studies that have reported limb salvage, complete ulcer healing was reported in only 17 studies (0.9%) according to a literature search from 1985 to 2005[2]. However, ulcer healing after revascularization is a major concern among patients, and the expected healing period is important in terms of health economics and the patient's quality of life (QOL)[3.4]. In particular, there has been a tremendous worldwide increase in the number of patients with diabetes mellitus (DM) and the percentage of CLI patients with DM is increasing markedly, currently accounting for 70%[5,6]. The increase in DM is accompanied by an increase in renal diseases, and the incidence of peripheral arterial disease (PAD) among dialysis patients is also increasing.

Historically, the outcomes of patients with peripheral arterial disease have been evaluated primarily with technical parameters such as graft patency or target lesion revascularization (TLR).In patients with CLI, clinical limb outcome was considered successful when the limb was rescued from major amputation. However, the "limb salvage rate" does not always represent successful limb outcome, because a significant number of patients die before their symptoms are relieved.[7]

Attempts to determine the independent factors that affect limb salvage have failed because these factors are overshadowed by survival factors. Moreover, AFS (Amputation free survival) also does not always indicate successful limb outcomes, because patients may survive a long time without major amputation but with painful ischemic wounds. The achievement of wound healing is a clear-cut indicator for evaluating the outcome of limbs with ischemic wounds.[8]

'*Each ulcer is unique in complexity and deserves flexible understanding and control of whole individual tissue recovery challenges*'

Review of Literature

Review of Literature

The essential role of multidisciplinary approach in ischemic ulcer healing

Increasing clinical evidence suggests that despite "well-suited" revascularization efforts, at least 25% of diabetic foot ulcers (DFU) will eventually not heal, and around 28% may end however with some form of amputation . It appears unmistakable that no current single therapy can enhance alone profitable healing results in a majority of CLI ulcers without concomitant management of all risk factors, including ischemic, metabolic, septic, local pressure, neuropathic, and adequate offloading appointed treatment.[10]

Wound healing embodies a complex cascade of molecular and clinical events in continuous dynamic interaction. It was stated that because CLI wound etiology is always multidimensional, specific therapy in turn requires a parallel multidisciplinary application.

Every individual risk factor requires accurate identification and management and represents a fundamental task for any multidisciplinary wound centre.

The recent guidelines document of the Society for Vascular Surgery connecting with the American Podiatric Medical Association and the Society for Vascular Medicine acts as a great reference to current evidence of ischemic wound treatment**.** [11] This noteworthy analysis addresses best available proofs and guidelines to date on the following main indicators: (1) prevention of diabetic foot ulceration, (2) off-loading (3) diagnosis of sepsis and foot osteomyelitis, (4) specific wound care, and (5) peripheral arterial disease in DFS (Diabetic foot syndrome).

Prevention following evidence-based program includes the patient and the referral General Practitioners (GP) as active members of the multidisciplinary group. Knowing that peripheral neuropathy can generate about 45–65% of DFS ulcers, patients with neuropathy hold >3.5-fold complementary risk for iterative neuro-ischemic ulceration .[2]

Adequate laboratory tests surveillance also represents a critical method as to minimize detrimental obstacles in tissue regeneration. It has been recorded that for every additional 1% increase in HbA1C, there is a 0.028 cm/day healing delay in DFS wounds[3]. The major importance of off- loading devices in the global healing process is acknowledged. Pressure reduction is reported to allow superior healing effects to any revascularization strategy .[3]

Early diagnostic and treatment of foot infection also have paramount consequences in correct tissue regeneration. Expeditious local wound debridement following timely re-evaluation schedule bears huge implications for maintaining tissue viability, parallel to revascularization .Since aggressively applied, early debridement can save millimetres of "time-dependent" irreversible damage. Appropriate wound dressing should help by maintaining a moist wound bed, providing exudate drainage, and urging granulation of tissue defect. The adapted dressing should match each specific CLI pathology, wound features and location, and individual amount of exudates, inflammation and pain.[3]

New complementary therapies including negative pressure therapy, living cellular therapy, extracellular matrix products, and hyperbaric oxygen therapy were equally developed in the last years. Their application should follow multidisciplinary team advises in ulcers that fail to demonstrate >50% area reduction per month, using standard therapy .[5]

Although revascularization still holds specific postoperative indicators , the global efficacy of multidisciplinary approach can be timely rated by percentage reduction in wound extent as an early predictor of clinical success .Wound surface diminution of 10–15% per week, or >50% in 4 weeks strongly suggests increased likelihood of healing and diminished probability for amputation.[6,7]

The location of the devitalized tissue also affects amputation risk, healing potential, and quality of life. Dosluoglu et al confirmed what we anecdotally know that necrotic heel ulcerations do poorly, and that even with revascularization, the short- and long-term amputation risk is significant. The patients who are at greatest risk are medically debilitated, nonambulatory and/or with end-stage renal disease.[8]

Factors Linked to Delayed Wound Healing After Revascularization

Clinical studies to date that have assessed ulcer healing after revascularization and the factors that impair ulcer healing are summarized in **Table 1.**

Table 1. Reports on Ulcer Healing After Revascularization and the Factors Possibly Affecting Ulcer Healing

Author (year)	Type of study	No. of limbs	Factors possibly affecting ulcer healing			
			DM	Renal failure	Wound status	Infection
Chung et al[21] (2006)	Single Retro	250	P=0.23	NS	Extensive TL(P – 0.01)	-
Soderstrom et al[11] (2009)	Single Pro	113	P=0.05	P=0.462	UTWCS (NS	-
Azuma et al[9] (2012)	Single Retro	249	P=0.03	P<0.001	Heel TL (P<0.001 R6 except heel (P=0.025)#	CRP (P=0.822)
Rashid et al[55] (2013)	Single Retro	167				
Varela et al[57] (2010)	Single Retro	76				
Apelqvist et al[8] (2011)	Single Retro	504		P=0.005	Multiple ulcers (P<0.001)# Wagner grade (P<0.001)	-
Alexandrescu et al[47] (2011)	Single Retro	232				
Kawarada et al[10] (2012)	Single Retro	106	P=0.008	P=0.133	Rutherford category (P=0.232)	Infected wound# (P=0.012
Soderstrom et al[52] (2013)	Single Retro	250		NS	NS) Heel TL (P=0.129)	
Iida et al[7] (2013)	Multi Pro	166	NS	P=0.15	NS	Infected wound# (P=0.04)
Kobayashi et al[41] (2014)	Single Retro	166	NS	P<0.001	Extensive TL (P=0.002) Heel TL (P=0.002	Infected wound# (P=0.046)

Table 1. Reports on Ulcer Healing After Revascularization and the Factors Possibly Affecting Ulcer Healing

Author (year)	Factors possibly affecting ulcer healing				Ulcer healing outcome
	DM	Renal failure	Wound status	Infection	
Chung et al[21] (2006)	P=0.23	NS	Extensive TL(P – 0.01)	-	76% healed @ 1Y Median healing time: 198 days
Soderstrom et al[11] (2009)	P=0.05	P=0.462	UTWCS (NS	-	74% healed @ 1Y Median healing time: 186 days
Azuma et al[9] (2012)	P=0.03	P<0.001	Heel TL (P<0.001 R6 except heel (P=0.025)#	CRP (P=0.822)	86.9% healed @ 1Y Median healing time: 82.96 days
Rashid et al[55] (2013)					Complete healing 87% (CPA); 85% (IPA); 64% (NPA)
Varela et al[57] (2010)					Complete ulcer healing @ 1Y 84% (bypass) vs. 87% (EVT), P=0.29 Median healing time 95 days (bypass) vs. 118 days (EVT), P=1
Apelqvist et al[8] (2011)		P=0.005	Multiple ulcers (P<0.001)# Wagner grade (P<0.001)	-	52% healed Median healing time 29 weeks
Alexandrescu et al[47] (2011)					71% healed
Kawarada et al[10] (2012)	P=0.008	P=0.133	Rutherford category (P=0.232)	Infected wound# (P=0.012	73.6% healed @ 1Y
Soderstrom et al[52] (2013)		NS	NS) Heel TL (P=0.129)		Complete ulcer healing @ 1Y 69% (DR) vs. 47% (IR), P=0.001
Iida et al[7] (2013)	NS	P=0.15	NS	Infected wound# (P=0.04)	Median healing time 97 days
Kobayashi et al[41] (2014)	NS	P<0.001	Extensive TL (P=0.002) Heel TL (P=0.002	Infected wound# (P=0.046)	Median healing time 64 days (T); 168 days (H); 267 days (E)

–, not reported. #Statistical significance.
BMI, body mass index; CPA, complete pedal arch; DM, diabetes mellitus; DR, direct revascularization; E, extensive TL; ESRD, endstage renal disease; EVT, endovascular treatment; H, heel ulcer or gangrene; IPA, incomplete pedal arch; IR, indirect revascularization; Multi, multicenter; NPA, no pedal arch; NS, not significant; Pro, prospective; Retro, retrospective; Single, single center; T, toe ulcer or gangrene; TL, tissue loss; UTWCS, University of Texas wound classification system; Y, year

Although studies investigating ulcer healing after revascularization are slowly accumulating, most are retrospective single-center studies, and the level of evidence is still low.

As a result of reviewing the literature documenting ulcer healing, the factors related to delayed ulcer healing can be classified into 5 categories: (1) systemic factors (comorbidities); (2) tissue defect factors; (3) infection; (4) inadequate wound management; and (5) inadequate revascularization strategy.

Systemic Factors

Factors affecting ulcer healing that must not be forgotten and are normally raised are systemic diseases and clinical conditions that impair the wound healing process. Among reports to date, many note ESRD and DM as potent factors that impair ulcer healing.[5,8–12] These disease conditions have been shown to induce decreased skin blood flow because of microcirculatory disorder and they likely trigger abnormalities even in the molecular biological process involved in the wound healing process, which has not been fully explored. In addition, several studies report that indices of nutritional state (ie, low BMI and hypoalbuminemia), also cause reduce the speed of ulcer healing.[13] The reason for this association is not simply that such indices reflect the patient's nutritional state, but the possibility that protein hypercatabolism caused by inflammation may also cause further complications.[14,15] The serum albumin level is an important indicator that affects wound healing and survival prognosis, but more sensitive biomarkers that have a faster turnover than albumin are desirable.

Tissue Defect Factors

As guidelines on revascularization, TASC II focus on the nature of vascular lesions, while AHA guideline focuses on patients' prognostic survival.[16,17] Although guidance is given on the choice of revascularization procedure, none of the guidelines mention anything about the tissue defect status of the ischemic foot in regard to the revascularization strategy.

Classifications such as that by Wagner and the University of Texas (UT) are commonly used, and all are based on the depth of tissue loss and infection status.[18,19] However, these were originally intended for diabetic foot lesions, not for PAD. On the other hand, the Rutherford classification is for ischemic limbs, and Rutherford category 5 or 6 is based on the extent of tissue loss with an indication of whether the trans metatarsal level is exceeded.[20]

In a study of ulcer healing after revascularization that was the first detailed study of ulcer healing after bypass surgery, Chung et al reported a cumulative ulcer healing curve by extent of tissue loss, and their results indicated that extensive pedal necrosis at presentation independently predicted delayed wound healing.[21]

Soderstrom et al investigated the time to complete ulcer healing in relation to the UT(University of Texas) classification or the duration of the ischemic tissue defect but reported no statistical significance for either.[11] Compared with other sites, mid- and hindfoot tissue loss showed significantly poor ulcer healing.

The heel ulcers are most difficult to heal and its involvement is directly linked to major amputation.[22] Diabetes clinicians, diabetes care nurses, dialysis nurses and other relevant care givers should be informed about this association, and early consultation with a vascular specialist must be recommended.

Extensive tissue loss requires sufficient blood flow and usually needs a longer period to cure compared with smaller areas of tissue loss. Thus, extent of tissue loss should matter, and it can be an important factor in determining the revascularization strategy.

Because the preoperative state of tissue loss should have a major influence on the revascularization decision-making process, detailed recordings of the preoperative ulcer state should have important significance in ongoing or future clinical studies.

Infection

Whether the patient's condition is complicated by infection is also significantly involved in ulcer healing and limb salvage. For some time, the following 3 factors were repeatedly proposed as factors in the formation of diabetic foot lesions: (1) neuropathy; (2) ischemia; and (3) infection.[1,18]

Terashi et al who proposed the Kobe classification, stress that it is difficult to diagnose infection, particularly in patients with both ischemia and infection.[23] In cases of severe ischemia, the manifestation of clinical infection such as local reddening, swelling, and fever is often masked, because the increase in blood flow with accumulating leukocytes by infection is suppressed. This masked infection worsens rapidly after revascularization and is often missed, likely resulting in major tissue loss. Infections, particularly abscess-forming ones, further aggravate the vascular network of the ischemic limb, inflicting damage; therefore, the tissue loss caused by infection becomes massive.

Rogers et al used the expression "stairway to an amputation" for neuropathy and circulatory disturbances complicated by infection that eventually ends in amputation; they asserted the importance of a team approach between those performing the revascularization and those responsible for wound management.[1]

Osteomyelitis is difficult to treat, and resection of infected bone will be needed in most cases. Furthermore, if osteomyelitis is missed, the infection spreads proximally, and if it reaches the heel bone or another ankle-forming bone, major amputation is unavoidable. If deep infection is suspected, MRI examination is recommended.[25]

Patients with CLI often have a complicating comorbidity that increases susceptibility to infection, such as DM or ESRD, or oral immunosuppressant drugs. Moreover, chronic wound infection is often accompanied by antibiotic-resistant bacteria. Therefore, adequate selection of antibiotics is crucial. For optimal prevention, it is vital to submit a wound culture for testing to clarify antibiotic sensitivity prior to revascularization. Observation, care, and early response at the onset of an abnormality are indispensable in practicable limb-length preservation.

Wound Management

Even when revascularization is successful, subsequent wound management still carries the possibility of prolonged ulcer healing and major amputation in some cases. Many wound management guidelines for diabetic foot lesions have been proposed.[26,27] However, medical personnel in charge of revascularization and wound management should understand the difference between wound treatment post-revascularization and ulcer management in the absence of revascularization; the former is characterized by inflammation and the onset of edema because of the rapid recovery of blood flow. As edema increases the intercellular space, with time it may become a medium or a passageway for infection. Therefore, after revascularization, it is important that necrotic tissue is removed promptly, drainage is performed properly, and the site is observed closely to confirm that no infection has spread proximally.

By properly performing the wound bed preparation, granulation will grow in due course.[28] The proliferation of granulation and improvement of the environment are very important. Therefore, if one does not make full use of established evidence regarding wound management, such as selecting an ointment that maintains adequate moisture environment and applying vacuum-assisted closure therapy, wounds in patients with diabetes- and dialysis-related microcirculatory disorders accompanied by increased susceptibility to infection will not heal. It is also imperative to maintain current knowledge about proliferation factors, medications, and new wound dressings [29–31] Eventually, complete healing will occur whether one simply waits for secondary healing, or performs a skin grafting, stump closure, or plastic surgery, such as a musculocutaneous flap. Free flap transfer is the ultimate procedure to salvage limbs facing major amputation.[32,33] Because a vein bypass graft can work as a reliable source of blood supply for the flap, to select bypass surgery as the first line of revascularization may be reasonable in cases of extensive tissue loss that potentially necessitate free flap transfer.

The most important factors in wound management after revascularization are the following: (1) checking whether the revascularized tissue circulation is being maintained or has deteriorated because of restenosis, and (2) checking for signs of infection advancing. If one of these signs is suspected, immediate examination followed by prompt clinical action is essential.

Revascularization Procedure and Target Selection

The choice of an appropriate treatment measure, the revascularization strategy, and the choice of treatment target have a major effect not only on limb salvage but also on the achievement of complete ulcer healing and shortening of the ulcer healing period. By contrast, incorrect revascularization strategy will prolong the ulcer healing period, increasing the opportunity for infection to set in and leading eventually to limb loss.

EVT or Open Repair

There is an ongoing debate about the choice of revascularization measure, namely, whether to use EVT or bypass surgery and how to perform it.[34–37] The AHA guideline based on the results of the BASIL trial[38,39] emphasizes predicting the survival prognosis and determining the status of available veins. By comparison, the European guideline published the same year recommends EVT as the first-line revascularization procedure.[40] The opinions of both these guidelines are completely inconsistent. However, no report has discussed whether bypass or EVT should be selected while considering the status of tissue loss before revascularization. For example, in the case of extensive tissue loss, continuous and ample long term blood supply is indispensable for complete healing.

According to the clinical results of EVT reported by Kobayashi et al, the healing rate of an ulcer in the toe is 75%, whereas in heel tissue loss cases, the healing rate is 52%, and in cases of extensive tissue loss located somewhere other than the heel, the rate is 13%, showing a marked decrease in the ulcer healing rate.[41] This highlights the possibility that EVT has a limited role in extensive tissue loss.

To derive parameters conducive to the choice of revascularization method, patient background and wound treatment procedures should be aligned to some extent, and EVT and bypass should be compared.

Restenosis After Revascularization Procedure

If the appropriate choice of revascularization procedure is important, then restenosis and obstruction have a major effect on ulcer healing.
A clinical study observing patency angiographically after crural artery EVT elucidated that the patency of the revascularized artery segment had a great effect on delayed ulcer healing.[43] In that investigation, restenosis or re-occlusion

was found in 72% of treated arteries 3 months after balloon angioplasty, and the time to ulcer healing in the restenosis group was significantly delayed compared with the non-restenosis group (127 vs. 66 days). This result demonstrated that it is not easy to maintain adequate blood supply with EVT for the crural artery in patients with extensive tissue loss associated with a lengthy ulcer healing period. Therefore, before initiating treatment in cases of extensive tissue loss, properly predicting the time to ulcer healing will inform the decision about whether to select bypass surgery or to perform repeated EVT.

Is the Angiosome Concept Fact or Fiction?

Since Attinger et al advocated the importance of the angiosome concept in lower limb revascularization,[44] the clinical significance has been widely debated (Table 2).[45]

Table 2. List of Reports Studying Angiosome

Author (year)	Complete ulcer healing rate				Limb salvage rate			
	DR (%)	IR (%)	P value	Months	DR (%)	IR (%)	P value	Months
Alexandrescu et al[47] (2011)	79.1	55.1	<0.018#	12	97.0	84.5	<0.030#	12
Iida et al[51] (2012)	-	-	-	24	82	68	0.01	24
Kawarada et al[10] (2012)	-	-	0.886	-	-	-	0.524	-
Soderstrom et al[52] (2013)	69	47	0.021	12	86	77	0.086	12
Fossacecca et al[49] (2013)	57.4	32.3	NM	12	90.4	91.2	NS	12
Varela et al[57] (2010)	92	73	0.008	24	93.0	72.0	0.02	24
Kabra et al[68] (2013)	96.4	83.3	0.21	6	84	75	0.06	6
Neville et al[53] (2009)	91	62	0.03	-	-	-	-	-
Deguchi et al[69] (2011)	73.3	72.2	0.43	-	-	-	-	-
Azuma et al[9] (2012)	95.8	91.7	0.185	24	97.8	92.3	0.855	24
Rashid et al[55] (2013)	86	79	0.2736	-	-	-	-	-
Kret et al[54] (2014)	78	46	0.01	-	-	-	0.82	-

As reported by Alexandrescu et al in their study titled "Angiosome concept: fact or fiction? ", some reports state that the angiosome concept is very useful clinically, while others state that the angiosome concept, though important as a concept, is not of any particular importance clinically.[46]
Most papers on ulcer healing post-EVT demonstrate the usefulness of the angiosome concept,[47–52] whereas those on ulcer healing post-bypass are divided on that usefulness.

Neville et al reported that the angiosome concept was also relevant to the field of bypass surgery.[53]

Kret et al found no difference in limb salvage rate but reported that in terms of time to ulcer healing, angiosome-direct revascularization (DR) produced significantly better results than angiosome-indirect revascularization (IR).[54]

Why do the clinical results regarding the angiosome vary?

To answer this question, 3 possible reasons are proposed: (1) a background bias may exist between the DR and IR groups; (2) the significance of the angiosome concept may differ between EVT and bypass surgery; and (3) the arterial-arterial connection between angiosomes may have a greater effect on ulcer healing than does the angiosome concept.

Background bias regarding the condition of ischemic tissue loss and systemic factors etc is likely. Angiosome-oriented bypass surgery is not always possible, because of infection, extensive tissue loss, and the absence of run-off; therefore, feet that have undergone angiosome-indirect bypass were often subject to more severe conditions before revascularization compared with those that had undergone angiosome-direct bypass. By contrast, other authors reporting their clinical results after EVT indicate that ulcer healing in the DR group is still

significantly superior to that of the IR group, even after minimizing background bias via the propensity score method.[54]

EVT can treat arteries running near the ischemic tissue loss and can approach the infectious area, which is a possible explanation for the difference between EVT and bypass surgery. Another important difference between bypass and EVT is the amount of blood supply to the tissue defect. The role of the angiosome concept may be more relevant for EVT, in which a limited blood supply through the treated crural artery can irrigate and focus into tissue loss efficiently if DR can be achieved. The blood pressure loading on the foot artery may also differ between EVT and bypass surgery. Pedal bypass can bring systemic blood pressure directly down the foot arteries: therefore, the possibility that it can cause chocked vessels to function more effectively as a network between angiosomes. The clinical results of IR revascularization may depend on whether the procedure can provide blood supply beyond the angiosome.

Impact of Pedal Arch Quality and the Arterial-Arterial Connection Between Angiosomes

Several authors have focused on the role of the arterial-arterial connection between angiosomes. Rashid et al proved the important role of pedal arch quality.[55] They divided it into 3 groups (complete pedal arch, incomplete pedal arch, and no pedal arch), observing ulcer healing after bypass surgery, and concluded that time to healing was directly influenced by the quality of the pedal arch rather than angiosome-oriented revascularization.

Kawarada et al also reported that their pedal arch classification had a great effect on ulcer healing after EVT, and that ulcer healing times were similar between DR and IR.[10] There are also reports stating that IR should be differentiated as IR without collateral and IR with collateral (IRc).[56,57] However, difficult problems remain regarding how to evaluate the reliability of collateral blood flow on ulcer healing if a stenotic lesion is present in the collateral vessels

or the inflow artery of the collateral circulation. There are reports of attempts to evaluate the arterial-arterial connection between angiosomes using local hemodynamic parameters and new imaging methods. [58–61]

Connections between angiosomes and the development of collateral pathways will differ according to the background disease and state of infection. Microcirculatory disorder is often serious in long-term diabetes patients and dialysis patients. Infection also destroys the microcirculatory network of tissues. Iida et al verified this finding using clinical data and concluded that the angiosome concept is important in diabetic and infected patients.[62] As such, studies examining the type of patients who benefit from revascularization strategies based on the angiosome concept need to be pursued hereafter.

Time to Wound Healing

Most patients who undergo revascularization with the hope for limb salvage will ask when the ulcer healing will take place. However, clinical data addressing that question are very limited. Moreover, the ulcer healing speed differs according to the many factors described before. Even with the same revascularization method, the time course to healing differs notably according to patient background and ulcer state. Furthermore, there is no established evidence indicating whether EVT is inferior to bypass in terms of ulcer healing speed. Predicting the time course of healing preoperatively is very important to both the patient and interventionalist, as it facilitates the choice of revascularization procedure and affects the patient's QOL.[62]

Prediction of Ulcer Healing Probability in Individual Patients

To predict the probability of ulcer healing in individual patients, several methods are now being studied. The transcutaneous oxygen tension (TcPO2) measurement method has been used to predict the ulcer healing probability during or immediately after revascularization.

Recently, the usefulness of skin perfusion pressure,tissue oxygen saturation (StO2),and hyperspectral technology[63] for assessing the blood supply to each angiosome has been reported. Moreover, several studies have reported the usefulness of indocyanine green (ICG) imaging as a method for predicting ulcer healing perioperatively.[64,65] After ICG was injected, the contrast effect in the skin in the area of interest is measured, and the degree of ischemia improvement is determined.

In addition, there is also a report on the use of conventional DSA to predict ulcer healing. Utsunomiya et al focused on densely stained, newly formed capillary blood vessels resulting from ischemia in completion angiography during EVT and called such a finding "wound brush".[66]The researcher reported that the ulcer healing rate of feet confirmed to have wound brush was significantly superior compared with feet without wound brush.

A reliable assessment method confirming well-improved circulation around ischemic tissue or the ulcer bottom intraoperatively or postoperatively could contribute to decisions about whether to wait for granulation tissue growth or conduct another revascularization.

WIfI and Wound healing

A new classification system for critical ischemic limbs, the WIfI system, was proposed to systemically assess extent of wound ("W" factor) and severity of ischemia ("I" factor) and status of foot infection ("fI" factor) in the era of vascular disease with diabetes.[67] This recommendation is an epoch-making proposal for filling the gap in current evidence and establishing the viewpoint from ulcer healing in future guidelines regarding revascularization of CLI. As mentioned earlier, we must not forget that the systemic state and the associated disease state may affect ulcer healing more strongly than the factors defined by the WIfI system. These considerations are very important for providing guidance on treatment strategies for the heterogeneous CLI patient population.

Aims and Objectives

Aims and Objectives

- **Primary endpoint** :

- To determine factors related to delayed healing of ischaemic foot wounds after revascularization.

- **Secondary end point**:

- Wound healing time

- Limb salvage

Materials and methods

Materials and methods

Study population:

All patients with CLI (Rutherford 5 and 6) who underwent successful revascularization (open / hybrid/ endovascular) between August 2017 and August 2018 (13 months)

- Number of patients : 113 (successfully revascularized)
- Follow up:- 6 months (at 1st , 3rd and 6th month)

Inclusion Criteria : All patients with CLI (Rutherford category 5 and 6).

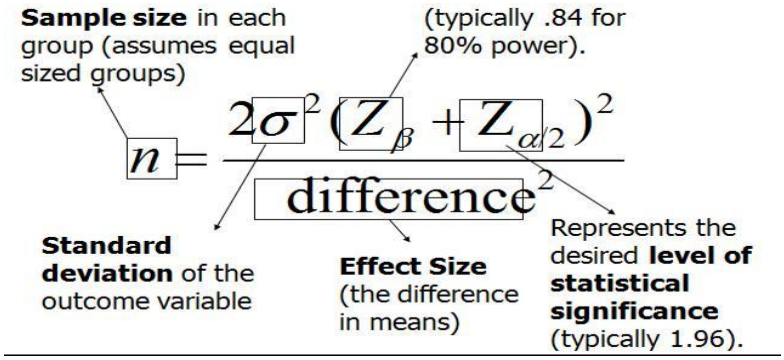
Exclusion criteria :

1. Previous revascularization for the index limb.
2. Patients who do not consent for study.
3. Unsuccessful revascularization

Study design: Prospective, observational, open ended study

Procedure : Data to be recorded (Refer Study proforma)

- Sample size calculation: The sample size is calculated based on data from previous similar studies.



Minimum sample size required is 60 for an 80% power of the study.

Methodology:

1.**Patient enrolment**:

Demographic data of patients were recorded with history and physical examination findings pre operatively in form of chief complaints, personal history of smoking, tobacco if any and previous revascularisation procedure done in the index limb .

They were assessed for known medical risk factors delaying ischemic wound healing like diabetes mellitus (DM), chronic kidney disease (CKD) along with other comorbidities like hypertension (HTN) and Ischaemic heart disease (IHD).

In all patients general and local examination were carried out with careful documentation of vascular status of both lower limbs along with non invasive vascular lab measurements including ankle brachial index (ABI), toe brachial index (TBI) and transcutaneous oximetry (TcPO2) - supine and foot down.

Preoperative imaging was based on clinical findings and was performed in form of arterial Duplex, CT angiography, MR angiography and MR angiography-Time of flight (TOF) sequence.

In patients with non invasive vascular lab findings and clinical examination ruling out arterial disease in the aorta, iliac, femoral and popliteal segments, digital subtraction angiogram of the infrapopliteal segment was done to detect and intervene on any significant lesion requiring intervention.

The eGFR of all patients were calculated using the Modification of diet in renal disease (MDRD) formula and based on this value the decision to use CO2 angiogram during the procedure was taken.

2. **Laboratory analysis**:

After enrollment in study all patients were recorded for Haemoglobin ,Total WBC count,Urea ,Creatinine ,HbA1C,Serum albumin ,ESR,CRP,Total Cholesterol ,LDL and 2D ECHO.

3.**Wound Characteristics** :

Wound characteristics were recorded as per the study proforma and documented. Wounds were divided into 3 groups according to their location (Figure 1). Group A (toe) comprised wounds localized only to the toes, group B (heel) comprised wounds localized to the heel and group C - comprised wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces or multiple wounds.

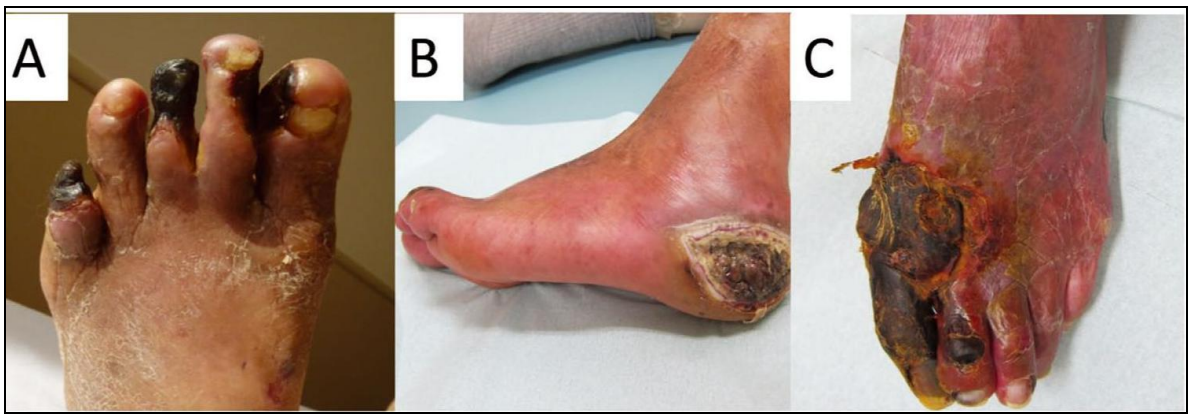


Fig 1. Wound location

4. **Medical management** :

Medication for diabetes, hypertension, cardiac conditions and medical ailments were continued as per physician's advice. The antibiotics and analgesics were prescribed as per patient and procedure requirements.

4 .**Revascularization**:

Strategies for revascularization were decided by consensus among our team of vascular surgeons depending on general condition, comorbidity and extent of ischaemia. All revascularization procedures were considered technically successful before enrollment in study.

5. **Secondary procedures**:

Patients with infected ulcers or gangrene underwent wound debridement and toe amputation before or following angioplasty. Depending upon the type of wound, they were either dressed with hydrocolloids or vacuum assisted device were used. In follow up period, unplanned toe amputations and debridements done as necessary for wound healing. Wound care was performed until wound healing at our outpatient foot care clinic or as inpatients and offered local surgical debridement /minor amputation in case of infected wounds and gangrene.

The level of amputation is chosen on clinical grounds to be the most distal level possible in which healing could be anticipated, the minimal requirement being intact skin with no signs of local infection or severe ischemia.

All patients were counselled about life style modification, daily foot care and appropriate foot wear/offloading.

6. **Follow up**:

All enrolled patients had surveillance at 1,3 and 6 months post procedure with thorough clinical examination and necessary investigations as mentioned in the

study proforma and ABI/TBI, TcPO2 (supine and foot down). For this study, follow-up terminated 6 months after the initial revascularization.

Patients will undergo Ambulatory 24 hr blood sugar monitoring (Freestyle Libre system) for 2 weeks postoperatively to start with and Serial home GRBS according to protocol.

To analyse factors influencing wound healing patients were divided into two groups as Wound healed and Wound not healed.[1]

Statistical analysis:

Statistical analyses were performed with SPSS version 18.5 (SPSS Inc., Chicago, IL, USA).Data are expressed as mean and standard deviation for continuous variables or as percentage for dichotomous variables, unless otherwise mentioned. Multivariate Cox proportional hazards regression models were used to investigate the association of variables with wound non healing. Variables with statistical significance in the multivariate model were determined as independent risk factors for outcome. A p value $< .05$ was considered statistically significant.

8.**Ethical and Scientific committee**:

Present study is approved by ethic and scientific committee of Bhagwan Mahaveer Jain Hospital, Bengaluru (annexure 4, 5).

Results

Results

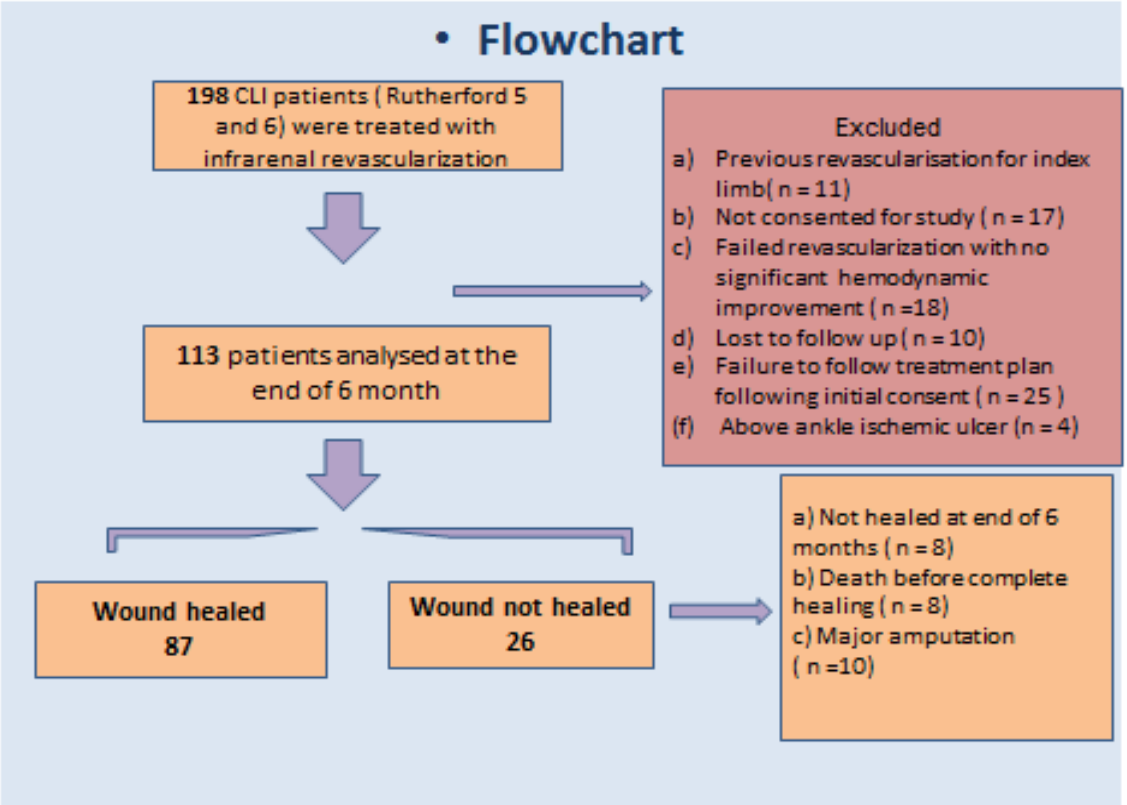


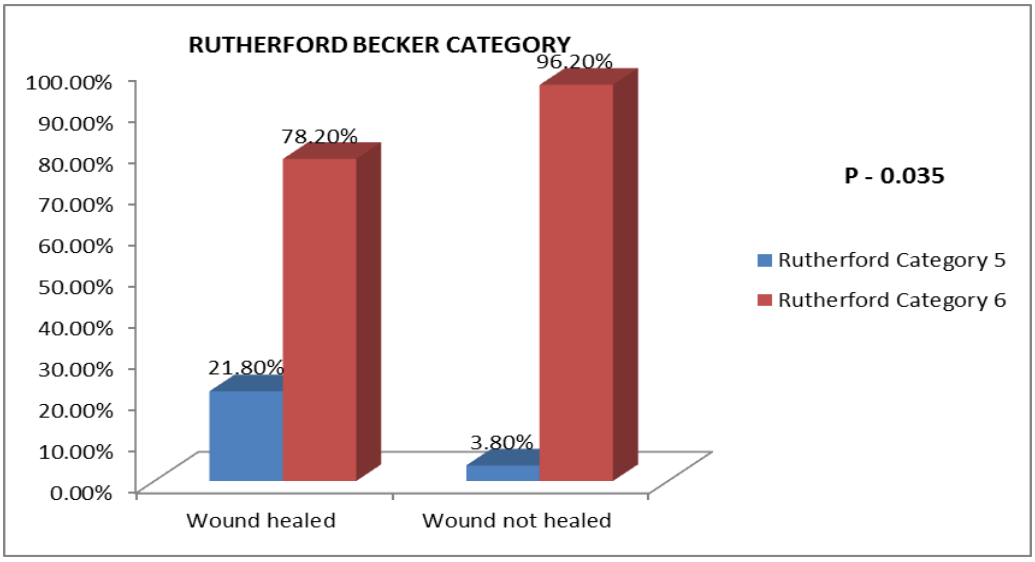
Fig 2: Flowchart

Baseline characteristics among study groups

Variables	Wound healed (n= 87)	Wound Not healed (n=26)	P value
Demography			
Age, years	63.7+/-6.8	65.2+/-8.5	0.361
Age >= 60 years	55 (63.2%)	21 (80.8%)	0.094
Male	73 (83.9%)	17 (65.4%)	***0.040***
Risk factors			
Diabetes Mellitus	58 (66.7%)	24 (92.3%)	***0.010***
Hypertension	56 (64.4%)	23 (88.5%)	***0.019***
Ischaemic heart disease	19 (21.8%)	16 (61.5%)	***<0.001***
Chronic Kidney disease	7 (8.0%)	5 (19.2%)	0.104
Tobacco	65 (74.7%)	13 (50.0%)	***0.017***

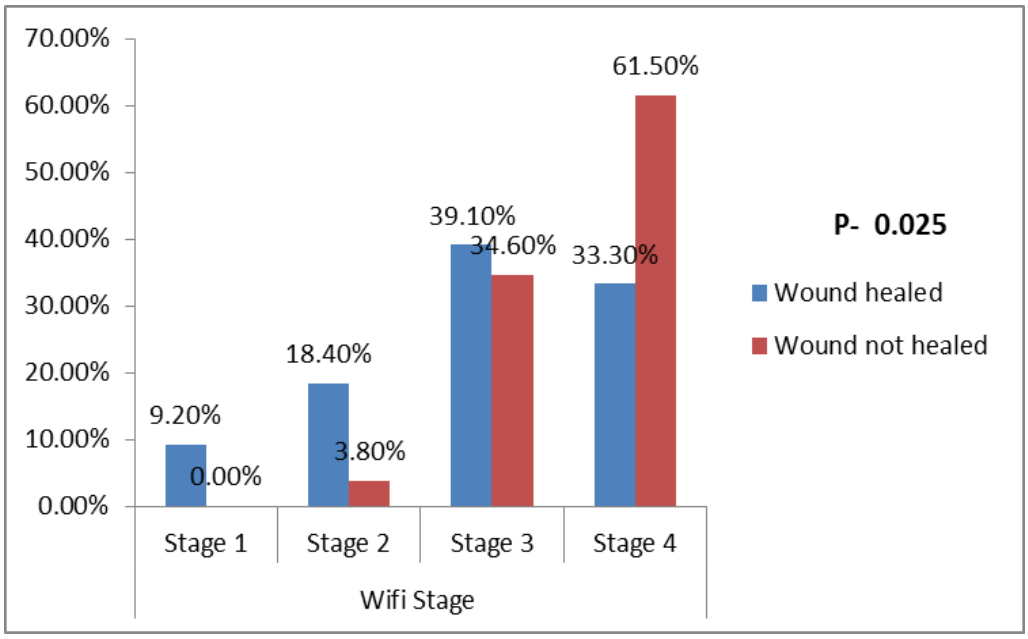
There was no significant difference between the two groups in terms of age. Prevalence of diabetes, hypertension , IHD was significantly higher in the wound not healed group .Majority of the patients were males and had history of tobacco consumption in this analysis henceforth showing significant difference in terms of sex and tobacco consumption between both groups.

Distribution of Rutherford Category among the Study Groups



Majority of the patients were belonging to Rutherford Category 6 (78% in the Wound healed group and 96 % in the Wound not healed group) but in terms of wound non healing there was significantly higher prevalence of Rutherford 6 as compared to Rutherford 5.

Distribution of WIfI Staging among the Study groups



Most patients were in WIfI Stage 3 (38%) and WIfI Stage 4 (40%). Wound healed group had 33% and Wound not healed group had 61% patients in the WIfI stage 4 which was statistically significant.

Distribution of Hemoglobin and WBC Levels among the Study groups

Visit		Hb		P value	WBC		P value
		Low (<11.0g/dl)	Normal (>=11.0g/dl)		Normal <=11 x 10^3 / cu mm	High > 11x 10^3 /cu mm	
Pre Op	Wound Healed	19	68	0.185	10	77	0.070
		21.8%	78.2%		11.5%	88.5%	
	Wound Not Healed	9	17		0	26	
		34.6%	65.4%		.0%	100.0%	
Post Op	Wound Healed	11	76	***0.030***	64	23	0.122
		12.6%	87.4%		73.6%	26.4%	
	Wound Not Healed	8	18		15	11	
		30.8%	69.2%		57.7%	42.3%	
Month 3	Wound Healed	8	79	0.065			
		9.2%	90.8%				
	Wound Not Healed	5	16				
		23.8%	76.2%				
Month 6	Wound Healed	8	79	0.051			
		9.2%	90.8%				
	Wound Not Healed	5	15				
		25.0%	75.0%				

Regarding **haemoglobin** significant difference was observed in post op where low HB was observed in 12.6% in wound healed group and 30.8 % in wound not healed group.There was no statistical difference between two groups in terms of pre op and post op WBC counts.

Distribution of Urea and Creatinine Levels among the Study groups

Visit		Urea		P value	Creatinine		P value
		Normal < =40 mg/dl	High > 40 mg/dl		Normal <=1.3 mg/dl	High > 1.3 mg/dl	
Pre Op	Wound Healed	80	7	0.104	80	7	***0.035***
		92.0%	8.0%		92.0%	8.0%	
	Wound Not Healed	21	5		20	6	
		80.8%	19.2%		76.9%	23.1%	
Month 1	Wound healed	80	7	0.089	80	7	0.089
		92.0%	8.0%		92.0%	8.0%	
	Wound not healed	20	5		20	5	
		80.0%	20.0%		80.0%	20.0%	
Month 3	Wound Healed	80	7	***0.030***	80	7	***0.030***
		92.0%	8.0%		92.0%	8.0%	
	Wound Not Healed	15	5		15	5	
		75.0%	25.0%		75.0%	25.0%	
Month 6	Wound Healed	78	7	0.081	78	7	0.081
		91.8%	8.2%		91.8%	8.2%	
	Wound Not Healed	14	4		14	4	
		77.8%	22.2%		77.8%	22.2%	

With respect to **Blood Urea** significant difference was observed in 3rd month where high Blood Urea was observed in 8% in wound healed group and 25 % in wound not healed group.

Regarding **Serum creatinine** statistical significant difference was observed in pre op and 3rd month.

Distribution of ESR and CRP Levels among the Study groups

Visit		ESR		P value	CRP		P value
		High (>10.0mm/hr)	Normal (<=10.0mm/hr)		High (>=5.1mg/dl)	Normal (<5.1mg/dl)	
Pre Op	Wound Healed	75	12	*0.045*	75	12	*0.045*
		86.2%	13.8%		86.2%	13.8%	
	Wound Not Healed	26	0		26	0	
		100.0%	.0%		100.0%	.0%	
1st month	Wound healed	8	79	*0.001*	8	79	*0.001*
		9.2%	90.8%		9.2%	90.8%	
	Wound not healed	8	14		8	14	
		36.4%	63.6%		36.4%	63.6%	
Month 3	Wound Healed	0	47	*0.001*	0	47	*0.001*
		.0%	100.0%		.0%	100.0%	
	Wound Not Healed	4	14		4	14	
		22.2%	77.8%		22.2%	77.8%	
Month 6	Wound Healed	0	1	0.764	0	1	0.764
		.0%	100.0%		.0%	100.0%	
	Wound Not Healed	1	11		1	11	
		8.3%	91.7%		8.3%	91.7%	

Regarding ESR and CRP, there were similar results in both groups which was statistically significant in pre op , 1st month and 3rd month.

Distribution of Serum Albumin and HbA1C levels among the Study groups

Visit		S.Albumin		P value	HbA1C		P value
		Low (<3.20 g/dl)	Normal (>=3.20 g/dl)		Normal (<6.5)	High (>=6.5)	
Pre Op	Wound Healed	15	72	*<0.001*	27	60	*0.048*
		17.2%	82.8%		31.0%	69.0%	
	Wound Not Healed	18	8		3	23	
		69.2%	30.8%		11.5%	88.5%	
1st month	Wound healed	15	72	*<0.001*			
		17.2%	82.8%				
	Wound not healed	17	8				
		68.0%	32.0%				
Month 3	Wound Healed	0	87	*<0.001*	25	62	0.057
		.0%	100.0%		28.7%	71.3%	
	Wound Not Healed	10	11		2	20	
		47.6%	52.4%		9.1%	90.9%	
Month 6	Wound Healed	0	86	*<0.001*	27	59	*0.043*
		.0%	100.0%		31.4%	68.6%	
	Wound Not Healed	3	17		2	19	
		15.0%	85.0%		9.5%	90.5%	

Hypoalbuminemia was more prevalent in wound not healed group during all the visits which was statistically significant and high HbA1c was significantly higher in the wound non healed group in pre op and 6th month.

Distribution of Total Cholestrol and LDL Levels among the Study groups

Visit		Total cholesterol		P value	LDL		P value
		High (>=200 mg/dl)	Normal (<200 mg/dl)		High (>=100 mg/dl)	Normal (<100/ mg/dl)	
Pre Op	Wound Healed	38	49		41	46	
		43.7%	56.3%	***0.001***	47.1%	52..9%	***0.001***
	Wound Not Healed	21	5		19	7	
		80.8%	19.2%		73.1%	26.9%	

Regarding Total cholesterol and LDL, **dyslipidemia** was significantly higher in the wound not healed group

Distribution of Ejection fraction Levels among the Study groups

	EF%		Total	P value
	<40%	>=40%		
Wound Healed	3	84	87	
	3.5%	96.6%	100.0%	***0.032***
Wound Not Healed	5	21	26	
	19.2%	80.8%	100.0%	

Regarding **ejection fraction** , low EF < 40 % was observed in 19.2% in wound not healed group and only 3.5% in wound healed group which was statistically statistically significant.

Distribution of X ray foot Osteomyelitis among the Study groups at different visits

Visit		XRAY foot osteomyelitis		Total	P value
		Yes	No		
Pre Op	Wound Healed	9	73	82	***0.001***
		11.0%	89.0%	100.0%	
	Wound Not Healed	10	16	26	
		38.5%	61.5%	100.0%	
Month 1	Wound Healed		83	83	
			100.0%	100.0%	
	Wound Not Healed		24	24	
			100.0%	100.0%	
Month 3	Wound Healed	0	46	46	***0.001***
		.0%	100.0%	100.0%	
	Wound Not Healed	4	14	18	
		22.2%	77.8%	100.0%	
Month 6	Wound Healed	0	1	1	0.764
		.0%	100.0%	100.0%	
	Wound Not Healed	1	11	12	
		8.3%	91.7%	100.0%	

Pre op **Osteomyelitis** was observed in 11 % of patients in wound healed group and 38 5 of patients in wound not healed group.Significant difference was also observed in the 3rd month between the two groups.

Distribution of Wound location among the Study groups

	Wound Location			Total	P value
	A	B	C		
Wound Healed	17	3	67	87	***0.002***
	19.5%	3.4%	77.0%	100.0%	
Wound Not Healed	2	6	18	26	
	7.7%	23.1%	69.2%	100.0%	
Total	19	9	85	113	
	16.8%	7.9%	75.2%	100.0%	

- Group A (Toe wounds)
- Group B (Heel wounds) and
- Group C (Wounds extending onto the fore- or mid-foot along with dorsum or plantar surfaces or multiple wounds)

Regarding wound location, majority of wounds were in Location C . Significant difference observed in terms of wound healed and not healed in all wound locations more so in location B (heel) wounds where in 21 % of wounds were not healed and only 3.4 % of wounds in location B had healed.

Distribution of Wound status among the Study groups at different visits

Visit		Infected	Not Infected	P value
Pre Op	**Wound Healed**	68	19	***0.035***
		78.2%	21.8%	
	Wound Not Healed	25	1	
		96.2%	3.8%	
Post Op	**Wound Healed**	1	86	0.069
		1.1%	98.9%	
	Wound Not Healed	2	24	
		7.7%	92.3%	
Month 1	**Wound Healed**	5	82	***<0.001***
		5.7%	94.3%	
	Wound Not Healed	8	13	
		38.1%	61.9%	
Month 3	**Wound Healed**	0	46	***<0.001***
		.0%	52.9%	
	Wound Not Healed	2	14	
		11.8%	82.4%	
Month 6	**Wound Healed**	0	0	***<0.001***
		.0%	.0%	
	Wound Not Healed	1	11	
		7.7%	84.6%	

Regarding prevalence of wound infection between the two groups at various visits significant difference was observed in pre op, 1st month , 3rd month and 6th month.

Distribution of pre op Wound culture growth among the Study groups

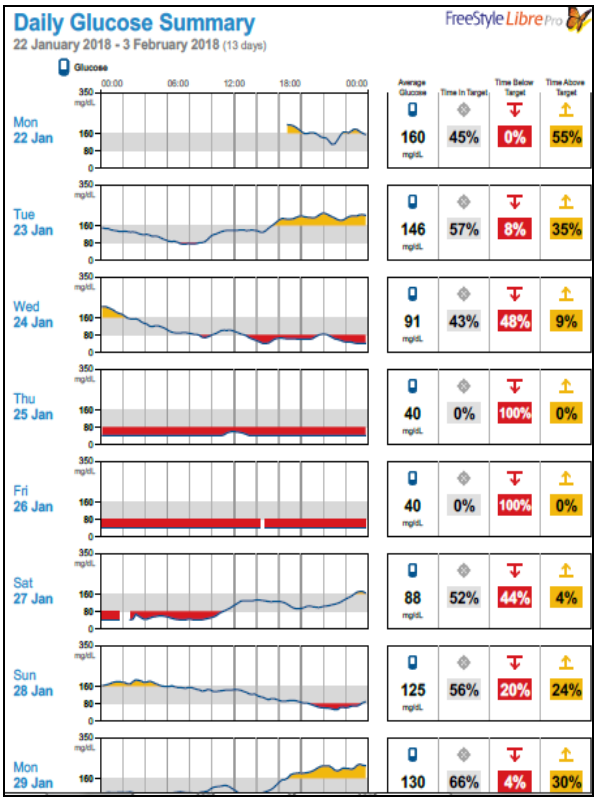
Visit		W.Culture Growth		Total	P value
		Yes	No		
Pre Op	**Wound Healed**	76	11	87	0.056
		87.4%	12.6%	100.0%	
	Wound Not Healed	26	0	26	
		100.0%	.0%	100.0%	

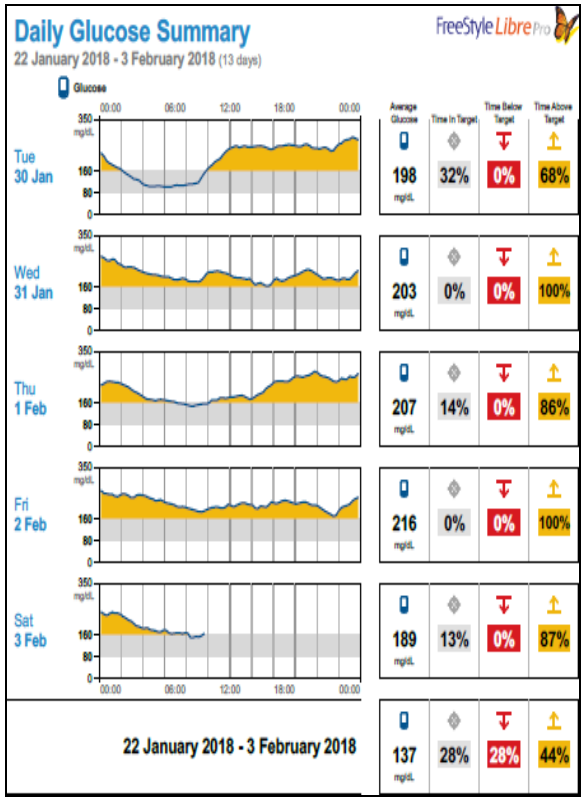
Of the 87 patient who had their wounds healed 87.4% had positive wound culture preoperatively and 100 % of patients who had their wounds not healed had positive wound culture.

Distribution of Ambulatory sugars / Home GRBS results among the Study groups

	Ambulatory / Home GRBS Glycaemic control		Total	P value
	Controlled	Uncontrolled		
Wound Healed	29	11	40	0.320
	72.5%	27.5%	100.0%	
Wound Not Healed	12	2	14	
	85.7%	14.3%	100.0%	
Total	41	13	54	
	75.9%	24.1%	100.0%	

Regarding Ambulatory Sugars / Home GRBS monitoring post op 2 weeks results , the difference was not statistically significant as both group of patients had almost equally matched controlled and uncontrolled sugars probably due to lesser sample size for analysis.





Ambulatory Sugars were analysed for individual patient based upon the above mentioned chart and mean sugars were taken into account and categorised as controlled and uncontrolled.

NEGATIVE PREDICTORS OF WOUND HEALING PER MULTIVARIATE ANALYSIS (COX REGRESSION ANALYSIS)

Variables in the Equation[b]				
		95.0% CI for Exp(B)		P value
	HR	Lower	Upper	
Age > 60 yrs	0.885	0.542	1.446	0.626
Male Sex	0.782	0.308	1.986	0.604
Rutherford Category 6	0.494	0.224	1.090	0.081
Wifi Stage 4	0.318	0.219	0.463	***<0.001***
DM	6.585	1.352	32.085	***0.020***
HTN	1.009	0.568	1.794	0.975
IHD	2.293	0.641	8.200	0.202
CKD	2.024	0.658	6.224	0.218
Tobacco	0.747	0.327	1.707	0.489
Hemoglobin < 11 g / dl	0.560	0.262	1.199	0.136
WBC count > 11 x 10^3 / mm^3	1.167	0.904	1.505	0.236.
Urea > 40 mg/dl	1.039	0.920	1.173	.0.537
Creatinine > 1.3 mg/dl	1.374	0.929	2.032	.0.111
Hba1c >= 6.5	5.134	1.056	24.960	***0.043***
Serum albumin < 3.2 g/dl	2.875	1.319	6.264	***0.008***
ESR > 10mm /hr	2.128	0.935	4.842	0.072
CRP > 5mg/dl				.
Total Cholestrol > 200 mg/dl	1.077	0.610	1.900	0.799
LDL > 100 mg/dl	0.984	0.949	1.020	0.367.
EF < 50 %	0.572	0.166	1.968	0.375
a. Degree of freedom reduced because of constant or linearly dependent covariates				
b. Constant or Linearly Dependent Covariates wbc = 2 ; urea = 2 ; creat= 2 ; crp = esr ; ldl= 3 - tchol ;				

Based upon multivariate analysis , **WIfI Stage 4**, **DM**, **HbA1C >=6.5** and **Serum Albumin < 3.2 g/dl** were identified as negative predictors of wound healing.

PATIENTS LIMB ,WOUND AND SURVIVAL OUTCOME AFTER SUCCESSFUL REVASCULARIZATION

					Total (n = 113)
		Month 0-1	Month 1-3	Month 3-6	
Wound Healed		0	41	46	87
		0%	36.3%	40.7%	76.99%
Wound not healed	Not healed				8
					7.07%
	Major AmputatIon	3	4	3	10
		2.7%	3.5%	2.7 %	8.84%
	Death	2	3	3	8
		1.8%	2.7%	2.7 %	7.07%
Total					113
					100.0%

Out of 113 patients , 76.99 % of the wounds were healed and 7.07% of the wounds were not healed at the end of 6 months. 8.84 % of patients had major amputation and 7.07% of patients had died during the follow up.

Wound location and outcomes

	Outcome				Total	P value
	Healed	Not Healed	Major Amputation	Death		
A	17	0	0	2	19	
	89.5%	.0%	0%	10.5%	100.0%	
B	3	3	1	2	9	
	33.3%	33.3%	11.1%	22.2%	100.0%	***0.024***
C	67	5	9	4	85	
	78.8%	5.9%	10.6%	4.7%	100.0%	
Total	87	8	10	8	113	
	77.0%	7.1%	8.8%	7.1%	100.0%	

- Group A (Toe wounds)
- Group B (Heel wounds) and
- Group C (Wounds extending onto the fore- or mid-foot along with dorsum or plantar surfaces or multiple wounds)

Based upon wound location 89.5 % (Location A) and 78.8% (Location C) wounds were healed and only 33.3 %[Location B (Heel ulcers)] had their wound healed.
Overall 11 % of patients who had their wound in location B had underwent major amputation and 10.6 % of patients with in Location C had major amputation.

WIfI Stage and Outcomes

	Outcome				Total	P value
	Healed	Not Healed	Major Amputation	Death		
Stage 1	8	0	0	0	8	
	100.0%	.0%	.0%	.0%	100.0%	
Stage 2	16	0	0	1	17	
	94.1%	.0%	.0%	5.9%	100.0%	
Stage 3	34	3	1	5	43	***0.041***
	79.1%	6.9%	2.3%	11.6%	100.0%	
Stage 4	29	5	9	2	45	
	64.4%	11.1%	20.0%	4.4%	100.0%	
Total	87	8	10	8	113	
	77.0%	7.1%	8.8%	7.1%	100.0%	

Based upon WIfI Stage, 100 % (Stage 1) and 94.1 %(Stage 2) of patients had their wound healed and only 79.1 %(Stage 3) and 64.4% (Stage 4)of patients had their wound healed.

Major amputaions were seen only in patients with WIfI Stage 3(2.3%) and Stage 4(20%).

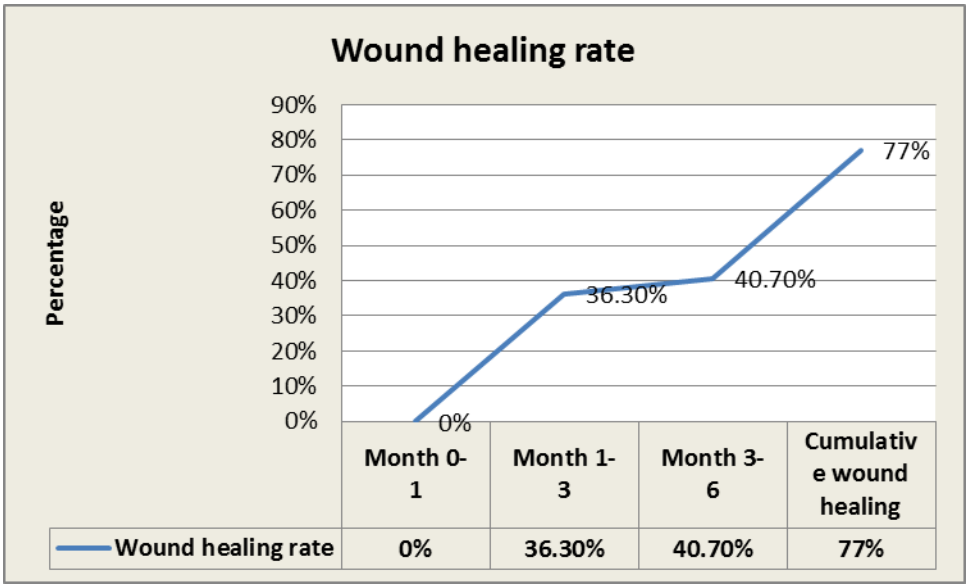


Fig 6.Wound healing rate

Wound healing rates were 0% (1st month), 36.3%(3rd month) and 40.7%(6th month) respectively and the cumulative wound healing rate was 77% .

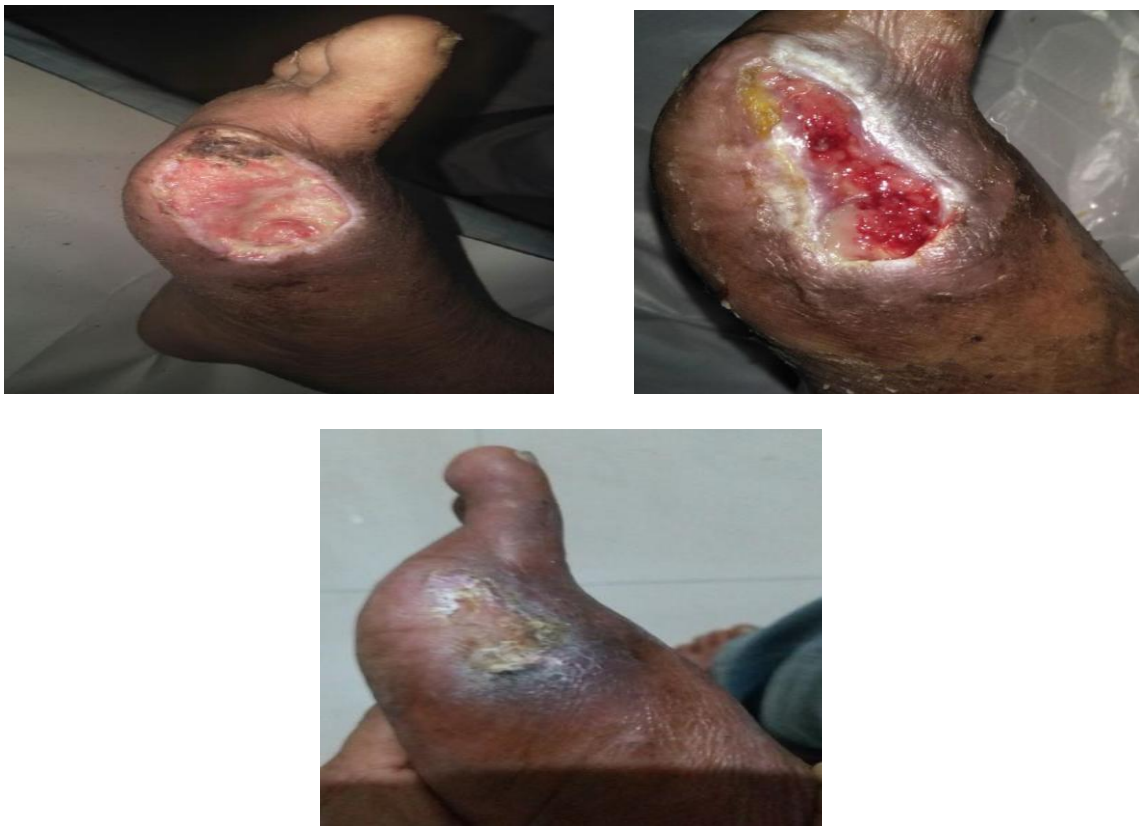


Fig 7. Serial image of a patient who achieved complete wound healing.

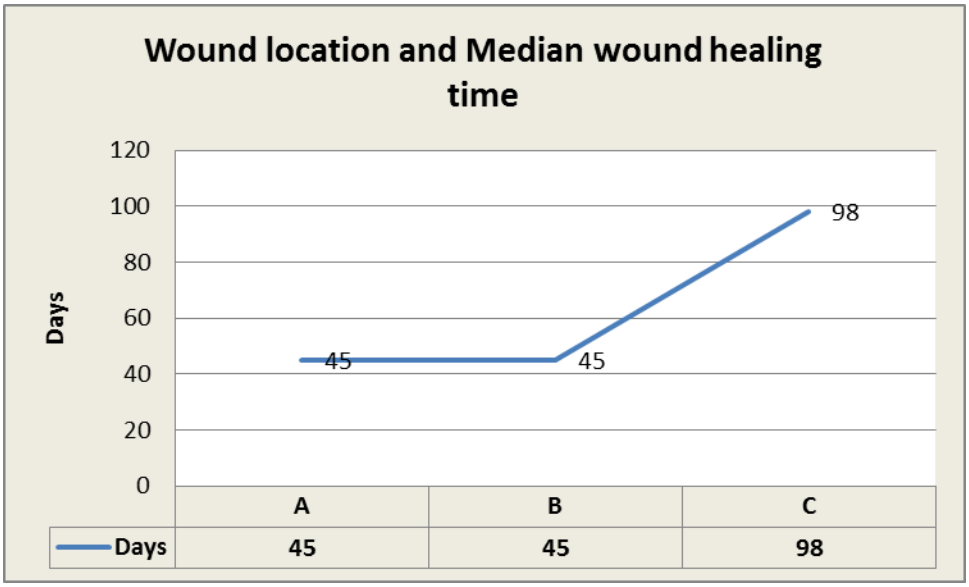


Fig 8.Wound Location and Median Wound healing time

The median wound healing time based upon wound location were 45 days(Location A), 45 days (Location B) and 98 days(Location C) respectively.

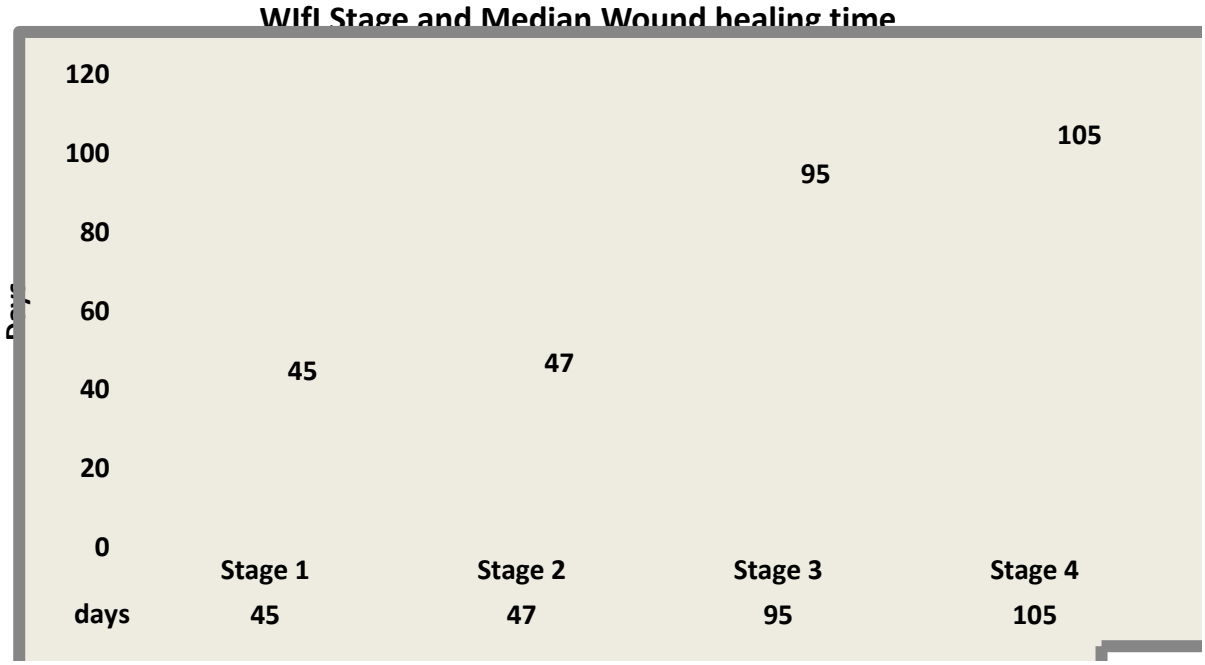


Fig 9. WIfI Stage and Median Wound healing time

The median wound healing time based upon WIfI Stage were 45 days(Stage 1), 47 days(Stage 2),95 days(Stage 3) and 105 days (Stage 4) respectively.

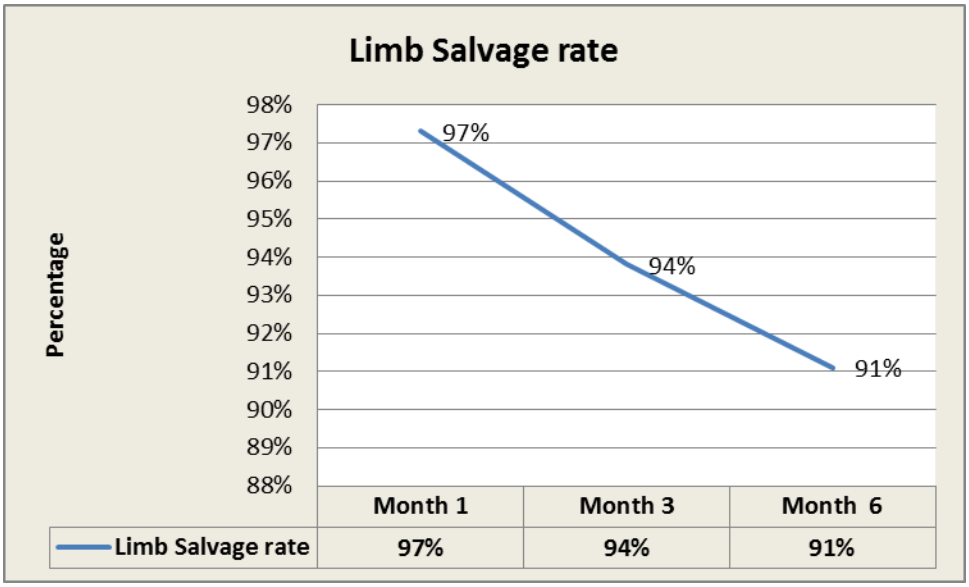


Fig 10. Limb Salvage rate

97% of the patients had their limb salvaged at the end of 1st month which became 94% at the end of 3rd month and only 91 % at the end of 6th month.

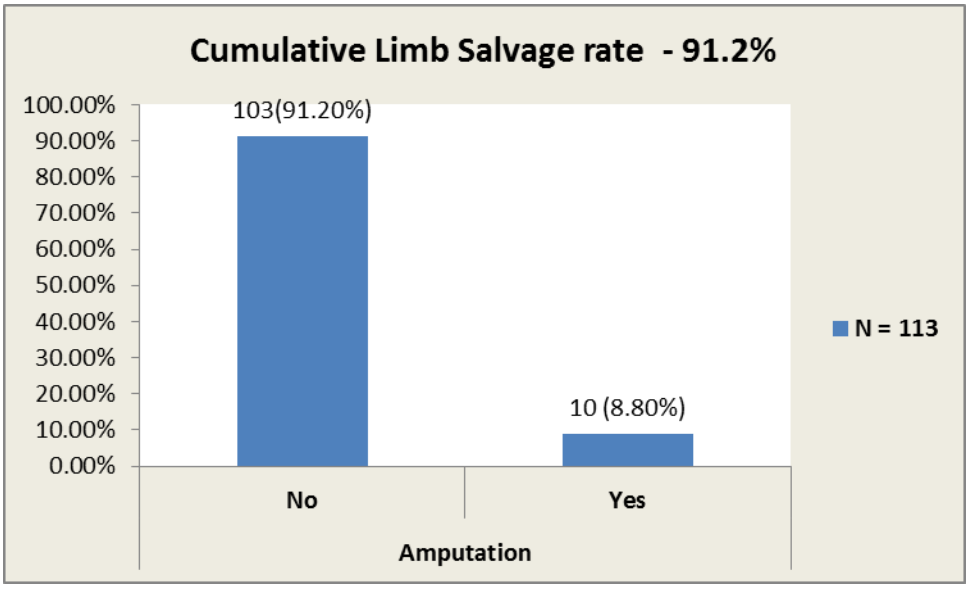


Fig 11. Cumulative Limb Salvage rate

During the study period 10(8.8%) patients underwent major amputation amounting to a 91.2% cumulative Limb Salvage rate.

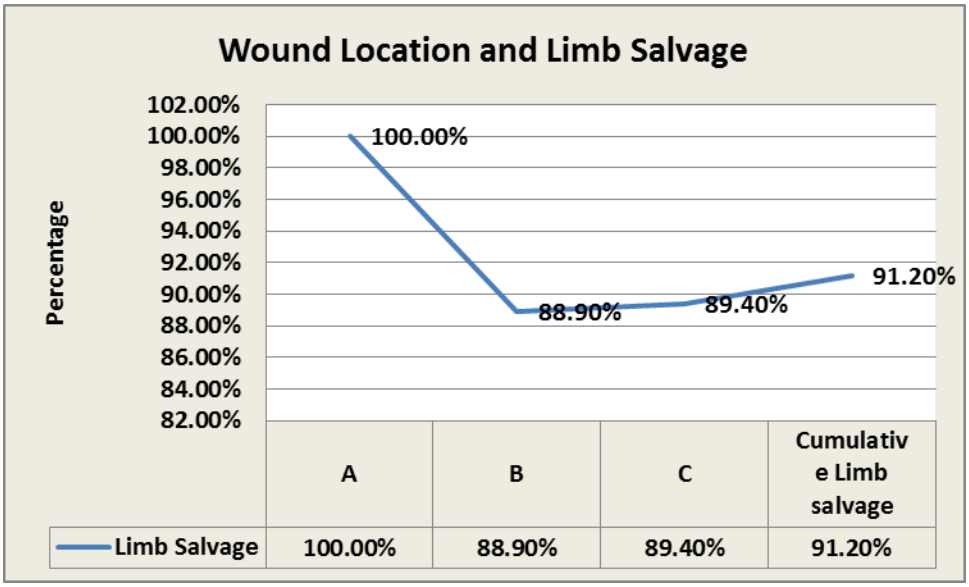


Fig 12. Wound Location and Limb Salvage rate.

Based upon wound location 100% of patients who had their wounds in Location A achieved limb salvage in comparison to Location B (88.9%) and Location C (89.4%).

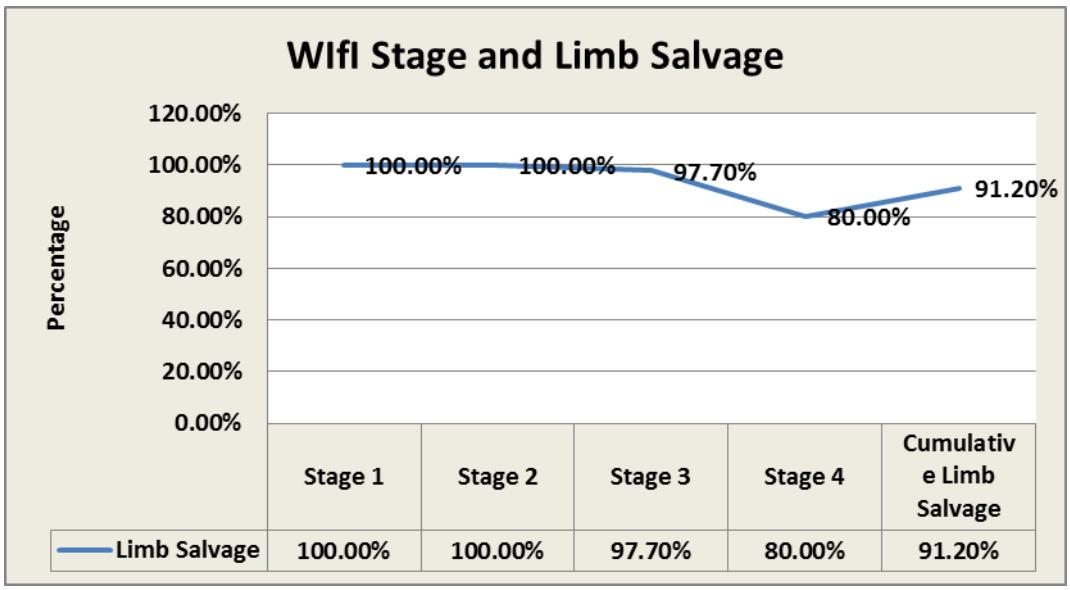


Fig 13. WIfI Stage and Limb Salvage rate

Based upon WIfI Stage 100% of patients in Stage 1 and 2 had their limb salvaged in comparison to Stage 3 (97.7%) and Stage 4 (80 %).

Wound status and outcomes

W.Status	Outcome				Total
	Healed	Not Healed	Amputated	Death	
Infected	68	8	10	7	93
	73.1%	8.6%	10.8%	7.5%	100.0%
Not Infected	19	0	0	1	20
	95.0%	.0%	.0%	5.0%	100.0%
Total	87	8	10	8	113
	77.0%	7.1%	8.8%	7.1%	100.0%

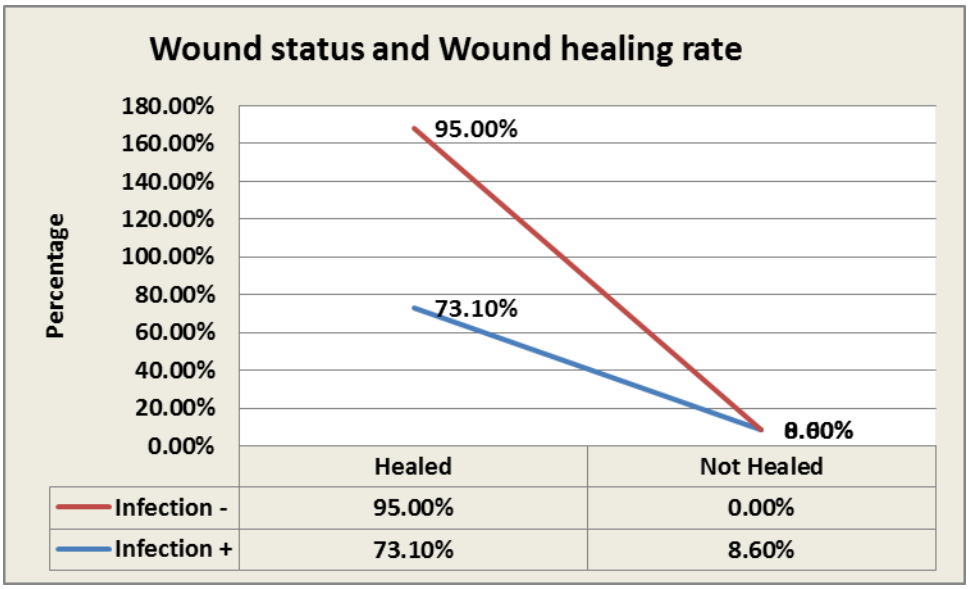


Fig 14. Wound status(Infection) and Wound healing rate.

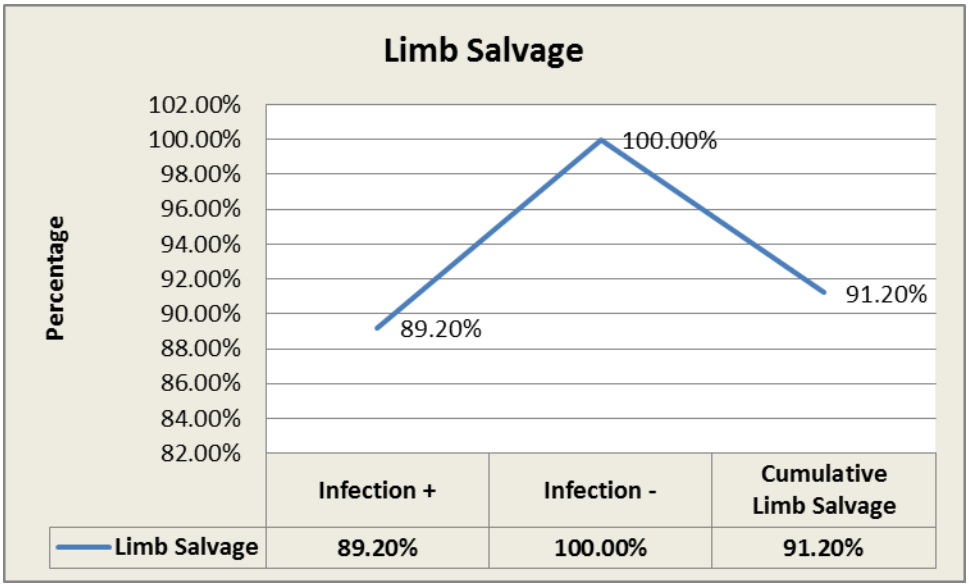


Fig 15. Wound status(Infection) and Limb Salvage

Of the total 87 patients who had their wound healed, only 73 % of patients who had infected wound preoperatively had achieved wound healing in comparison to 95% who wounds were not infected. 100 % of patients had their limb salvaged who had uninfected preoperative wounds and only 89.2% of patients had their limb salvaged whose wounds were infected.

ABI

Visit		N	Mean	SD	Min.	Max.	't' value	P value
Pre Op	Wound Healed	51	0.616	0.135	0.33	0.95	0.043	0.837
	Wound Not Healed	21	0.608	0.168	0.28	1.08		
	Total	72	0.614	0.144	0.28	1.08		
Post OP	Wound Healed	50	0.894	0.103	0.60	1.12	2.618	0.110
	Wound Not Healed	21	0.845	0.145	0.52	1.23		
	Total	71	0.879	0.118	0.52	1.23		
Month 1	Wound Healed	50	0.923	0.086	0.72	1.12	0.435	0.512
	Wound Not Healed	15	0.903	0.140	0.60	1.22		
	Total	65	0.918	0.100	0.60	1.22		
Month 3	Wound Healed	47	0.967	0.069	0.74	1.09	0.761	0.387
	Wound Not Healed	13	0.938	0.184	0.44	1.24		
	Total	60	0.961	0.104	0.44	1.24		
Month 6	Wound Healed	44	0.917	0.096	0.64	1.08	3.712	0.059
	Wound Not Healed	11	0.853	0.110	0.58	1.00		
	Total	55	0.904	0.101	0.58	1.08		

In the entire period of follow up there was no difference in the ABI levels between the Wound healed and Wound not healed groups. ABI was not available when then patient had non compressible vessels (N/C). ABI was available only for 50(1st month),47 (3rd month)and 44 patients(6th month) follow up in the Wound healed group respectively. Similarly in the Wound not healed group, ABI was available only for 15(1st month), 13 (3rd month)and 11 patients(6th month) respectively.

TBI

Visit		N	Mean	SD	Min.	Max.	't' value	P value
Pre Op	Wound Healed	25	0.216	0.053	0.14	0.37	1.488	0.231
	Wound Not Healed	11	0.241	0.062	0.19	0.41		
	Total	36	0.224	0.056	0.14	0.41		
Post OP	Wound Healed	24	0.307	0.102	0.18	0.60	0.965	0.333
	Wound Not Healed	11	0.344	0.107	0.22	0.60		
	Total	35	0.318	0.103	0.18	0.60		
Month 1	Wound Healed	21	0.356	0.092	0.23	0.56	0.165	0.688
	Wound Not Healed	6	0.373	0.101	0.24	0.50		
	Total	27	0.360	0.092	0.23	0.56		
Month 3	Wound Healed	14	0.391	0.119	0.22	0.59	0.119	0.734
	Wound Not Healed	5	0.412	0.117	0.22	0.52		
	Total	19	0.396	0.116	0.22	0.59		
Month 6	Wound Healed	10	0.365	0.114	0.22	0.51	0.262	0.618
	Wound Not Healed	5	0.398	0.127	0.20	0.51		
	Total	15	0.376	0.115	0.20	0.51		

In the entire period of follow up there was no significant difference in the TBI levels between the POBA and DCB groups. TBI was not available when the patient had the 1st or 2nd toes were amputated.

TcPO2 Foot Supine

Visit		N	Mean	SD	Min.	Max.	't' value	P value
Pre Op	Wound Healed	78	22.33	6.143	13	38	6.708	0.678
	Wound Not Healed	23	26.39	8.010	13	48		
	Total	101	23.26	6.789	13	48		
Post OP	Wound Healed	80	32.25	7.344	16	62	0.688	0.409
	Wound Not Healed	25	33.84	11.082	18	64		
	Total	105	32.63	8.353	16	64		
Month 1	Wound Healed	29	33.10	8.525	15	52	0.131	***0.042***
	Wound Not Healed	12	34.17	8.695	25	55		
	Total	41	33.41	8.479	15	55		
Month 3	Wound Healed	19	36.47	9.276	23	56	0.435	0.516
	Wound Not Healed	8	34.00	7.856	18	44		
	Total	27	35.74	8.804	18	56		
Month 6	Wound Healed	12	38.00	11.709	24	58	0.141	0.712
	Wound Not Healed	6	36.00	7.772	26	47		
	Total	18	37.33	10.364	24	58		

TcPO2 Foot Down

Visit		N	Mean	SD	Min.	Max.	't' value	P value
Pre Op	Wound Healed	78	32.27	7.510	17	52	3.607	0.060
	Wound Not Healed	23	35.78	8.723	15	52		
	Total	101	33.07	7.897	15	52		
Post OP	Wound Healed	80	43.61	7.520	22	68	1.203	0.275
	Wound Not Healed	25	45.64	9.660	27	69		
	Total	105	44.10	8.077	22	69		
Month 1	Wound Healed	29	44.34	9.317	24	63	0.237	0.629
	Wound Not Healed	12	45.83	7.802	36	60		
	Total	41	44.78	8.830	24	63		
Month 3	Wound Healed	19	47.37	8.146	35	61	0.252	0.620
	Wound Not Healed	8	45.63	8.450	28	56		
	Total	27	46.85	8.113	28	61		
Month 6	Wound Healed	12	46.83	9.193	33	64	0.033	0.858
	Wound Not Healed	6	47.67	9.114	34	61		
	Total	18	47.11	8.904	33	64		

TcPO2 was measured in the supine and in the dependent foot down provocative position .As indicated the TcPO2 (foot supine) levels at the 1st month follow up was significant between the Wound healed and Wound not healed group.

Discussion

Discussion

Wound healing after revascularisation has not been fully studied even though it is one of the most important outcomes of CLI treatment. Clinical outcomes in patients with critical limb ischemia (CLI) depend not only on restoration of macro vascular blood flow but also on aggressive peri-procedural wound care . Advances in revascularisation, vast improvements in the endovascular armamentarium, and clinical experience have revolutionised salvage of the ischaemic limb. The current study was prospectively designed to evaluate factors affecting wound healing , median wound healing time and limb salvage rates in patients with CLI after successful revascularization

The mean age of patients in the Wound healed group and the Wound not healed group were 63years and 65 years respectively which were comparable to patient groups in previously published studies where the mean age was 71 years.[4]

The proportion of males in our study was 83 % .Kawarada et al in their study analysing predictors of adverse clinical outcomes after successful infrapopliteal intervention had 74 % of males.[10]

Diabetics made up almost the entire cohort in both groups (Wound healed-66.7% and Wound not healed -92.3%) which is comparable to the study by Das et al who had 61.7% and 78.4% ($P < 0.06$) in the wound healing and wound non healing groups.[1]

Systemic hypertension was present in 64.4% and 88.5% of the patients in the Wound healed group and Wound not healed group respectively which is almost similar to the study by Soderstrom et al who had 76.4 % of their patients who were hypertensives. [11]

The prevalence of ischaemic heart disease in our study was 21.8% and 61.5% in the Wound healed and Wound not healed groups respectively. In a similar study conducted by Chung et al[21], 51 % of the patients had a history of coronary artery disease. Das et al had 23.5% and 37.8 % (P - 0.06) of coronary artery disease patients in their wound healing and wound non healing groups[1]. In a study by Kawarada et al analysing predictors of adverse clinical outcomes after successful infrapopliteal intervention in 106 limbs had 29 % of their patients had Ejection fraction (EF) < 40 %.[10] In our study only 7 % of patients had low EF < 40 % compared to the previously mentioned study.

Chronic kidney disease (CKD) was present in 8% and 19% of the patients in the Wound healed and Wound not healed groups respectively. This is similar to the study by Das et al where the prevalence of patients with end-stage renal disease (ESRD) receiving dialysis was significantly higher in the wound non-healing group (6.2 vs 32.4%; P < .0001).[1]

In this study the use of **tobacco** was present in 75% in the Wound healed group and 50 % in the Wound not healed group with a P value-0.017 implying unequally matched groups in terms of exposure to tobacco and its associated risks and effects. Previously published studies have varying proportions of smokers. Elbadawy et al in a comparative study analysing wound healing between direct revascularisation and indirect revascularisation groups had 65% of the patients in the DR group and 63.2% of the patients in the IR group who were smokers[2]. The study by Das et al included 118 patients with 46.9% and 48.6 % of current smokers in the Wound healing group and Wound non healing group respectively[1]. The present study included current and previous smokers with the duration of smoking not taken into consideration.

Dyslipidemia was diagnosed based upon preoperative Total cholesterol and LDL .In the present study 43% of the patients in the Wound healed group and 80 % in the Wound not healed group were dyslipidemic. This is fairly high compared to Das et al where 30.9% of the patients in the Wound healing group and 35.1% of the patients in the Wound non healing group had dyslipidemia (P - 0.67).[1] Kobayashi et al observed 33%, 29% and 38 % of their patients belonging to Group T, H and E respectively were dyslipidemic (P- 0.81).[41]

The level of chronic ischemia was stratified by the **Rutherford-Becker class** with category 4, 5 and 6 termed as critical ischemia in view of rest pain and tissue loss. Our study included only patients with Rutherford category 5 and 6. Many studies have proven that as the Rutherford class increases the limb salvage decreases, multilevel disease is more, patient is highly morbid, likelihood of cardiovascular events are more and that mortality rates are higher. Most patients were in Rutherford Becker category 6- 78% in the Wound healed group and 96 % in the Wound not healed group. A study conducted by Shiraki et al had 67 % of patients with Rutherford 5 and 33 % of patients in Rutherford category 6.[70] In a study by Elbadawy et al 61.5% of the patients in the DR group and 60% of the patients in the IR group belonged to Rutherford category 5 and 38.5% of the patients in the DR group and 40% of the patients in the IR group belonged to Rutherford category .[2]

In 2014, in response to changing patient demographics and increased treatment options for chronic limb threatening ischemia (CLTI), the Society for Vascular Surgery (SVS) Lower Extremity Guidelines Committee developed a new classification system for threatened limbs based on a thorough literature review and a Delphi consensus process .[67]

The SVS **Wound, Ischemia, and foot Infection (WIfI) classification** system was intended to be applicable across the entire spectrum of patients with CLTI and to aid in patient stratification according to initial disease burden in the affected limb. As patients with threatened limbs are more diverse than in the past, WIfI more completely describes the extent of limb threat than previously utilized classification systems such as those of Rutherford and Fontaine. The present study has stratified patients in both groups into their respective preoperative WIfI stages. Most patients are in Stage 3 (38%) and Stage 4 (40%) which indicates the worst combination of wound, ischemia and foot infection requiring definitive revascularisation and also indicating that higher chance of major amputation is present. Wound healed group had 33% and the Wound not healed group had 61% patients in the WIfI stage 4. The distribution of patients in both groups was similar (p value- 0.025) implying equally matched groups. In a study by Okazaki et al analysing wound healing time and wound-free period after surgical and endovascular revascularization for critical lower limb ischemia had wound grades according to the WIfI classification were 1 (31.6%), 2 (65.1%), and 3 (3.2%).[3]

Kobayashi et al analysed Wound healing time and 1‐year wound healing rate by Wound, Ischemia, and foot Infection clinical stage and found that as WIfI stage increased, so did WHT (all weighted means, Stage 1: 92.89 days (range 31–112), Stage 1: 94.32 (range 49–133), Stage 3: 141.30 days (range 125–163), Stage 4: 207.88 days (range 111–263)). The WHR at 1 year decreased with increasing WIfI stage (all weighted means, Stage 1: 92.0%, Stage 2: 69.32%, Stage 3: 62.38%, Stage 4: 44.89%).[41]

In our study the wound healing rate in patients with WIfI Stage 3 and Stage 4 were 79 and 64 % respectively. Median WHT was 95 days and 105 days in patients belonging to WIfI Stage 3 and 4.Overall limb salvage rate was only 80 % in WIfI Stage 4. Our results showed that WIfI wound grade affected the

achievement of wound healing , limb salvage and WHT directly and independently.

In the **clinical setting**, we generally divide wounds into 2 groups using the Rutherford classification, that is, into Rutherford 5 or Rutherford 6. However, the Rutherford classification is ambiguous and sometimes it is difficult to clearly categorize wounds into 2 groups because there are various types of wounds and sometimes multiple wounds on a single limb.

In our study we divided wounds into 3 groups according to their locations:

- Group A (Toe wounds, n=17),
- Group B (Heel wounds, n=8), and
- Group C (Extensive wounds extending onto the fore- or mid-foot along with dorsum or plantar surfaces or multiple wounds, n=88)

and revealed statistically significant (P – 0.002) results of wound healing rates, although there were differences in baseline characteristics.

Wound healing rates at 6 months were 90%(Group A),33% (Group B) and 79% (Group C) [P – 0.024] . The median WHT was 45 days(Group A and B) and 98 days(Group C) which was comparable to study conducted by Kobayashi et al which showed wound healing rates 75%,52 % and 13 % in group T, group H; and group E.[41] The median time to healing was 64 days (interquartile range 25-156 days) in group T, 168 days (interquartile range 123-316 days) in group H, and 267 days (interquartile range 177-316 days) in group E (P=0.038).

Das et al observed there was a higher prevalence of toe wounds in the wound healing group (65.2% vs 42.2%; P- 0 .02) and a higher prevalence of dorsal wounds in the non healing group (9.8% vs 28.9%; P -0 .006). These findings suggest that evaluation of wound locations is meaningful for the prediction of wound healing.[1]

Ulceration or gangrene located at the heel is considered difficult to treat. Soderstrom et al. showed that ischemic tissue lesions located on the mid- and hind-foot had significantly prolonged ulcer healing times (HR 0.4, P=0.044).[11] Our findings are in agreement with those of Soderstrom et al., and they indicate that the rate of healing of heel wounds was lower than that of toe wounds (37.5% vs 100 %) and that it took a considerably longer time to heal. This difficulty with successful healing most likely reflects many factors—limited soft tissue over the calcaneus, the frequent development of osteomyelitis, difficulty in keeping pressure off the wound, and differences in regional pedal perfusion.

In studies done by Shiraki et al [4] and Okazaki et al [2] 42 % of their patients wounds were infected .Das et al observed wound infection in 32.6% and 77.8% in their wound healing and wound non healing groups[1]. In our study wound infection was present in 78 % and 96 % of patients in the Wound healed and Wound not healed groups respectively (P- 0.035) . Diagnosis of wound infection was further proven by elevated pre op WBC counts, ESR , CRP levels in all the patients in wound not healed group. Pre op positive wound culture and Osteomyelitis was present in 100 %(P – 0.056) and 39 % (P - 0.001) of wounds respectively.

Previous studies have evaluated predictors of wound healing in patients with diabetic foot ulcers and reported that the wound's depth, area, and duration before treatment by a specialist were important factors related to failure of wound healing and major amputation. However, the effect of these wound characteristics on wound healing and limb salvage in CLI patients with tissue loss is poorly understood.

Das et al found in their study of predictors of delayed wound healing after successful isolated below-the-knee endovascular intervention in patients with ischemic foot ulcers identified the following as predictors of wound non healing after initial EVT: ESRD with dialysis (hazard ratio [HR], 2.6; 95% confidence interval [CI], 1.0-6.3; P ¼ .04); albumin level <3.0 g/dL (HR, 2.0; 95% CI, 1.1-3.8; P ¼ .02); CRP level >5.0 mg/dL (HR, 3.9; 95% CI, 1.6-9.6; P ¼ .003); major tissue loss (HR, 2.1; 95% CI, 1.3-3.4; P ¼ .003); wound infection (HR, 1.9; 95% CI, 1.2-2.9; P ¼ .005); gangrene (HR, 1.8; 95% CI, 1.2-2.8; P ¼ .008); wound depth (UT grade 3; HR, 3.4; 95% CI, 1.4-8.6; P ¼ .009); duration of ulcer ($2 months; HR, 2.9; 95% CI, 1.0-8.4; P ¼ .048); insulin use (HR, 1.7; 95% CI, 1.0-2.8; P ¼ .04); and no BTA runoff (HR, 1.9; 95% CI, 1.0-3.4; P ¼ .04).[1]

Kobayashi et al in their study identified that dependence on HD (hazard ratio [HR] 0.33, 95% CI 0.21–0.51, P<0.001), infectious wounds (HR 0.65, 95% CI 0.42–0.99, P=0.046), extensive wounds extending onto the fore- or mid-foot along the dorsal or plantar surfaces (HR 0.17, 95% CI 0.07–0.40, P<0.001), and heel wounds (HR 0.39, 95% CI 0.22–0.71, P=0.002) were negative predictors of wound healing.[41]

In our study, **independent negative predictors** of wound healing were determined by multivariable Cox proportional hazards model and identified the following as predictors :

- **WIfI stage 4** (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.2-0.4; P - <0.001);
- **Diabetes mellitus** (HR, 6.5; 95% CI, 1.3-32.08; P- 0.020);
- **HbA1C > 6.5** (HR, 5.1; 95% CI, 1.0-24.9; P- 0.043) ;
- **Serum Albumin < 3.20 g/ dl** (HR, 2.9; 95% CI, 1.3-6.2; P- 0.008).

Serum albumin <3.2 g/dl was strongly associated with wound non healing in the current study. Azuma et al. also reported albumin <3 g/dL as a negative predictor for wound healing after bypass surgery; however, it is unknown whether hypoalbuminemia was caused by inflammation or malnutrition.[9]

In this analysis, only technically successful revascularization cases were enrolled. Previous studies have reported time to wound healing and wound healing rates after revascularization.

Iida et al. performed a retrospective, propensity matched score analysis of 539 consecutive non-diabetic patients with CLI. They reported a 12 month complete wound healing rate of 75% versus 64% (p ¼ .01) for the DR and IR groups, respectively. Freedom from amputation (p ¼ .99) and AFS (p ¼ .17) were not significantly different at up to 24 months.[51]

However, Varela et al. demonstrated significantly better results for both complete wound healing (92% vs. 73%; p ¼ .008) at 12 months and limb salvage rates (93% vs. 72%; p ¼ .02) at 24 months among comparison groups.[57]

Alexandrescu et al in their retrospective case series of 208 diabetic patients with CLI treated by infrapopliteal angioplasty, reported complete wound healing in 73% versus 69% (p ¼ .018) and much better limb salvage rates (90% versus 84%; p ¼ .035) at 1 year.[48]

Söderström et al., in their study of 226 diabetic patients with CLI, reported lower complete wound healing rates (72% DR vs. 45% IR; p ¼ .001) at 12 months and limb salvage rates (86% DR vs. 77% IR; p ¼ .086) after propensity matched analysis of 84 pairs in comparison groups.[11]

Kobayashi et al observed at 3, 6, 9, and 12 months, wound healing rates were 51%, 64%, 75%, and 75%, respectively, in group T; 12%, 36%, 36%, and 52%, respectively, in group H; and 0%, 5%, 8%, and 13%, respectively, in group E. The median time to healing in completely healed wounds was 64 days (interquartile range 25–156 days) in group T, 168 days (123–316 days) in group H, and 267 days (177–316 days) in group E (group T vs. group H, P<0.001; group H vs. group E, P=0.49.[41]

The **present study** represents one of the few prospective study of ischaemic ulcer healing after revascularization. After revascularization for CLI with tissue loss, the wound healing rate at 1 month, 3 months and 6 months were 0% ,36.3 % and 40.7 % respectively and the cumulative wound healing rate was 77 %.The median wound healing time in the Group A and Group B was 45 days and in the Group C was 98 days.

Historically, the outcomes of patients with peripheral arterial disease have been evaluated primarily with technical parameters such as graft patency or TLR. In patients with CLI, clinical limb outcome was considered successful when the limb was rescued from major amputation. However, the "limb salvage rate" does not always represent successful limb outcome, because a significant number of patients die before their symptoms are relieved.The uncertainty about limb salvage in the subgroup of patients who die before symptom relief (wound healing or pain relief) makes the analysis of limb outcome difficult.

The incidence of major amputation and death before achieving complete healing during the follow-up period were 10 limbs (8.8%) and 87 of the 113 limbs (77 %) achieved complete wound healing. Of the 26 patients that did not achieve wound healing, wound observation was terminated by amputation in 10 and by death in 8, and 8 patients still had unhealed ulcer at 6 months after primary revascularization. Kobayshi et al found the incidence of major amputation and

death before achieving complete healing during the follow-up period were 6 limbs (5.7%) and 24 patients (28.6%) in group T, limbs (9.5%) and 5 patients (29.4%) in group H, and 19 limbs (47.5%) and 24 patients (64.9%) in group E.[41] On stratifying patients who had major amputations according to wound locations were 0[Group A], 1(12.5%)[Group B] and 9(10.2%)[Group C] respectively. In this study, the major amputation rate after revascularisation was significantly different between wounds with, versus without infection (10.8% vs. 0%, respectively). In our study majority of patients were belonging to WIfI Stage 3 and Stage 4.Major amputation rate was 2.4 % (WIfI Stage 3) and 20 % (WIfI Stage 4).The cumulative limb salvage rate at 6 months in our study was 91 % .

Technical success needs to translate to haemodynamic success in order to achieve resolution of symptoms and wound healing. On assessment of the haemodynamic status post procedure using non-invasive vascular lab methods, about 100% and 80% of the patients in the Wound healed and Wound not healed groups had achieved adequate improvement in the vascular status in the PVR (Pulse volume recording) at the end of 3months and about 20 % and 8 % of the patients in Wound healed and Wound not healed group respectively at the end of 6 months.

All patients underwent the three measurements (ABI, TBI,TCPO2) in follow up as those were the indirect measurements of adequate revascularization .At 1st month, 3rd month and 6th month of follow up, the ABI in both groups were similar implying that revascularization alone does not contribute to complete wound healing. However ABI was not available when then patient had non compressible vessels (N/C) .

To overcome the problem of N/C ABI is the measurement of TBI as the foot vessels are less prone for medial calcification. TBI was not available when the

patient had the 1st or 2nd toe amputated. In our study, there was no significant difference in mean TBI in both the groups during follow up.

ABI and TBI are direct monitors of determining the patency of a vessel post intervention. The same cannot be told of TcPO2 as it provides the perfusion at the tissue level and is not a direct modality to determine whether a vessel is patent or not. This is because TcPO2 may be maintained by collateral supply even in the presence of a blocked major artery. Also availability of TcPO2 is an advantage as there are not much factors which make it non measurable. However the multitude of factors which may vary the actual level should be kept in mind before proceeding with measuring the TcPO2. TcPO2 was measured in the supine and in the dependent foot down provocative position. Only for a few patients in both groups, TcPO2 was not available in follow up. Maintenance of foot perfusion by measurement of TcPO2 reveals that the Wound healed group and Wound not healed group had almost similar perfusion at all steps of follow up. Foot perfusion was maintained in 29 of 41 patients in 1st month (70.7%), 19 of 27 patients in 3rd month (70.4%) and 12 of 18 patients in 6th month (66.7%) in the Wound healed group. In the Wound not healed group, foot perfusion was maintained in 12 of 41 patients in the 1st month (29.3%), 8 of 27 patients in the 3rd month (29.6%) and 6 of 18 patients in the 6th month (33.3%). To our knowledge none of the published studies analysing ischaemic wound healing after successful revascularization have considered ABI,TBI and TcPO2 in their follow up protocol.

We also analysed the **Ambulatory blood glucose profile** for few CLI patients who consented for the device sensor whereas the rest monitored by Home GRBS monitoring. AGP is one of the most recent, innovative developments that are being used to monitor Glycaemic variability in DM patients. AGP is generated from the Flash Glucose Monitoring device which is like a CGM device attached to the patient for a maximum period of 14 days, which checks the ISF glucose at every 15 minutes[70]. In our study 75.9 % of patients had

controlled mean sugars at the end of 2 weeks whereas 24.1 % of patients had uncontrolled sugars. Out of the wound which were healed 72.5 % of patients had their sugars controlled as per the ambulatory glucose profile / Home GRBS monitoring and out of the wounds which were not healed 14.3 % of patients had uncontrolled sugars although the difference was not statistically significant . AGP in the patient provides the doctor with an opportunity to have a complete glycemic picture of the patient . It offers a reliable, predictive, standardized visualization of the glucose data.

Limitations :

Several limitations of our study must be acknowledged. This study was a single-centre study and selection of revascularization procedure was not randomized. Patient background was not controlled. Revascularization procedure, target artery, and wound management were not stratified. WHT may be overestimated because wound status was not checked daily in outpatients and, depending on the frequency of clinic visits, may have introduced error of up to approximately 1 month.

Conclusion

Conclusion

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Factors that impair ischaemic ulcer healing are broadly divided into 5 types:

(1) systemic condition and comorbidity;

(2) extent of tissue loss;

(3) infection;

(4) inadequate wound management; and

(5) inadequate revascularization strategy.

The combination of these factors would enable optimal wound management, leading to successful wound healing and improved limb salvage and survival rates. These viewpoints regarding ulcer healing must be incorporated into the next CLI treatment guideline to prepare for a coming era of vascular disease related to the global expansion of an aging population with increasing comorbid diseases.

Summary

Summary

A prospective, non randomised, single centre observational study was conducted at Jain Institute of Vascular Sciences (JIVAS), Bengaluru to analyse factors affecting ischaemic wound healing following successful revascularization. We have also analysed wound healing rate, time and cumulative limb salvage rate in this study.

All patients with CLI (Rutherford category 5 and 6) who had undergone primary revascularization between August 2017 to August 2018 (13 months) were included in this study. Only patients with technical and hemodynamic successful revascularization were included in this study.

During the study period of 13 months, 198 CLI patients presenting with ischaemic foot wounds were treated with revascularization and appropriate wound management. After exclusion, 113 CLI patients who had undergone successful revascularization were enrolled. The age, sex, co-morbidities, tobacco use, Rutherford class of critical ischaemia, WIfI stage, various laboratory parameters, haemodynamic success were recorded. Patients were divided into two groups as Wound healed and Wound not healed groups. The primary outcome of factors associated with delayed wound healing after revascularization were examined by multivariate analysis.The secondary outcome measures of this study were wound healing rate, median wound healing time after revascularization and limb salvage rate.
Clinical variables found to influence wound healing in previous studies were inserted into the multivariate analysis. All patients were followed up at the 1st month, 3rd month and 6th month. All patients received standardized wound therapy according to the institute protocol. All the wounds were evaluated accordingly and received débridement and removal of devitalized tissues and culture-based infection eradication. Offloading techniques were also used.

The wound healing rates were 0%(1st month), 36.3%(3rd month) and 40.7% (6th month) respectively and the cumulative wound healing rate was 77%. The median wound healing time is 95 days (WIfI Stage 3)and 105 days(WIfI Stage 4) and **overall limb salvage rate was 91.2%**.

Multivariate Cox proportional hazards analysis revealed the following as independent predictors of wound nonhealing after initial successful revascularization:

- **WIfI stage 4** (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.2-0.4; P - <0.001);
- **Diabetes mellitus** (HR, 6.5; 95% CI, 1.3-32.08; P- 0.020);
- **HbA1C > 6.5** (HR, 5.1; 95% CI, 1.0-24.9; P- 0.043) ;
- **Serum Albumin < 3.20 g/ dl** (HR, 2.9; 95% CI, 1.3-6.2; P- 0.008).

Hence we recommend that successful revascularization alone does not contribute to successful clinical limb outcome (complete wound healing and freedom from major amputation) and other factors influencing ischaemic wound healing has to be addressed and be a part of treatment armamentarium.

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Annexure

Annexure I

Annexure I

Definitions

Complete wound healing was defined as complete epithelialisation of the tissue defect by secondary intention (eg. VAC) or tertiary intention (eg. skin grafting) or after any additional local debridement.[1]

- Wounds were considered **not-healed** if they failed to heal within 6 months or in case of major amputation or death before complete healing.[1, 2]

Wound Healing time was defined as the number of days required to achieve complete wound healing after revascularization.[3]

Limb salvage defined as prevention of major amputation. [4]

Major amputation was defined as limb loss below or above the knee level.[4,5]

Minor amputation was defined as a transmetatarsal or more distal level amputation of the lower extremity.[4,5]

Diabetes mellitus defined as baseline fasting blood glucose levels of > 126mg/dl, HbA1c (>6.5%) or the need for glucose lowering treatment according to the World Health Organization Criteria.[6]

Hypertension defined as having high blood pressure (systolic blood pressure > 140mg Hg and /or diastolic blood pressure >90 mm Hg) and/or receiving antihypertensive treatment for at least 1 year before inclusion in study.[7]

Ischaemic heart disease (IHD) defined as a history of angina pectoris, myocardial infarction, congestive heart disease, or prior coronary artery revascularizations.[8]

Chronic kidney disease (CKD) defined as serum creatinine >1.5 mg/dL 24 hrs before surgery.[9]

Smoking habit defined as active smoker when the patient smoked at the time of the inclusion or gave up the habit in a period lower than 6 months.[10]

Dyslipidemia was defined as serum low density lipoprotein (LDL) cholesterol > 100 mg/dL or Total cholesterol > 200 mg/dl, or having been treated for dyslipidemia.[11]

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Variable	Normal Reference range
Hb	11 .0 to 18.0 g/dl
WBC	4.00 TO 11.00 X 10 ^3/cu.mm
Urea	15.00 to 40.00 mg/dl
Creat	0.6 to 1.3 mg/dl
HbA1C	< 6.5 OR > = 6.5 %
S.Albumin	3.20 to 4.50 g/dl
ESR	0 TO 10 mm/hr
CRP	0 TO 5 mg/dl
TC	< 200 mg/dl
LDL	< 100 mg/dl

Annexure II

Annexure II

STUDY PROFORMA :

Analysis of factors delaying healing of ischaemic foot wounds in patients who undergo lower limb revascularization.

Hosp. No.: _____ JIVAS No.: _____ Name : _____

Telephone No.: _____ Age : _____years Sex : Male / Female

Type of Ulcer : Superficial / Deep / Abscess / Gangrene

Site of Ulcer : Big toe / Other toes / Forefoot / Midfoot / Plantar / Heel /Dorsal surface / Multiple

Side of Ulcer : Right / Left

Ulcer group : A/B/C

Diabetes : Yes / No ,

Hypertension : Yes / No

Ischaemic heart disease : Yes / No

Chronic Kidney Disease : Yes / No

Any Use of Tobacco : Yes / No

Rutherford Category : _____ Wifi Stage : _____

DIAGNOSIS : Critical Limb Ischemia (Right/ Left/ Bilateral)

Treatment plan : Revascularization (Endovascular / Open / Hybrid)

Ambulatory Glycaemic Control / Home GRBS post op 2 Weeks : Controlled / Not Controlled

Parameters	Pre Op	Post Op	1 month	3 month	6 month
Haemoglobin g/dl	Low / Normal	Low / Normal	--------	Low / Normal	Low / Normal
Total WBC count	Normal / High	Normal / High	--------	--------	--------
Urea mg/dl	Normal / High	--------	Normal / High	Normal / High	Normal / High
Creatinine mg/dl	Normal / High	--------	Normal / High	Normal / High	Normal / High
HbA1C %	Normal / High	--------	--------	Normal / High	Normal / High
Serum albumin mg/dl	Low/ Normal	--------	Low/ Normal	Low/ Normal	Low/ Normal
ESR	Normal / High	--------	Normal / High	Normal / High	Normal / High
CRP	Normal / High	--------	Normal / High	Normal / High	Normal / High
Total Cholesterol	Normal / High	--------	--------	--------	--------
LDL	Normal / High	--------	--------	--------	--------
ABI (index limb)					
TBI					
TCPO2 mm/Hg					
Cardiac Ejection fraction %		--------	--------	--------	--------
Wound Culture Growth	Yes / No	--------	Yes / No	Yes / No	Yes / No
X-ray foot (Osteomyelitis)	Yes / No	--------	Yes / No	Yes / No	Yes / No
Wound status	Infected. / Not Infected.	Infected. / Not Infected.	Infected. / Not Infected.	Infected. / Not Infected./	Infected. / Not Infected.
Wound Healed	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No

- **Wound healing time : ----- Days**
- **Amputation : Yes / No, If Yes : Minor / Major.**
- **Death : Yes / No**

Annexure III

Annexure III

Informed Consent

I hereby give consent to undergo the procedure-

_____

_____

for the study conducted by Dr.Roshan Rodney S under the guidance of Dr.Vivekanand of Jain Institute of Vascular Sciences(JIVAS), Bhagwan Mahaveer Jain Hospital, Bangalore.

I have been informed that i will be receiving treatment in the form of revascularization (endovascular/open) for my limb ischemia and surgical debridement or minor amputation for the wound .Prior to the procedure, detailed clinical history and examination ,relevant preoperative laboratory investigations ,ABI,TBI. PVR, TCPO2 & CT/ MR Angiography will be done for which no extra cost will be charged .After

revascularization; i will be enrolled for study. Postoperatively, I will be followed at 1^{st},3^{rd} and 6 th month and the investigations explained to me will be done to assess assess the wound healing clinically and limb salvage .

I consent to the usage of the data observed during the course of my treatment, photography of the wounds for the purpose of advancing medical education or its publication in scientific journals provided my identity is not revealed by the pictures or description in the accompanying texts.

I have been explained the above details in my own language-_____ understood by me and I give consent and absolve the hospital authorities, its doctors and the staff in the event of any complication.

	Name	Signature	Date	Time
Patient				
Witness				
Doctor				

Annexure III

Patient information sheet

Arterial ulcers can take a long time to heal and individuals are likely to vary in their rate of healing, which depends on how good the circulation is. To improve the blood supply to the ulcer an angioplasty is often used, or surgery to clear out a blockage from a leg artery (endarterectomy) or a bypass operation to put in a new route for blood flow in the leg.

There are many dressing used to help leg ulcers heal, keeping them clean and protected. Some will aim to reduce discharge, some will try and help old tissue or slough lift off allowing the healthy tissue to come through.

Even after successful revascularization many of the ulcers fail to heal or have delayed healing. There are multitude of factors which may delay in ulcer healing apart from poor circulation.

Factors Affecting Wound Healing :

1. Age of Patient. There are many overall changes in healing capacity that are related to age.
2. Type of Wound. The characteristics of a wound can affect the speed of wound healing.
3. Infection.
4. Chronic Diseases. (Diabetes, Hypertension, Ischaemic heart disease, Chronic kidney disease etc)
5. Poor Nutrition.
6. Poor Blood Circulation.
7. Edema

These should be considered and addressed as part of a holistic approach to wound management.

Annexure IV

Bhagwan Mahaveer
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A Unit of Bhagwan Mahaveer Memorial Jain Trust
BMJH
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Bengaluru 560052
website - www.bmjh.org

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with
compassion

SCIENTIFIC COMMITTEE

APPROVAL CERTIFICATE OF DISSERTATION FOR NBE

Approval has been granted by Scientific Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement **ANALYSIS OF FACTORS DELAYING HEALING OF ISCHAEMIC FOOT WOUNDS IN PATIENTS WHO UNDERGO LOWER LIMB REVASCULARIZATION** Conducted by **Dr. ROSHAN RODNEY.S** Department of **VASCULAR SCIENCES** under the guidance of **Dr. VIVEKANAND,** approximate period of study is from **JULY 2017 TO JUNE 2018.**

Scientific Committee meeting held on **21/06/2017.**

Date : 22/06/2017

Dr. Preethi Adoni
Chair Person
Scientific Committee

Deputy Medical Director
BHAGWAN MAHAVEER JAIN HOSPITAL
BANGALORE - 560 052

Annexure V

ETHICS COMMITTEE ON HUMAN RESEARCH
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APPROVAL CERTIFICATE OF DISSERTATION FOR NBE

Approval has been granted by Ethics Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement **ANALYSIS OF FACTORS DELAYING HEALING OF ISCHAEMIC FOOT WOUNDS IN PATIENTS WHO UNDERGO LOWER LIMB REVASCULARIZATION** Conducted by **Dr. ROSHAN RODNEY.S** Department of **VASCULAR SCIENCES** under the guidance of **Dr. VIVEKANAND,** approximate period of study is from **JULY 2017 TO JUNE 2018.**

Ethics Committee meeting held on **22/06/2017.**

Dr. (Wg Cdr) M.D.Marker
Member Secretary
BMJH Ethics Committee

Date :22/06/2017

Master Chart