COMPARATIVE STUDY OF OUTCOMES BETWEEN SINGLE VERSUS MULTIPLE INFRAPOPLITEAL VESSEL ANGIOPLASTIES IN PATIENTS WITH CRITICAL LIMB ISCHEMIA

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

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December 2019 **Dr.Hemant K Chaudhari**

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Bengaluru

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled "**COMPARATIVE STUDY OF OUTCOMES BETWEEN SINGLE VERSUS MULTIPLE INFRAPOPLITEAL VESSEL ANGIOPLASTIES IN PATIENTS WITH CRITICAL LIMB ISCHEMIA**" is a bonafide and genuine research work carried out by me under the guidance and supervision of **Dr.Sumanthraj K B,** Vascular surgeon, Jain Institute of Vascular Sciences (JIVAS), Bhagwan Mahaveer Jain Hospital, Bengaluru, in partial fulfilment 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. Hemant K Chaudhari**

Place: Bengaluru

CERTIFICATE

This is to certify that the dissertation titled **"COMPARATIVE STUDY OF OUTCOMES BETWEEN SINGLE VERSUS MULTIPLE INFRAPOPLITEAL VESSEL ANGIOPLASTIES IN PATIENTS WITH CRITICAL LIMB ISCHEMIA**" is a bonafide research work done by **Dr. Hemant K Chaudhari, MBBS, DNB(Gen surg)** under my guidance at Jain Institute of Vascular Sciences (JIVAS), a unit of Bhagwan Mahaveer Jain Hospital, Bangalore in partial fulfilment 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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I express my sincere thanks to ***Dr. Vivekanand, Dr. Vishnu Motukuru, Dr. Indushekar, Dr. Mamatha S H,*** *and* ***Dr. Girija,*** *Consultants, JIVAS for their valuable help and the encouragement and support they provided me, during my work.*

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Last but not the least; I sincerely thank all the patients who were part of the study for their cooperation

Place: Bengaluru

June 2019 ***Dr. Hemant K Chaudhari***

❖ LIST OF ABBREVATIONS:

PAD = Peripheral Arterial Disease
CLI = Critical Limb Ischemia
DM = Diabetes Mellitus
HTN = Hypertension
IHD = Ischemic Heart Disease
CRF = Chronic Renal Failure
CVA = Cerebro Vascular Accidents
ATA = Anterior Tibial Artery
PTA = Posterior Tibial Artery
TPT = Tibio-Peroneal Trunk
SV group = Single vessel infrapopliteal angioplasty group
MV group = Multiple vessel infrapopliteal angioplasty group
PAQ = Plantar Arch Quality
CPA = Complete Plantar Arch
IPA = Incomplete Plantar Arch
APA = Absent Plantar Arch
VIZ = Videlicet (Namely)
Vs = Versus
et al = Et alia

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Annexure I

Definitions

Wound healing was defined as complete epithelialisation of the tissue defect by secondary intention (eg. VAC) or by tertiary intention (eg. skin grafting). [1]

- Wounds were considered **not-healed** if they failed to heal within 6 months or in case of major amputation.[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 freedom from major amputation (below or above knee. [4]

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

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

Diabetes mellitus (DM) 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 (HTN) 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 Renal Failure (CRF) 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]

Procedural technical success is obtaining one straight in line flow (direct/indirect) to the foot without any flow limiting dissection, with less than 30% residual stenosis of the target vessel being angioplastied

Technical success - in single-vessel interventions was defined as a residual stenosis <30%, where success in multiple-vessel interventions was defined as interventions in which at least two intervened vessels achieved technical success[12, 13]

All cause death: death occurring postoperatively or during the follow up due to cardiac or any non cardiac cause.

The **plantar arch** was classified as a complete plantar arch (CPA), incomplete plantar arch (IPA), or absent plantar arch (APA) [14]

CPA was defined as the presence of both dorsalis pedis arteries and at least one plantar artery, with the communication of these arteries through the deep plantar artery or lateral tarsal artery.

IPA was defined as the presence of one pedal artery but no plantar arch.

APA was defined as no identifiable pedal artery, with only side branches detectable in the foot

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14. Rashid, Hisham et al. The impact of arterial pedal arch quality and angiosome revascularization on foot tissue loss healing and infrapopliteal bypass outcome. Journal of Vascular Surgery, Volume 57, Issue 5, 1219 - 1226

Annexure II

STUDY PROFORMA

NAME :	**AGE/SEX :** **HOSPITAL No. :** **JIVAS No. :** **TELEPHONE :** **DATEOF ADMISSION :**

Laboratory Investigations:

Haemoglobin	
Creatinine pre operative	
Creatinine post operative at 48 hr	
2 D ECHO	
HbA1C	
Lipid profile	

Tests:

ABI (index limb)	
Arterial Doppler	
DSA/MRI/CT Angiogram	

Intra operative:

Procedure performed- vessels undergoing angioplasty-

ATA PTA TPT Peroneal

Brief description –

Technically Successful - Yes No

Quality of plantar arch- complete incomplete absent

MACE:

Mortality:

Post procedure: (baseline for evaluation in subsequent visits)

Follow up included

	Preoperative	Postoperative	1 month	3 month	6 month
ABI(index limb)					
Duplex scan(If needed)					
Wound Status					
Major Amputation					
HbA1c					
Lipid profile					

Reintervention over period of 6months if any (In brief):

Annexure III

Informed Consent

I hereby give consent to undergo the procedure-____ for the study conducted by Dr. Hemant K Chaudhari, under the guidance of Dr. Sumanthraj K B of Jain Institute of Vascular Sciences(JIVAS), Bhagwan Mahaveer Jain Hospital, Bangalore.

I have been advised of the benefits, costs, reasons for the procedure as indicated by the clinical observation and the diagnostics performed. I acknowledge that no guarantees have been or can be made regarding the likelihood of success or outcome. I have been advised that the major risks involved in the above procedure are pain, bleeding, infection, procedure failure (10-20%), limb loss, minor/major amputation (10-20%), non healing of wound, need for further procedures to improve vascularity, myocardial infarction, deep venous thrombosis, pulmonary embolism, renal failure, respiratory failure, allergic reactions to the contrast dye/paclitaxel or excipient coated in the balloon and need of ICU care. I have been advised the existing alternatives in treatment and prognosis of the same and the risks of not having the procedure done. I also consent and authorize the surgeon and/or his designee to treat any of the above complications in the event it may occur due to unforeseeable events.

I consent to the usage of the data observed during the course of my treatment, photography or televising of the procedure 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				

Patient information sheet

Angioplasty (or Balloon angioplasty) is an endovascular procedure to widen narrowed or obstructed arteries. An empty, collapsed balloon, known as a balloon catheter, is passed over a wire into the narrowed locations and then inflated to a fixed size. The balloon forces expansion of the stenosis (narrowing) within the vessel and the surrounding muscular wall, opening up the blood vessel for improved flow, and the balloon is then deflated and withdrawn.

Balloon used for angioplasty may be a plain (non medicated) balloon or a drug coated balloon. DCB coating is a non-polymer based formulation, consisting of paclitaxel as the active pharmaceutical ingredient and excipients polysorbate and sorbitol. The paclitaxel coating is distributed evenly across the working length of the balloon. This would result in faster healing of the wounds, lesser need for re-intervention to maintain the blood supply and economical in long term.

Potential adverse events which may be associated with a peripheral balloon dilatation procedure include:

- Additional intervention
- Allergic reaction to drugs, excipients or contrast medium
- Amputation/loss of limb
- Aneurysm or pseudoaneurysm
- Arrythmias
- Embolization
- Hematoma
- Haemorrhage, including bleeding at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness
- Pneumothorax or hemothorax

- Sepsis/infection
- Shock
- Stroke
- Thrombosis
- Vessel dissection, perforation, rupture or spasm.

Potential adverse events which may be unique to the paclitaxel drug coating include:

- Allergic/immunologic reaction to the drug coating (paclitaxel)
- Alopecia
- Anemia
- Myalgia/Arthralgia
- Myelosuppression
- Peripheral neuropathy

Annexure IV

Bhagwan Mahaveer
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GreenOT

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 **COMPARATIVE STUDY OF OUTCOMES BETWEEN SINGLE VERSUS MULTIPLE INFRAPOPLITEAL VESSELS ANGIOPLASTIES IN PATIENTS WITH CRITICAL LIMB ISCHEMIA** Conducted by **Dr. CHAUDHARI HEMANT KADU** Department of **VASCULAR SCIENCES** under the guidance of **Dr. SUMANTHRAJ,** approximate period of study is from **JULY 2017 TO JUNE 2018.**

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

Date : 22/06/2017

22/6/17

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Chair Person
Scientific Committee
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Annexure V

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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 **COMPARATIVE STUDY OF OUTCOMES BETWEEN SINGLE VERSUS MULTIPLE INFRAPOPLITEAL VESSELS ANGIOPLASTIES IN PATIENTS WITH CRITICAL LIMB ISCHEMIA** Conducted by **Dr. CHAUDHARI HEMANT KADU** Department of **VASCULAR SCIENCES** under the guidance of **Dr. SUMANTHRAJ** approximate period of study is from **JULY 2017 TO JUNE 2018.**

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

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Annexure VI

INTRODUCTION

REVIEW OF LITERATURE

AIMS AND OBJECTIVE

MATERIAL AND METHODS

RESULTS

DISCUSSION

CONCLUSION

SUMMERY

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INTRODUCTION

Peripheral arterial disease (PAD) is growing health problem across globe. Peripheral arterial disease of the lower extremity is an important cause of morbidity in terms of limb loss and affects 10 million people in India as shown by Dutta et al.[1] The number of people living with limb loss in the country is expected to double by 2050 due to growing rates of diabetes and peripheral arterial disease.

Critical limb ischemia (CLI) is result of inadequate blood flow, to supply and sustain metabolic need of resting muscle and tissue in limbs and is devastating manifestation of ischemia. Clinical and economic impact with morbidity and mortality in CLI patients has been well described by Allie et al[2], mortality can be as high as 25% and 30% require major amputation within 1 year after diagnosis. Expeditious and appropriate evaluation and management of these PAD patients can lead to 50% reduction in amputation rate.

Among the revascularization method for CLI surgical bypass is regarded as a gold standard, with better anatomical and clinical durability. However, most of the patients with CLI are often aged, have highest likelihood of coronary artery disease with increasing perioperative mortality rates and poor autogenous conduit because of which they are not optimal candidates for surgical bypasses.[3] This group of patients are at increased risk of developing complications related to open surgical interventions, less invasive approach is more appealing in them.

Development of endovascular therapy has raised expectations for improvement of traditionally poor prognosis of CLI patients in infrapopliteal disease. In addition patient with significant medical co-morbidities and unsuitable vein conduit find percutaneous intervention to be less morbid and more realistic therapeutic alternative. In last few decades, development in devices with technical advances have widened therapeutic spectrum of angioplasty to more distal and complex infrapopliteal lesions with lower complication rates. Endovascular therapy for infrapopliteal diseases has gained acceptance as there is growing evidence demonstrating its safety and effectiveness.

Inspite of these vast advances in revascularization techniques for infrapopliteal diseases, some infrapopliteal angioplasty and vascular bypass surgery fails to heal ischemic lower extremity wounds even in the presence of patent target vessels and palpable pulses .[4,5] The failures may be due in part to inadequate postoperative wound care,[6] but part of the problem may also be due to the inadequate revascularization of the local ischemic area, because the vascular connections between the revascularized vessel and the source vessel nourishing the ischemic area are occluded. Thus, successful revascularization for ischemic wounds obviously is more complex than simply restoring circulation to a specific artery

In distal vein bypass planning, the choice of tibial target vessel requires the selection of the best single outflow vessel; however, the endovascular approach offers the possibility of concomitantly treating more than one tibial vessel and may provide comparable clinical outcomes.[7-9] Regarding the multiple vessel approach, some articles have suggested that recanalisation of more than one artery could improve wound healing,[10-12] clinical success,[13] and amputation free survival.[8] One possible explanation is that a multiple vessel approach could provide continuing healing of the wound; even if restenosis occurs in one vessel, the perfusion from the other vessel could compensate.[12] Therefore, a possible delay in restenosis time achieved by having more inflow vessels to the foot could result in a better wound healing course.[12] Another explanation is that the multiple vessel approach could provide greater perfusion to the foot and, therefore, improve healing speed. Perfusing the foot with two or three arteries could compensate for an incomplete pedal arch, improving wound healing and limb salvage.[13] Despite the potential benefit of concomitantly recanalising more than one arteries in CLI patients, risk of major amputation and mortality in failed endovascular interventions, risk of renal impairment with the use of a greater contrast volume,[14] extended procedure time, radiation exposure, and potential complications in recanalisation should also be considered.[15]Understanding whether this strategy proves beneficial is important. Studies have shown that at least one patent tibial artery to the foot is often needed to achieve a sufficient amount of blood flow necessary for limb salvage and wound healing, [16-19] but the potential benefit(s) of treating multiple infrapopliteal arteries remains uncertain.

Revascularization of the infrapopliteal and pedal arteries is widely accepted as part of the treatment for CLI [20,] and multiple studies have focused on various factors such as the plantar arch quality/ pedal runoff score, role of angiosome based revascularization to improve vascular patency and to improve limb salvage in CLI patients.[21, 22, 23] but very few studies have examined the impact of the number of infrapopliteal arteries treated on the limb salvage and wound healing. Therefore, the aims of this study were to evaluate if the number of infrapopliteal arteries treated with endovascular intervention is associated with increased limb salvage rate and wound healing.

REVIEW OF LITERATURE

Peripheral Arterial Disease and Critical Limb Ischemia:

Peripheral arterial disease (PAD) is defined as chronic, atherosclerotic steno-occlusive disease of the lower extremities (Rutherford). Risk of developing peripheral arterial disease is higher amongst diabetic patients as compared to non-diabetics, because of predominant involvement of infrapopliteal and pedal vessels with long and multilevel steno-occlusive disease in diabetics.[24-26]

Critical limb ischemia (CLI) is the most advanced stage of peripheral vascular disease.27 CLI patients are tip of the iceberg representing approximately 1% of the total number of patients with peripheral vascular disease.[28-30]. In critical limb ischemia patients there is an issue of supply versus demand, that is, there is chronic inadequate blood flow to supply vital oxygen demanded of the limb, setting off a cascade of pathophysiologic events that ultimately lead to rest pain, tissue loss and gangrene.[31] Thus, CLI is considered the “end stage” of peripheral arterial disease.

Lower extremity arterial disease is known to be located predominantly in the superficial femoral artery in patients with claudication and in the below-the-knee region in patients with critical limb ischemia (CLI).Patients with isolated infrapopliteal atherosclerotic disease may be asymptomatic due to the excellent collateral network which develops between infrapopliteal arteries. Often one patent tibial artery is sufficient to keep a patient free from ischaemic symptoms. [32] When these patients present with CLI they often have severe, extensive atherosclerotic disease involving all three-vessel and only 20–30% have a simple, focal lesion with good distal run-off. [33, 34] Multilevel lesion distribution is not infrequent and requires treatment of both the superficial femoral artery and more challengingly, below-the-knee vessels. These patients are usually elderly with multiple comorbidities, such as diabetes, hypertension, coronary artery disease and cerebrovascular accidents, which increases the overall surgical risk

REVIEW OF EVOLUTION HISTORY OF INFRAPOPLITEAL ANGIOPLASTY CONCEPT:

Peripheral vascular disease can be a severe and complex condition that is still a challenge for both surgical and endovascular therapies.[35] multilevel lesion distribution like simultaneous superficial femoral artery and infrapopliteal vessels involvement is not infrequent and requires treatment of both the superficial femoral artery and more challengingly, infrapopliteal vessels.

The traditional surgical treatment for critical limb ischemia patients was bypass or primary amputation. In those with significant medical co-morbidities, absence of suitable veins to act as conduits for bypass, or inadequate sites for distal anastomosis (no angiographically visible tibial vessels, vessels1 mm in diameter, or diffusely diseased vessels), percutaneous transluminal angioplasty (PTA) may be the only realistic therapeutic option.

Percutaneous transluminal angioplasty (PTA) of infrapopliteal arteries dates back to the time of Dotter and Judkins. In present era, endovascular treatment of infrapopliteal arteries has been considered as a most acceptable and commonly used revascularisation modality, but it has limitation of high restenosis as compared with open surgery.[35-37]

To achieve best possible results in infrapopliteal revascularisation with respect to wound healing and limb salvage, various strategies have been studied like

1) **Angiosome concept**- angiosome based revascularization

2) **Plantar Arch Quality (PAQ) and Pedal Run off (PR)score concept**
3) Most recently **role of single versus multiple infrapopliteal vessel angioplasties**.

The results of these studies are equivocal.

ANGIOSOME CONCEPT

Understanding vascular anatomy of foot and ankle is very important for limb salvage in critical limb ischemia patients. Angiosome concept was first described in 1987 by Ian Taylor's in his landmark anatomic paper. Angiosome is defined as anatomic three-dimensional tissue blocks consisting of skin, subcutaneous tissue, fascia, muscle and bone which are supplied and drained by specific vessels. Most tissue supplied by two or more angiosomes. As foot is end organ, there are numerous direct arterial-arterial connections amongst main supplying arteries which allow alternative routes of blood flow to develop if the main direct supplying artery is occluded. Knowledge of the boundaries of the angiosome and the vascular connections among neighbouring angiosomes, described by Taylor as "Choke vessels" help vascular surgeon in deciding target vessel for endovascular / open (bypass) revascularization so as to achieve better limb salvage and wound healing in ischemic ulcers

ANGIOSOMES OF THE FOOT AND ANKLE

At least total 40 angiosomes has been defined in the body by Taylor[38], of which 6 were described in the foot and ankle region. Steno-occlusive disease of source artery results in systemic manipulation in such a way that blood will flow through the neighbouring choke vessels and supply affected angiosome. These changes were described by Taylor as "delay phenomenon." [39, 40] While the choke vessels provide an indirect connection between the adjacent angiosomes, there are also direct arterial-arterial connections that allow blood flow to immediately bypass local vascular occlusion.

The six angiosomes of the foot and ankle are supplied by the three main infrapopliteal arteries viz Anterior Tibial Artery (ATA), Posterior Tibial Artery (PTA) and peroneal artery. The large angiosomes of the foot can be further broken into angiosomes of the major branches of the above arteries.

I. **Angiosome 1**- dorsal surface of the foot- Dorsalis Pedis Artery
II. **Angiosome 2-** Covers a small surface of the lateral malleolous- anterior malleolar branch of Peroneal artery
III. **Angiosome 3-** Covers the lateroposterior and plantar surface of the heel-calcaneal branch of peroneal artery.
IV. **Angiosome4-** the mediodorsal and plantar heel - calcaneal branch of Posterior Tibial Artery.
V. **Angiosome 5 -** medial instep via the medial plantar artery.
VI. **Angiosome 6-** the lateral instep and the plantar forefoot – lateral plantar artery.

- Angiosome 1: The main source artery is Anterior Tibial Artery
- Angiosomes 2-3: The main source artery is Peroneal artery
- Angiosomes 4–6: The main source artery is Posterior Tibial Artery

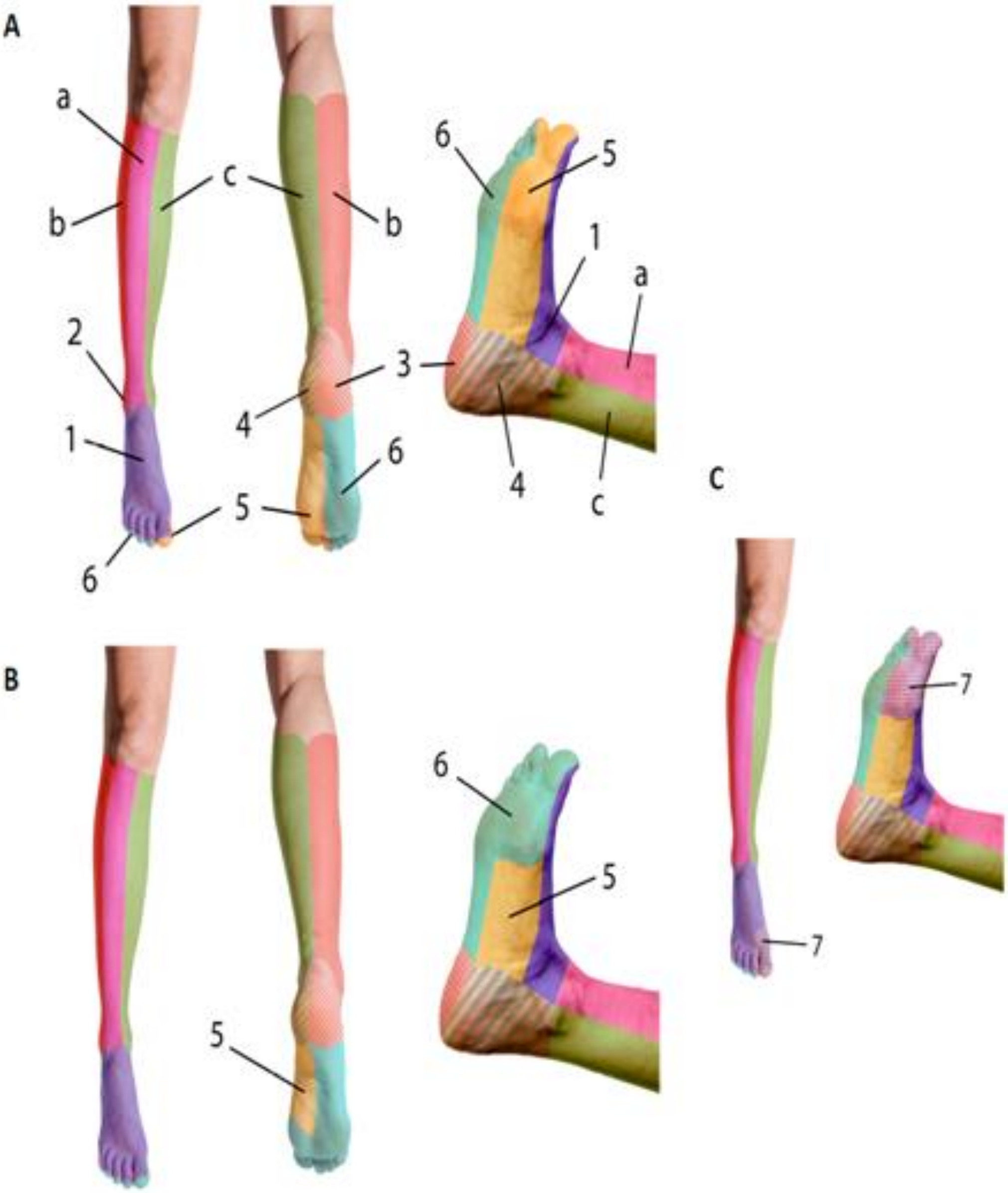

Figure 3. Angiosomal distribution (A) and its variations (B, C)

a, the angiosome of ATA; b, the angiosome of AP including the lateral malleolar angiosome (2); c, the angiosome of ATP. 1, dorsal angiosome, source = ADP; 2, lateral malleolar angiosome, source = AP; 3, dorsolateral and plantar angiosome, source = calcanear branch of the AP; 4, dorsomedial and plantar angiosome, source = calcanear branch of ATP ; 5, medial plantar instep and forefoot angiosome, source = medial plantar artery,; 6, lateral plantar foot and forefoot angiosome, source = lateral plantar artery and 7, angiosome of the hallux and medial side of the second toe, source = dorsal metatarsal artery (78%), plantar metatarsal artery (22%).

Figure 1: Foot angiosome distribution

The Anterior Tibial Artery and Dorsalis Pedis Angiosome

Anterior tibial artery's angiosome in the leg, supplies the area overlying the anterior compartment, with the fibula as the lateral boundary and the anterior tibia as the medial boundary. This artery originates from the popliteal artery and pierces the interosseous membrane to travel deep in the anterior compartment between the tibialis anterior muscle and extensor hallucis longus muscle.

At the ankle, the anterior tibial artery gives off the anterior lateral malleolar artery at the level of the lateral malleolous that joins with the anterior perforating branch of the peroneal artery. At the same level, it also gives off the anterior medial malleolar artery, which anastomoses with the posteromedial artery of the posterior tibial artery. The anterior tibial artery then emerges under the extensor retinaculum of the ankle to become the dorsalis pedis artery.

The dorsalis pedis artery's angiosome (Angiosome 1) encompasses the entire dorsum of the foot. Typically, the dorsalis pedis artery has three lateral arterial branches, the proximal and distal tarsal arteries and the arcuate artery, and two medial branches, the medial tarsal arteries. The proximal lateral tarsal artery communicates with the calcaneal branch of the peroneal artery. It may also connect superiorly to the lateral malleolar artery and inferiorly to the arcuate artery. The third lateral branch of the dorsalis pedis, the arcuate artery, travels laterally over the bases of the second, third, and fourth metatarsals. It gives off the second, third and fourth dorsal metatarsal arteries before it join the lateral tarsal artery. Medially, the dorsalis pedis artery (usually) gives off two medial tarsal arteries. Usually, one of these joins with the superficial branch of the medial plantar artery. After giving off the arcuate artery, the dorsalis pedis artery enters into the proximal first inter-metatarsal space and in the process gives off the first dorsal metatarsal artery. The dorsal metatarsal arteries, which supply the toes, both originate from the dorsal system (the arcuate artery) and receive additional blood supply from the deep plantar system (the proximal perforating arteries). At the metatarsal heads, the dorsal metatarsal arteries divide into two dorsal digital arteries and then travel to the plantar area via the distal perforating arteries (also called anterior perforating arteries). These perforating arteries join the plantar metatarsal artery to supply the plantar digits. In this way, the web space and the toes on either side of the web space receive dorsal and plantar blood supply from a dual system: the dorsalis pedis artery and the lateral plantar artery.

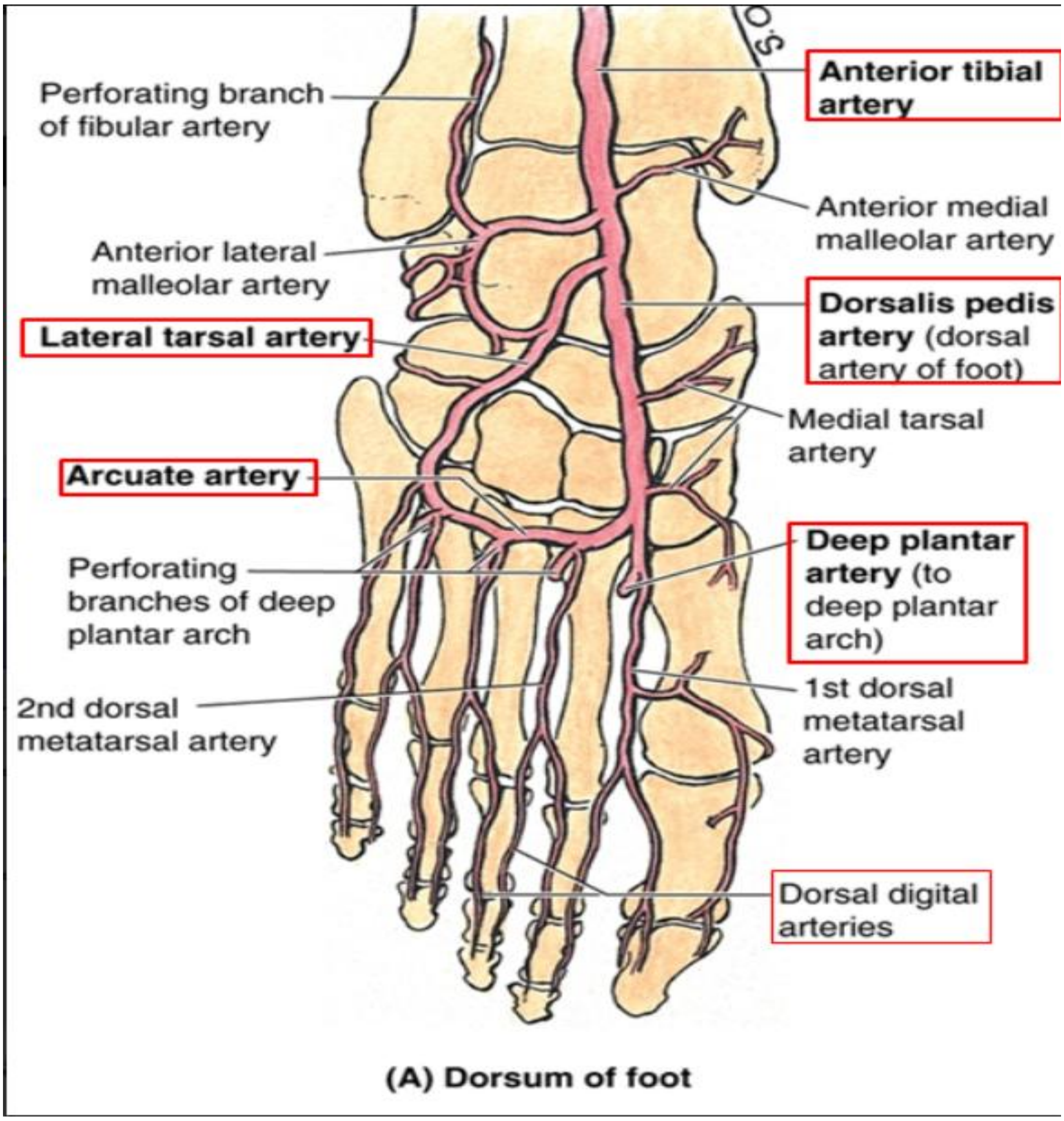

Figure 2: ATA angiosome

Angiosome from the Peroneal Artery Fed by Anterior Perforating Branches and the Calcaneal Branch

The peroneal artery arises from the tibial peroneal trunk and courses along the medial side of the fibula, supplying the poster lateral lower leg, ankle, and heel. The peroneal artery angiosome is bounded laterally by the central raphe overlying the Achilles tendon and medially by the anterior edge of the lateral compartment. The posterior lateral skin of the leg is supplied by peroneal artery angiosome. Before the peroneal artery emerges at the level of the lateral malleolous, it bifurcates into the anterior perforating branch and the lateral calcaneal branch.

The anterior perforating branch's angiosome (ANGIOSOME 2) extends over the anterolateral ankle. The anterior perforating artery then connects directly with the anterior lateral malleolar artery.

The lateral calcaneal branch's angiosome (ANGIOSOME 3) includes the plantar and lateral heel. More specifically, the proximal boundaries extend medially to the medial glabrous junction of the heel, distally to the proximal fifth metatarsal, and superiorly to the lateral malleolous.

The heel is privileged in that it has two overlapping source arteries: the medial and lateral calcaneal arteries. This ensures duplicate blood supply to heel.

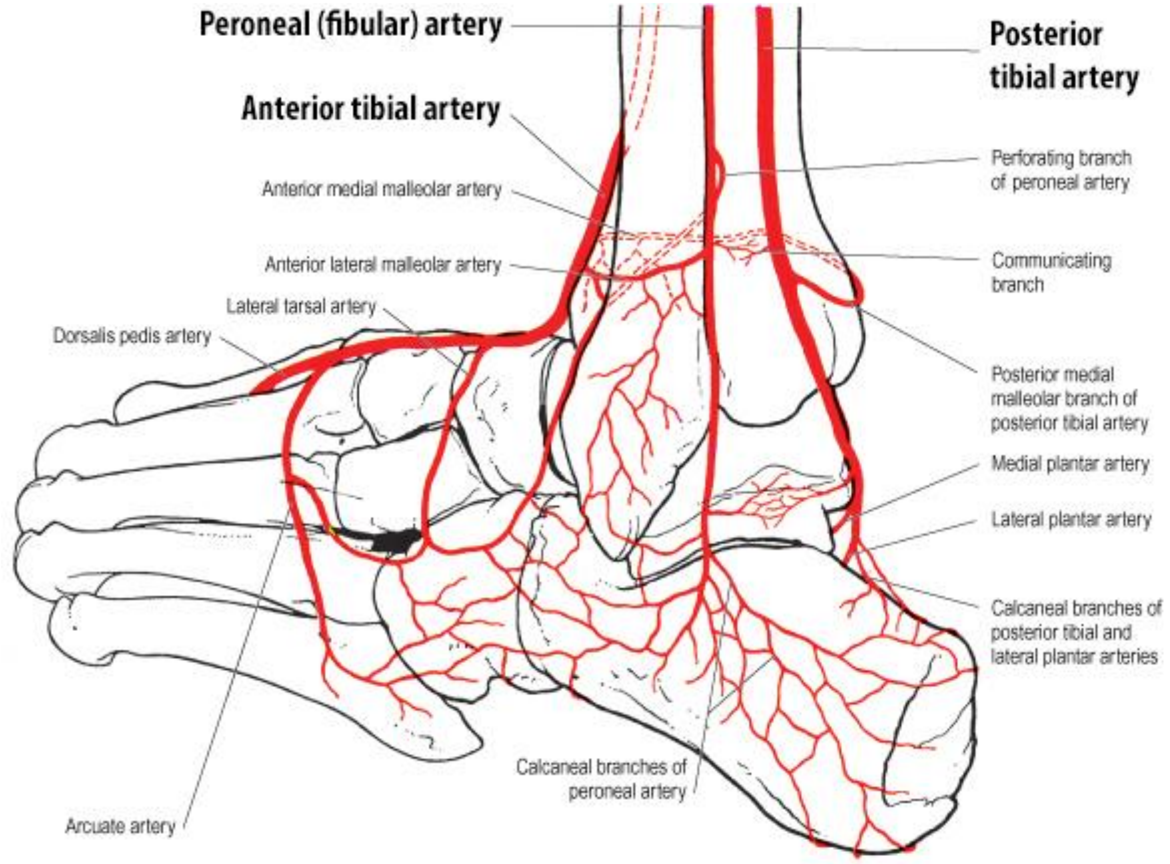

Figure 3: Peroneal and posterior tibial angiosome

The Posterior Tibial Artery Angiosomes 4-6- Fed by the Calcaneal, Medial Plantar, and Lateral Plantar Arteries

The posterior tibial artery in the leg, supplies the medial part of lower leg, starting from the anterior medial border of the tibia and extending posteriorly to the midline of the calf over the central raphe of the Achilles tendon. There are smaller perforator arteries along the course of the posterior tibial artery that perforate through the flexor digitorum longus and/or soleus to supply the overlying skin.[41, 6]

In the foot, posterior tibial artery gives off the **posterior medial malleolar branch (ANGIOSOME 4)** at the medial malleolous. The posterior medial malleolar branch joins the anterior medial malleolar branch from the dorsalis pedis artery, giving rise to an important interconnection between the posterior tibial artery and the anterior tibial artery. This system supplies the medial malleolar area. At the same level, posterior tibial artery gives off **the medial** calcaneal **artery** to supply the medial part of the heel. The medial calcaneal artery's angiosome boundary includes the medial and plantar heel, with its most distal boundary being the glabrous junction of the lateral posterior and plantar heel.[42] The posterior tibial artery then enters the calcaneal canal underneath the flexor retinaculum and bifurcates into the medial and lateral plantar arteries.

The medial plantar artery's angiosome (ANGIOSOME 5) boundaries encompass the instep (Fig. 5). Its boundaries are as follows: posteriorly, the distal-medial edge of the plantar heel; laterally, the midline of the plantar midfoot; distally, the proximal edge of the plantar forefoot; and medially, an arc 2 to 3 cm above the medial glabrous junction.

The lateral plantar artery's angiosome (ANGIOSOME 6) includes the lateral plantar surface as well as the plantar forefoot. The borders are as follows: posteriorly, the distal-lateral edge of the plantar heel; medially, the central raphe of the plantar midfoot; more distally, the glabrous juncture between the medial plantar forefoot and the medial distal dorsal forefoot; and laterally, the glabrous junction between the lateral dorsum of the foot and the plantar surface of the foot (Fig. 4, *below*). The distal border includes the entire plantar forefoot. Note that while the hallux is usually part of the lateral plantar angiosome, it can also be part of the medial plantar artery angiosome or the dorsalis pedis angiosome.

The lateral plantar artery travels toward the base of the fifth metatarsal, then turns medially, forming the deep plantar arch, and crosses the proximal (two, three, and four) metatarsals. It finally anastomoses directly with the dorsalis pedis artery in the proximal first interspace. This direct anastomosis between the dorsal and plantar circulation helps ensure that if either the dorsalis pedis or lateral plantar artery become occluded, flow is maintained to the entire foot. The four plantar metatarsal arteries originate from the deep plantar arch to nourish the plantar forefoot. They travel along each metatarsal shaft and bifurcate distally and are joined by the deep plantar arteries and the plantar intermetatarsal arteries to form an arcade of arterial triangles.[43] The common digital arteries arise at the apices of these triangles in the proximal web spaces. The common digital arteries bifurcate into two digital arteries for each toe and are joined by distal perforating branches that originate from the dorsal metatarsal arteries. The proper plantar digital arteries are the predominant blood supply to the lesser toes, except for the medial side of the second toe, which is supplied by the first metatarsal artery .[44]

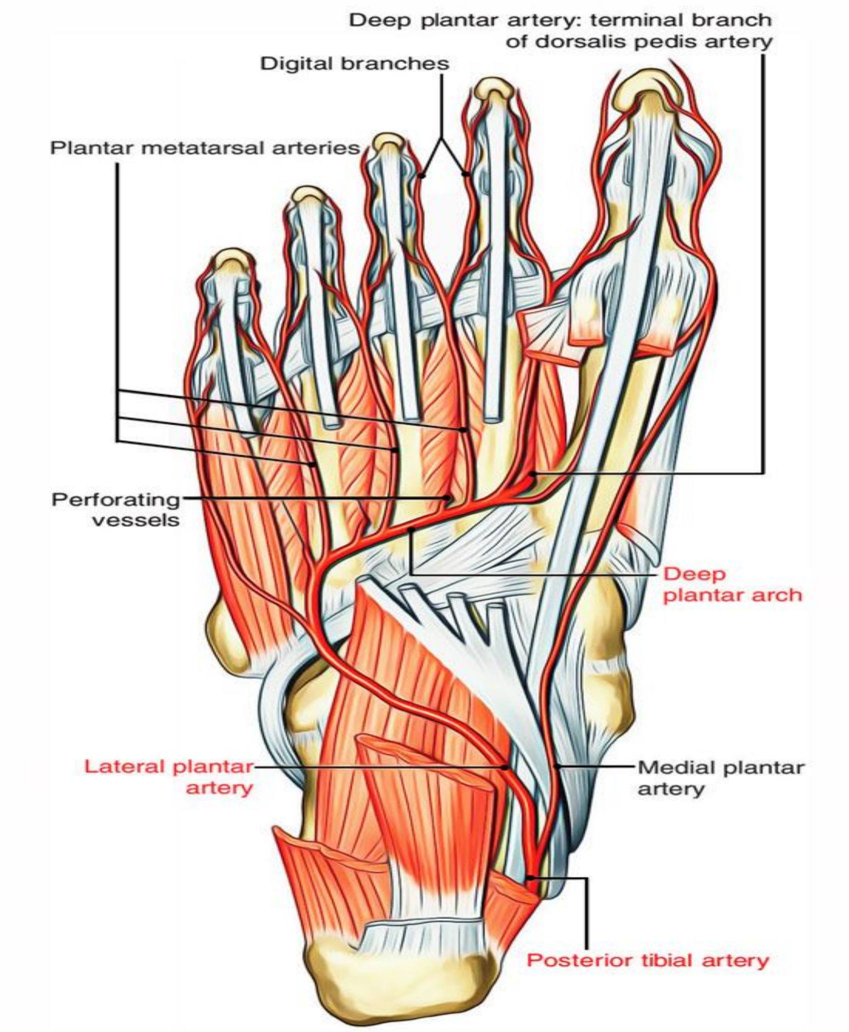

Figure 4: Posterior tibial artery (PTA) angiosome

ANGIOSOME STUDIES

Aadarsh Kabra et al (J Vasc Surg 2013)[44] studied outcomes of angiosome and non-angiosome targeted revascularization in critical lower limb ischemia. They prospectively studied 56 patients with continuous single crural vessel runoff to the foot presenting with critical limb ischemia from January 2007 to September 2008. Direct revascularization (DR) of the ischemic angiosome was performed in 61% (n =39), indirect revascularization (IR) in 39% (n = 25). Open surgery was performed in 60.9%and endovascular interventions in 39.1%. All patients were evaluated for the status of the wound and limb salvage at 1, 3, and 6 months. The study end points were major amputation or death, limb salvage, and wound epithelialisation at 6months.In the study, 81.2% of patients had forefoot ischemia, 17.2% had ischemic heel, whereas 1.6% had midfoot nonhealing ischemic ulceration. The single vessel runoff distributions were the anterior tibial artery in 42.2% (27/64), posterior tibial artery in34.4% (22/64), and the peroneal artery in 23.4% (15/64). All patients were followed at 1, 3, and 6 months postoperatively for ulcer healing, major amputation, or death. At the end of 6 months, nine patients expired, and six were lost to follow-up. Of 49 patients who completed 6 months, nine underwent major amputation, and 40 had limb salvage. Ulcer healing at 1, 3, and 6 months for DR vs IR were 7.9% vs 5%, 57.6% vs 12.5%, and 96.4% vs 83.3%, respectively. This difference in the **rates of ulcer healing between the DR and IR groups was statistically significant (*P* = .021).** The limb salvage in the DR group (84%) and IR group (75%) was not statistically significant (*P* = .06). The mortality was 10.2%for DR and 20% for IR at 6 months. They concluded that direct revascularization of the ischemic angiosome should be considered whenever possible, to achieve better ulcer healing rates combined with higher limb salvage. Revascularization should not be denied to patients with indirect perfusion of the ischemic angiosome as acceptable rates of limb salvage can be obtained.

Marcus R. Kret et al (J Vasc Surg 2014)[45] studied Utility of direct angiosome revascularization and runoff scores in predicting outcomes in patients undergoing revascularization for critical limb ischemia. They compared both runoff scores and direct (DR) vs indirect revascularization (IR) according to pedal angiosomes in CLI patients undergoing infrapopliteal bypass for foot wounds. Patients who underwent tibial/pedal bypass for a foot/ankle wound from 2005-2011 were identified and operations classified as DR or IR based on wound location and bypass target. A blinded observer reviewed angiograms for an intact pedal arch and calculated standard Society for Vascular Surgery (single tibial) and modified (composite tibial) runoff scores. Comorbidities, wound characteristics, wound healing, major amputation, and overall survival were determined. A total of 106 limbs were revascularized in 97 patients; 54 limbs had DR and 52 had IR, although only 36% of wounds corresponded to a single, distinct angiosome. Wound characteristics and comorbidities were similar between groups. Mean standard (7.9 vs 7.2; P = .001) and modified (22.2 vs 20.0; P = .02) runoff scores were worse (higher number indicates worse runoff) in the IR vs DR groups; 33% had a complete pedal arch. Complete wound healing (78% vs 46%; P = .001) and time to complete healing (99 vs 195 days; P = .002) were superior with DR vs IR but were not influenced by runoff score, modified runoff score or presence of complete plantar arch. In multivariate models controlling for runoff score, DR remained a significant predictor for wound healing (odds ratio, 2.9; 95% confidence interval, 1.1-7.4; P = .028) and reduced healing time (hazard ratio, 2.1; 95% confidence interval, 1.2-3.7; P = .012). Mean amputation free survival (75 vs 71 months for DR vs IR; P=.82) and median survival (36 vs 33 months DR vs IR; P=.22) were not different for DR vs IR .Conclusion of the study showed **DR provides more efficient wound healing, but** is possible in only one-half of the patients and **does not affect amputation-free or overall survival.**

Mohamed Farag et al[46], conducted retrospective study of Angiosome-targeted isolated tibial angioplasty for healing of ischemic foot ulcer in critical limb ischemia patients. Aim of the study was to evaluate and compare clinical outcomes, ulcer healing, and amputation-free survival between patients with successful angiosome-targeted tibial angioplasty alone [direct revascularization (DR)], patients with indirect revascularization (IR) in whom the vessels angioplastied successfully were the nonangiosome target, and those who underwent combined revascularization (CR) (both DR and IR were achieved). Total of 66 critical limb ischemia patients who presented with ischemic foot ulcer with isolated tibial vessel lesions at Mansura University Hospital during the period from January 2014 to January 2016 were included in study. DR of the ischemic angiosome was performed in 37.8% (n=25), IR in 33.3% (n=22), and CR in 28.7% (n=19) of patients. All patients were evaluated for the status of wound healing and limb salvage at 1, 3, 6, 9, and 12 months. The study endpoints were major amputation or death, limb salvage, and ulcer epithelialization at 12 months. The mean follow-up was 11.08±3.2, ranging from 3 to 13 months. On Kaplan–Meier analysis, 65% of patients were diabetic. Ulcer healing rate at 12-month follow-up based on angiosome hypothesis among groups CR, DR, and IR was 94.7, 66.7, and 57.17%, respectively, with a significant P value (0.013) between CR and DR and a significant P value (<0.001) between CR and IR. However, on comparing the DR and the IR group, mean time to complete ulcer healing was not statistically significant (P=0.222). Amputation-free survival rate was 94.7, 75.6, and 72.7% in CR, DR, and IR, respectively. They finally concluded that **if technically feasible, dilation of angiosome target artery plus any other significant nonangiosome based tibial artery lesions should be considered.**

Systematic reviews and meta-analysis

Over the last few years, several systematic reviews have been published and their conclusions are not equivocal.

The first systematic review, dating back to September 2013, evaluated 11 studies, involving 1,616 patients and 1,757 limbs[47]. The authors noticed an important heterogeneity of the published data, not only with regard to the technique used, but also the definition of direct revascularization, follow-up, and reporting of outcome. They emphasize the lack of prospective trials; large patient populations; and a consistent, uniform vocabulary to compare study findings. All of these factors prevent (according to the authors) a recommendation of the conceptual model for the guidance of revascularization attempts at a wider level.

The second published review (January 2014) included a total of nine studies (of note, fewer studies were included compared to the review mentioned previously[48]. A total of 715 legs were treated using a direct approach, while 575 legs were treated with indirect revascularization. The risks of unhealed wound and major amputation were significantly lower after direct revascularization compared with indirect revascularization. Pooled limb salvage rates after direct and indirect revascularization were 86.2% versus 77.8% at 1 year and 84.9% versus 70.1% at 2 years, respectively. The analysis of three studies reporting only on patients with diabetes confirmed the benefit of direct revascularization in terms of limb salvage. Amputation-free survival (evaluated only in two of the included studies) showed a trend in favour of direct revascularization. When feasible, direct revascularization of the foot angiosome affected by ischemic tissue lesions may improve wound healing and limb salvage rates compared with indirect revascularization. A limitation of all of the studies evaluated was their retrospective nature, with a lack of proper comparability of the studies. Not having data on the angiographic status of the foot arteries limits the analysis of the data further and most data involve diabetic patients, making it uncertain whether angiosome-targeted revascularization is also of benefit in non-diabetic patients.

The third review, Bosanquet D.C et al[49], conducted Systematic Review and Meta-analysis. The aim of this systematic review was to evaluate outcomes of direct revascularisation (DR) versus indirect revascularisation (IR) of infrapopliteal arteries to the affected angiosome for critical limb ischaemia. Both open and endovascular techniques were included. A systematic review of key electronic journal databases was undertaken from inception to 22 March 2014. Studies comparing DR versus IR in patients with localised tissue loss were included. Meta-analysis was performed for wound healing, limb salvage, mortality, and re-intervention rates, with numerous sensitivity analyses. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Total 15 cohort studies consisting of 1,868 individual limbs were included (endovascular revascularisation, 1,284 limbs; surgical revascularisation, 508 limbs; both methods, 76 limbs). GRADE quality of evidence was low or very low for all outcomes. DR resulted in improved wound healing rates compared with IR (odds ratio [OR] 0.40, 95% confidence interval [CI] 0.29-0.54) and improved limb salvage rates (OR 0.24, 95% CI 0.13-0.45), although this latter effect was lost on high-quality study sensitivity analysis. Wound healing and limb salvage was improved for both open and endovascular intervention. There was no effect on mortality (OR 0.77, 95% CI 0.50-1.19) or reintervention rates (OR: 0.44, 95% CI 0.10-1.88). **Conclusion of study was DR of the tibial vessels appears to result in improved wound healing and limb salvage rates compared with IR, with no effect on mortality or reintervention rates**. However, the quality of evidence on which these conclusions are based on is low. In addition, as mentioned, combining indirect and direct revascularization has been demonstrated to lead to better outcomes[50]. This meta-analysis suggests that in patients where both options of the direct and indirect approach are feasible, direct revascularization should be the preferred approach.

The fourth meta-analysis selected only 4 of 518 publications[51]. The largest number of papers was excluded because they were duplicate publications or papers from an institution describing an increasing number of patients in prospectively recruited cohorts in various papers. This review was also limited to diabetic patients treated by endovascular means. It was found that both the overall limb salvage rate and wound healing were significantly better after angiosome-targeted angioplasty.

Another recent systematic review and meta-analysis enrolled studies including open and endovascular revascularization, as well as diabetic and non-diabetic patients with CLI [52]. A total of 19 cohort studies (with 3,932 patients) were evaluated. Nine of these were considered as high quality. It was found that direct revascularization led to significantly better wound healing. Direct revascularization in bypass studies did not show a reduction of major amputations compared to indirect revascularization. A significant reduction of major amputations was seen in high-quality studies, and those studies evaluating endovascular treatment. Survival rates were similar. In 3 of 19 studies, stratification was made for collaterals. In the presence of collaterals, no differences in wound healing and major amputation rate were seen between angiosome-targeted and non-angiosome targeted revascularization

The most recent systematic review and meta-analysis by **Dilaver N, et al**[53] (European Journal of Vascular and Endovascular Surgery, 2018), they studied outcomes of Direct (revascularisation to the angiosome of tissue loss; DR) vs. Indirect Angiosomal Revascularisation (IR) in Infrapopliteal Arteries. They updated previously conducted systemic reviews according to PRISMA guidelines. Studies comparing DR with IR by both endovascular and surgical means for patients with localised tissue loss were included. Meta-analyses were performed to assess the effect of DR versus IR on wound healing (total and time to healing), limb salvage, mortality, and re-intervention rates. Outcome data quality was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. Total 22 studies, comprising 4146 limbs, were included. Wound healing rates (odds ratio [OR] 0.51; 95% CI 0.39-0.68, $p < 0.001$), time to wound healing (standard mean difference [SMD] -1.70; 95% CI-3.34 to -0.07, p =0 .04) and limb salvage (OR 0.37; 95% CI 0.24-0.58, $p < .0001$) were significantly better with DR compared with IR. Sensitivity analyses were concordant with the primary analysis for these outcomes, with the exception of the effect of wound healing rates between DR and IR, which was lost on sensitivity analysis for bypass surgery. Mode of revascularisation had no effect on mortality or on re-intervention rates. GRADE outcomes were very low. So they concluded DR of the tibial vessels appears to result in improved wound healing and limb salvage rates compared with IR, with no effect on mortality or re-intervention rates. For surgical revascularisation the importance of DR appears to be lost for wound healing.

PEDAL RUNOFF/ PLANTAR ARCH

Various studies have conducted to find whether improved circulation in pedal arteries is more important factor than angiosome based revascularisation, for healing of ischemic ulcer in critical limb ischemia. Results of these studies showed positive impact of good pedal runoff / complete plantar arch over wound healing rate and time in critical limb ischemia patients.

Studies

Hisham Rashid et al[54], studied impact of arterial pedal arch quality and angiosome revascularization on foot tissue loss healing and infrapopliteal bypass outcome in patients with critical limb ischemia (CLI). Between 2004 and 2011, patients undergoing distal bypass for CLI (Rutherford 4-6) were divided in groups taking into consideration the state of the pedal arch and direct angiosome revascularization (DAR) and non-DAR. Angiography was used to divide the pedal arch into three groups: complete pedal arch (CPA), incomplete pedal arch (IPA), and no pedal arch (NPA). The primary end points were patency rates at 12 months, amputation-free survival at 48 months, and the rate of healing and time to healing of foot tissue loss. Total of 154 patients (75% men) with CLI underwent 167 infrapopliteal bypasses. Patients were a median age of 75 years (range, 46-96 years). Diabetic mellitus was present in 76%, chronic renal failure in 28%, and ischemic heart disease in 44%. The primary patency rates at 1 year in the CPA, IPA, and NPA groups were 58.4%, 54.6%, and 63.8%, respectively (P = .5168), the secondary patency rates were 86.0%, 84.7%, and 88.8%, respectively (P = .8940), and the amputation-free survival at 48 months was 67.2%, 69.7%, and 45.9%, respectively (P = .3883). Tissue loss was present in 141 of the 167 bypasses. In the CPA group, 83% of tissue loss with DAR healed compared with 92% in the non-DAR (median time to healing, 66 vs 74 days). Similarly in the IPA group, 90%

with DAR healed compared with 81% in the non-DAR (median time to healing, 96 vs 86 days). In the NPA group, only 75% with DAR healed compared with 73% in the non-DAR (median time to healing, 90 vs 135 days). There was a significant difference in healing and time to healing between the CPA/IPA and NPA groups (P = .0264). So they concluded the quality of the pedal arch did not influence the patency or the amputation-free survival rates. However, the rates for healing and time to healing were directly influenced by the quality of the pedal arch rather than the angiosome revascularized.

Hallie E. et al[55], conducted study to examine the impact of pedal runoff on patient-centered outcomes after tibial endovascular intervention in critical limb ischemia patients. Patients who underwent lower extremity endovascular interventions for critical ischemia (Rutherford 5 and 6) at a single urban academic medical center between 2006 and 2016 were retrospectively identified. Pre-intervention angiograms of these patients were reviewed to assess pedal runoff. Each dorsalis pedis, lateral plantar, and medial plantar artery was assigned a score according to the reporting standards of the Society for Vascular Surgery (0, no stenosis >20%; 1, 21%-49% stenosis; 2, 50%-99% stenosis; 2.5, half or less of the vessel length occluded; 3,more than half the vessel length occluded). A foot score (dorsalis pedis + medial plantar + lateral plantar + 1) was calculated for each foot (1-10). Two runoff score groups were identified: good vs poor, <7 and ≥7, respectively. Patient oriented outcomes of clinical efficacy (absence of recurrent symptoms, maintenance of ambulation, and absence of major amputation), amputation-free survival (survival without major amputation), and freedom from major adverse limb events (above-ankle amputation of the index limb or major reintervention [new bypass graft, jump/interposition graft revision]) were evaluated. There were 1134 patients (56% male; average age, 59 years) who underwent tibial intervention for critical ischemia, with a mean of two vessels treated per patient and a mean pedal runoff score of 6 (47% had a runoff score ≥7). Overall major adverse cardiac events were equivalent at 30 days after the procedure in both groups. At 5 years, vessels with compromised runoff (score ≥7) had significantly lower ulcer healing (25% ± 3% vs 73% ± 4%, mean ± standard error of the mean [SEM]) and a lower 5-year limb salvage rate (45% ± 6% vs 69% ± 4%, mean ±SEM) compared with those with good runoff (score <7). Patients with poor pedal runoff (score ≥7) had significantly lower clinical efficacy (23% ± 8% vs 38% ± 4%, mean ± SEM), amputation-free survival (32% ± 6% vs 48% ± 5%, mean ± SEM), and freedom from major adverse limb events (23% ± 6 9% vs 41% ± 8%, mean ± SEM) at 5 years compared with patients with good runoff (score <7). So they concluded pedal runoff score can identify those patients who will not achieve ulcer healing and patient-centered outcomes after tibial intervention. Defining such subgroups will allow stratification of the patients and appropriate application of interventions.

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SINGLE Vs MULTIPLE VESSEL INFRAPOPLITEAL ANGIOPLASTIES

The endovascular approach offers the possibility of concomitantly treating more than one tibial vessel and may provide comparable clinical outcomes.[7-9]

Regarding the multiple vessel approach, some articles have suggested that recanalisation of more than one artery could improve wound healing,[13-15] clinical success,[4] and amputation free survival.[11] One possible explanation is that a multiple vessel approach could provide continuing healing of the wound; even if restenosis occurs in one vessel, the perfusion from the other vessel could compensate.[15] Therefore, a possible delay in restenosis time achieved by having more inflow vessels to the foot could result in a better wound healing course.[15] Another explanation is that the multiple vessel approach could provide greater perfusion to the foot and, therefore, improve healing speed. Perfusing the foot with two or three arteries could compensate for an incomplete pedal arch, improving wound healing and limb salvage.[13] Despite the potential benefit of concomitantly recanalising more than one arteries in CLI patients, risk of major amputation and mortality in failed endovascular interventions, risk of renal impairment with the use of a greater contrast volume,[17] extended procedure time, radiation exposure, and potential complications in recanalisation should also be considered.[18]

Understanding whether this strategy proves beneficial is important. Studies have shown that at least one patent tibial artery to the foot is often needed to achieve a sufficient amount of blood flow necessary for limb salvage and wound healing, [19-22] but the potential benefit(s) of treating multiple infrapopliteal arteries remains uncertain.

Revascularization of the infrapopliteal and pedal arteries is widely accepted as part of the treatment for CLI 23, but very few studies have examined the impact of the number of infrapopliteal arteries treated on the limb salvage and wound healing. Therefore, the aims of this study were to evaluate if the number of infrapopliteal arteries treated with endovascular intervention is associated with increased limb salvage rate and wound healing.

Kobayashi et al [12] in there retrospective study of Clinical effects of single or double tibial artery revascularization in critical limb ischemia patients with tissue loss; studied 123 CLI patients (137 limbs) with lesions in both the anterior tibial artery and the posterior tibial artery. Amongst these, patients with single tibial artery (anterior or posterior tibial artery) revascularization was included in Single tibial group (group S, n= 84 limbs) and double tibial artery (both anterior and posterior tibial arteries) revascularization included in Double tibial group (group D, n= 53).They showed better wound healing rate (87% vs 79%; P=0.003), shorter wound healing time (median, 83 vs 142 days; P= 0 .01), and the repeat peripheral vascular intervention rate was lower (15% vs 35%; P=0 .03) in group D than in group S. The wound healing rate was similar between both groups in patients with a low clinical WIfI stage (90% in group D vs 93% in group S (P =0 .20); however, the wound healing rate was significantly higher in group D in patients with a high clinical WIfI stage (85% vs 72%; P =0 .007).

Biagioni et al[55], conducted single center prospective, unblinded randomized control trial to analyse the effect of the treatment of more than one infrapopliteal artery with respect to wound healing and limb salvage. Total 78 patients (80 limbs) were enrolled prospectively in the study and were randomly divided into two groups: single vessel (SV) group (n = 40) and multiple vessel (MV) groups (n = 40). Patients with more than 70% stenosis or total occlusion of all three infrapopliteal arteries, tissue loss (Rutherford 5), one or more patent distal vessels of the pedal arch, and adequate proximal inflow (less than 30% stenosis of the femoral or popliteal artery) were included in study. Exclusion criteria included TASC (Trans-Atlantic Intersociety Consensus) II D femoral or popliteal atherosclerotic disease, previous angioplasty of the distal arteries. Choice amongst which artery to target first was based on an analysis of two factors: the technical ease of the required endovascular intervention (shorter stenosis/occlusion, less calcified, proximal segment lesions) and the presence of adequate distal outflow (better artery in the pedal arch). When two arteries had the same quality, the artery that fed the wound area (angiosome) was treated. The tibio-peroneal trunk (TPT) is considered an extension of the peroneal or posterior tibial artery. The patients were randomised after the first successful distal artery angioplasty. Primary endpoints studied were the wound healing rate and limb salvage rate while secondary endpoints were primary patency, secondary patency, and amputation free survival. Demographic characteristics and technical aspects were statistically comparable in both groups. The mean age of the patients was 69.1 $\pm$ 4.3 years, and 56% were male. Concomitant inflow correction of the femoral and popliteal arteries was performed in 38.8% of patients. Infrapopliteal arterial stents were used in 15.7% of cases, and the kissing balloon technique was used in 20.5% of cases (all in the MV group). In 60% of the MV group, two arteries were treated, and in 40 % three arteries were treated. The limb salvage rates after 1 and 3 years, respectively, were 75.9% and 67% for the SV group and 91.1% and 91.1% for the MV group (p= 0 .052). The wound healing rates after 1 and 3 years, respectively, were 33.6% and 70.9% for the SV and 63.9% and 78.4% for MV group (p = 0 .006). The mean wound healing time for the SV group was 428 $\pm$ 250 days, and for MV group 183 $\pm$ 103 days (p = 0.0001). Overall survival rate at 1 and 3 years, respectively, were 84.2% and 72.6% for the SV group, and 95.0% and 83.6% for the MV group , respectively (p=0 .191). There is no statistically significant difference in primary patency, secondary patency and amputation free survival rate in both groups. So they concluded endovascular treatment of more than one artery was associated with better wound healing rates but there is no added advantage with respect to limb salvage.

Darling et al[15] conducted a single center retrospective study to understand the effects of concomitant endovascular interventions on multiple infrapopliteal vessels. Patients undergoing an infrapopliteal angioplasty /stent for CLI between January 2004 and May 2014 were included in the study. During this period total 528 patients (673 limbs) underwent an infrapopliteal endovascular intervention for tissue loss (77%), rest pain (13%), stenosis of a previously treated vessel (5%), acute limb ischemia (3%), or claudication (2%). In final analysis 448 patients (558 limbs) with successful infrapopliteal angioplasty for critical limb ischemia (86% tissue loss and 14% rest pain) were analysed. Number of infrapopliteal vessel angioplastied is as per operator's choice. Single-vessel interventions was considered technically successful when residual stenosis in treated vessel was <30%, whereas in multiple vessel it was defined as residual stenosis < 30% in at least two intervened vessels. Tibial peroneal trunk (TPT) was considered as an extension of the peroneal or posterior tibial artery (PTA) vessels (as opposed to an additional vessel); an intervention was considered multiple-vessel when an anterior tibial artery (ATA) or dorsalis pedis artery (DPA) was angioplastied in an addition to the TPT, peroneal, or PTA (or any combination of the three). Out of 558 limbs, 503(90%) limbs underwent single vessel interventions while 55(10%) underwent multiple vessel intervention. There is no significant difference amongst two groups in baseline characteristics, WIfI stage. Majority of patients were in WIfI stage 4 (41 Vs 47%).Postoperative outcomes analysis showed no significant difference in two groups with respect to one year mortality rate (4.6 Vs 7.3%, P=0.38), 6 month wound healing rate (37 Vs 41%, P = 0.13), major amputation rate (16 Vs 10%, P = 0.24). survival rate at 1 and 3 years did not differ between two groups (76% vs 75% [P = 0 .78] and (52% vs 47% [P =0 .42], respectively. So they concluded that a multiple-vessel intervention does not improve outcomes when compared to a single-vessel intervention.

AIMS AND OBJECTIVES

Aims

To study correlation between number of infrapopliteal arteries treated with endovascular intervention and limb salvage rate, wound healing in critical limb ischemia patients.

Objectives

- **Primary: -** To evaluate if the number of infrapopliteal arteries treated with endovascular intervention is associated with increased limb salvage rate and wound healing.

- **Secondary:**

1. To compare plantar arch quality
2. To compare changes in ABI and PVR
3. To compare peri-operative outcomes in terms of MACE

In patients with single versus multiple infrapopliteal arteries treated with endovascular intervention in critical limb ischemia.

MATERIAL AND METHODS:

Study Design: - Single centre, prospective, non randomised, double arm, comparative, open ended study

Study Duration: - Recruitment Period: 1st May 2017 to 31stOct 2018 (18 month)

Follow up: 6 month (at1st, 3rd and 6th month)

Study Site: - Jain Institute of Vascular Sciences (JIVAS), a Unit of Bhagwan Mahaveer Jain Hospital, Bengaluru

Study Population:-

During study period, 256 patients were admitted in JIVAS with critical limb ischemia who underwent infrainguinal revascularisation. Among these, 73patients required revascularisation of isolated femoropopliteal segment (endovascular/open) and open infrainguinal surgery (Fem-distal bypass), so they were excluded from study. The remaining 183 patients underwent infrapopliteal angioplasty $\pm$inflow correction in the form of femoro-popliteal open surgical revascularisation or endovascular intervention. Amongst these, 19 patients were lost to follow up and in 13 patients procedure was technically unsuccessful and 8 patient had history of previous vascular intervention in the same lower limb, so were excluded from the study. Thus finally 143 patient were analysed, 91 in single vessel infrapopliteal angioplasty group (SV) and 52 in multiple vessel infrapopliteal angioplasty group (MV). Out of 143 patients, 23 patients had mortality in 6 month follow up (14 in SV group and 9 in MV group), so for all limb outcome analysis (wound healing, limb salvage rate) these mortality patients were excluded and all limb outcomes were calculated for remaining 120 patients.

Sample size calculation:-

Minimum 82 undergoing successful revascularization

By using following formula we have calculated sample size

N = 4*P*Q / L^2

Where P = Proportion of outcome i.e Overall wound healing rate 83% as per the previous hospital data

Q = 100 - P = 100 - 83 = 17

L = Experimental error

Experimental error taking 10 % of P i.e. 8.3%

Overall Sample size becomes 82

The Above total sample size divided in 2 two groups, multiple vessel and Single vessel infrapopliteal angioplasty group.

Inclusion Criteria:

- 18 years and above
- Critical limb ischemia (Rutherford class 5 and 6)
- Single or sequential denovo steno-occlusive lesions
- In-flow vessel (Superficial Femoral Artery and Popliteal Artery) free from flow-limiting lesion or in-flow lesion correction with bypass or endovascular intervention during index procedure.

Exclusion Criteria:

- Restenotic lesions
- Acute thrombus in target vessel
- Previous vascular intervention either bypass or endovascular ,in target limb
- Technically unsuccessful infrapopliteal angioplasty
- Patients with aorto-illiac steno-occlusive disease.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men who are intending to become father
- Known case of Vasculitis
- Patient allergic to contrast
- Not willing for participation in 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 use if any. They were assessed for medical risk factors like diabetes mellitus (DM), hypertension (HTN), Ischemic Heart Disease (IHD), chronic Renal Failure (CRF), cerebro-vascular accidents (CVA) and Dyslipedemia. If any history of documented allergy following the use of iodinated contrasts media then the patient was excluded from the study. In all patients' general and local examination were carried out with careful documentation of ulcer/ gangrene location as toe, plantar, foot dorsum, and heel or ankle ulcer. If ulcer/ gangrene is involving multiple areas of foot like toes and dorsum, it was counted separately both in toes and dorsum. All patients were stratified as per level of chronic ischemia by Rutherford- Becker classification and risk stratification was done in all patients as per Wound, Ischemia and foot Infection (WIfI Stage).In all patients documentation was done for vascular status of both lower limbs, along with non invasive vascular lab measurements including ankle brachial index (ABI), toe brachial index (TBI), pulse volume recording (PVR) 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. 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.

. Patients with non invasive vascular lab, imaging and clinical examination indicating arterial disease in the aorta, iliac, were excluded from the study. All patients were explained preoperatively regarding the pros and cons of the intervention and if willing, they were considered for the study. Patients with infrapopliteal disease $\pm$ femoral and popliteal lesion, with successful one or more than one infrapopliteal angioplasty with successful inflow lesion correction (if any) were enrolled in the study.

2. **Laboratory analysis:-**

Along with routine blood investigations including hematocrit, coagulation profile, renal function tests, serum electrolytes, urine analysis, chest X ray, 2 D Echocardiogram, ECG, glycosylated hemoglobin (HbA1c) and fasting lipid profile was recorded for all patients after enrolment in study.

3. **Medical management**:-

Patients were started on IV hydration with 0.9% NaCl at 1 ml/kg/hr (0.5ml/kg/hr if ejection fraction was <40%) for 12 hours pre- procedure and for a minimum of 12 hours post-procedure based on the urine output. Infusion of 150mEq/L sodium bicarbonate as a bolus of 3 mL/kg/hour for 1 hour before the administration of contrast, followed by 1 mL/kg/hour for 6 hours during and after the procedure.. N-acetyl cysteine of 1200mg twice daily was started one day prior to procedure and continued for two days post procedure. All DM patients who were on oral hypoglycemic agents were switched over to regular insulin and strict glycemic control was ensured peri-operatively. All patients were started on aspirin 150mg once daily preoperatively and if the patient was already on double antiplatelets (aspirin + clopidogrel or aspirin + ticagrelol), they were continued. Post operatively all patients were put on dual antiplatelets (aspirin 150mg and clopidogrel 75mg or preoperative combination continued) once daily for a period of 1 months (3monthsin patients with inflow correction in the form of femoro-popliteal stenting). All patients received Statins (atorvastatin 20mg once daily or higher if dyslipidemic) or additional fibrates (based on fasting lipid profile) for 6 months. Non-steroidal anti-inflammatory drugs (NSAIDs) use was restricted for 2 days prior to the procedure. 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. **Endovascular intervention:-**

Non-ionic contrast media Iohexol 300mg per ml (Omnipaque®) or CO2 angiogram for indicated patients was used for imaging. Most of the procedures were carried out under local anaesthesia with monitored anaesthesia care (MAC) unless patient opted for general anaesthesia. Ultrasound guided femoropopliteal nerve blocks were used as the anaesthetic modality for CO2 angiograms. Angioset CO2 gas delivery system was used for CO2 angiograms. All cases were done by 3 different consultant vascular surgeons with more than 10 years experience in open vascular and endovascular revascularisation. In patients undergoing a total endovascular procedure for infrainguinal revascularisation approach to the target site was by an ipsilateral antegrade CFA puncture or a contralateral retrograde CFA puncture. In patients requiring hybrid procedures, access site for endovascular intervention was decided based on the open surgical procedure done. Systemic heparinisation was done at 80U/kg body weight and then 1000units IV for every passing hour. Once inflow to the infrapopliteal segment was corrected (if any inflow lesion), standard wire and catheter techniques were used to cross the infrapopliteal lesions and the diseased segments were treated with plain balloon angioplasty, inflated to nominal pressure for a period of two minutes. Check angiogram was done to record the result of a plain balloon angioplasty and to rule out reocclusion, residual stenosis, spasm, dissection, recoil and thrombus.

Intraoperative decision making and data recording- Number of infrapopliteal vessels treated was at the discretion of the treating surgeon. The choice of the first artery to treat was based on an analysis of three factors: the easiest artery technically to cross (shorter stenosis/occlusion, less calcified, proximal segment, stenosis preferable to occlusion), the presence of adequate distal outflow (better distal runoff forming plantar arch) and angiosome based vessel. When two arteries had the same quality, the artery that fed the wound area (angiosome) was treated first. Multiple vessel interventions were defined as interventions on infrapopliteal vessels in parallel rather than in series. Considering the tibial peroneal trunk (TPT) as an extension of the peroneal and posterior tibial artery (PTA) (as opposed to an additional vessel), an intervention was considered multiple-vessel when an anterior tibial artery (ATA) or dorsalis pedis artery (DPA) or ATA and DPA was intervened on in addition to the TPT, peroneal, or PTA (or any combination of the three). For example, an angioplasty of the TPT and PTA vessels within one procedure would be categorized as a single-vessel intervention (because the TPT and PTA are in-line), while an angioplasty of the TPT and the ATA would be categorized as multiple-vessel. Balloon diameter was selected based on the angiographic measurements of the healthy distal artery segment diameter (from 2 mm to 3.5 mm). In each group, we classified the status of the plantar arch on the basis of completion digital substraction angiogram, to determine whether the artery that underwent endovascular treatment had adequate outflow and to evaluate the effect of number of infrapopliteal vessels angioplastied on type of the plantar arch.

Check angiogram was done post angioplasty in all cases to record the final result and type of plantar arch. Activated clotting time (ACT) was used to keep track of the patient anticoagulation status for quick and efficient monitoring and was maintained at 250-300 seconds throughout the procedure. After the procedure, the sheath was removed when the ACT was dropped to less than 180 seconds. Manual compression was applied after sheath removal, for 10 minutes or till there was no bleeding with continuous hemodynamic monitoring in the recovery room.

Post procedure pulse/doppler signals status was noted and the PVR, ABI/TBI and TcPO2 noted within 48 hours post procedure.

Perioperative- Any other significant perioperative events in form of morbidity (ACS etc) and mortality were also recorded, complications were identified by review of operative reports, discharge summaries, and physician progress notes

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, antiseptic spray or vacuum assisted device were used. In follow up period, unplanned toe amputations and debridement done as necessary for wound healing. All patients were counselled about life style modification, daily foot care and appropriate foot wear.

6. **Follow up:-**

All enrolled patients had thorough clinical examination and PVR, ABI/TBI, TcPO2 (supine and foot down) surveillance done at 1, 3, and 6 months post procedure. Duplex ultrasound examination was performed if there was a worsening in their symptoms with an increase in one category in the Rutherford scale, decrease in ABI >0.15/TBI>0.1/TcPO2>10 from the maximum post procedural level or clinical worsening of tissue loss. Duplex ultrasound examination was performed in an accredited vascular laboratory by experienced sonologist.

Revascularisation was then planned if needed. Unplanned toe amputations and debridement were done as necessary for wound healing.

7. Statistical analysis:-

Statistical analysis was performed using SPSS, version 17.0 (SPSS, Chicago, IL). Descriptive statistics were evaluated in terms of frequencies, percentages or mean ± standard deviations. Categorical variables were evaluated by Fischer's exact test and continuous variables were assessed by the t-test. Data before and after procedures, comparison of repeated measures for continuous variables were analyzed using unpaired t-tests. P value of <0.05 was considered significant. Kaplan Meier analysis was used to estimate cumulative wound healing and limb salvage.

8. Ethical and Scientific committee:-

Present study is approved by ethic and scientific committee of Bhagwan Mahaveer Jain Hospital, Bengaluru

RESULTS

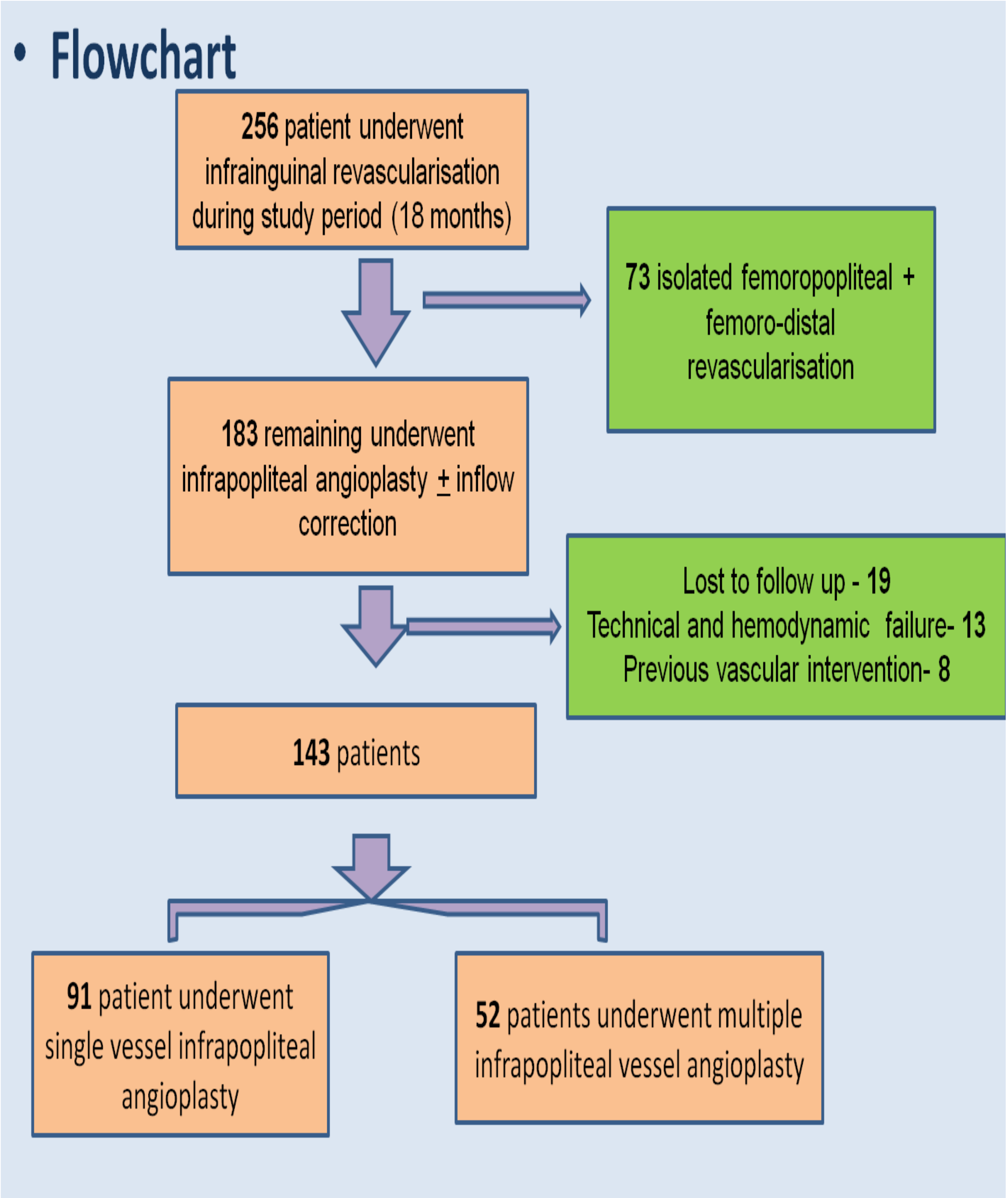

Figure 5:- Patient selection flowchart

Months	Death – Total (Cardiac)	Total No of patients remaining for limb outcome analysis
0---1	4 (2)	139
1---3	7 (4)	132
3---6	12 (5)	120
Total at 6 month	23	120

Table 1: Total and cardiac related mortality at end of 1, 3 and 6 month with total number of patients available at end of 6 month for limb related outcome analysis

During the study period of 18 month (May 1, 2017 to Oct 31, 2018), 256 patients underwent infrainguinal revascularisation in JIVAS, for critical limb ischemia. Amongst these, 73 patients who underwent isolated femoro-popliteal revascularisation and other open infrainguinal revascularisation were excluded from study. The remaining 183 patients underwent infrapopliteal angioplasty with or without inflow femoro-popliteal open/ endovascular/ hybrid correction. Amongst these, 19 patients were lost to follow up and in 13 patients procedure was technically unsuccessful and 8 patient had history of previous vascular intervention in the same lower limb, so were excluded from the study. Thus finally 143 patient were analysed, 91 in single vessel infrapopliteal angioplasty group (SV) and 52 in multiple vessel infrapopliteal angioplasty group (MV). Out of 143 patients, 23 patients had mortality in 6 month follow up (14 in SV group and 9 in MV group), so for limb outcome analysis (wound healing, limb salvage rate) these mortality patients were excluded and all limb outcomes were calculated for remaining 120 patients.

Technical success rate was 92.90% (170/183). Lost to follow up rate was 10.38% (19/183).

Age Distribution

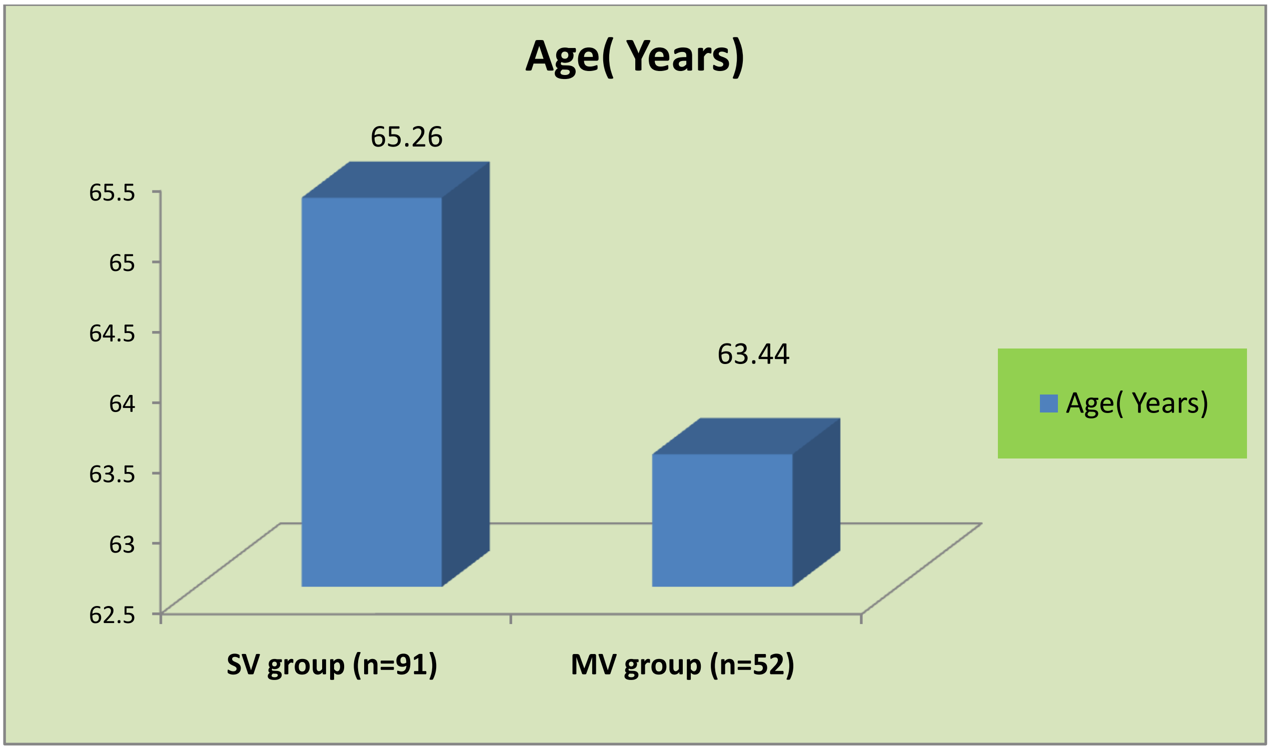

Figure 6: Age distribution

Mean age in Single Vessel (SV) group was 65.26 $\pm$ 11.32 years and Multiple Vessel (MV) group was 63.44 $\pm$ 8.79 years. (P = 0.28).

Gender Distribution

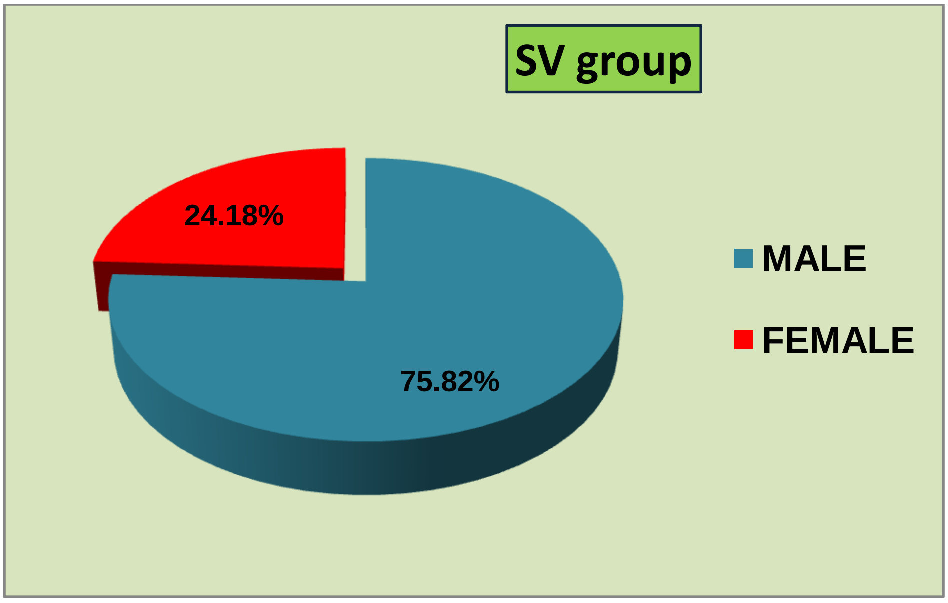

Figure 7: Gender distribution in SV group

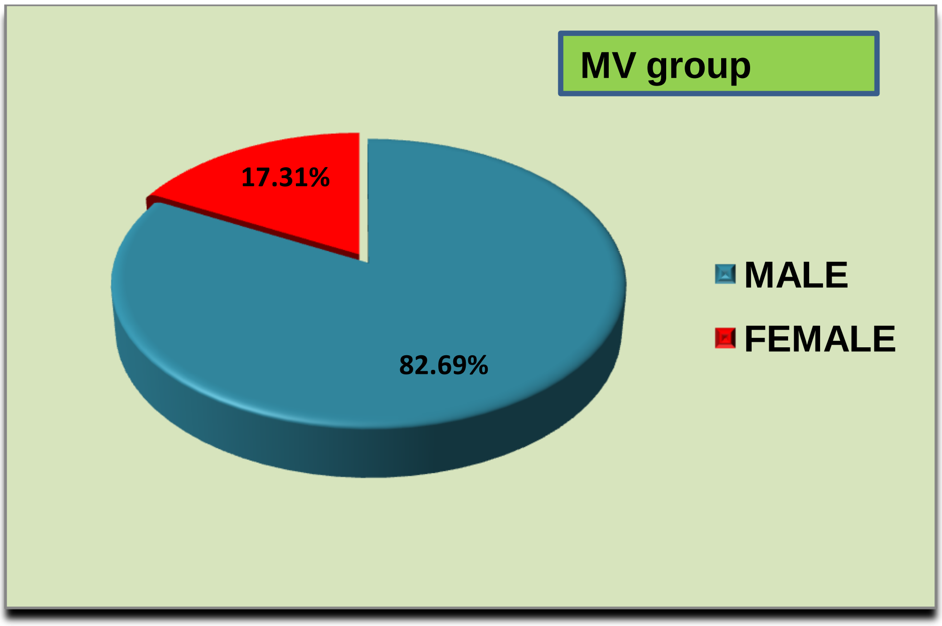

Figure 8: Gender distribution in MV group

In both groups male gender was predominant, 75.82% (69/91) in Single Vessel (SV) group and 82.69% (43/52) in Multiple Vessel (MV) group. (P=0.34)

Comorbidities

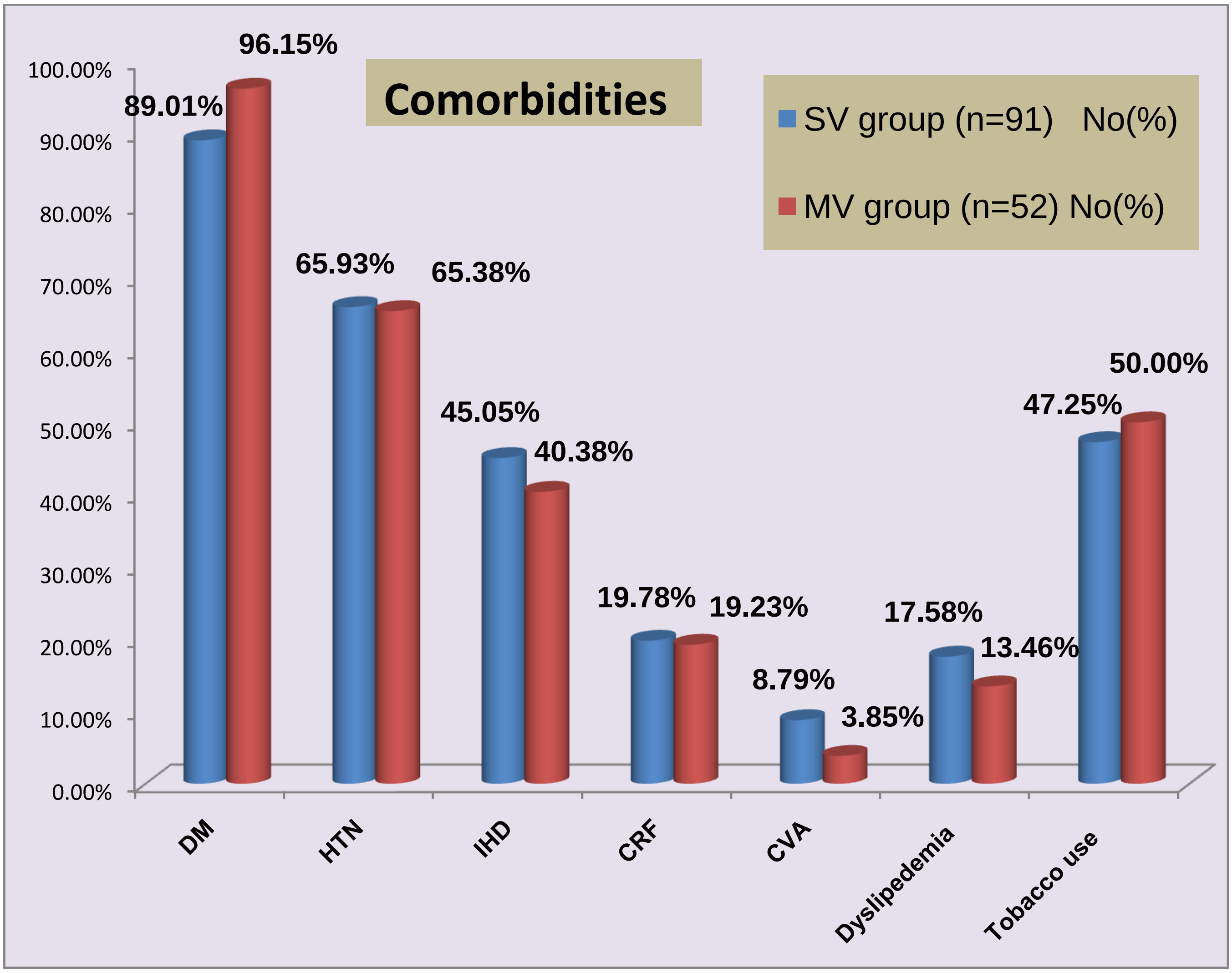

Figure 9: Co-morbidities distribution

Co-morbidities distribution amongst both group were equally matched. Diabetes mellitus was the most common co-morbidity in both groups followed by hypertension and ischemic heart disease. Diabetics were 89.01% (81/91) in SV group and 96.15% (50/52) in MV group (P = 0.21). Hypertension was present in 65.93% (60/91) in SV group while in MV group it was 65.38% (34/52) (P=0.94). Ischemic heart disease (medically treated or percutaneous angioplasty/stenting or coronary artery bypass grafting done) was present in 45.05% (41/91) and 40.38% (21/52) of the patients in SV and MV group respectively (P = 0.58). Chronic renal failure was present in 19.78% (18/91) patients in SV group while 19.23% (10/52) in MV group (P=0.94).History of cerebro vascular accidents (ischemic or haemorrhagic) was present in 8.79% (8/91) in SV group and in 3.85% (2/51) in MV group (P=0.33). Dyslipedemia was present in 17.58% (16/91) and 13.46% (7/52) of the patients in SV and MV group respectively (P=0.52). The use of tobacco was present in 47.25% (43/91) in SV group and 50% (26/52) in MV group (P=0.75).

Ulcer Location

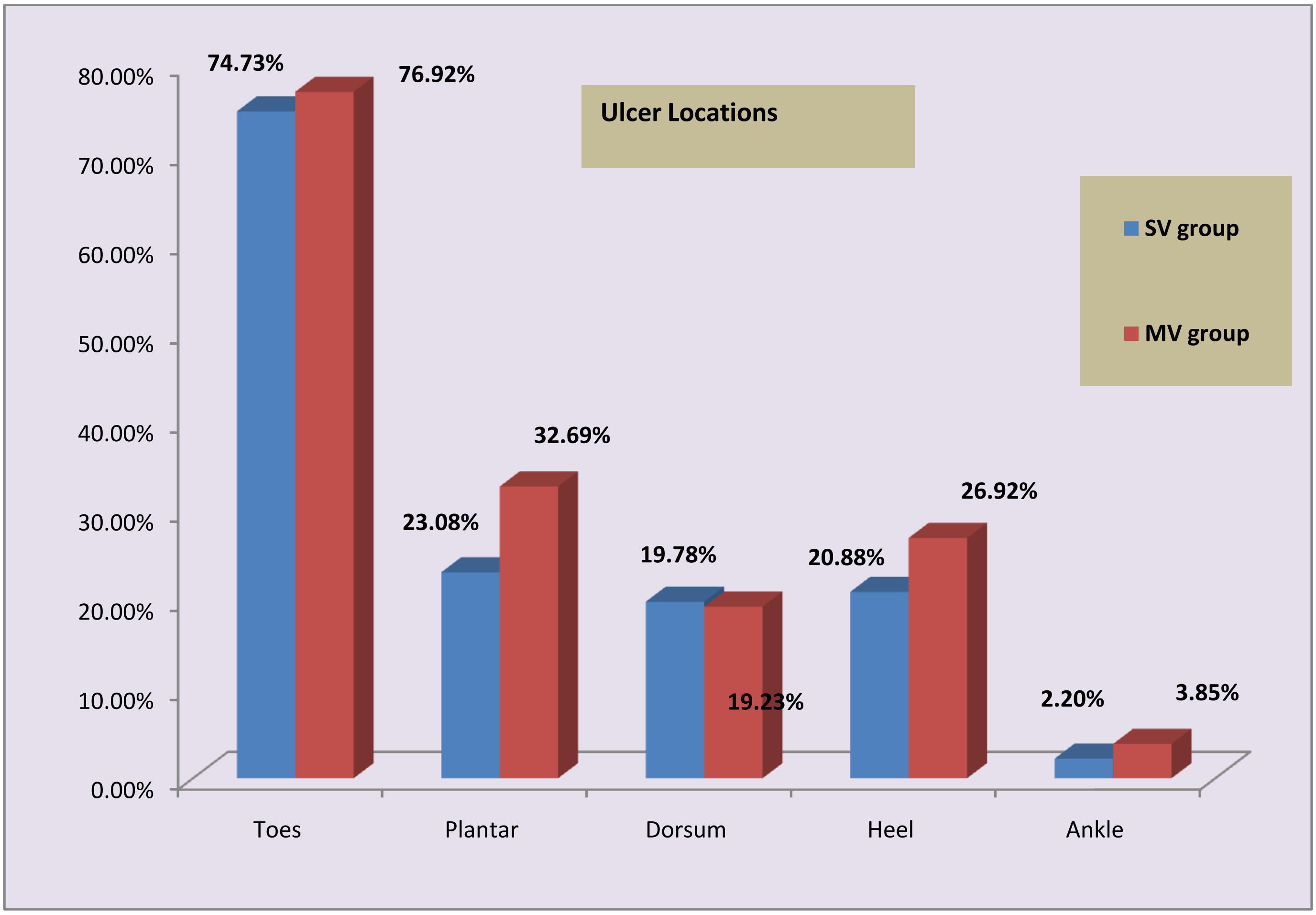

Figure 10: Ulcer location

Foot ulcer location was equally distributed amongst two groups. Most common site of ulcer location was toes in both groups. Ulcer was located over toes in 74.73% (68/91) in SV group and in 76.92% (40/52) in MV group (P=0.76). Plantar ulcer location was present in 23.08% (21/91) in SV group while in MV group it was 32.69% (17/52) (p= 0.21). Ulcer was located over dorsum of foot in 19.78% (18/91) in SV group and in 19.23% (10/52) in MV group (P=0.93). Heel ulcer was present in 20.88% (19/91) in SV group and 26.92% (14/52) in MV group (P=0.40). Ankle ulcer location was present in 2.20% (2/91) and 3.85% (2/52) in SV group and MV group respectively (P= 0.62)

Wound, Ischemia, Foot Infection (WIfI) stage:-

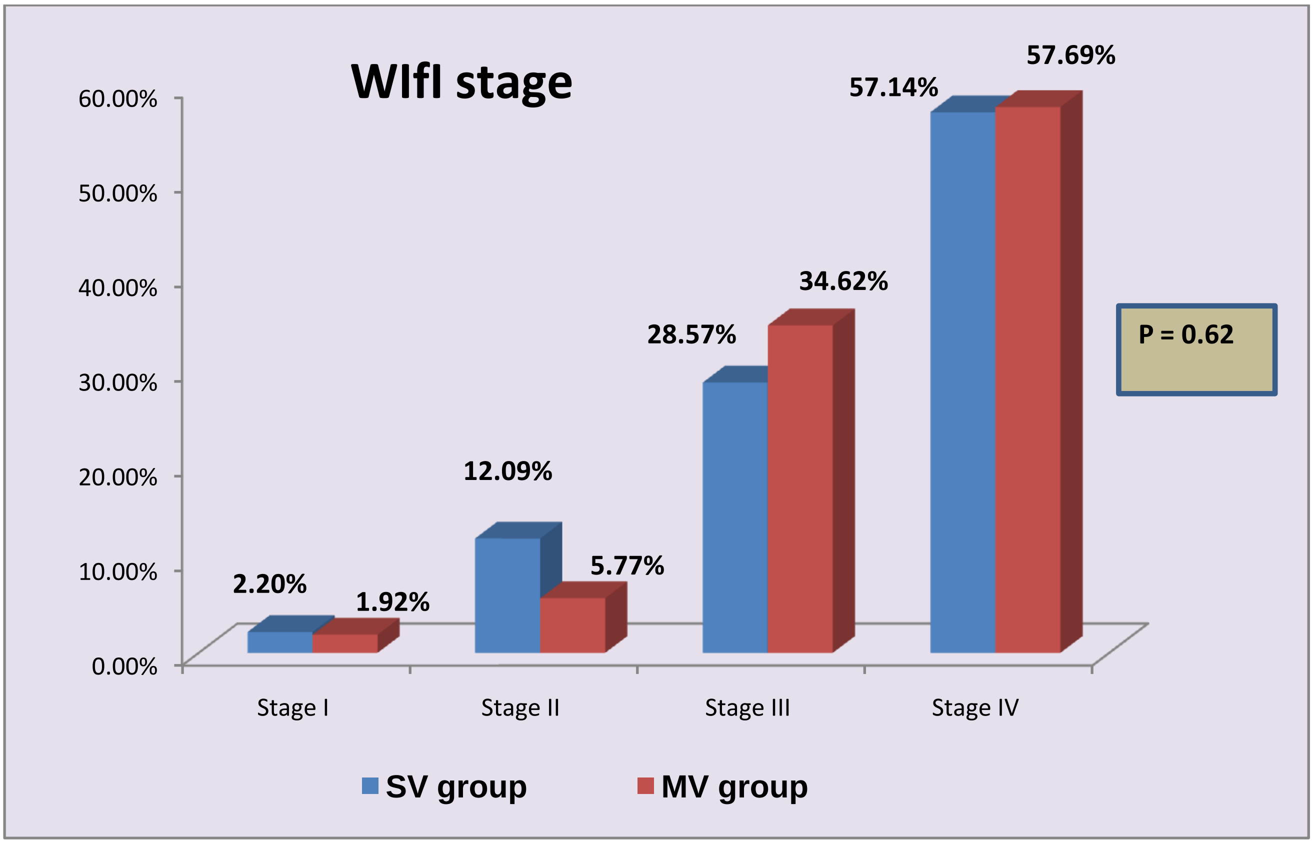

Figure 11: WIfI stage

On comparing both study groups with respect to WIfI stage distribution, there was no statistically significant difference (p = 0.62). Majority of the patients were in WIfI Stage 4 and Stage 3 which indicate worst combination of wound, ischemia and foot infection. SV group had 57.14% (52/91) patients and MV group 57.69% (30/52) patients in WIfI Stage 4. Distribution of WIfI Stage 3, 2, 1 in SV group were 28.57% (26/91), 12.09% (11/91) and 2.2 %(2/91) while in MV group it was 34.62% (18/52), 5.77 %(3/52) and 1.92 %(1/52).

Rutherford Becker class:

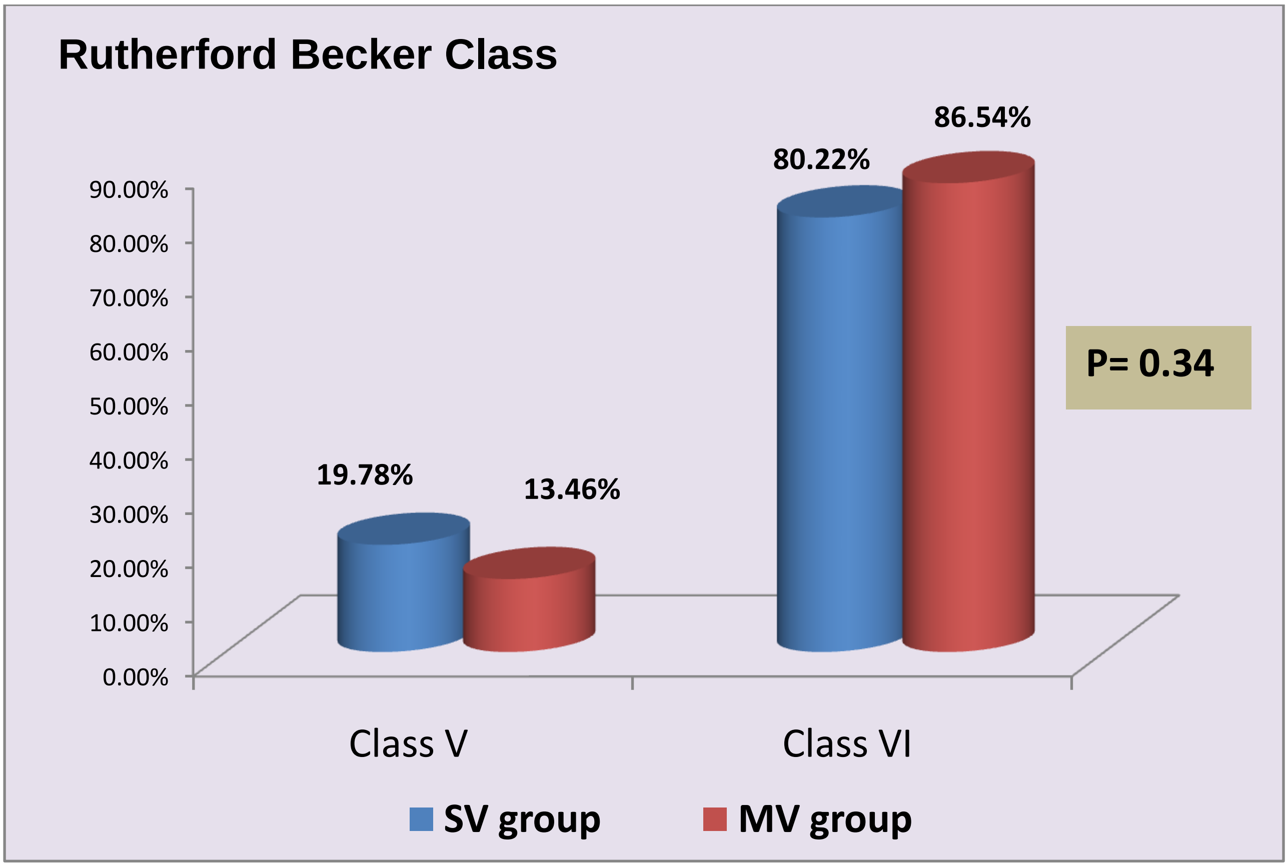

Figure 12: - Rutherford Becker class

All patients in the study group were suffered from critical limb ischemia with equal distribution in terms of Rutherford Becker class (p = 0.34). Most of the patients were in Rutherford Becker class 6, comprising 80.22% (73/91) in SV group and 86.54% (45/91) in MV group while 19.78 % (18/91) in SV group and 13.46% (7/52) patients in MV group were in Rutherford Becker class 5.

Inflow correction data:

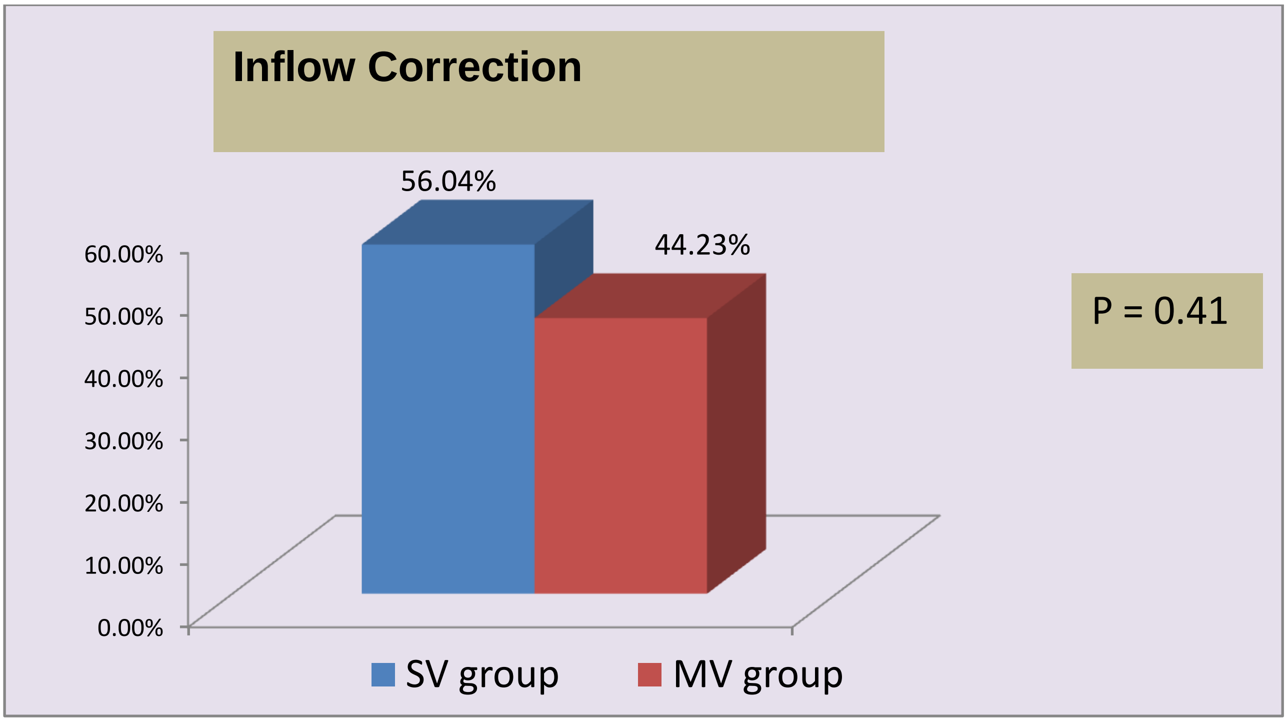

Figure 13: - Inflow correction

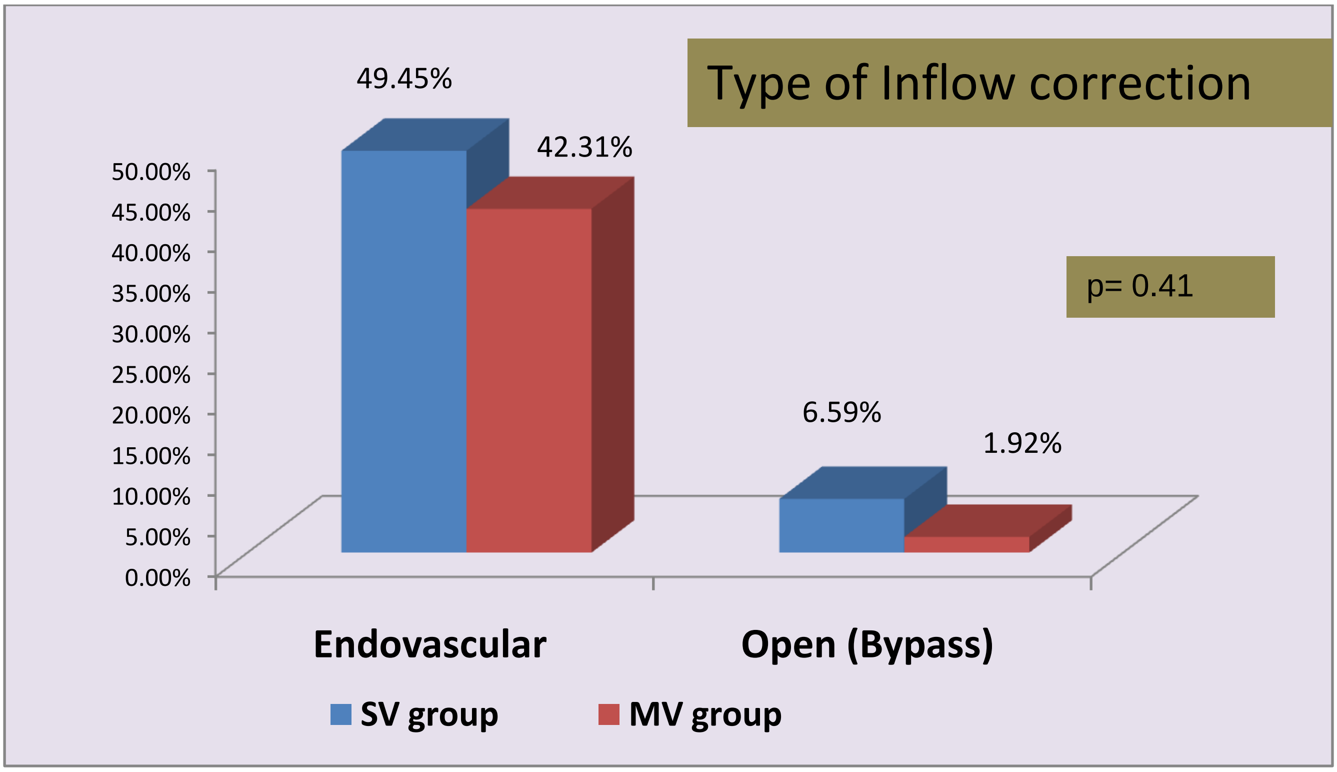

Figure 14: Type of Inflow correction

Both groups are equal in terms of inflow correction. In SV group 56.04% (51/91) while in MV group 44.23% (23/52) underwent inflow correction for Superficial Femoral Artery / Popliteal steno-occlusive lesions. Most common modality for inflow correction was endovascular intervention (Superficial Femoral Artery and Popliteal Artery angioplasty/ stenting) and was performed in 49.45% (45/91) of patients in SV group and 42.31% (22/52) of patients in MV group. Open femoro-popliteal bypass were performed in only 6.59 % (6/91) in SV group and 1.92% (1/52) in MV group. (P=0.41)

Infrapopliteal vessel angioplasty data:

Vessel Targeted	Single Vessel group (SV group) (n=91) (91 vessels)	Multiple Vessel group (group) (n=52) (116 Vessels)	P value
ATA	39 (42.86%)	44 (84.62%)	<0.001
PTA	30 (32.97%)	34 (65.38%)	<0.001
Peroneal	18 (19.78%)	36 (69.23%)	<0.001
TPT	4 (4.40%)	2 (3.85%)	1

Table 2: Angioplasty data

Infrapopliteal vessels angioplastied were recorded in both groups. There is significant difference between two groups with respective targeted infrapopliteal vessels. ATA were targeted in 42.86% in SV group in contrast to 84.6% in MV group (P < 0.001). Similarly PTA and Peroneal artery were targeted more in MV group as compared with SV group, 32.97 Vs 65.38% for PTA and 19.78% Vs 69.23% for peroneal artery in SV and MV group respectively **(P< 0.001).** TPT angioplasties were comparable amongst two groups.

Wound healing rate at 6 month:

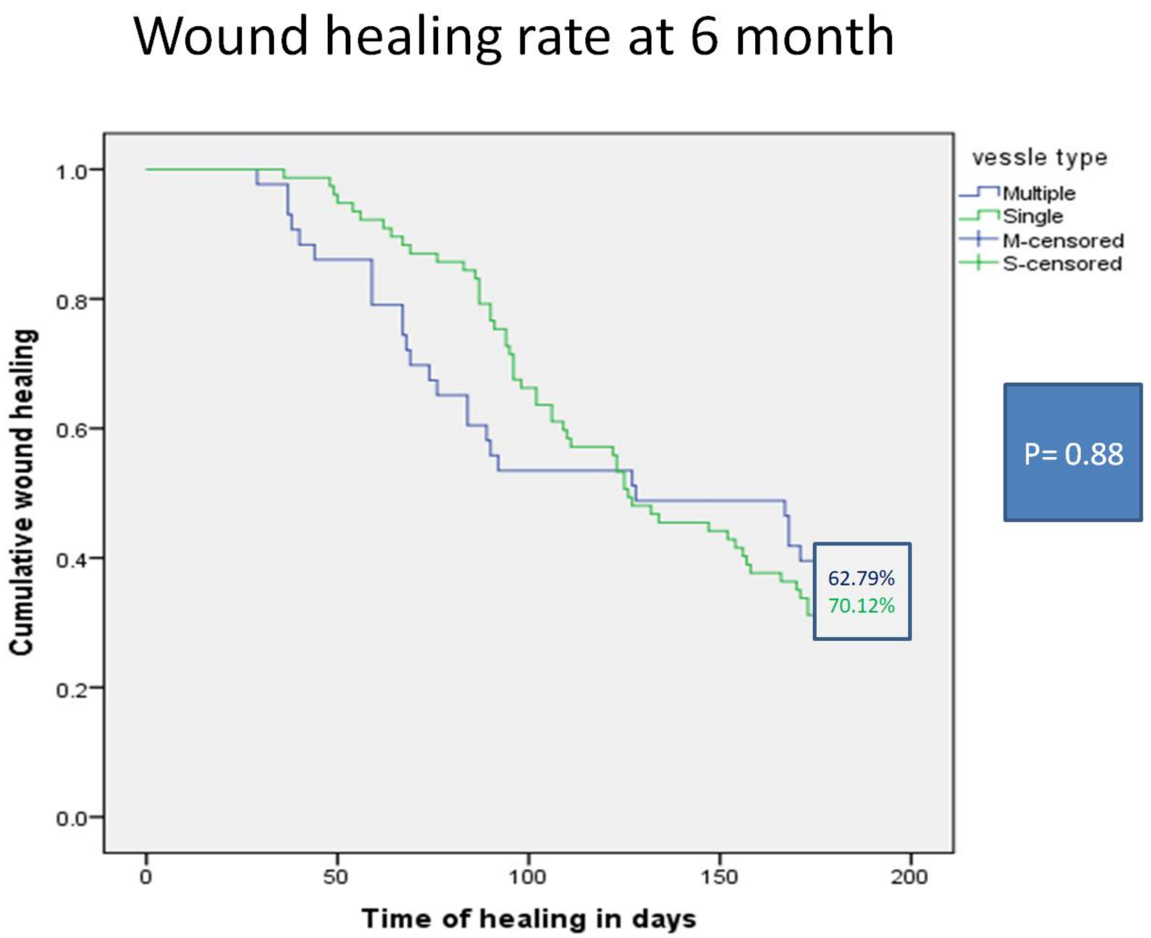

Figure 15: - Wound healing rate

Mortality patients were excluded for wound healing analysis. Complete wound healing occurred in 70.12% (54/77) of patients in SV group and 62.79% (27/43) patients in MV group, over 6 month follow up. As per the Kaplan Meier curve wound healing rate was better in MV group compared to SV group for initial 4 months but beyond 4 months and up to 6 months wound healing rate was better in SV group as compared with MV group.

Wound healing time:-

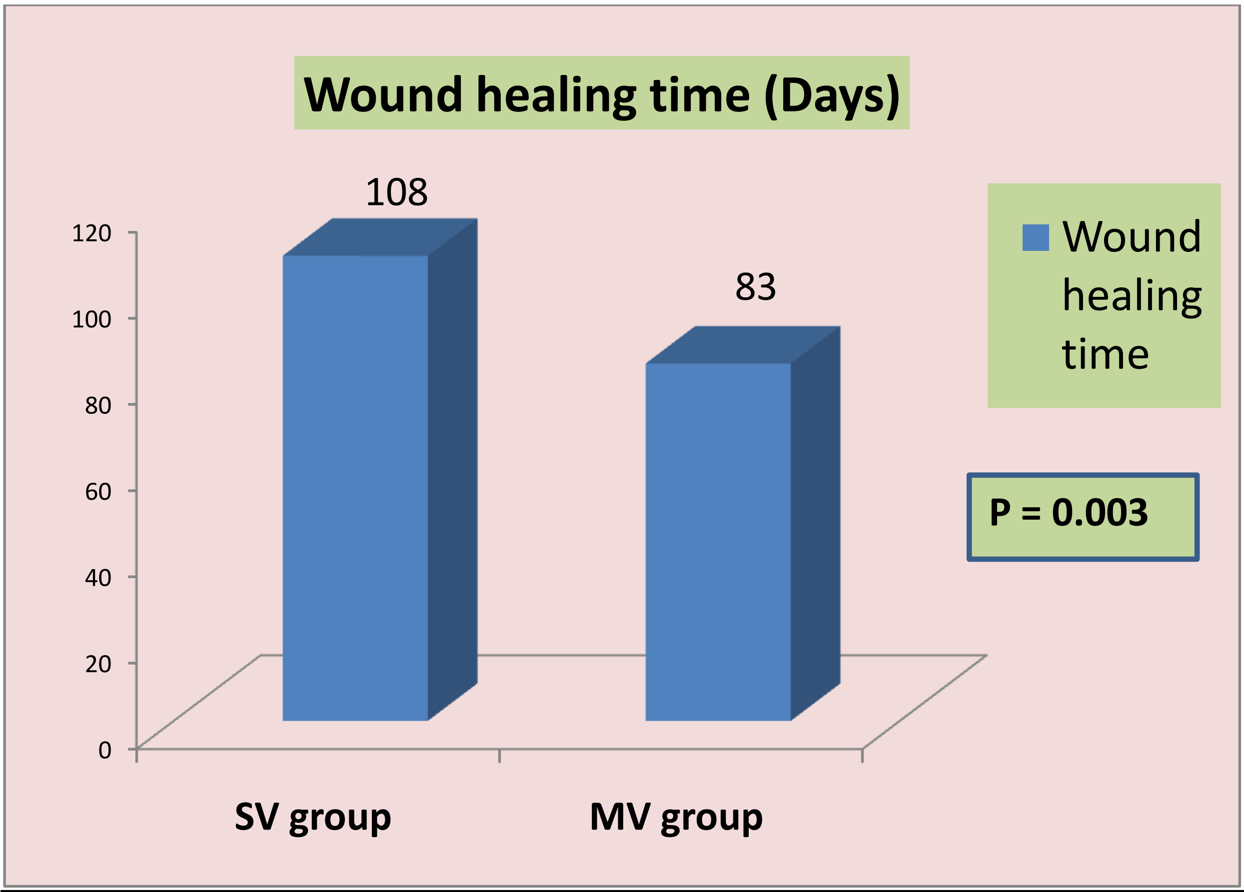

Figure 16:-Wound healing time

Wound healing time was recorded in days in both groups. Mean wound healing time was 108 ± 43 days in SV group and 83 ± 40 days in MV group. **(P=0.003).** This observed difference is statistically significant.

Limb salvage rate:-

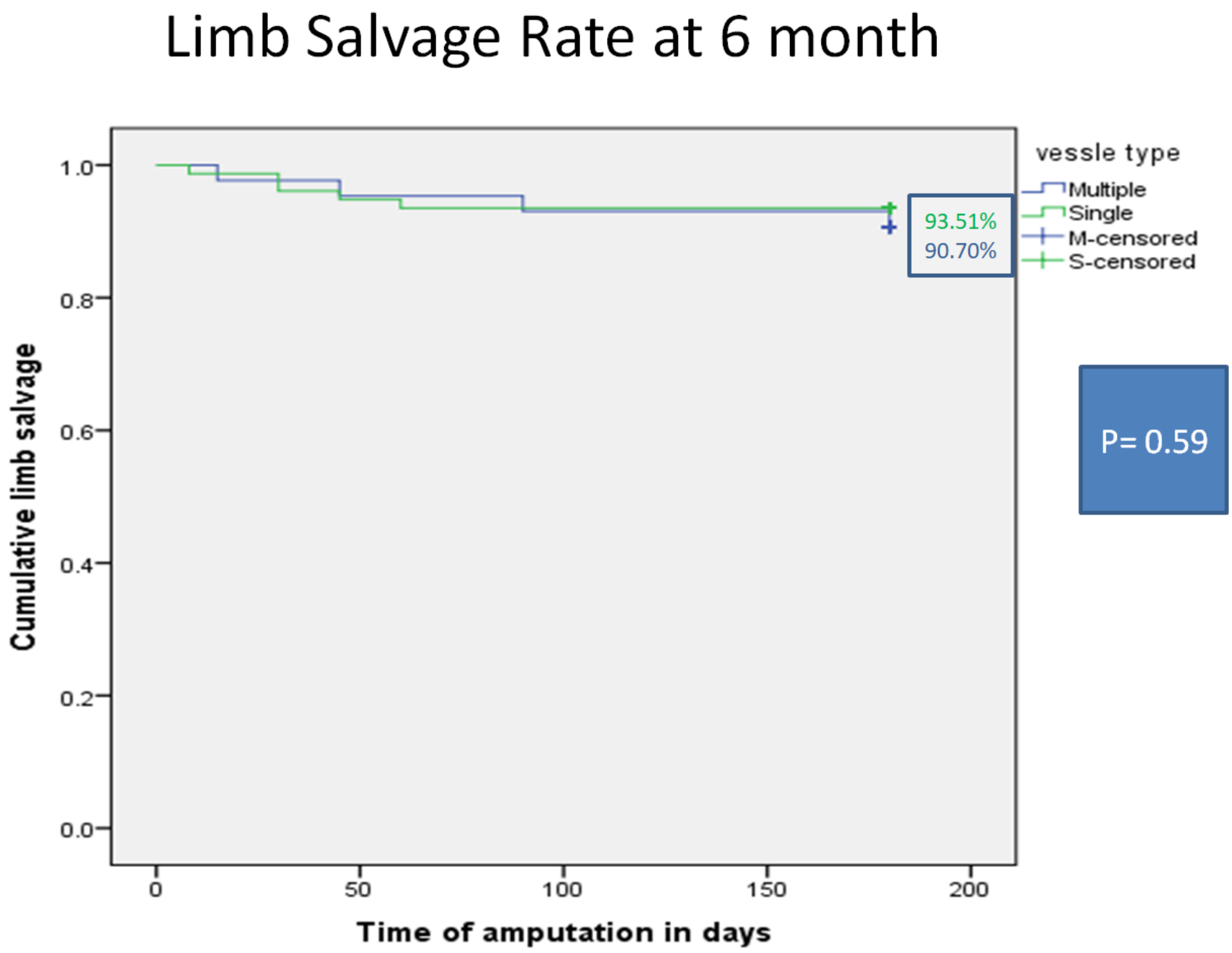

Figure: 17 - Limb salvage rate

Mortality patients were excluded for limb salvage analysis. Limb salvage rate at the end of 6 months in SV group was 93.51% (72/77) while in MV group it was 90.70 % (39/43), but this observed difference was not statistically significant. (P= 0.59)

Effect of Plantar Arch Quality (PAQ):

Type of Plantar arch	SV group (n=91)	MV group (n=52)	P Value
Complete	29 (31.87%)	19 (36.54%)	0.07
Incomplete	44 (48.35%)	30 (57.69%)	
Absent	18 (19.78%)	3 (5.76%)	

Table 3: Plantar Arch Quality (PAQ)

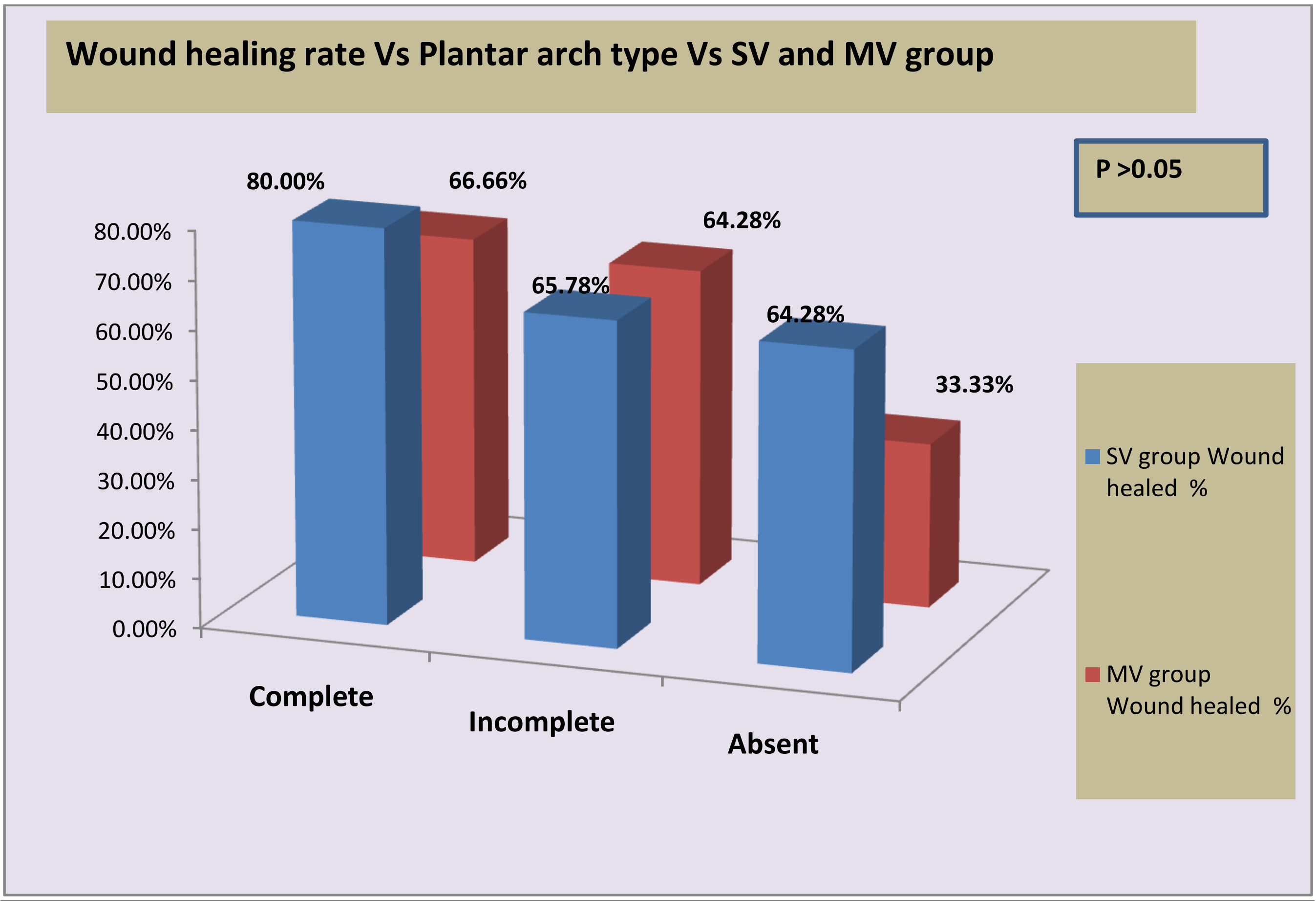

Figure 18: - Wound healing rate Vs Plantar arch type Vs SV and MV group

Considering the effect on plantar arch quality (PAQ), complete, incomplete and absent plantar arch was achieved in 31.87% (29/91), 48.35% (44/91) and 19.78% (18/91) of the patients in SV group and 36.54% (19/52), 57.69% (30/52) and 5.76% (3/52) of the patients in MV group, respectively.(P=0.07) Excluding mortality patients, wound healing rate amongst complete, incomplete and absent plantar arch was 80% (20/25), 65.78% (25/38) and 64.28% (9/14) in SV group while in MV group it was 66.66% (8/12), 64.28% (18/28) and 33.33% (1/3) respectively (P value 0.95,0.22 and 0.09 respectively). This observed difference of wound healing rate amongst plantar arch type was not statistically significant in two groups.

Ankle Brachial Index (ABI):

ABI	SV group	MV group	P value
Preoperative	0.59 ± 0.15	0.63 ± 0.14	0.20
Postoperative	0.87 ± 0.13	0.89 ± 0.10	0.32
1 month	0.90 ± 0.11	0.93 ± 0.08	0.29
3 month	0.95 ± 0.09	0.99 ± 0.12	0.11
6 month	0.92 ± 0.06	0.90 ± 0.10	0.60

Table 4:- Ankle Brachial Index (ABI)

All patients underwent preoperative, postoperative, follow up 1 month, 3 month and 6 month ABI which showed no significant difference between two study groups (P>0.05). Preoperative, postoperative, 1 month, 3 month and 6 month ABI in SV group were 0.59 ± 0.15, 0.87 ± 0.13, 0.90 ± 0.11, 0.95 ± 0.09 and 0.92 ± 0.06 while in MV group it was 0.63 ± 0.14, 0.89 ± 0.10, 0.93 ± 0.08, 0.99 ± 0.12 and 0.90 ± 0.10 respectively.

Toe Brachial Index (TBI):

TBI	SV group	MV group	P value
Preoperative	0.21 ± 0.05	0.21 ± 0.03	0.96
postoperative	0.29 ± 0.07	0.28 ± 0.10	0.76
1 month	0.35 ±0.08	0.34 ± 0.08	0.84
3 month	0.38 ± 0.11	0.38 ± 0.09	0.89
6 month	0.35 ± 0.11	0.38 ± 0.08	0.53

Table 5:-Toe Brachial Index (TBI)

All patients underwent preoperative, postoperative, follow up 1 month, 3 month and 6 month TBI which showed no significant difference between two study groups (P>0.05). Preoperative, postoperative, 1 month, 3 month and 6 month ABI in SV group were 0.21 ± 0.05, 0.29 ± 0.07, 0.35 ± 0.08, 0.38 ± 0.11 and 0.35 ± 0.11 while in MV group it was 0.21 ± 0.03, 0.28 ± 0.10, 0.34 ± 0.08, 0.38 ± 0.09 and 0.38 ± 0.08 respectively.

Transcutaneous oxygen saturation (TcPO2)

TCPO2 Supine	SV group	MV group	P value
Preoperative	23.18 ± 7.02	22.93 ± 5.88	0.83
postoperative	32.50 ± 7.84	34.34 ± 8.07	0.20
1 month	33.21 ± 7.58	37.58 ± 8.03	0.03
3 month	35.73 ± 9.14	41 ± 11.92	0.18
6 month	37.11 ± 11.20	42.66 ± 10.89	0.66

Table 6:-Transcutaneous oxygen saturation (TcPO2) - supine

TCPO2 Foot down	SV group	MV group	P value
Preoperative	32.71 ± 7.97	32.36 ± 7.45	0.81
postoperative	43.81 ± 7.90	46.32 ± 7.86	0.08
1 month	43.98 ± 8.06	49.58 ± 10.05	0.03
3 month	46.94 ± 7.56	50.11 ± 9.30	0.34
6 month	47.33 ± 7.33	50.50 ± 10.85	0.81

Table 7:-Transcutaneous oxygen saturation (TcPO2) - foot down

TcPO2 supine and foot down in both study groups recorded at preoperative, postoperative, follow up 1 month, 3 month and 6 month. Both supine and foot down TcPO2 at 1 month showed significant improvement in MV group as compared to SV group(Supine TcPO2 37.58 $\pm$ 8.03 Vs 33.21 $\pm$ 7.58, P = 0.03 and foot down TcPO2 49.58 ± 10.05 Vs 43.98 ± 8.06 , P = 0.03 respectively.) Preoperative, postoperative, follow up 3 month and 6 month Supine and foot down TcPO2 showed no significant difference between two groups.

Major Adverse Cardiac Events (MACE)

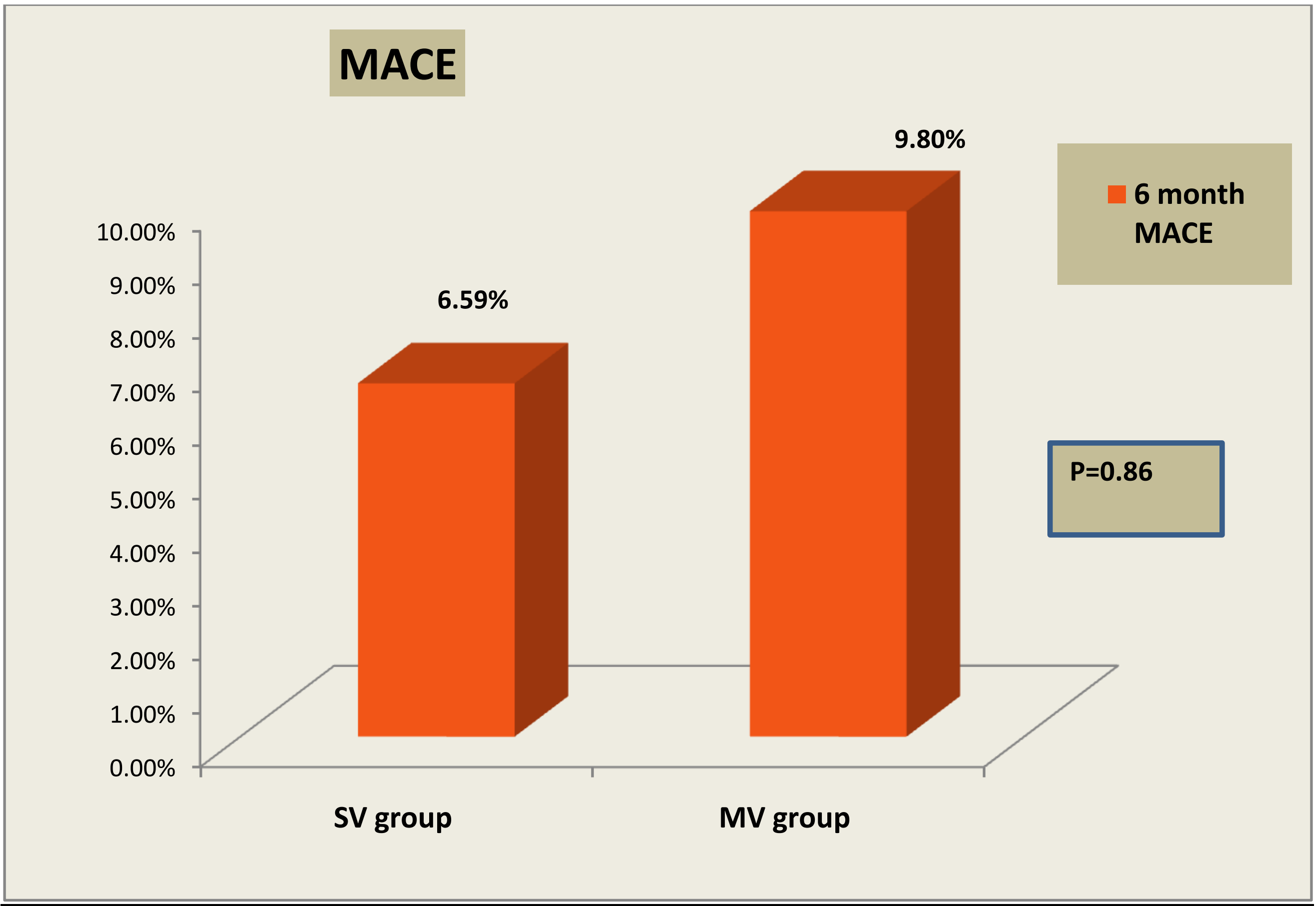

Figure 19: - MACE

Over 6 months major adverse cardiac events (MACE) occurred in 6.59% (6/91) in SV group and 9.80% (5/52) in MV group, but this observed difference is not statistically significant (P=0.86).

All Cause Mortality:

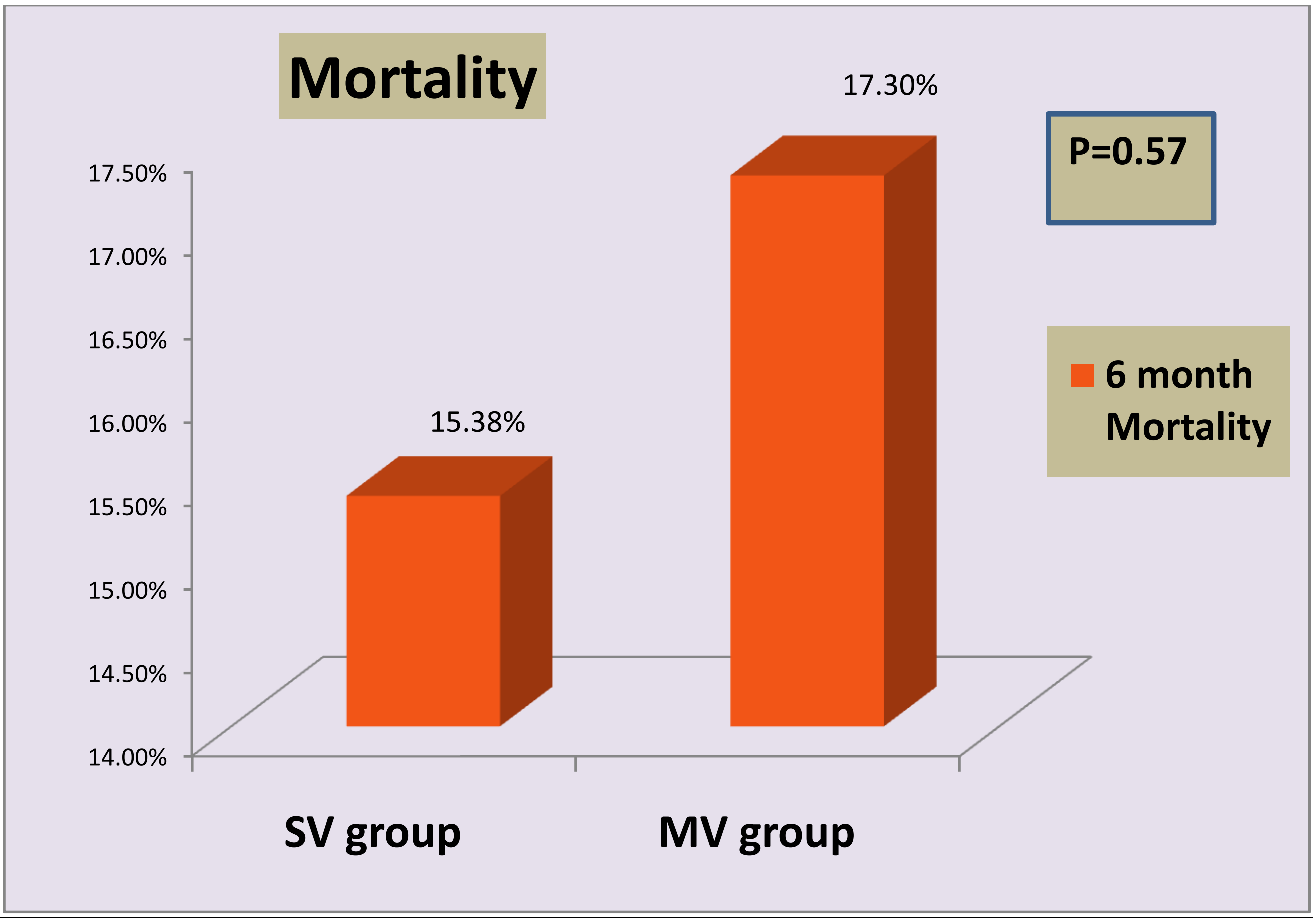

Figure 20: - All cause mortality at 6 month

Mortality from all cause occurred in 15.38% (14/91) and 17.30% (9/52) of the patients in SV and MV groups respectively. Though the all cause mortality was high amongst MV group, this observed difference is not statistically significant (P=0.57).

DISCUSSION

In this prospective study we have compared outcomes of single infrapopliteal vessel angioplasty with multiple infrapopliteal vessel angioplasties. We have analysed the various pre-operative, intraoperative angiographic factors and both groups seems to be matched with this regard. The clinical outcomes like wound healing rate, wound healing time, limb salvage rate, effect on plantar arch, PVR changes, cardiac events (MACE) and mortality were also analysed amongst single and multiple vessel infrapopliteal angioplasty group.

The mean age of patients in the SV group and MV group were 65.26 $\pm$ 11.32 yrs and 63.44 $\pm$ 8.79 yrs respectively which are comparable with Darling et al[15] study where they found mean age of 71.5yrs and 68.2 yrs and Rodrigo B. Biagioni et al[55] where they noticed 70.9 yrs and 66.9 yrs in SV and MV groups respectively.

In our study, the predominant gender is male, 75.82% and 82.69% in SV and MV group while other studies found almost equal gender distribution, 52% and 62 % male in darling et al[15] study and 57.5% and 55% in Rodrigo B. Biagioni et al[55] study in SV and MV group respectively.

In present study, most common co-morbidity was Diabetes while other studies [55, 15, 12] showed hypertension as most common comorbidities.
Diabetics distribution was 89.01% in SV group and 96.15% in MV group while it was79% and 87%in Darling et al study[15] and 76.9% and 78.7 % in Rodrigo B. Biagioni et al[55] study in SV and MV group respectively.

Hypertension distribution amongst two groups in our study was 65.93% and 65.38% in SV and MV group while Darling et al[15] noticed hypertension in 84% and 87% and Rodrigo B. Biagioni et al[55] found it in 97.4% and 87.8% in SV and MV group.

Prevalence of ischemic heart disease (IHD) in our study was 40.05% and 40.38% in the SV and MV group respectively which is similar to previously published studies

In the present study, chronic renal failure (CRF) was present in 19.78% and 19.23% patients in SV and MV group respectively. Darling et al[15], in their study found 25% and 27% CRF patients in SV and MV group respectively. De Athayde Soares et al[14] also noticed similar finding, 23.9 % in SV and 27.1% in MV group while Kobayashi et al[12] noticed CRF in almost half of the patients, 57 % and 50 % in SV and MV group.

In this study, prevalence of Cerebro-vascular disease was noticed in 8.79% and 3.85% while Darling et al[15] found it in13% and 17 % in SV and MV groups respectively.

Dyslipedemia was noticed in 17.58% and 13.46% patients in SV and MV group respectively, in our study. Kobayashi et al[12] found it in 29 % and 35 % patients in SV and MV groups respectively.

In the present study, 42.50% patients in SV group and 50% patients in MV group had history of tobacco use in the form of smoking or tobacco chewer. Darling et al[15], in their study found smoking history in 55 % in SV group and 59% in MV group while Rodrigo B. Biagioni et al[55], in their study found active smoking and tobacco use history in 48.6% patients in SV group and 42.3%patients in MV group.

In the present study all patients were having ischemic ulcers. Most common site of ulcer location in our study was toes and least common site was ankle. Ulcer location distribution in present study was 74.73% and76.92%, 23.08% and 32.69%, 19.78% and 19.23%, 20. 88% and 26.92%, 2.20 % and 3.85 % over toes, plantar, dorsum, heel and ankle region in SV and MV groups respectively.

Kobayashi et al[12] also, in their study noticed most common ulcer location site as toes but least common site as plantar ulcer. They found ulcer location distribution as 70 % and 75%, 2% and 0 %, 16% and 17%, 12% and 4 % 0 % and 4 % over toes, plantar, dorsum, and heel and ankle region in SV and MV groups respectively.

Risk stratifications based on three major factors that impact amputation risk and clinical management: Wound, Ischemia and foot Infection (WIfI) [57]. The present study has stratified patients in both groups into their respective WIfI stage. Most of the patients were in Stage 4which indicate worst combination of wound, ischemia and foot infection. In present study, 57.14 % patients in SV group and 57.69% patients in MV groups were in WIfI stage 4, while 28.57% in SV group and 34.62% in MV groups were in WIfI stage 3. 12.09% patients in SV group and 5.77% patients In MV group were in WIfI Stage 2. The distribution of WIfI stage in both SV and MV group was similar. (P=0.62)
Darling et al[15], in their study found, 41% and 47% patients, 35% and 37% patients , 22% and 14 % patients, 1.6 % and 2% patients in SV and MV groups in WIfI Stage 4, WIfI Stage 3, WIfI Stage 2 and WIfI Stage 1 respectively.(p=0.63) Kobayashi et al[12], in their study noticed , 43% and 34% patients, 26% and 30% patients , 21% and 15 % patients, 10 % and 21% patients in SV and MV groups in WIfI Stage 4, WIfI Stage 3, WIfI Stage 2 and WIfI Stage 1 respectively.(p=0.21)

The level of chronic ischemia was stratified by the Rutherford- Becker class. All patients were having tissue loss (Rutherford class 5 and 6). Many studies have proven that as Rutherford class increases the limb salvage decreases, multilevel disease is more and increased likelihood of cardiovascular events and mortality. In present study, most of the patients were in Rutherford class 6, 80.22% patients in SV group and 86.54% in MV group were in

Rutherford class 6 while remaining were in Rutherford class 5. Distribution of Rutherford class amongst two groups was equal (P= 0.34)

Kobayashi et al[12], in their study observed 61% in SV group and 62% patients in MV group were in Rutherford class 6 and remaining in Rutherford class 5 (p=0.86), while De Athayde Soares et al[14], in their study, noticed 32.6% patients in SV group and 76.7% patients in MV group were in Rutherford stage 6 while 63% patients in SV group and 35.9% patients in MV group belongs to Rutherford class 5. (P>0.05)

In our study, Infrapopliteal disease patients with inflow lesion in the form of femoro popliteal steno-occlusive disease were treated with endovascular/open repair in addition to infrapopliteal angioplasty. In present study, 56.04% patients in SV group and 44.23% patients in MV group underwent endovascular/open repair of inflow femoro-popliteal lesions. Most common modality used for inflow correction was endovascular (angioplasty/stenting) and was done in 49.45% patients in SV group and 42.31% patients in MV group while open in flow repair in the form of femoro-popliteal bypass was done in 6.59% patients in SV group and 1.92% patients in MV group. Both the groups are comparable in the form of inflow correction. (P=0.41). Darling et al[15], in their study reported inflow correction in 54% patients in SV group and 40% patients in MV group.

Infrapopliteal vessels angioplastied data were recorded in both groups. There is significant difference between two groups with respective targeted infrapopliteal vessels. ATA were targeted in 42.86% in SV group in contrast to 84.6% in MV group (P< 0.001). Similarly PTA and Peroneal artery were targeted more in MV group as compared with SV group, 32.97 Vs 65.38% for PTA and 19.78% Vs 69.23% for peroneal artery in SV and MV group respectively (P< 0.001). TPT angioplasties were comparable amongst two groups. This significant difference is expected because in MV group more than one vessels were angioplastied.

De Athayde Soares et al[14], in their study found similar results, ATA was predominantly treated in SV group (41.70% Vs 29.73%) while PTA (8.33% Vs 35.1%), peroneal (36.11% Vs 67.5%) and TPT (13.8% Vs 67.6%) (P=0.001)

Wound healing was defined as complete epithelisation of wound. For all limb based outcome analysis like wound healing rate, wound healing time and limb salvage rate, mortality patients were excluded to avoid bias because in some patients wound were healed before mortality while some patients had death before complete healing. So all limb based outcomes were calculated for n=77 patients in SV group and n=43 patients in MV group. All major amputations were due to non-salvageable foot either due to extensive tissue loss or extensive infection so in all amputation patients wounds were considered to be not healed.

In present study, complete wound healing occurred in 70.12% (54/77) of patients in SV group and 62.79% (27/43) patients in MV group, over 6 month follow up.(P=0.88). This indicates the difference in wound healing rate at 6 month is not statistically significant amongst SV and MV group. Kaplan Meier curve of wound healing rate indicate wound healing was better in MV group compared to SV group for initial 4 months but beyond 4 months and up to 6 months wound healing rate was better in SV group as compared with MV group.

Like our study, Darling et al[15], also didn't found any significant difference amongst two groups, in 6 month wound healing rate (37% in SV group and 41% in MV group) (P=0.13)

Rodrigo B. Biagioni et al[55], in their study reported better 1 yr complete wound healing rate of 33.60% in SV group and 63.90% in SV group.(p=0.006).

Kobayashi et al[12], also showed better 1 yr wound healing rate in MV group as compared to SV group (87% Vs 79%, P=0.003).

In our study, limb salvage rate is better in SV group (though the difference is not statistically significant) as opposed with Rodrigo B. Biagioni et al[55] and Kobayashi et al[12], where wound healing rate is better in MV group. Possible explanation for this is, more number of diabetes patients in MV group as compared to SV group (96.15% Vs 89.01%), more number of patients with Rutherford class 6 (large wound burden) (86.54%Vs 80.22%) and less number of patients with Rutherford class 5 (small wound burden) (5.76% Vs 19.78%), though these parameters were not statistically significant amongst two group, they might have contributed for less wound healing rate in MV group.

In our study, Wound healing times were recorded in days in both groups. Mean wound healing time was better in MV group (83 $\pm$ 40 days) as compared with SV group (108 $\pm$ 43 days) (P=0.003). This observed difference is statistically significant.

Kobayashi et al[12], in their study found similar results; time of wound healing was shorter in MV group than in single vessel group, median 83 days Vs142 days. (P=0.01) This shorter wound healing time in MV group, might be because multiple vessel approach could provide greater perfusion to the foot and, therefore, improve healing speed and multiple vessel approach could provide continuing healing of the wound; even if restenosis occurs in one vessel, the perfusion from the other vessel could compensate.15

In our study, Limb salvage rate at the end of 6 months in SV group was 93.51% (72/77) while in MV group it was 90.70 % (39/43), but this observed difference was not statistically significant. (P= 0.59)

De Athayde Soares et al[55], found limb salvage rate of 89.3% in SV group and 93.8% in MV group at 6 month. (P=0.595)

In their study, Kobayashi et al[12], found that limb salvage rate at 3 year was 85.6% in SV group and 93.9% in MV group. (P=0.18)

Thus limb salvage rate is not affected by number of infrapopliteal vessels angioplastied.

Improved circulation in pedal arteries is one of the important factor, to achieve better wound healing rate and limb salvage rate in critical limb ischemia patients. To evaluate impact of number of infrapopliteal vessel angioplastied on plantar arch quality, all patients were classified in complete, incomplete and absent plantar arch based on post-operative check angiogram. Complete, incomplete and absent plantar arch was achieved in 31.87%, 48.35% and 19.78% of the patients in SV group and 36.54%, 57.69% and 5.76% of the patients in MV group, respectively.(P= 0.07)

De Athayde Soares et al[55], in their study found that complete, incomplete and absent plantar arch was achieved in 38.9%,38.9% and 22.2% in SV group and 27%, 54% and 19% in MV group (P=0.29, P=0.29 and P =0.52) respectively.

Wound healing rate amongst complete, incomplete and absent plantar arch was 80%, 65.78% and 64.28% in SV group while in MV group it was 66.66%, 64.28% and 33.33%, respectively (P value 0.95,0.22 and 0.09 respectively).

Patients underwent preoperative, postoperative, follow up 1 month, 3 month and 6 month ABI and TBI. Preoperative and postoperative, ABI and TBI were comparable amongst the two groups. Follow up 1st month, 3rd month and 6th month ABI, TBI in both SV and MV group showed no significant difference (P>0.05) implying multiple vessel angioplasties does not give the desired advantage.

Kobayashi et al[12], in their study found comparable pre operative ABI and TBI amongst SV and MV group with no significant improvement in post operative

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TcPO2 supine and foot down in both study groups recorded at preoperative, postoperative, follow up 1st month, 3rd month and 6th month. Both supine and foot down TcPO2 at 1 month showed significant improvement in MV group as compared to SV group (Supine TcPO2 37.58 ± 8.03 Vs 33.21 ± 7.58, P = 0.03 and foot down TcPO2 49.58 ± 10.05 Vs 43.98 ± 8.06 , P = 0.03 respectively). Preoperative, postoperative, follow up 3 month and 6 month Supine and foot down TcPO2 showed no significant difference between two groups. This indicate multiple vessel angioplasty has advantage of improving tissue oxygen saturation probably by providing greater perfusion to the foot, effect of which is maximum at 1 month and it wears off at 3 month follow up.

Kobayashi et al[12], in their study found no significant difference between pre operative and postoperative TcPO2.

Major Adverse Cardiac Events (MACE) Over 6 months occurred in 6.59% in SV group and 9.80% in MV group, but this observed difference is not statistically significant (P=0.86).Indicating that targeting more than one vessel does not increases risk of MACE.

Six month mortality from all causes occurred in 15.38% and 17.30% of the patients in SV and MV groups respectively. Though the all cause mortality was high amongst MV group, this observed difference is not statistically significant (P=0.57).

De Athayde Soares et al[55], in their study found lower perioperative mortality in SV group as compared with MV group (4.2% Vs 16.2%). (P=0.039)

In our study, mortality rate is higher in SV group which was probably due to higher number of IHD patients in SV group. (45.05% vs 40.38 %)

CONCLUSION

Peripheral arterial disease is growing health problem, especially in diabetic patients. Infrapopliteal disease constitutes about 30-40% of peripheral arterial disease burden.[58] Although surgical bypass is gold standard in these patients, advances in endovascular technology and hardware's led it to become endovascular as first treatment option.

Inspite of these vast advances in revascularization techniques for infrapopliteal diseases, some infrapopliteal angioplasty fails to heal ischemic lower extremity wounds even in the presence of patent target vessels and palpable pulses.[4, 5] Thus, successful revascularization for ischemic wounds obviously is more complex than simply restoring circulation to a specific artery

Multiple studies have focused on various factors such as the plantar arch quality/ pedal runoff score, role of angiosome based revascularization to improve vascular patency and to improve limb salvage in CLI patients.[21, 22, 23] but very few studies have examined the impact of the number of infrapopliteal arteries treated on the limb salvage and wound healing.

From this study we conclude that multiple vessel infrapopliteal angioplasties are associated with shorter time to wound healing, but have no effect on wound healing rate and limb salvage rate.

SUMMARY

A prospective, single centre, non randomised, double arm, comparative, open ended study was conducted at Jain Institute of Vascular Sciences (JIVAS), Bengaluru to evaluate whether the number of infrapopliteal arteries treated with endovascular intervention is associated with increased limb salvage rate and wound healing.

During study period, 256 patients were admitted in JIVAS with critical limb ischemia who underwent infrainguinal revascularisation. Among these, 73 patients required revascularisation of isolated femoropopliteal segment (endovascular/open) and open infrainguinal surgery (Fem-distal bypass), so they were excluded from study. The remaining 183 patients underwent infrapopliteal angioplasty ± inflow correction in the form of femoro-popliteal open surgical revascularisation or endovascular intervention. Amongst these, 19 patients were lost to follow up and in 13 patients procedure was technically unsuccessful and 8 patient had history of previous vascular intervention in the same lower limb, so were excluded from the study. Thus finally 143 patient were analysed, 91 in single vessel infrapopliteal angioplasty group (SV) and 52 in multiple vessel infrapopliteal angioplasty group (MV). Out of 143 patients, 23 patients had mortality in 6 month follow up (14 in SV group and 9 in MV group), so for all limb outcome analysis (wound healing, limb salvage rate) these mortality patients were excluded and all limb outcomes were calculated for remaining 120 patients.

The age, gender, co-morbidities, tobacco use, Rutherford Becker class, WIfI Stage, ulcer location, Inflow correction data, angioplasty data, technical and hemodynamic success were recorded. Both groups are comparable with regards to these above factors except angioplasty data which showed ATA, PTA and

peroneal angioplastied more often in MV group as compared to SV group. All patients were followed up at 1st month, 3rd month and 6th month by clinical examination and non-invasive vascular lab modalities (ABI, TBI, TcPO2- supine and foot down position) ABI, TBI were comparable amongst two groups at all stages of follow up. Both supine and foot down TcPO2 at 1 month showed significant improvement in MV group as compared to SV group Preoperative, postoperative, follow up 3 month and 6 month Supine and foot down TcPO2 showed no significant difference between two groups, indicating multiple vessel angioplasty has advantage of improving tissue oxygen saturation probably by providing greater perfusion to the foot, effect of which is maximum at 1 month and it wears off by 3 month follow up.

In present study, complete wound healing rate over 6 month was comparable amongst SV and MV group (70.12% Vs 62.79%) (P=0.88). Wound healing rate was better in MV group compared to SV group for initial 4 months but beyond 4 months and up to 6 months wound healing rate was better in SV group as compared with MV group, but this observed difference is not significant.

Mean wound healing time was significantly better in MV group (83 $\pm$ 40 days) as compared with SV group (108 $\pm$ 43 days) **(P=0.003).**

Limb salvage rate at the end of 6 months in SV group was 93.51% (72/77) while in MV group it was 90.70 % (39/43), but this observed difference was not statistically significant. (P= 0.59)

Complete, incomplete and absent plantar arch was achieved in 31.87%, 48.35% and 19.78% of the patients in SV group and 36.54%, 57.69% and 5.76% of the patients in MV group, respectively.(P= 0.07)

Six month Major Adverse Cardiac Events (MACE) was not statistically significant amongst SV and MV group. (6.59% Vs 9.80%).Indicating that targeting more than one vessel does not increases risk of MACE.

Six month all causes mortality occurred in 15.38% and 17.30% of the patients in SV and MV groups respectively, this difference is not statistically significant (P=0.57).

Hence we recommend that multiple infrapopliteal vessel angioplasties can be considered in CLI patients so as to achieve shorter wound healing time without any added advantage of better wound healing rate or limb salvage rate. As the various studies showed equivocal results further larger prospective studies are required to established exact clinical impact of targeting multiple vessels in CLI patients.

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