

## COMPARATIVE STUDY BETWEEN INFRAGENICULAR BALLOON ANGIOPLASTY AND CONSERVATIVE MANAGEMENT IN TREATMENT OF PATIENTS WITH CRITICAL LOWER LIMB ISCHEMIA

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### ABSTRACT

**Background:** Critical limb ischemia (CLI) is a severe degree of peripheral arterial occlusive disease (PAD) that requires rapid intervention to avoid limb loss and its associated mortality and morbidity. The mainstay of treating of a patient with critical limb ischemia is to reperfuse his limb which can be achieved by direct revascularization by surgical interference or endovascular management or indirect revascularization through other conservative measures as medical therapy, spinal cord stimulation and hyperbaric oxygen. This study aims to compare between the outcomes of endovascular intervention and conservative management of patients with critical limb ischemia.

**Subjects & methods:** The study included 76 patients with critical limb ischemia CLI, 38 patients were treated by endovascular intervention and the other 38 patients were conservatively.

**Results:** Results proved that revascularization of critical limb ischemia patients by endovascular intervention was better than conservative management in terms of limb salvagability and patient survival.

**Conclusion:** Endovascular intervention was found to be a promising and more effective procedure than conservative management in patients with critical limb ischemia and the conservative procedure should be limited to patients not feasible to revascularization.

**Keywords:** Critical limb ischemia, Balloon Angioplasty, conservative.

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### INTRODUCTION

Most patients with rest pain or tissue necrosis had complex, multilevel occlusive disease in patterns that appeared unfavorable to treat surgically, and these patients were often subjected to primary amputation. This situation had changed dramatically in the last 20 -25 years as interventional management strategies to treat virtually all patterns of arteriosclerotic disease underlying severe limb ischemia<sup>[1]</sup>

Despite the benefits of pharmacologic therapy, arterial revascularization remains a mainstay in the management of CLI for restoration of arterial blood flow. The clinical objective of treating CLI is to avoid amputations, achieving limb salvage, and it is considered successful when the lesions are healed and the plantar stand is maintained, even when achieved by minor tarsal-metatarsal amputation. Due to good clinical results, endovascular treatment of CLI is gaining acceptance as a primary therapeutic strategy, with acceptable limb salvage and amputation-free survival rate<sup>[2]</sup>.

Endovascular intervention has emerged as an accepted modality of therapy for these patients, it poses multiple challenges to the interventionalist due to the presence of widespread multilevel disease, long and complex occlusive lesions, and

involvement of the tibial vessels, which itself poses specific interventional challenges<sup>[3]</sup>

CLI, in both diabetic and non diabetic patients can be presented either by persistently recurring ischemic rest pain requiring regular adequate analgesia for more than 2 weeks with an ankle systolic pressure  $\leq 50$  mmHg and/or toe systolic pressure  $\leq 30$  mmHg or ulceration or gangrene of the foot or toes, with an ankle systolic pressure  $\leq 50$  mmHg or toe systolic pressure  $\leq 30$  mmHg.<sup>[4]</sup>

There are multiple classification systems for chronic limb ischemia as Anatomic classification Trans Atlantic Inter-Society Consensus (TASC II) and Joint Endovascular and Noninvasive Assessment of Limb Perfusion (JENALI) Classification and Symptom classification as Rutherford and Fontaine Classifications and WiFi classifications.<sup>[5]</sup>

The objective of diagnostic testing in patients with CLI is to confirm the presence of PAD, identify the distribution and hemodynamic significance of disease, and provide anatomic information to plan a revascularization procedure<sup>[6]</sup>

The Noninvasive Physiologic Tests include Handheld Continuous Wave Doppler

(CWD), ankle-brachial systolic pressure index (ABI), transcutaneous oxygen pressure (TcPO<sub>2</sub>) and Skin Perfusion Pressure by Laser Doppler while the Noninvasive Anatomic Imaging include Duplex ultrasonography (US) examination, Ankle peak systolic velocity, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) [7]

The ultimate goal of critical limb ischemia treatment is to reestablish the normal perfusion which based on upon the balance between risk of the intervention and the durability of the improvement that can be expected from this intervention [8]

The treatment strategies have been practiced in order to preserve the limb can be classified into endovascular treatment and bypass surgery. The endovascular treatment of peripheral arterial disease (PAD) has gained widespread interest. This is because of the development of new technologies and an increasing operator experience,[9]. Therefore, endovascular treatment has replaced open surgical procedures as the first line of treatment for many arterial lesions. Also reintervention is relatively easier with endovascular than with surgery [10]

However, The technical success and subsequent durability of crural angioplasty are limited compared with bypass surgery, but the clinical benefit is acceptable because limb salvage rates are equivalent to bypass surgery” It has been shown that tibial restenosis can delay wound healing, but this does not mean that once healed, that restenosis will lead to recurrent ulcerations[11]The indications of infrapopliteal angioplasty are: if no suitable vein available for bypass, focal lesions, severe infection near the sites of planned anastomosis, poor general conditions, high surgical risk, and if the patient refuses surgery, [9]

The conservative management is confined to patients with extensive co morbidities not fit for surgery, absent collateral run off to the foot as a last option before lry amputation [9]

#### **PATIENTS & METHODS**

This study was conducted as a Non randomized control study" that included 76 critical lower limb ischemia patients of different age & sex who were admitted to the Department of Vascular Surgery at Zagazig Universities Hospitals.

38 patients were scheduled for below knee angioplasty, while the other 38 patients underwent conservative management and follow up from the beginning of August 2015 till the end of April 2018. These patients underwent a follow up period of 12 months.

The *Inclusion Criteria* are: Patients with critical lower limb ischaemia (Rutherford categories 4,5&6), Patients with solely infragenicular occlusion (presence of popliteal pulse) and presence of collateral distal refilling of at least one of the foot vessels (Revascularization Group) and Absent of Distal Collateral Refilling (Conservative group) while the *Exclusion Criteria* are Patients with supragenicular artery occlusion, patients with unsalvageable limb or threatening infections and patients with suspected unavailability throughout the study.

#### **Description of Technique:**

Patients would be allocated into either of two groups:

Group A (n =38) Endovascular management:

Patients undergoing PTA will receive transfemoral antegrade angioplasty and if failed retrograde transpedal or tibial angioplasty will be done.

Group B (n =38) Conservative management:

Patients undergoing conservative management will receive PGE1, antiplatelets (clopidogril or aspirin) and cilostazol.

Pre-Procedural: Prior to our therapy, all patients were counseled, signed a consent and had a full vascular assessment, including clinical history, physical examination, preoperative duplex with assessment of the ABI, risk factor profile and serum creatinine , X-ray imaging and Photos of the foot lesion and CT Angiography.

Initial broad-spectrum antibiotics in addition to Pre and postoperative debridement and minor amputations (toe/s or trans metatarsal without affecting the pedal arch) for patients presenting with wet gangrene/ necrotic tissue or sloughs in the wound bedand, this was done in both groups. The wounds were subsequently reassessed for possibility of limb salvage. Cardiac, pulmonary, renal, and glycemic status were optimized preoperatively with the assistance of the concerned specialist physicians.

#### **Intra-procedural (Group A):**

##### *Peri-procedural medications:*

Peri-procedural medications used were clopidogril loading dose (300mg) and oral acetylcystine 600mg once with good hydration at a rate of 0.5 ml/kg/hr normal saline for 6 hrs before and after the procedure.

##### *Imaging Technique:*

The procedure was done under local anaesthesia in a vascular surgery room with a mobile C-arm with vascular imaging capabilities

##### *Access:*

Intra-procedural 5000-10000 units of unfractionated heparin were administered. Obtaining of intraarterial access through CFA through pulse palpation or under fluoroscopy in cases of severe calcification is by using cutting sheath 6 Fr.

Diagnostic digital subtraction angiography was first done using iodinated contrast dye where the angiographic information regarding diseased segment location, length and degree of stenosis or occlusion, and extent of distal run-off were available.

#### *Crossing the lesion:*

Crossing the lesion with mainly (0.035" hydrophilic guide wire Terumo) or low-profile (0.018" V-18 control wire Boston Scientific). In 2 cases, retrograde approach through ATA. It was done by exploring it at the ankle and insertion of micropuncture set and then crossing the lesion. We used guiding catheter (Bern 4Fr) for selective angioplasty and in tight lesions, we used support catheter (Rubicon, Boston Scientific).

#### *Dye Used:*

In most patients, we used non ionized contrast (Telebrix) or (Ultravest) while in renal patients, we used CO2 angiography.

#### *Balloon Used:*

Dilatation was done through long tibial balloons 3Fr and 2.5Fr semi compliant (Amphirion, INVATEC) and high pressure (Mustang, Boston Scientific) for highly calcified lesions. In the case of arterial spasm, 0.1 to 0.2 mg nitroglycerin was administered as intra-arterial bolus.

#### *Criteria of success and failure:*

Technical success is defined as restored patency of the vessel with an angiographic residual diameter stenosis of < 30% of the target vessel with an inline flow in at least one tibial vessel down to the foot. Clinical success is defined as some combination of symptomatic improvement and objective haemodynamic success. Haemodynamic success is defined as an increase in the ABI of more than 0.10. Haemodynamic failure occurred if the ABI declined or the rise was < 0.10 or if the stenosis or occlusion recurred confirmed by duplex scanning or arteriography.

#### *Post-procedural:*

The patients puncture site was 24 hours inspected for hematoma or pseudoaneurysm. ABI was measured and compared to preprocedural level and recorded. After the procedure all

patients were prescribed low molecular weight heparin (LMWH) anticoagulation for 72 hrs. Then aspirin (150mg/day), clopidogril (75 mg/ day) and statins (20mg/day) were given during the whole follow up period. The patients followed an appropriate risk factor modification program.

#### **Group B**

The patients were hospitalized and underwent conservative therapy in the form of alprostadil (PGE1), Prostavasin or Alpropristin, at a dose of 80 – 100 mic in 250 cc normal saline I.V infusion over an hour per day for 6-8 weeks beside other antiplatelet as aspirin (150mg/day), clopidogril (75 mg/ day) and statins (20mg/day) and cilostazol 100mg bid.

#### **Follow Up and Surveillance**

All patients were followed up to the endpoints of limb salvage, patency rate, major amputation or deaths at the end of the follow up period.

A foot ulcer was defined as a full-thickness skin defect distal to the malleolar level present for at least 2 weeks.

Ulcer healing was defined as complete epithelialization of the tissue defect by secondary intent or after any additional local ulcer surgery. The foot ulcer was considered non-healed if it did not heal during the follow-up period.

Major amputation was defined as an amputation proximal to the ankle level.

Limb salvage was considered if the ulcer/gangrenous segment had healed completely or if at the end of the follow up period, the ulcer persisted but with a significant reduction in size and progression of the healing process.

All wounds were classified as either granulating with ongoing healing progress, complicating in the form of infection or gangrene or getting lost at the time of each review.

All dressings were performed depending on the wound status. Dressings and wound evaluation were performed daily, initially after the arterial intervention and later at alternate day/every third day, once adequate granulation tissue was noted to cover the wound and wound epithelialization had started.

Further Intermittent debridement was performed as dictated by the wound status either as an outpatient procedure or in the operating room. Foot counseling and appropriate offloading footwear were advised to all patients to help early ambulation.

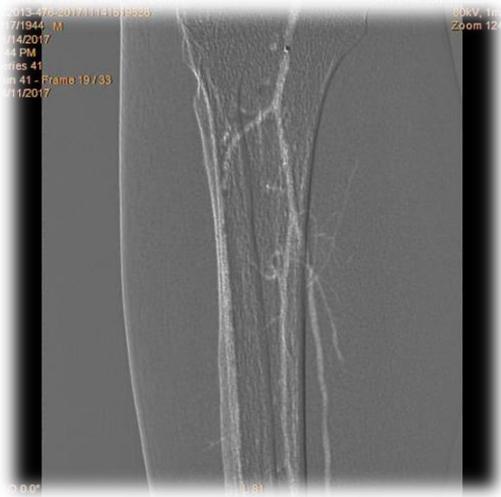


Fig (1): CO<sub>2</sub> angiography showing stenosis of tibioperoneal trunk, peroneal a.



Fig (2): After infragenicular angioplasty using CO<sub>2</sub>

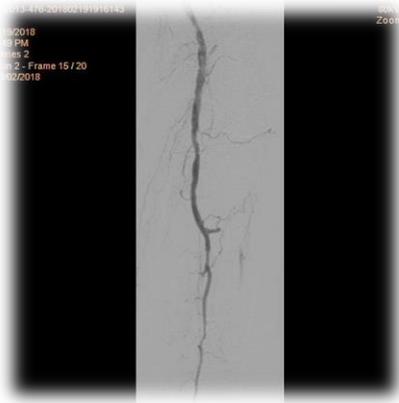
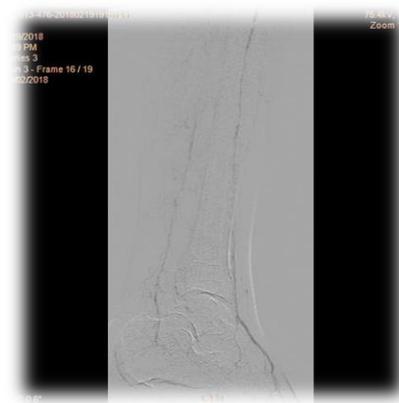


Fig (3): ATA occlusion



Fig(4): Distal multiple stenotic ATA segments



Fig (50): Dilatation of distal ATA



Fig (5): Dilatation of proximal ATA

**RESULTS**

In our study, all patients who met the inclusion criteria in the Department of Vascular and Endovascular Surgery at Zagazig University Hospitals were enrolled. The study started from beginning of August

2015 till the end of April 2018. These patients underwent a follow up period of 12 months. We categorized our patients in two major categories endovascular and conservative groups according to the presence of suitable run off.

**Sex distribution between groups**

		Group		Total	P
		Conservative	Endovascular		
Gender	Female	N	<b>13</b>	<b>8</b>	<b>21</b>
		%	<b>34.2%</b>	<b>21.1%</b>	
	Male	N	<b>25</b>	<b>30</b>	<b>55</b>
		%	<b>65.8%</b>	<b>78.9%</b>	
Total	N	<b>38</b>	<b>38</b>	<b>76</b>	
	%	<b>100.0%</b>	<b>100.0%</b>	<b>100.0%</b>	

**Table (1):** showing sex distribution among the study patients

There was no significance difference between groups as male represent 65.8% from conservative and 78.9% from endovascular groups.

Most of the study patients were diabetics;85.5%,68%of the study patients (52 patients) were smokers , 13.2% (10 patients) had cerebro-vascular strokes (CVS) , 44.8 % (34 patients) had ischemic heart disease (IHD) , and 86.8% (67% patients) were hypertensive (HTN).

**Risk Factors and Co-morbidities:**

	Conservative	Endovascular	Total	Percentage
DM	31	34	65	85.5%
HTN	4	5	9	88.2%
SMOKING	28	24	52	68.4%
IHD	17	17	34	44.8%
COPD	0	2	2	2.6%
RENAL	11	4	15	19.7%
STROKE	5	5	10	13.2%

**Table (2):** Risk Factors and Co-morbidities

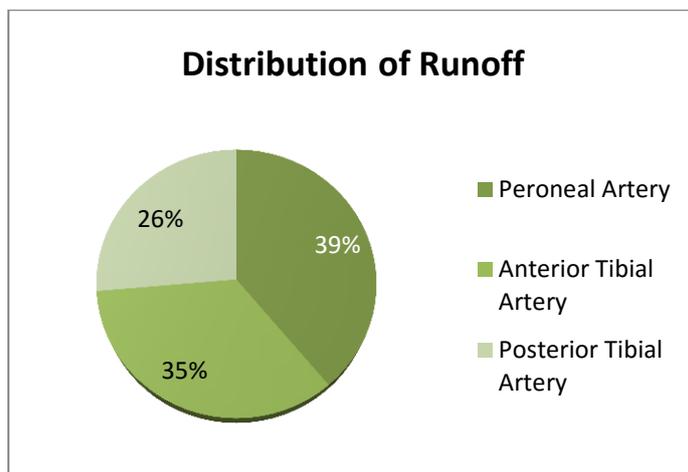
**Patients Complaints at the beginning of the study:**

**Table (3):** showing patients Complaints at presentation

	Endovascular Group	Conservative Group
<b>Rest Pain</b>	8	7
<b>Rutherford 4</b>	21%	18.4%
<b>Minor Tissue Loss</b>	30	12
<b>Rutherford 5</b>	79%	32%
<b>Major Tissue loss</b>	6	19
<b>Rutherford 6</b>	15.7%	50%

It was noticed that most patients in the study presented with tissue loss which was much severe in conservative group.

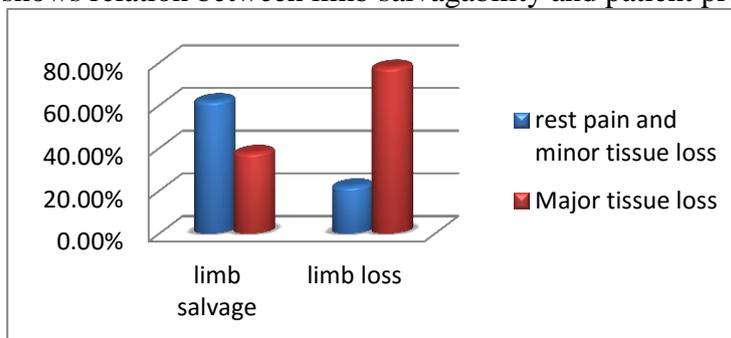
**Runoff Vessel Distribution**



**Predictors of success and failure in both groups**

**Patient presentation at the study time:**

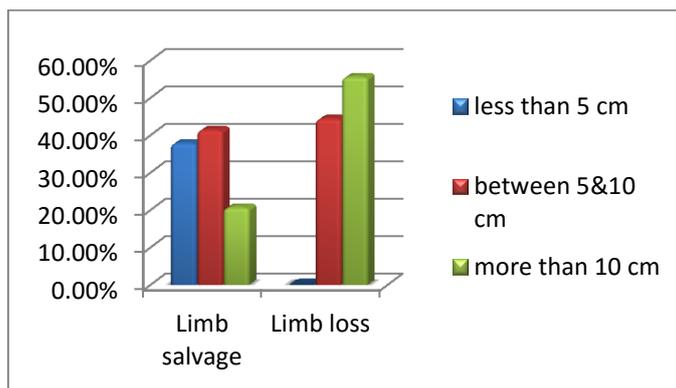
**Fig (6):** shows relation between limb salvagability and patient presentation



Most salvaged limbs were presented with rest pain and minor tissue loss (ulcer or toe amputation) 62% while, most patients with amputations were presented with major tissue loss (77%) e.g. .forefoot amputation.

**Target Lesion Length:**

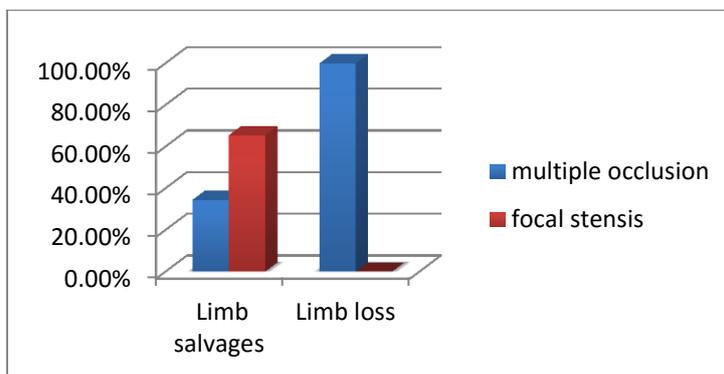
**Fig (7):** shows lesion length and its relation to limb salvagability



Limb salvagability was considered with shorter lesion especially in lesions less than 5 cm and vice versa.

**Nature of Target Lesion**

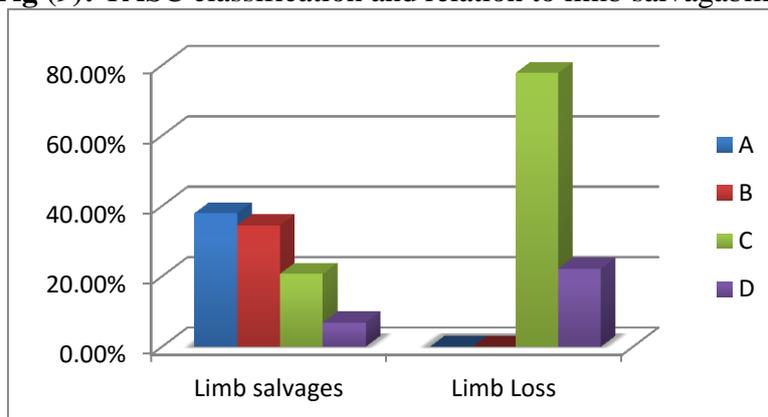
**Fig (8):** shows lesion length and its relation to limb salvagability



It was noticed that limb salvagability significantly correlated to focal and stenotic lesions rather than occlusive and multiple ones.

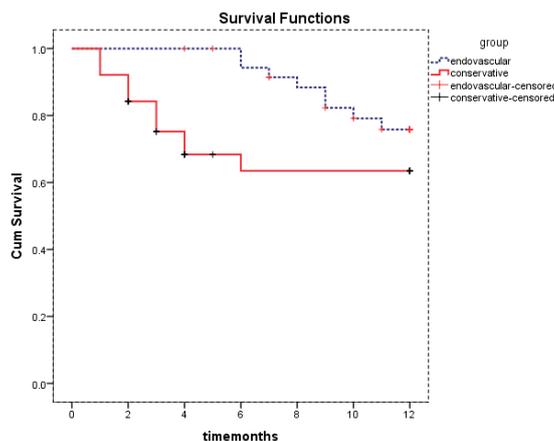
**TASC Classification**

**Fig (9):** TASC classification and relation to limb salvagability



Limb salvage was associated with earlier stages of TASC classification and vice versa.

**Fig (10):** Kaplan Meier curve shows cumulative freedom from major amputation following infrapopliteal angioplasty and conservative treatment over the study period.



**Overall Comparisons**

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.135	1	.042

Test of equality of survival distributions for the different levels of group.

**DISCUSSION**

Critical leg ischemia (CLI) leads to significant morbidity and mortality and to the consumption of considerable health and social care resources in developed and developing countries [11]

If the critical limb ischaemia is not revascularized, Up to 40% of extremities with ischemic non healing ulcers, gangrenous digits or rest pain may require a major amputation within 6 months of onset [12]

For these reasons, infrapopliteal PTA is currently proposed as the primary treatment for critical limb ischaemia [13]

Nevertheless, conservative treatment can be used for critical limb ischemia patients not feasible for revascularization. They include prostanoids, spinal cord stimulation, and hyperbaric oxygen and wound management [14]

This study was designed to assess and to compare the outcomes of the percutaneous transluminal angioplasty and conservative management in patients with critical limb ischemia with infragenicular lesions regarding its efficacy on wound healing and limb salvage.

In January 2018, **Mustapha and coauthors** published a meta-analysis of Percutaneous Transluminal Angioplasty in Patients with Infrapopliteal Arterial Disease including a total of 6769 distinct patients, so we compared our patients' demographic characteristics, risk factors and comorbidities to those of patients in their meta-analysis.

Regarding patients characteristics, in our study the majority of cases were male (78.9%) with mean age of 64 years old.

A look into the patients' characteristics in the meta- analysis done by [15] revealed that the average of male gender was 66.2% and the mean age of all patients included in the study was 70 years old.

So, the percent of male gender in our study is higher in comparison to other studies on patients with critical limb ischemia On the other hand, we had lower mean age. This could be explained by the fact that we are a developing country with low health care standards and more exposure to risk factors in comparison to the developed countries and that leads to low life expectancy in the general population.

Regarding risk factors and medical history we found , 52 patients were smokers (68.3%), hypertension was present in 67 patients (88.7%), diabetes mellitus in 65 patients (89%), 15 patients with end stage renal disease (ESRD) on regular dialysis (19.5%), ischemic heart disease (IHD) in 34 patients (44.8%), COPD in 2 patients (2.6%) and previous stroke in 10 patients (13.2%).

In **Neupane et al. (2016)** who conducted a study to evaluate the clinical, angiographic characteristics and outcomes of patients with popliteal and infrapopliteal peripheral arterial disease (PAD) undergoing peripheral vascular intervention (PVI) , the smokers percentage was (66.5%), hypertension was present in (95%) of patients, diabetes mellitus in (65%) of patients, (16.7%) of patients with end stage renal disease (ESRD) on regular dialysis, ischemic heart disease (IHD) in (74.6%)of patients, and previous stroke in (26%) of patients [16].

In our study, the patients were divided into 2 groups according to feasibility of intervention, the endovascular group and conservative group, and because there is no previous data on such comparison, so we evaluate each group alone in non-randomized fashion to evaluate each group.

In endovascular group, we found that 8 patients (21%) presented with rest pain while the vast majority presented with minor tissue loss (79%) and the lowest category (15.7%) was the Rutherford 6 group.

According to **Abdelaziz, 2012** who conducted a paper on 40 patients to evaluate the results of percutaneous transluminal balloon angioplasty in patients suffering from infragenicular arterial diseases in patients with critical lower limb ischaemia, he found that the patient's clinical criteria at the time of angioplasty according to Rutherford category 4 (rest pain) was in 6 patients (18.7%) and Rutherford category 5 (minor tissue loss) was in 16 patients (50%) and Rutherford category 6 (major tissue loss) was in 10 patients (31.2%). [17]

In conservative group our results versus **Martini and Andreozzi 2012** ,who conducted a study on 90 patients with CLI not suitable for revascularization and underwent conservative management, show that patients were presented with rest pain (18, 4% vs. 31%) while patients major tissue loss (50% vs. 68%).

Discussing the state of runoff crural vessels in our study, we found that peroneal artery was present in the most cases in 28 patients with a percent (73%), (ATA) in 25 patients and lastly (PTA) in 19 patients with a percent (50%).

This was not comparable with **Zafarghandi et al., 2015**, who found in a study conducted to examine the outcome of angioplasty in patients with below-the-knee critical ischemia that peroneal artery was present in (50%) of patients, (ATA) in (26.92%) of patients, while the (PTA) in (84.61%) patients.<sup>[18]</sup>

Moving to technical success in our study, we find that 92% (36 patients) technically succeeded regarding crossing the lesion, dilatation with residual stenosis less than 30% while failure restricted in two cases due to failure to pass the lesion because of heavy calcification which can be correlated to **Conrad et al., 2009**, who conducted a study on Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease, they recorded technical success up to 71.6%. Similarly, **Vraux et al., 2000** who evaluated the feasibility and preliminary results at 1 year of angioplasty of tibial occlusions in critical limb ischaemia (CLI) reported a technical success rate of 78% in 40 patients undergoing infrapopliteal PTA for CLI.<sup>[18]</sup>

Technical success was lower in patients with TASC D lesions at 50%, compared with 63% as reported previously by **Kok et al., 2017** and technical success for the remaining A–C lesions was as higher at 100% as **Kok et al., 2017**, 81%.<sup>[13]</sup>

After excluding mortality, the overall clinical success, wound healing and limb salvagability in our study was 76.3% while in **Conrad et al., 2009** it was 86.2%.<sup>[14]</sup>

Our study agree with **Mustapha et al., (2018)** regarding the major predictives of clinical success were Rutherford category of patients, failure was more associated with tissue loss  $P=0.02$ , length of lesion, the longer the lesion the more failure ( $>10$  cm)  $P=0.041$ , type of the lesion, failure was associated with multiple and occlusive lesions  $P=0.001$  rather than stenotic and focal lesions.<sup>[15]</sup>

Looking to conservative group lesion characteristics, we found that cases had lesion 5-10 cm were 6 cases (15.8%) while the rest had long lesions more than 10 cm (84.2%), multiple occlusions in 21 patients (55.3%) and single long occlusion in 17 patients (44.7%). Studying the association

with success and failure in conservative group, the incidence of limb loss for patients with stroke was (23.8%) compared with (0%), ( $P$  value 0.031) for those without previous cerebrovascular accident and this can explain that patients with stroke have extensive atherosclerotic disease. Moreover, failure also was associated significantly with length of lesion more than 10 cm (95.2%), ( $P$  value 0.038).

(**Marston et al., 2006**) found that multivariate risk factor analyses revealed that ABI was independently associated with amputation at 1 year. At 12 months, 32% of limbs with an ABI  $\leq 0.5$  and 43% of limbs with an ABI  $\leq 0.4$  required amputation compared with 15% of limbs with an ABI between 0.5 and 0.7 ( $P=0.01$ ).<sup>[18]</sup>

Looking at the amputation as a failure representative, we found that 16 patients underwent major amputation (41.8%) and in **Brass et al., 2006** study was (16.2%) while in the endovascular group, it was (23%).<sup>[17]</sup>

Regarding mortality in conservative group, 10 patients (26.3%) expired due to extensive co morbidities associated as MI and stroke and in **Brass et al., 2006** it was (10%) while in endovascular group it was (21%).<sup>[17]</sup>

## CONCLUSION

From our study we conclude that endovascular intervention is better than conservative management regarding limb salvagability, wound healing and life quality. Conservative management should be restricted for patients with poor runoff as a last treatment option.

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