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ORIGINAL RESEARCH

Surgical management and outcomes of late-presenting acute limb ischaemia at 2 referral hospitals in Addis Ababa, Ethiopia: A 1-year prospective study

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Running title: Acute limb ischemia in Addis Ababa, Ethiopia

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Abstract

Objective: The study was performed to show the overall perspective of surgical management for acute limb ischemia specific to Ethiopian population.
Methods: A prospective planned cohort study was conducted to analyze the socio-demography, clinical presentation, causes of limb ischemia, and outcomes of surgical intervention, and variables associated with complications of acute limb ischemia.

Results: A total of 102 patients were operated upon. The male to female ratio was 2:1; the mean age of presentation was 54±17 years. Patients presented after an average of 9±4.8 days of symptom onset. The type of procedures performed were, thrombectomy 51(47.2%), primary amputation 24(22.2%), bypass or interposition vascular grafts 10(9.2%), embolectomy 10(9.2%), primary vascular repair 7(6.4%), and femoro-femoral graft 6(5.5%). Local and systemic complications occurred in 35.3% and 17.6% respectively. Amputation after re-vascularization surgery was seen in 32.4%. A 30-day total amputation & mortality rate was 52.9% and 9.8% respectively. Clinical variables found to have a statistical significant association (P<0.05) with complications were age ≥ 60 years, late presentation (≥ 9 days), patients with hypertensive disease and previous myocardial infarction.

Conclusions: Optimizing co-morbidities, timely detection and treating immediately on arrival could potentially play a key role in improving surgical outcomes of acute limb ischemia.

Keywords: Acute Limb Ischemia, Thrombosis, Embolism, Re-vascularization

Introduction

Acute limb ischemia (ALI) is a medical emergency, which is responsible for a high proportion of morbidity and mortality attributable to cardiovascular disease [1]. According to the 2007 Transatlantic Intersociety Consensus (TASCII) for the management of peripheral arterial disease (PAD), ALI is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability in patients who present within two weeks of acute onset of symptoms [1].

A recent review of the literature showed that, despite urgent revascularization with thrombolytic, endovascular, or open vascular surgery, the one-year amputation and mortality rates are high, ranging between 15-20% and 15-40% respectively [2]. In the USA, ALI affects 1.28% of the adult population aged ≥40 years [3,4]. A population-based estimate of ALI in low and middle-income countries (LMICs) like Ethiopia is difficult to determine. However, data from the Global Burden of Diseases Program [3,4,5] and a systematic review of prevalence surveys...
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[6] showed that the rate of growth of ALI prevalence between 1990 and 2010 was faster in LMICs than in developed nations [7,8].

The majority of the Ethiopian population is young with a median age of 19.8 years. The age demographic pyramid of Ethiopia is an expandable type with a wider base where 60% of the population is <24 years, and only 3% are >65 years. Despite this type of population structure, a study conducted on the Ethiopian national mortality burden during 1990-2015 showed that diseases like cardiovascular, diabetes, cancer, and other non-communicable diseases have become the leading causes of hospital death in 2015 [8].

In Ethiopia, surgical services to treat ALI have started very recently in a few hospitals in the country. Our experience in surgically treating ALI is limited. To date, the literature review performed showed very few reports from sub-Saharan Africa and none from Ethiopia. Accordingly, the report shows our experience on the risk factors, etiologies, outcome, and associated factors influencing the surgical outcome of ALI.

Methods

An institutional-based prospective planned cohort study was conducted on all patients operated for ALI at TASH and Teklehaimanot General Hospitals in Addis Ababa, Ethiopia from January 1, 2018, to December 31, 2018. Patients were referred from regional hospitals or received direct assistance at TASH and Teklehaimanot General hospitals. Diagnosis with ALI was made, using a combination of clinical imaging by Doppler US, CT-Angiography and intraoperative findings.

All patients with ALI due to thrombosis, emboli, or trauma were included in the study.

After patients arrived at the hospitals, the primary treatment strategy was determined according to the clinical assessment of limb viability. After the clinical diagnosis of non-traumatic ALI, 5000 Units of unfractionated heparin was initially given intravenously, then 17500 Units was given subcutaneously for a few days. Later, this was switched to oral anticoagulant medications. For patients with a history of atherosclerosis and in-situ thrombosis, Aspirin 81mg or Clopedogrile 75mg was given orally.

Patients with PAD without ischemia, who self-discharge before the intervention or refused surgery, and had incomplete data for analysis were excluded from the study. All patients were operated by Consultant Vascular
Surgeons and were followed up on the 1st and 3rd. Patients were treated with either revascularization procedures or amputations. The different types of revascularization procedures conducted were thrombectomy, embolectomy, reversed great saphenous vein bypass graft (RGSV), extra-anatomic crossover femoro-femoral bypass graft, and primary repair for traumatic vascular injury.

**Statistical analysis**

The measurable (independent) variables used for this study were age, sex, duration of acute limb pain, risk factors, and comorbidities. Amputation, local/systemic complications, and mortality were used as dependent variables. The primary outcome was identified as the occurrence of amputation, systemic or local complications, and death at 30 days and 3 months after surgical intervention. The same events were similarly analyzed separately as a secondary outcome. Predesigned structured questionnaires were used for data collection during the initial presentation of the patients and subsequently at 1st and 3rd month of post-surgical intervention period. After appropriate training, six final year general surgery residents collected data and the principal investigator subsequently checked and cleaned the content. Data were entered and analyzed using SPSS software version 22. Results of univariate analysis were expressed in a ratio, frequency, and percentage. The occurrence of the dependent variables by several of the independent variables was tested using a 2-test and P-value < 0.05 was used as an acceptable level of significance. The logistic regression model was applied to see the relation between possible risk factors and amputation, systemic or local complications, and mortality.

**Operational definitions**

ALI - A patient who presented within two weeks of acute symptom onset.

Thrombosis- Acute thrombus with no documented cardio-embolic source.

Major amputation – Above or below knee amputation

Minor amputation – digital or fore foot amputation
Results

Baseline characteristics

During the study period, a total of 124 patients presented at the hospitals with ALI. Surgical intervention was performed for 116 patients. 8 patients refused surgery and self-discharged against medical advice. This occurs, as there is a cultural trend for patients to go to traditional healers. Among those operated patients, 102 were found eligible for this study. The other 14 patients were excluded from the study because there was no data from the follow-up clinic. The male to female ratio was 2:1 and the mean age at presentation was 54±17 years (age ranges 23-95 years). The average duration of symptoms before presentation was 9 ± 4.8 days (ranges 1-15 days). All the patients presented after 24 hours of the onset of symptoms. Eighteen (17.6%) patients presented within 1-3 days, 35 (34.4%) within 4-9 days & 49 (48%) patients within 9-15 days.

The main causes of ALI in the cohort were thrombosis, 77 (75.5%), embolism, 14 (13.7%), and trauma, 11 (10.8%). Risk factors for thrombosis, hypertension and diabetes mellitus were among the most common, accounting for 40(39.2%) and 32(31.4%) respectively. Smoking [7(6.9%)] and dyslipidemia [4(3.9%)] were the least contributing risk factors identified. The source of all emboli was from the heart, because of previous ischemic heart disease; rheumatic valvular heart disease, and dilated cardiomyopathy. (Table 1). The lower limb was affected six times more than the upper limb [88(86.3% Vs 14(13.7%)]. Bilateral lower limb ischemia was seen in only 5(4.9%) patients.

During the initial presentation, 47 (45.9%) of patients had gangrene and 58(56.9%) had neurologic deficits of the affected limb. Among those patients presented with gangrene, 43 (42.2%) of them was treated with amputation (24 primary & 19 secondary amputations) & 4 (3.9%) had digital gangrene, which sloughed off after the revascularization procedure.

Surgical intervention

Patients were treated either with revascularization procedures or amputation. A total of 108 procedures were conducted for 102 patients. Thrombectomy was the most frequent revascularization procedure, [51(47.2%)], followed by thrombectomy with primary major amputation, [8(7.8%)], thrombectomy with reversed great saphenous vein bypass graft (RGSV), [3(2.9%)], RGSV graft alone, [5(4.8)], and an extra-anatomic crossover.
femoro-femoral bypass graft performed for unilateral common an external iliac thrombosis, [6(5.5%]. For those with traumatic vascular injury, primary repair and RGSV interposition graft were carried out on 7(6.4%) patients and RGSV interposition graft on 5 (4.6%) patients. Primary major amputation and embolectomy were performed on 23 (21.3%) and 10(9.2%) procedures respectively. (Table 2).

Outcomes of surgical Intervention at 30 postoperative days and 3 postoperative months

There were 10(9.8%) deaths and 54 (52.9%) amputations conducted in the cohort of patients investigated. The total limb salvage rate was 48(47.1%). Causes of death were acute coronary syndrome, 6(5.9%), overwhelming sepsis, 3 (2.9%), and acute respiratory insufficiency, 1 (0.9%). Amputation after an attempt of revascularization was performed for 33(32.4%) patients. During the study period, 36(35.3%) patients developed procedure-related local complications in which re-thrombosis of native vessels and surgical site infections were seen in 14.7% & 12.6% of patients respectively. Systemic complications occurred in 18 (17.6%) patients, the most common was acute coronary syndrome, 6 (5.9%), and acute kidney injury, 5 (4.9%).

During the subsequent 3-month follow up, 3 more patients required amputations due to re-thrombosis and one patient died because of overwhelming sepsis of a wound site infection. The final amputation and mortality rates after a 3-month follow up were 55.9% & 10.8% respectively. (Table 3)

Short-term predicators of amputation and death

On logistic regression bivariate analysis, age > 60 years as compared to those with 20-40 years, was found to have significantly associated with an increased rate of limb amputation and mortality. [(p = 0.017; OR = 3.8; 95% CI, 1.26 to 11.11) (p = 0.037; OR = 9.72; 95% CI, 1.15 to 82.32)]. Significantly more patients with combined hypertension and diabetes mellitus underwent amputation (p = 0.028; OR = 10.15; 95% CI, 1.29 to 80.12) compared to patients who had neither hypertension nor diabetes mellitus. Similarly, patients with hypertension alone showed significant association with increased risk of amputation (p = 0.031; OR = 2.76; 95% CI, 1.05 to 6.32) compared to non-hypertensive.

In the same way, the duration of symptoms before presentation at the hospital had a strong association with increased risk of amputation and a patient who came after 9 days (average time in this study) underwent more amputation (p = 0.013; OR = 4.22; 95% CI, 1.36 to13.12) than those who presented within 3 days. However, a
similar association was not demonstrated with mortality. A significant rate of mortality was observed in patients who had Ischemic heart disease compared to those who didn't have it. \((P = 0.036; \text{OR} = 5.31; 95\% \text{ CI}, 1.11 \text{ to } 25.38)\).

Patients with diabetes mellitus alone, smoking, dyslipidemia, and cardiac risk factors other than Ischemic heart disease (atrial fibrillation, rheumatic valvular heart disease, dilated cardiomyopathy) were statistically tested separately & in combination and showed no significant association with amputation or mortality rate.

**Discussion**

In this study, it was found that patients generally presented very late with a significant number of them arriving at the hospital with irreversible limb ischemia and tissue loss. The two most important explanations for the delay in presentation was a lack of awareness on the part of the health professionals, and patients need to travel a long distance to reach the vascular centre and had issues related to finance, transportation, and accommodations in the capital Addis Ababa.

Age >60 years, hypertension, previous ischemic heart disease, and delay in the presentation were factors that were significantly associated with higher morbidity and mortality. Therefore, a recommendation from this study is to ensure that patients are advised about the risk factors such as hypertension and diabetes mellitus and to have regular check-ups for PVD.

The male predominance of 67.6 %, in this study, is consistent with other reports [9,10,11]. The predominance of elderly male patients was similarly seen in other studies too [19, 22, 27]. Bivariate analysis showed that age > 60 years was associated with a three-fold increase in limb loss and a nine-fold increase in mortality as compared to those with 20-40 years of age. A similarly high rate of limb loss and death was also reported by other studies too [15,18,19].

As opposed to trends seen in developed countries [8,23], all our patients presented after 24 hours (mean, 9±4.8 days) with many of them having either a neurologic deficit or a gangrene limb. Multivariate analysis also showed that patients who presented after 9 days of acute symptom onset had a five-fold increase in limb loss as compared to those presented within 3 days. Because of this late presentation, the overall 3 months’ secondary amputation rate (55.9\%) was found 2-3-fold higher than similar studies done in developed countries [22-27]. Similarly, the
rate of limb loss following a revascularization procedure (32.4%) was higher than data from other studies too [24,25, 27].

Most literature agrees that ischemic conditions of the lower limb are more common than the upper limb [10,14,]. Such a difference was attributed to the unequal distribution of atherosclerotic occlusive diseases affecting both limbs [22].

Previous studies report that smoking is the most common predisposing factor for ALI [19, 22, 25]. However, in this study only 6.7% of patients smoke. Studies also showed that the relative risk of developing thrombosis is 2-3-fold higher in hypertensive patients who smoke. That is why the current guideline for hypertensive diseases with PAD supports aggressive treatment with a target blood pressure of 130/80 mmHg [17, 18, 20, 21].

In our study, hypertensive patients with ALI had a three times higher risk of amputation than those without it. Besides, when hypertension was combined with diabetes mellitus, the relative risk of limb loss increased tenfold. A similar finding was also reported in other articles. [21,24]

In this study, we observed that primary vascular repair and RGSV interposition graft conducted for the vascular injury had a better limb salvage rate as compared to bypass graft performed for all other causes of ALI. These patients usually arrive early and go treatment immediately, most of them were young and with better disease-free vessels than otherwise older patients.

At Thirty days postoperatively, systemic and procedure-related complications occurred in 17.6% and 35.3% of patients respectively. This figure was higher compared to experience from South Africa [25]. The 30-day mortality rate of ALI in this study was 9.8%; only one patient died in a subsequent 3 month follow up making an overall mortality rate of 10.8%. This finding was much lower than a report from other authors [26,27] but comparable with reviews made in Iran and Lithuania [23,28,33].

**Conclusions**

ALI caused by thrombosis, embolism, or trauma was identified as one of the major events in TASH and Teklehaimanot General hospitals and was significantly associated with higher morbidity and mortality. In general, age > 60 years, hypertension, combined hypertension & diabetes mellitus, myocardial infarction, and delayed...
presentation were strongly associated with a high rate of morbidity and mortality. Therefore, treating and optimizing co-morbidities, timely detection, and early intervention are the most important modifiable risk factors that can play a key role in improving the surgical outcome of ALI.

Limitations

This study has several limitations. First, the analysis of clinical records was conducted in only two centers. Therefore, it is difficult to generalize the results to a national level. Secondly, some of the patients’ data were found incomplete during data coding and a few patients were lost at follow-up, so they were excluded from the analysis. Thirdly, the duration of the follow-up is only 3 months hence the long-term effect is not known.

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References

Surgical management and outcomes of late-presenting acute limb ischaemia at 2 referral hospitals in Addis Ababa, Ethiopia: A 1-year prospective study
Table 1. Demographics and associated risk factors of patients with ALI and its relationship with amputation

<table>
<thead>
<tr>
<th>Risk factors for ALI</th>
<th>No, (%)</th>
<th>Amputation rate (%)</th>
<th>P-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>69 (67.6)</td>
<td>38.2</td>
<td>0.596</td>
<td>1.2</td>
</tr>
<tr>
<td>Age (years) - &gt; 60 years</td>
<td>34 (33.3)</td>
<td>19.6</td>
<td>0.017</td>
<td>3.75</td>
</tr>
<tr>
<td>- 40-60 years</td>
<td>40 (39.2)</td>
<td>26.5</td>
<td>0.032</td>
<td>3.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (39.2)</td>
<td>29.4</td>
<td>0.031</td>
<td>2.76</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>32 (31.4)</td>
<td>17.6</td>
<td>0.163</td>
<td>2.1</td>
</tr>
<tr>
<td>Hypertension &amp; Diabetes Mellitus</td>
<td>20 (19.6)</td>
<td>13.7</td>
<td>0.028</td>
<td>10.1</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (6.9)</td>
<td>3.9</td>
<td>0.478</td>
<td>1.8</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4 (3.9)</td>
<td>1.9</td>
<td>0.999</td>
<td>1.1</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>4 (3.9)</td>
<td>2.9</td>
<td>0.370</td>
<td>0.6</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>3 (2.9)</td>
<td>1.9</td>
<td>0.345</td>
<td>2.2</td>
</tr>
<tr>
<td>Ischemic Heart Disease &amp; Atrial fibrillation</td>
<td>2 (1.9)</td>
<td>1.9</td>
<td>0.761</td>
<td>1.6</td>
</tr>
<tr>
<td>RVHD and atrial fibrillation</td>
<td>3 (2.9)</td>
<td>1.9</td>
<td>0.496</td>
<td>0.8</td>
</tr>
<tr>
<td>Rheumatic Valvular Heart Disease</td>
<td>1 (0.9)</td>
<td>0.9</td>
<td>0.703</td>
<td>0.5</td>
</tr>
<tr>
<td>Dilated Cardiomyopathy</td>
<td>1 (0.9)</td>
<td>0.9</td>
<td>0.703</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Table 2. Types of surgical procedures done for ALI and subsequent amputation rates at 3 months follow up

<table>
<thead>
<tr>
<th>Primary Surgical Procedure</th>
<th>Number (%)</th>
<th>Amputation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombectomy</td>
<td>51 (47.2)</td>
<td>17.6</td>
</tr>
<tr>
<td>Primary major amputation</td>
<td>23 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Embolectomy</td>
<td>10 (9.2)</td>
<td>3.9</td>
</tr>
<tr>
<td>Primary vascular repair</td>
<td>7 (6.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Extra-anatomic crossover</td>
<td>6 (5.5)</td>
<td>3.9</td>
</tr>
<tr>
<td>Femoro-femoral graft (PTFE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interposition graft (Reversed GSV)</td>
<td>5 (4.6)</td>
<td>1.9</td>
</tr>
<tr>
<td>Bypass graft (Reversed GSV)</td>
<td>5 (4.6)</td>
<td>3.9</td>
</tr>
<tr>
<td>Primary minor amputation</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>108 (100)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Local and Systemic complications of Acute Limb Ischemia at 30th day and 3rd month of follow up time

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Complications</th>
<th>At 30th day No. (%)</th>
<th>At 3rd month No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Acute coronary syndrome</td>
<td>6 (5.9)</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td></td>
<td>Acute kidney injury</td>
<td>5 (4.9)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>3 (2.9)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular attack</td>
<td>3 (2.9)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Acute respiratory insufficiency</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Local</td>
<td>Re-thrombosis of native vessels</td>
<td>15 (14.7)</td>
<td>20 (19.6)</td>
</tr>
<tr>
<td></td>
<td>Surgical site infection</td>
<td>13 (12.6)</td>
<td>15 (14.7)</td>
</tr>
<tr>
<td></td>
<td>Graft failure</td>
<td>6 (5.9)</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>2 (1.9)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>No complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>48 (47.1)</td>
<td>40 (39.2)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>102 (100)</td>
<td>102 (100)</td>
</tr>
</tbody>
</table>

Table 4. Duration of symptoms versus amputation rate

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th>Limb Salvage (%)</th>
<th>Amputation rate (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 days</td>
<td>12 (66.7)</td>
<td>6 (33.3)</td>
<td>18 (17.7)</td>
</tr>
<tr>
<td>4-9 days</td>
<td>8 (22.9)</td>
<td>27 (77.1)</td>
<td>35 (34.3)</td>
</tr>
<tr>
<td>&gt; 9 days</td>
<td>14 (28.6)</td>
<td>35 (71.4)</td>
<td>49 (48)</td>
</tr>
<tr>
<td>Total</td>
<td>34 (33.3)</td>
<td>68 (66.7)</td>
<td>102 (100)</td>
</tr>
</tbody>
</table>