LONG TERM EFFECTS OF BELOW-THE-KNEE ANGIOPLASTY IN DIABETIC PATIENTS WITH CRITICAL ISCHEMIA OF LOWER LIMBS REFERRED TO SINA HOSPITAL DURING 2010-2011

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Despite significant advances in the treatment of diabetic foot ulcers and below-the-knee critical ischemia, there are ongoing efforts to achieve a method with low complication, high success rate and persistence of long-term effects.

The aim of the study was to examine the outcome of angioplasty in patients with below-the-knee critical ischemia referred to Hospital.

Material and methods. This semi-experimental study conducted on diabetics patients treated with PTA (Percutaneous transluminal angioplasty) with critical ischemia of lower limbs referred to Sina Hospital. After discharge, the patients were followed weekly for the first month and then monthly up to 12 months. The procedure short-term effects were examined through evaluation of wound healing as well as patients' recovery and pain relief, after one month. Given the distribution type, parametric and non-parametric test were used to compare the results before and after treatment. Pearson's correlation coefficient was used to determine the correlation between variables.

Results. Twenty four patients participated in this study. The mean ankle-brachial index (ABI) at baseline was 0.55±0.17. A month after angioplasty, the index increased statistically significant to 0.93±0.16. The mean health score expressed by the patients at baseline was 5.48±1.39. A month after angioplasty, it was significantly increased (6.32±1.24). The mean pain score before enrollment was 6.68±2.52 (according to VAS scale). There was a significant decrease over time (3.45±1.13). The overall mean score of all patients at Rutherford Classification was 3.88±0.63 at baseline. During the 1st month and 6th month follow-up, it was changed to Class 0 that was statistically significant in the first month.

Conclusions. This study represents the mid-term outcomes of PTA. Although PTA treatment was associated with improved pain scores, satisfaction with health, classification of limb ischemia and diabetic foot ulcers, the effects only remain short-term and mid-term. However, long-term efficacy of PTA needs to be investigated further.

Key words: diabetic foot, critical ischemic, PTA, lower limbs, ankle-brachial index

Diabetes is a disorder leading to peripheral arterial occlusive disease (PAOD) and its prevalence is increasing (1). Diabetics with PAOD have a worse prognosis compared to non-diabetic patients with PAOD. Patients with PAOD constitute more than half of non-traumatic amputation cases (2). In developed communities, incidence of critical limb isch-
emias characterized by tissue destruction (gangrene or ulceration) and pain at rest or at night is estimated approximately 50 to 100 per 100,000 cases per year. It leads to significant morbidity and mortality as well as waste of medical and social resources (3). According to Beach and colleagues, 42-48% of men and 28-35% of women with type 2 diabetes suffer from peripheral arterial disease (4).

One of the serious problems of arterial occlusive disease (PAOD) in humans is gangrene accounted for half of the cases of lower limb amputation in diabetics in Western societies (5). Critical limb ischemia (CLI) and severe claudication (LLC) limiting daily activities are often caused by narrowing or blockage of the below-the-knee arteries (6). The most common treatment methods include artery bypass and balloon angioplasty. Those physicians, who usually prefer artery bypass surgery, are also well aware of long term anatomical patency and clinical durability (7).

Unfortunately, in most cases, it is not possible to provide proper vein or good arterial run off for by-pass. On the other hand, long-term prognosis of synthetic materials established less satisfaction (8, 9). In the past, percutaneous revascularization of lower limb arteries (angioplasty) has only been used for patients with contraindication for open artery bypass surgery. All other surgical methods have also been used. In recent years, the number of patients treated with percutaneous surgery (angioplasty) as the first-line treatment of arterial occlusive disease of the lower limb is increasing (10).

Successful revascularization reduces amputation cases expediting the healing process and improves the quality of life of diabetics with peripheral arterial occlusive disease. On the other hand, the use of percutaneous procedures including laser angioplasty, absorbable metal stents and many other methods is rising. Thus, the range and scope of damages that are suitable candidates for percutaneous treatment have increased (11). Percutaneous transluminal angioplasty (PTA) is a treatment method for critical limb ischemia (CLI). The outcome of this procedure is similar to artery bypass procedure (12).

The use of angioplasty for critical limb ischemia backs to about 50 years ago (13). In a study conducted by Hanna et al. on balloon angioplasty, complications such as embolization and thrombosis were observed in 21% of patients with critical limb ischemia (14). According to Dorros et al., below-the-knee arterial angioplasty is a safe procedure with satisfactory outcomes (15). In a retrospective study by Kudo et al., PTA was introduced as an alternative to open surgery with almost similar outcomes. Accordingly, angioplasty is not only a safe procedure, but is an effective and selective method for primary and secondary therapy of chronic ischemic lesions (16). In addition, the mortality rate in PTA is equal to 1-3% compared with 1.8-6% in distal bypass (17, 18).

The objective of the present study is to examine the long-term effects and recurrence rates in diabetic patients with critical limb ischemia treated with percutaneous angioplasty procedure.

**MATERIAL AND METHODS**

This is a semi-experimental study conducted on a group of patients during which the outcome of each individual is compared with previous results. Due to the unknown desired effects and adverse events, a total of 24 patients were enrolled. The patients underwent angioplasty in the operating room of Sina Hospital during 2010-2011.

According to TASC II criteria, patients with critical limb ischemia (CLI) who met following criteria will be enrolled: 1) A history of diabetes according to American Diabetes Association criteria, 2) Ischemic foot lesions (Fontine stage 4 or Rutherford category 5-6), 3) Absence of any critical damage (more than 70% stenosis in the arteries above the knee and proximal popliteal artery), 4) CLI in small arteries below the knee (more than 70% stenosis or blockages in leg arteries, anterior and posterior tibial and peroneal artery or tibiopronal trunk) with or without involvement of the leg arteries (pedal or plantar arteries) or involvement of one or two leg vessels and involvement of at least a foot vessel.

Treatment protocol

1. **Pre-PTA**
   a) surgery to remove necrotic tissue and to drain the abscess and phlegmon, broad-spec-
trum antibiotic therapy until more specific treatment based on culture indication is found,
b) control of blood sugar,
c) a double-dose antiplatelet therapy with aspirin (100 mg daily) and 300 mg of clopi-
d) protective kidney treatment in patients with CR greater than 1.3 mg/dl with an infu-
sion of normal saline solution at a dose of 1 ml/kg per hour (0.5 ml/kg per hour in pa-
tients with a history of heart failure) 12 hours before and 24 hours after the pro-
dure and the use of N-acetyl cysteine with a dose of 600 mg twice daily before and after surgery.

2. Angiography and PTA
The procedure was simultaneously per-
fomed by two surgeons under local anesthe-
sia. The unilateral common femoral artery
was systematically punctured. The arterial
tree imaging was performed using a non-
Ionic contrast agent as digital subtracted angiography with multiple oblique views and lateral foot projection. A wire with a diameter of 0.014” was used to cross the lesion. Full stenosis preferably was re-canalized through the arterial lumen with a specific coronary wire with a diameter of 0.014”. For this pur-
pose, small profile balloons were filled with air up to 12 to 15 ATM for TWO minutes The balloon size was selected based on the diam-
eter of artery and lesion length. Stenting was
only performed in cases where occlusion was not removed with prolonged inflation from five to 10 minutes. At the beginning of the PTA procedure, 5000 units of heparin was routinely intra-arterially injected to reach the active clotting time of approximately 250 mil-
iseconds. In the case of arterial spasm, 0.1
to 0.2 mg nitroglycerin was administered as intra-arterial bolus. At the end of the pro-
dure, hemostasis was established using the local press.

3. Post-PTA treatment
Elective surgery was performed with the aim of restoring a proper stamp/walk after 1 week. All patients received double-dose anti-
platelet for a month (100 mg aspirin and 75 mg clopidogrel). None of the patients received prostanoids and none of them underwent lumbar sympathectomy. After discharge, patients were followed in the outpatient clinic weekly for one month and then monthly up to 12 months. The short-term effects of the procedure were examined through evaluation of wound healing as well as patient recovery and pain relief (via Questionnaire 1) one month after PTA. All patients received medical treatment to reduce atherosclerosis risk factors.

Assessments

**ABI (ankle-brachial index).** ABI was evaluated at baseline and one day and six months after surgery. Pressure cuff and a portable Doppler ultrasound device (for pulse detection) were used to measure the ABI.

**End points.** In cases where the arterial flow to the plantar arch is established at least in a leg artery with stenosis less than 30%, the procedure was considered successful.

In cases where the PTA was only performed on the peroneal artery, the success of the pro-
cedure was defined as good collateralization toward the plantar arch. The primary end point was the improvement of ABI one month after the procedure compared to the baseline. The secondary endpoints include the incidence of death from any cause during the follow-ups, wound healing according to classification of diabetic foot ulcers, self-assessed patient re-
covery and pain relief according to Question-
naire 1 one month after the procedure, limb salvage rate during follow-up (which is defined as the ability to stand on the plantar surface of the foot, even with the need for a small am-
putation below ankle) and the need for addi-
tional intervention to open vessels in the same limb.

**Data analysis.** Given distribution type, parametric test (paired t) and nonparametric test (e.g. Wilcoxon) were used to compare outcome before and after treatment. Pearson’s correlation coefficient was used to determine the correlation between variables. A signifi-
ance level of 0.02 was considered.

**RESULTS**

A total of 24 diabetic patients with below the knee critical ischemia who were candidates
for angioplasty to keep the lower limbs were enrolled. In total, 26 limbs were treated by angioplasty. Table 1 shows characteristics of patients.

The pattern of vascular involvement and treatments

- Involved vessel: the pattern of vascular involvement at baseline was as follows: anterior tibial artery in six limbs (26.92%), posterior tibial artery in 22 limbs (84.61%), and popliteal artery in 14 limbs (53.84%) and peroneal artery in 13 limbs (50%) (tab. 2).
- The type of required angioplasty: in all cases (100%), balloon angioplasty was performed as the main intervention.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Standard deviation/ percentage</th>
<th>Mean/ number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>±5.7</td>
<td>57.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>79.16%</td>
<td>19</td>
</tr>
<tr>
<td>female</td>
<td>20.83%</td>
<td>5</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>45.83%</td>
<td>11</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>75%</td>
<td>18</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>20.83%</td>
<td>5</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>8.33%</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simultaneous treatment with two drugs</td>
<td>41.66%</td>
<td>10</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>8.33%</td>
<td>2</td>
</tr>
<tr>
<td>Metformine</td>
<td>20.83%</td>
<td>5</td>
</tr>
<tr>
<td>Insulin</td>
<td>29.16%</td>
<td>7</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>±9.53</td>
<td>14.56</td>
</tr>
<tr>
<td>HBA1c</td>
<td>±2.6</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Table 2. Frequency of vessels involvement undergoing angioplasty

<table>
<thead>
<tr>
<th>The type of involved vein</th>
<th>Number of limbs (26 limbs) (n)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior tibial</td>
<td>7</td>
<td>26.92%</td>
</tr>
<tr>
<td>Posterior tibial</td>
<td>22</td>
<td>84.61%</td>
</tr>
<tr>
<td>Popliteal</td>
<td>14</td>
<td>53.84%</td>
</tr>
<tr>
<td>Peroneal</td>
<td>13</td>
<td>50%</td>
</tr>
</tbody>
</table>

Table 3. Involvement of vessels during different time intervals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6th month</th>
<th>1st month</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>0.91±0.17</td>
<td>0.93±0.16</td>
<td>0.55±0.17</td>
</tr>
</tbody>
</table>
Table 4. Improvement of vascular involvement based on patients’ view

<table>
<thead>
<tr>
<th></th>
<th>p Value</th>
<th>6th month</th>
<th>p Value</th>
<th>1st month</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall health status expressed by patient (mean)</td>
<td>&gt;0.01</td>
<td>0.92±7.39</td>
<td>&gt;0.01</td>
<td>6.32±1.24</td>
<td>5.48±1.39</td>
</tr>
<tr>
<td>The pain score expressed by patient (mean)</td>
<td>&gt;0.01</td>
<td>2.29±0.72</td>
<td>&gt;0.01</td>
<td>3.45±1.13</td>
<td>6.68±2.54</td>
</tr>
</tbody>
</table>

Table 5. The frequency of involved vessels treated with angioplasty based on various classification criteria

<table>
<thead>
<tr>
<th>Classification</th>
<th>p Value</th>
<th>6th month (26 limbs) n (%)</th>
<th>p Value</th>
<th>1st month (26 limbs) n (%)</th>
<th>Baseline (26 limbs) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutheford Classification</td>
<td>&gt; 0.01</td>
<td>0.48±1.7</td>
<td>&lt; 0.01</td>
<td>0.96±1.92</td>
<td>0.63±3.88</td>
</tr>
<tr>
<td>class 0</td>
<td>13 (50)</td>
<td>10 (38)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 1</td>
<td>4 (15.4)</td>
<td>6 (23.1)</td>
<td>2 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 2</td>
<td>3 (11.5)</td>
<td>4 (15.4)</td>
<td>3 (11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (19.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (30.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 5</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 6</td>
<td>6 (23.1)</td>
<td>6 (23.1)</td>
<td>6 (23.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fontaine Classification</td>
<td>&gt; 0.01</td>
<td>0.49±1.96</td>
<td>&lt; 0.01</td>
<td>0.47±2.07</td>
<td>0.34±2.92</td>
</tr>
<tr>
<td>class 1</td>
<td>13 (50)</td>
<td>10 (38.5)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 2</td>
<td>7 (26.9)</td>
<td>10 (38.5)</td>
<td>10 (38.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (30.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 4</td>
<td>6 (23.1)</td>
<td>6 (23.1)</td>
<td>8 (30.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

increase in 6th months was not significant compared to 1st month (p>0.01).

– The overall health status of the patient’s view: the mean Well Being score represents an increase in patient satisfaction over time. Nevertheless, the increase was only statistically significant in the 1st month compared to baseline (p<0.01). No significant difference was observed in subsequent follow-ups (p>0.01).

The pain scores expressed by the patient: the pain score was significantly reduced after one month follow-up compared to baseline (p<0.01). However, mid-term follow-up of 6 months showed no significant changes in the pain expressed by the patients (p>0.01).

– The Rutheford Classification Score: Consecutive review of patients at three time periods represents an enormous change in Rutheford class in 1st and 6th months compared to the baseline. Within the first month follow-up, the classification was significantly reduced to class 0 in most cases (p<0.01). No change was observed in 6th month compared to 1st month (p>0.01).

– Fontaine Classification Score: the changes in Fontaine mean score in the 1st month indicate a significant decrease compared to the baseline (p<0.01). The change in 6th month was not significant compared to the 1st month (p>0.01).

DISCUSSION

Lower limb amputation is one of the prevalent complications observed in diabetics mainly due to peripheral arterial disease (19). In most patients, a small skin lesion with no critical appearance often occurring by trivial accidents becomes infectious. In most cases, it will result in gangrene of extremities (20). There are many evidences that distal artery revascularization is the best chance for diabetics with vascular insufficiency (10). According to Tan, the success rate of maintaining an affected limb over a year was 78% (21). The results of the present study showed that successful endovascular treatment leads to maintaining a high percentage of limbs with critical limb ischemia and isolated tibial artery and peroneal artery during follow-up. This finding is consistent with the results of other studies in which patients with failed revascularization had a poor prognosis (22).

In the present study, a mortality rate of 3.57% was observed during follow-up after treatment. This was due to reasons other than the limb failure such as heart disease/brain stroke. Many other studies reported mortality and morbidity rates of 0 and 8.1% in patients with diseases threatening PTA-treated limbs (23). Tan et al. also reported six mortalities. It is worth noting that the mortalities were not
due to acute organ failure and mainly caused by diabetes or its complications. Many patients suffered from other diseases in addition to diabetes. Issues such as sepsis can be involved (21).

The success rate of angioplasty to maintain limbs with arterial insufficiency for three years was 77% to 94% (15, 16). The findings of previous studies are consistent with the results of the present study. Thus, the ability to maintain limbs in the present study was 93%.

In 40% to 45% of cases, amputation occurs in diabetic patients (24) and the possible need for amputation in diabetic patients is higher than non-diabetic patients (25). In the present study where all patients were diabetics, major and minor amputation rates was 3.84% and 38.7%, respectively.

The clinical outcome and limb maintain following PTA was higher than hemodynamics capacity. This frequently shows that improved ischemic lesions do not recur even after dilated artery restenosis. So less blood flow is needed to keep the improved wounds than wound healing. In addition, the majority of patients were improved in terms of symptoms such as pain and gangrene of the extremities (21). During the follow-up procedures, after 100 PTA, only three patients out of 94 patients who had success with this treatment again suffered from critical limb ischemia in the same limb. In the study conducted by Balmer et al., 69% of patients with acute organ failure treated with balloon angioplasty showed restenosis. Despite the incidence of restenosis during a 12-month follow-up after angioplasty, amputation was avoided in more than 90% of treated patients with PTA. Less than 50% of patients with restenosis required revascularization (26).

Faglia et al. found that extensive distal thrombosis only occurred in one patient treated with PTA. In this case, thrombolytic therapy was not effective and surgical revascularization was ineffective leading to extensive amputation (27). According to Hanna et al., angioplasty for treatment of critical limb ischemia was associated with 21% of treatment-related complications like embolism and thrombosis (14). However, Dorros et al. believes that PTA treatment for below the knee arteries is associated with safe and satisfactory results (16). In the present study, only in two cases (1.9%), treatment-related complications were manifested as groin hematoma that required no treatment.

Bosch and Hunink compared the efficiency of PTA and drug stenting. They found that the technical success rate of stenting for the treatment of occlusive lesions is higher than the PTA. However, the difference was not statistically significant (28). In some other studies, the initial three-year performance of PTA was less than 60% (16), while the performance of stenting was higher than 90% (29).

In the study conducted by Gargiulo et al., of 39 limbs with stenosis, 24 limbs re-experienced symptoms caused by the restenosis and again underwent angioplasty. But 15 limbs with restenosis with no clinical symptoms were followed up without re-treatment (30).

In the present study, ABI index was significantly increased following PTA. This increase was maintained even in the 6th month. None of the patients experience restenosis during the study. As a result, there was no need for any intervention. According to the limb ischemia and diabetic foot classification, PTA treatment was evidently associated with significant improvements in limb ischemia. It has improved so much such that in Rutherford classification, most patients in class 4 at baseline were placed in class 0 in the 1st and 6th months. In Fontine’s classification, the patients were placed in class 2 at baseline and reached to class 2 and 1 in subsequent months. Patient satisfaction with their health showed a significant increase after the treatment.

It should be noted that satisfaction with health and quality of life are also affected by other factors. Although the foot pain after angioplasty was significantly reduced, the pain relief did not change significantly over time and remained relatively constant. Ferrari et al. conducted a retrospective study on 107 limbs with ischemia (Rutherford 5, 6). Limb salvage, restenosis and mortality of 93%, 42% and 9% was respectively reported during one year. These results represent a high percentage of reperfusion and long-term preservation of limbs. However, the evidence shows that in patients with acute organ failure, the time required for wound healing after endovascular surgery and significant improvements in the final outcome of patients varies and often takes more than 12 months (31).
CONCLUSION

The long-term follow-up should be done to demonstrate the efficacy of PTA in treatment of wounds caused by critical limb ischemia. In fact, the results of the present study indicate the mid-term outcome of PTA. Although PTA is associated with improved pain scores, satisfaction with health as well as classification of limb ischemia and diabetic foot ulcers, these are only short term and mid-term results. There is doubt on long-term efficacy of PTA and needs further investigation. Thus, definitive conclusion about the long-term effects of PTA is not possible. Definitive conclusions will require further investigation and long-term follow-up through studies with adequate sample size (multi-center). However, long-term efficacy of PTA needs to be investigated further.

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Authors’ contribution

Study concept, design and Scientific Content: Mohammad-Reza Zafarghandi and Iraj Nazari Abdoul and Morteza Taghavi; Acquisition of relevant references: Abbas Rashidi and Sanaz Karimi Dardashti; data collection: Donya Sadid, Sanaz Karimi Dardashti and Leyli Esmaili; data Analysis and manuscript preparation: Mohammad-Reza Zafarghandi, Iraj Nazari and Seyed Masood Mahmoodi; critical revision of the manuscript for important intellectual content: Iraj Nazari and Abbas Rashidi; approval of the final version: Mohammad-Reza Zafarghandi; interpretation of results: Iraj Nazari, Seyed Mostafa Mahmoodi and Donya Sadid; drafting the article: Dr. Seyed Masood Mahmoodi and Leyli Esmaili; Administrative, technical, and material support: Ahvaz Jundishapur University of Medical Sciences.

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