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Role of balloon angioplasty in the treatment of critical limb ischemia due to infrapopliteal lesions in diabetic patients

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Abstract

Diabetes Mellitus is one of the diseases that is affecting the health system medically and financially. Its incidence and prevalence have been growing, and its management and control of its complication have been a necessity. One of the complications that often occurred is a peripheral arterial disease with its multiple stages. Peripheral arterial diseases affect not only the management of diabetes itself but also the patients' quality of life. Since the peripheral arterial disease is much higher in diabetics than the non-diabetics, we are discussing in this review article epidemiology, different treatment modalities including medical management, intervention angioplasty versus bypass surgery. We also flash the light on some new methods that are not well studied yet in diabetics.

Keywords

diabetics; below the knee vessels; angioplasty

Introduction

The incidence and prevalence of Diabetes Mellitus (DM) have increased over the last decades. Subsequently, huge efforts have been made to improve the patients' quality of life. Peripheral artery disease (PAD) is one of the most serious complications of DM that adversely affect the quality of life. Critical Limb Ischemia (CLI) is the most severe form of chronic PAD and its treatment in the diabetic population is the main focus of this review [1].

Epidemiology

Diabetes mellitus is most prevalent in the middle-aged and elderly populations, with the prevalence estimated at 11% for those persons aged 65 years and older [2,3]. It is estimated that 25% of patients with diabetes will develop a lower extremity ulcer during the course of their disease [4-6].

Several reports from population-based studies indicate an annual cumulative incidence for diabetic

foot ulcers of 2–3% [7,8]. In one study of a large cohort of neuropathic patients, there was a 7% one-year incidence of first foot ulcer [9]. Reported foot ulcer prevalence in a variety of populations has ranged between 2% and 10% [5,7,9,10]. The cumulative effects of neuropathy, deformity, high plantar pressure, poor glucose control, duration of diabetes, and gender are all contributory factors for foot ulceration [11]. Also, while most ulcers can be successfully treated in the office or outpatient setting, infected and/or ischemic foot ulcers are a major cause for diabetes-related hospitalization [12-14].

Critical limb ischemia in diabetics

Diabetes mellitus is a significant contributing factor to limb loss due to a combination of ischemia, infection, and neuropathy. [15] According to the United Kingdom Prospective Diabetes Study (UKPDS), aggressive glycemic control is associated with a significant fall in diabetes endpoints and myocardial infarction; however, intensive glycemic treatment did not appear to reduce the risk of PAD, underpinning the importance of cessation of smoking and other risk factor management [16].

Diagnosis of CLI

Critical limb ischemia is manifested by pain at rest, nonhealing wounds and gangrene. Ischemic rest pain is typically described as a burning pain in the arch or distal foot that occurs while the patient is recumbent but is relieved when the patient returns to a position in which the feet are dependent. Objective hemodynamic parameters that support the diagnosis of critical limb ischemia include an ankle-brachial index of 0.4 or less, an ankle systolic pressure of 50 mm Hg or less, or a toe systolic pressure of 30 mm Hg or less. Also Imaging with doppler US and CT angiography of the lower extremities will support the diagnosis [17].

Medical treatment of critical limb ischemia in diabetic patients

Smoking cessation and treatment of hypertension, hyperlipidemia, and diabetes all reduce the mortality rate in those with PAD. Antiplatelet agents, aspirin or clopidogrel are recommended to reduce both the incidence of cardiovascular events and risk of arterial occlusion. A meta-analysis of 54 RCTs of patients with intermittent claudication demonstrated that aspirin reduced the risk of arterial occlusion compared with placebo, and ticlopidine reduced the need for revascularization [18].

Routine use of anticoagulation, warfarin or heparin is not recommended. Treatment of the limbs themselves is often more challenging. Prostanoids may have some efficacy for treating CLI and iloprost can reduce the risk of major amputations, but long-term follow-up data regarding disease progression are lacking. There is insufficient evidence to support the use of naftidrofuryl or cilostazol, and pentoxifylline is not beneficial [19].

Furthermore, there is no evidence of a proven benefit of hyperbaric oxygen. A number of angiogenic growth factors have been studied in Phase I studies and randomized controlled trials. They appear to be safe, but efficacy results have been mixed. Treatment with stem cells also shows some potential from early trials, but further larger RCTs are needed to demonstrate a clear benefit. However, newer endovascular

techniques are likely to have a greater role in the future [19].

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Invasive treatment of critical limb ischemia in diabetic patients

Role of angioplasty has been well studied and established as the first line of invasive treatment of PAD especially in diabetic patients, while Surgery will be kept to the end of treatment lines, given the co-morbidities of diabetes and surgery complications [20].

Iida et al. reported that endovascular treatment of below the knee (BTK) vessels has acceptable limb salvage outcomes after treating 465 limbs with CLI and isolated BTK lesions between 2004 to 2010. They also identified diabetes as one of the factors associated with major amputation [21]. Supporting this data, Zhan et al. in 2012 compared early and initial hemodynamic outcomes of endovascular therapy and open revascularization in 85 consecutive patients with diabetes and CLI who underwent 109 interventions collectively. There was a similar significant initial hemodynamic improvement between the two interventions [22].

This suggests that the inferior intermediate or long-term results were seen in diabetic patients is not necessarily due to the initial hemodynamic response but more likely due to the effects of diabetes on plaque characteristics and cardiovascular health and the durability of the intervention in such patients. Ryu et al. compared clinical outcomes between diabetic and non-diabetic patients with CLI who underwent infrapopliteal angioplasty, diabetic patients had unfavorable primary patency at 2 years compared to non-diabetic patients. However, there was no significant difference between the two groups in terms of limb salvage and survival. The authors noted that the main obstacles to recanalization or long-term patency include long, multiple, and calcified stenosis or small-diameter vessels that have a tendency towards restenosis [23].

Role of balloon angioplasty

Angioplasty has been the first line of treatment of below the knee lesions in diabetics. Ferraresi et al. studied 634 patients with CLI retrospectively, selected a consecutive series of 101 diabetics (16%) with 107 critically ischemic limbs (33 Rutherford 5 and 74 Rutherford 6) and no critical ATK lesion, who underwent PTA on isolated BTK lesions. The limb salvage rate was 93% after a mean follow-up of 1048 ± 525 days. Transcutaneous oxygen saturation significantly increased after 1 month with $p < 0.05$. After 1 year, target-vessel restenosis had occurred in 42% of the non-amputated limbs, nine patients (9%) had died because of medical conditions unrelated to PTA and three patients had undergone repeat PTA for recurrent CLI [24].

Faglia et al. employed PTA as first choice revascularization in a consecutive series of diabetic patients hospitalized for CLI and it was successfully performed in 993 patients with 1.7% major amputations. Mean follow-up was 26±15 months. Clinical restenosis was observed in 87 patients. The 5 years primary patency was 88%, 95% CI 86–91% [25].

Introducing the angiosome protocol, Alexandrescu et al. reported 232 limb-threatening neuroischemic wounds in 208 diabetic patients were treated by below-the-knee endoluminal and/or subintimal angioplasty. Patients treated prior to 2005 when the angiosome-targeted revascularization protocol was introduced (89 limbs, group 1) were compared to 134 limbs treated subsequently according to the angiosome model (group 2). Patients in group 2 treated with angiosome-targeted revascularization had significantly better wound healing ($p<0.018$) and limb preservation ($p<0.030$) [26].

Fossaceca et al. have conducted a retrospective analysis of the results of PTA performed in 201 diabetic patients with BTK-only disease assessing the rates and values of partial and complete ulcer healing, restenosis, major and minor amputation, limb salvage, and percutaneous oximetry (TcPO2) using the angiosome model to compare different clinic-laboratory outcomes in patients treated by direct revascularization (DR) from patients treated with indirect revascularization (IR) technique. During the follow-up period of 17.5 ± 12 months, in both groups, there was a statistically significant increase of TcPO2 values at follow-up compared to baseline ($p < 0.05$) which means successful limb salvage, without statistically significant differences in therapeutic efficacy [27].

Following the procedure success, TcPO2 was used. Redlich et al. performed PTA in 28 diabetic patients with CLI confined to infrapopliteal vessels and recorded patency of crural vessels, including the vascular supply of the foot as well as the ABI and TcPO2 of the foot. The limb-salvage rate at 12 months was 60.7%. The number of patent straight vessels above and below the level of the malleoli increased significantly in patients avoiding amputation. Amputation was unnecessary in 88.2%. In 72.7% of patients, patency of the peroneal artery alone was not sufficient for limb salvage. ABI was of no predictive value for limb salvage. TcPO2 values increased significantly only in patients not requiring amputation ($P = 0.015$). In patients with only one tibial artery supplying the foot or only a patent peroneal artery in postprocedural angiograms, TcPO2 was capable of reliably predicting the outcome [28].

Changes to the techniques help in limb salvage and mortality terms not only in diabetics but in all patients of CLI, as Gandini et al. stated. 1,035 patients underwent endovascular treatment for critical limb ischemia. Transfemoral antegrade revascularization attempt failed, and an alternative approach was used. Follow-up was performed at 1 and 6 months. Results were compared with 56 patients, in whom conventional technique was unsuccessful and unconventional techniques were not adopted. The limb-salvage rates were 96.8% and 83% at 1- and 6-month follow-up, respectively. Transcutaneous oxygen tension increased at 1 month (44.7 ± 1.1 vs. 15.7 ± 0.8 mmHg; $p < 0.001$) and remained stable at follow-up. they stated that the use of alternative techniques seems feasible in case of a failed antegrade BTK revascularization attempt and could minimize failure rates in the treatment of complex occlusions while providing satisfying clinical success rates at 6 months [29].

Arterial Bypass

CLI patients with DM are at a significantly higher risk of major amputation than CLI patients without DM [30].

Arterial bypasses and various vascular surgeries are of lower outcomes compared to angioplasty in diabetics as Malmstedt et al. have stated in his study on 1,840 patients in a population-based cohort study by linking nationwide databases in Sweden. Patients had their first leg bypass procedure for critical lower-limb ischemia between 1 January 2001 and 31 December 2003-742 with and 1,098 without diabetes. Individuals were followed up until 31 December 2005 through the National Hospital Patient Registry and the Cause-of-Death Registry.

Incidence of ipsilateral amputation or death was higher in patients with diabetes than in patients without (30.2 vs. 22 events/100 person-years; crude hazard ratio [HR] 1.32 [95% CI 1.17–1.50]). Similarly, individuals with diabetes had a shorter amputation-free survival period than individuals without (2.3 years, range 1.9–2.8 vs. 3.4 years, range 3.1–3.7). Adjustment for demographic characteristics, comorbidities, and risk factors for amputation or death did not substantially affect the risk (HR 1.46 [95% CI 1.26–1.69]). The effect was more pronounced in male (1.75 [1.47–2.08]) than in female (1.35 [1.11–1.64]) patients after adjustment for age [31].

Nguyen et al. have reported that quality of life improvements are lower in diabetic patients and those who develop graft-related events. The study included 1404 patients with lower extremity vein bypass for CLI at 83 centers in the United States and Canada as part of the PREVENT III clinical trial. Surveys were completed in 1296 patients at baseline, 862 patients at 3 months, and 732 patients at 12 months. The global QoL score (mean ± SD) was 2.8 ± 1.1 at baseline and was 4.7 ± 1.4 and 5.1 ± 1.4 at 3 and 12 months, respectively. Mean changes from baseline at 3 and 12 months were statistically significant ($P < .0001$) [32].

New endovascular modalities

Introducing recent modalities in the field of BTK vessels, Siablis et al. have compared paclitaxel-coated balloon (PCB) with drug-eluting stents (DES) in long infrapopliteal lesions, and cleared that DES are related with significantly lower residual immediate post-procedure stenosis and have shown significantly reduced vessel restenosis at 6 months. PCB may produce positive vessel remodeling [33].

Different stents of the BTK vessels also have been used. Sirolimus-Eluting Stents (SES) implantation may offer a promising therapeutic alternative to PTA for treatment of infrapopliteal peripheral arterial disease as Scheinert et al. reported when he studied two hundred patients with total lesion length 27 ± 21 mm, were randomized to infrapopliteal SES stenting or percutaneous transluminal balloon angioplasty (PTA). After 1 year, there were lower angiographic restenosis rates (22.4% vs. 41.9%, $p = 0.019$), greater vessel patency (75.0% vs. 57.1%, $p =0.025$), and improved Rutherford class for SES versus PTA [34].

Zeller reported that in patients with CLI, IA-DEB had comparable efficacy to PTA. Primary safety was met, but there was a trend towards an increased major amputation rate through 12 months compared to PTA [35].

Conclusion

Percutaneous Transluminal Angioplasty is the first line of treatment in CLI, especially when it comes to diabetic patients with BTK lesions. Given the other comorbidities, surgery should be avoided or at least be kept to be the last choice. Various drug-eluting stents and balloons showed promising results in the treatment of CLI and should be studied more and widely in diabetics, in terms of limb salvage and mortality benefits.

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