CURRENT TRENDS IN CRITICAL LIMB ISCHEMIA - REVIEW

General Surgery

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ABSTRACT

Critical limb ischemia (CLI) is considered the most severe clinical manifestation of peripheral artery disease (PAD). These patients carry high risk of amputation and mortality. CLI patients face many problems like restriction of movement, starvation of services and depression. Therapeutic goals in treating these patients include relieving ischemic pain, reducing cardiovascular risk factors, preventing major amputation, improving quality of life and increasing survival. Revascularization is the primary treatment strategy in critical limb ischemia patients. Many patients are not treatable by conventional techniques. This review article provides a comprehensive summary that includes current trends in the management of Critical limb ischemia like endovascular revascularization, gene and cell based therapies and drug eluting stents (DESs) etc.

KEYWORDS

Critical, limb, ischemia, current, trends

INTRODUCTION

Critical limb ischemia is (CLI) a most severe stage of peripheral arterial disease (PAD) resulting from impaired circulation to the lower limbs. It can be defined as > 2 weeks of rest pain, ulcers or loss of tissue. CLI carries a 25% risk of mortality and another 25% risk of amputation over the next year [1]. According to the Global Burden of Disease study approx 202 million adults worldwide have Peripheral arterial disease [2]. Although most of them are asymptomatic but if left untreated, increases the risk of cardiovascular events, amputation and death. Approximately 1-3 % patients of PAD may present with Critical limb ischemia (CLI); these estimates are likely to increase as life expectancy, prevalence of diabetes, obesity and sedentary lifestyles are increasing [3-4]. Many of them present to the health care facility very late when the arteries are severely damaged. In many centers, amputation without revascularization is continued to be performed. Therapeutic goals in treating these patients include curtailing known etiologic factors, relieving ischemic pain, reducing cardiovascular risk factors, healing ulcers, preventing major amputation, improving quality of life and increasing survival. These aims may be achieved through medical therapy, revascularization, or amputation [1].

DIAGNOSIS AND ASSESSMENT

CLI is primarily a clinical diagnosis. Any of the '6P' arises suspicion of ALI i.e. pain, pallor, paralysis, paresthesia, pulse deficit and poikilothermia. ALI can be classified on the basis of symptoms of limb ischemia by Fontaine or Rutherford classification. The holistic approach is to be taken to evaluate peripheral pulses and identify cardiovascular risk factors. Various examinations are helpful like ankle-brachial index (ABI), Toe-brachial index (TBI), transcutaneous partial pressure of oxygen (TcPO₂), ankle systolic pressure and ultrasound color duplex scan. To demonstrate location and degree of arterial obstruction, Digital subtraction angiography, computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) plays an important role.

HOLISTIC MANAGEMENT OF CLI

Treatment goals in the management of CLI includes relieving ischemic pain, optimization of cardiovascular risk factors, ulcer healing, improve limb perfusion, prevent further deformity by which improving quality of life and patient survival. These goals can be achieved by curtailing known etiologic factors, patient care, medical therapy, revascularization and amputation.

Wound care and risk factor modification

Initial treatment includes relieving of pain, which may require narcotics, ulcer care, sheepskin boots to increase superficial collateral supply, and tilting the patient's bed downward which is required to keep limb in dependent position and so is to increase perfusion. [5] Relieving of pain is essential to improve quality of life and mobility. Usually, NSAIDs and paracetamol is used to relieve pain. Sometimes opioids are also needed. Wound care includes cleaning and dressing, treating

infection, avoiding pressure over wound, improving nutrition and debridement, if necrosis developed in the wound. Local application of platelet-derived growth factor helps in the healing of chronic ulcer. The Sheepskin (Rooke) boots help to improve superficial collateral flow of limbs by increasing the local temperature. [6] Cessation of smoking, control of hypercholesterolemia & hypertension must be ensured in these patients with strict glycemic control to achieve cardio protection.

Medical Therapy

In CLI patients coexisting cerebrovascular and coronary artery disease (CAD) accounts for considerable mortality and morbidity; hence, optimization of these risk factors is of prime importance in the management of CLI patients. Medical therapy is primarily used to optimize these cardiovascular risk factors. [7]. Various CLI guidelines consider the effectiveness of antiplatelet therapy, statins and ACE inhibitors to reduce cardiovascular events and mortality. Aspirin or clopidogrel is indicated for secondary prevention in patients with PAD and other cardiovascular diseases. Low dose of aspirin (75–160 mg) is safe and effective. [8] Monotherapy with P2Y₁₂ inhibitors viz. clopidogrel and ticagrelor has been studied in the context of single antiplatelet therapy for symptomatic PAD. Dual antiplatelet therapy (aspirin+clopidogrel or ticlopidine) is recommended in diabetic patients who undergo lower limb revascularization for at least 1 month after endovascular procedure; after 1 month, aspirin or clopidogrel should be continued lifelong. [9] In patients with CLI, Cilostazol (phosphodiesterase III inhibitor having antiplatelet, antimitogenic and vasodilator properties) has been shown to favorably increase skin perfusion pressure and wound healing. [10] Cilostazol (100 mg orally 2 times per day) is indicated in patients of PAD with intermittent claudication as an effective therapy to improve symptoms and increase walking distance. Due to the increased risk of bleeding, most surgeons reserve anticoagulation therapy for graft thrombosis or hypercoagulable disorders.

Endovascular Revascularization

Endovascular revascularization is the favored approach to CLI in many centers because of lower morbidity and mortality than open surgery. It aims to re-establish continuous in line pulsatile flow to the pedal arch and to reduce the surgery related complications without affecting the limb salvage rate. Various patient and procedure specific factors such as age and associated co-morbidity, vascular anatomy, severity of the ischemia, presence of usable vein graft and extent of involvement determines choice between surgical versus endovascular treatment. This minimally invasive treatment option has significantly evolved over the past decades. Today many revascularization modalities are being practiced like plain balloon or percutaneous transluminal angioplasty (PTA), several novel endovascular approaches and devices have been released on the market for example, stent-grafts, bare metal stents, atherectomy devices, cryoplasty, drug-eluting stents, and drug-eluting balloons. [11] PTA involves placing a wire intra-luminally beyond the lesion of interest and then expanding the inserted balloon at the lesion with the appropriate pressure which

leads to fracture of the lesion and stretching of the arterial wall. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) study was a randomized controlled trial that compared percutaneous transluminal angioplasty (PTA) with bypass surgery in 452 patients presenting with CLI.[12] According to this study, amputation-free survival, was similar for PTA and bypass surgery at 1 year (71% vs. 68%, $P = \text{NS}$) and 3 years (52% vs. 57%, $P = \text{NS}$). Surgery was associated with a higher post-procedure morbidity with no significant difference in mortality at 30 days. Usually, in patients of CLI with active co-morbidities, planned for angioplasty does not require general anesthesia. Percutaneous transluminal angioplasty (PTA) can be performed in patients not fit for bypass procedure, like in the presence of several co-morbidities, unavailability of veins, reduced life expectancy, absence of appropriate site for distal bypass and infection of the foot at the site of potential anastomosis.

Surgical Revascularization

It includes; Balloon catheter thrombectomy, Endarterectomy with or without patch angioplasty and Intraoperative isolated limb thrombolysis. The aims of surgical revascularization are to provide straightline flow into the foot arch. The risk of perioperative myocardial infarction (MI), death, and stroke are higher in open surgery than endovascular revascularization. Surgical revascularization is advocated for the lesions that are not amenable to catheter-based intervention and in cases of younger patients with prolonged life expectancy who require a more durable revascularization. In case of long occlusion of femoro-popliteal and infra popliteal vessels, bypass is usually more effective and ensures patency of long segment. These aortoiliac diseases may be treated with anatomic or extra-anatomic bypass (e.g. axillobifemoral, axillofemoral, or femorofemoral bypass). Extra-anatomic repair are generally done in Patients who are older, more likely to have advanced ischemia, previous aorto-femoral inflow operation, renal insufficiency, and severe chronic obstructive pulmonary disease (COPD).[13]

Hybrid Revascularization

Hybrid revascularization refers to the combination of open surgery and endovascular approach that achieves complete revascularization with decreased complications. Some patients of CLI might not benefit completely from percutaneous endovascular revascularization due to difficult access to the lesion or complex anatomy. These patients need hybrid therapy to achieve complete revascularization. Some of the advantages of this therapy are low risk compared to open surgery, less invasive technique, decreased complications and shorter duration of operation.[14-16] According to a study, 125 patients underwent hybrid therapy for de novo arterial reconstruction or revision of a bypass graft in which the perioperative mortality was $< 1\%$ and morbidity was 15.4%. After follow-up over 27.6 months, the primary patency was 39.6%, primary B assisted patency 65.1%, and secondary patency 73.5%.[17].

Amputation

Amputations are to be reserved for patients unfit for surgical revascularization with no endovascular options available. Prior to concluding major amputations (at or above the knee), efforts should be made to salvage the ischemic limb using surgery or endovascular techniques. Adequate blood supply is needed into the foot to maximize healing in minor amputations like toe, metatarsal or transmetatarsal. After the major amputations (at or above the knee), prosthesis is required and it limits functional independence. Due to poor perfusion and healing, up to one third of below-knee amputations may require further surgery/revision surgery or an above-knee amputation.[18] While taking decision of amputation, efforts should be made to preserve knee joint because compared to above knee amputation, below knee amputation is associated with reduced 30-day mortality (5% versus 16%) and increased long-term survival rate (74.5% versus 50.6%) [19-20]. Bilateral amputation or above-knee amputation, dementia, increasing age are some of the factors related to poor prosthesis use.

Evolving treatment options

Gene and cell based therapies are emerging treatment options in CLI management. These therapies are the new hope for non-revascularizable patients and showed promising results by inducing local angiogenesis and neovascularization. Various gene therapies viz. fibroblast growth factor (FGF), hypoxia inducible factor 1, vascular endothelial growth factor (VEGF), hepatocyte growth factor

and hypoxia inducible factor 1 have been tried. Out of these, hepatocyte growth factor seems the most promising. Cell based therapies are bone marrow mononuclear cells, mesenchymal stem cells, and endothelial progenitor cells. Bone marrow-mononuclear cells were studied in a randomized, placebo controlled study, in which these cells were injected into the gastrocnemius muscle in 45 CLI patients. Significant improvements were noted at 4 weeks in terms of rest pain scale, TcPO₂, ABI, and pain-free walking time. It was observed that number of collaterals was increased compared to baseline in 27 of 45 patients, as evident by the Angiographic evaluation. [21]

The results of both the gene and cell based therapies are encouraging in the management of CLI. More double blinded control studies are needed to be done to evaluate long term outcome in terms of amputation, healing of wound and quality of life. **Stenting**: Restenosis significantly affects outcomes after PTA done. Stent placement can prevent restenosis and also helps when balloon angioplasty is failed. Different types of drug eluting stents (DESs) were tried in PAD patients. They were created in an attempt to overcome stent thrombosis and in-stent restenosis. ZilverPTX trial showed that use of paclitaxel benefited much in femoro-popliteal lesions, which allowed its FDA approval in 2012 for use in PAD. [22-23] Paclitaxel has superior lipophilicity which reduces its systemic absorption and it can be applied directly over metal. This property makes it bio-compatible, and used in Bilayered stents (paclitaxel & growth factor). Further, ongoing research on Bilayered stents (paclitaxel & growth factor) may help in improving the outcome in these patients. **Platelet rich plasma** contains many growth factors like chemokines and cytokines. These growth factors help in wound healing by improving microcirculation and angiogenesis. In CLI patients, Use of platelet rich plasma has shown beneficial effect for limb salvage and ulcer healing process.[24-25] **Deep venous arterialization (DVA)** has shown promising results in patients of CLI to prevent major amputation and it is a feasible and safe alternative.[26-27] It enables wound healing by providing arterialized blood. **Atherectomy** evolved as an additional option in anatomic locations not normally amenable to stents, including the common femoral artery or popliteal artery. Atherectomy has become widely adopted across specialties and four main methods of function are: rotational, directional, orbital, and laser atherectomy.[28] **Lithoplasty** is a new technology currently under investigation. It uses same technology used in the treatment of renal calculi. It is the Shockwave Lithoplasty System (Shockwave Medical, Fremont, CA, USA). In this technology, a catheter guided balloon produces powerful acoustic shockwaves which disrupt plaques. The technology is being studied in the DISRUPT PAD III clinical trial.[28-29] Cryoplasty Endovascular cryoplasty (Boston Scientific, Natick, MA, USA) has been introduced as an alternative to traditional angioplasty. Additional research is necessary for a better understanding of the feasibility and efficacy of advancements in angioplasty balloons (cryoplasty, laser, or vibrational angioplasty) which may help in improving the outcome in CLI patients.

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