Rok Luciano Perme[1]

Caring for Chronic Limb-Threatening Ischemia Patients Undergoing Vascular Interventions

ABSTRACT

KEY WORDS: chronic limb-threatening ischemia, peripheral arterial disease, antithrombotic regimen

Chronic limb-threatening ischemia (CLTI) is a clinical diagnosis with objectively confirmed atherosclerotic peripheral arterial disease, leading to varying degrees of ischemia and presenting as ischemic rest pain and/or tissue loss, such as ulceration or gangrene. Hemodynamic parameters usually associated with CLTI are an ankle-brachial index < 0.4, absolute ankle perfusion pressure < 50 mmHg, toe pressure < 30 mmHg, or transcutaneous oximetry < 30 mmHg. The following article will cover the topics of CLTI prognosis and risk factor treatment as well as the approach to revascularisation procedures with periprocedural or postprocedural treatment especially regarding antithrombotic regimens to improve vessel patency.

[1] Rok Luciano Perme, dr. med., Klinični oddelek za žilne bolezni, Univerzitetni klinični center Ljubljana, Zaloška cesta 7, 1000 Ljubljana; rok.perme@kclj.si

EPIDEMIOLOGY OF PERIPHERAL ARTERIAL DISEASE

Chronic limb-threatening ischemia (CLTI) is a manifestation of peripheral arterial disease (PAD), which is a consequence of the pathological process of atherosclerosis. PAD is defined by ankle-brachial index values ≤ 0.9. Based on these measurements, the worldwide prevalence of PAD is estimated at around 3–10%, in other words, in 2010, there were approximately 200 million persons globally having PAD with a ratio of asymptomatic versus symptomatic patients being 4 : 1 *(1)*. Epidemiological data on CLTI prevalence is unreliable and limited but possibly about 21% of patients with intermittent claudication progress to CLTI in 5-year period *(2)*. CLTI as the most serious clinical form of PAD increases patient risk of lower extremity tissue loss or amputation as well as causes a very high risk of cardiovascular adverse events. One-year mortality in CLTI patients is estimated at around 25%, mostly due to cardiovascular events, comorbidities or advanced age *(3)*. Therefore, there are two aims of treatment.

MEDICAL TREATMENT OF PATIENTS WITH CHRONIC LIMB-THREATENING ISCHEMIA

The first aim of the treatment is to reduce the risk of atherothrombotic events such as myocardial infarction or cerebrovascular insult. This is done by controlling risk factors following established guidelines *(4)*. Every CLTI patient should be treated with antiplatelet medications, usually low dose acetylsalicylic acid (ASA) with the possible addition of low dose (2.5 mg twice a day) rivaroxaban (RIVA) unless there are indications for anticoagulant treatment. Dyslipidemia should be addressed with potent statins with or without ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors to reach low-density lipoprotein (LDL) cholesterol goal levels. Arterial hypertension and diabetes mellitus must also be treated according to the guidelines. It is of utmost importance that the patient adopts lifestyle changes with smoking cessation, a healthy diet and regular exercise if feasible *(4)*.

IMAGING METHODS

The second aim of treatment in CLTI patients is the improvement of perfusion to enable the healing process and possibly avoid amputation. A good morphological preprocedural diagnostic should be made to enable decision making. This is usually done with a duplex ultrasound, which also provides hemodynamic information, CT angiography or digital subtraction angiography (DSA) during the therapeutic procedure. An MRI is rarely utilised. After obtaining the imaging information, a decision is made on the revascularisation approach. Since patients with CLTI are often of advanced age, have multiple comorbidities, could have had several previous procedures and have multi-level disease, a shared decision is taken on the best approach. The decision making process usually involves an angiologist, an interventional radiologist and a vascular surgeon. Revascularisation can be done endovascularly, surgically or as a hybrid procedure *(1)*. A precise description of these methods is beyond the scope of this article.

LABORATORY MEASUREMENTS

Before the procedure, the patient should be adequately prepared to minimise the risk of complications. Laboratory work-up must include hemogram, myoglobin, electrolytes and creatinine as well as hemostatic parameters. Thresholds may vary between different centres, but generally, hemoglobin levels should be > 90 g/L in case of bleeding, and platelet count should be > 100×10^9/L for primary hemostasis. Electrolyte imbalances must be corrected and a reflection on parenteral hydration should be done to

prevent acute contrast-induced kidney injury in patients with advanced kidney disease.

With respect to hemostasis parameters in patients on vitamin K antagonists, the international normalised ratio (INR) value should be < 1.5, although there are reports that endovascular procedures can be done safely with higher values. Since more and more patients are taking direct oral anticoagulants (DOAC), strict instructions must be given on when to interrupt treatment. Percutaneous endovascular procedures carry an intermediate bleeding risk, and the last dose of DOAC should be taken at least 24 hours before the planned procedure. In case of kidney disease, this time window can increase to 48 hours. Vascular surgery operations carry a high bleeding risk, usually at least 48 hours should pass from the last dose of DOAC. It is also important to keep in mind the possible need for bridging anticoagulant treatment with low-molecular-weight or unfractionated heparin to avoid thrombotic complications *(5)*.

PAIN TREATMENT

One important component of treatment in CLTI patients is analgesia. It is well known that ischemic pain can be very strong and debilitating. Particularly for endovascular procedures, which are predominately performed under local anesthesia, patient cooperation must be good. A supine position during procedure can worsen perfusion, increase the level of pain and cause agitation, making the procedure difficult to perform successfully and without complications. Because of the above-mentioned reasons, sufficient analgetic treatment before and during the procedure is necessary, if needed, sedation can also be utilised. The choice of analgesic medication is at the discretion of the treating physician but usually a combination of several drugs including opioids is necessary *(1)*.

ANTITHROMBOTIC TREATMENT AFTER THE PROCEDURE – OUR EXPERIENCES

Improving patency-rates following revascularisation procedures is the ultimate goal in treating CLTI patients. Dissection, elastic recoil, and arterial thrombosis are the mechanisms of restenosis or occlusion after angioplasty; the last two occur during or in the first few weeks after the procedure. Later, neointimal hyperplasia becomes a significant factor, typically peaking around four to six months post-procedure. This process is driven by the activation, proliferation, and migration of vascular smooth muscle cells to the intima, and the production of an extracellular matrix. Patency-rates differ depending on the vascular region, type of procedure, implanted materials, and comorbidities. There is a lack of quality data on the best antiplatelet/antithrombotic treatment, which is important to optimise procedural outcome. In our clinical department, decisions about antithrombotic treatment are made based on different factors like the vascular region being treated, the implantation of devices or usage of drug-eluting techniques, the indication for anticoagulation treatment, known clopidogrel resistance and bleeding risk.

In patients without anticoagulation, low-dose (100 mg) ASA is given regardless of procedure type. Clopidogrel (75 mg) is added for one month in case of stent or stent-graft implantation, the usage of drug-coated balloon or plain old balloon angioplasty (POBA) of popliteal or tibial arteries. In case of POBA of the superficial femoral artery (SFA), low-dose RIVA is added to ASA. If there is proven clopidogrel resistance, it can be substituted with RIVA or ticagrelor.

If the patient has an indication for anticoagulation treatment, ASA is added only in case of POBA in the iliofemoral region, otherwise clopidogrel is added for one month. If bleeding risk is considered to be

high, usually only monotherapy with anticoagulant drug is continued. Bleeding risk is evaluated based on several factors, such as clinical impression, advanced age (above 75 years), prior large bleeding, anaemia, thrombocytopenia, kidney or liver failure, metastatic cancer or a history of cerebrovascular insult.

There are certain scenarios where optimal treatment choice is individual and at the discretion of the treating interventionalist or a result of a team decision-making process. Such scenarios are for example combined »triple« treatment with dual antiplatelet medication and an anticoagulant, or treatment after catheter-directed thrombolysis or other percutaneous thrombectomy intervention.

Data on patency-rates after surgical (bypass) procedures is sparse so patients usually receive antiplatelet or anticoagulant treatment based on primary indication. There is a possible benefit of dual antiplatelet medication in case of synthetic infrapopliteal bypass, whereas there is no strong indication for DOAC or VKA to improve bypass patency *(6, 7)*.

FOLLOW-UP OF PATIENTS WITH CHRONIC LIMB-THREATENING ISCHEMIA

In the follow-up process, CLTI patients should be seen on a regular basis and encouraged to take cardiovascular risk reducing medications and introduce lifestyle modifications. Patency after a revascularisation procedure should be checked with clinical examination, Doppler pressure measurements and possibly duplex ultrasound to detect restenosis or reocclusion and enable timely re-intervention if needed.

CONCLUSIONS

In summary, patients with CLTI represent a heterogeneous group endangered by a very high risk of fatal and non-fatal cardiovascular events as well as risk of amputation. Therefore, treatment is complex, also due to the lack of high-quality evidence and should be individually tailored by weighing the risks and benefits.

REFERENCES

1. Frank U, Nikol S, Belch J, et al. ESVM guideline on peripheral arterial disease. Vasa. 2019; 48 (Suppl 102): 1–79. doi: 10.1024/0301-1526/a000834
2. Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: A meta-analysis of mortality and disease progression in peripheral arterial disease. Eur J Vasc Endovasc Surg. 2016; 51 (3): 395–403. doi: 10.1016/j.ejvs.2015.10.022
3. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease. Int Angiol. 2007; 26 (2): 81–157. doi:10.1016/j.jvs.2006.12.037
4. Visseren FLJ, Mach F, Smulders YM, et al. ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42 (34): 3227–337. doi: 10.1093/eurheartj/ehab484
5. Spyropoulos AC, Al-Badri A, Sherwood MW, et al. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. J Thromb Haemost. 2016; 14 (5): 875–85. doi:10.1111/jth.13305
6. Belch JJF, Dormandy J. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. J Vasc Surg. 2010; 52 (4): 825–33.e2. doi:10.1016/j.jvs.2010.04.027
7. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch bypass oral anticoagulants or aspirin study): A randomised trial. The Lancet. 2000; 355 (9201): 346–51.