

Management of critical limb ischemia

Cornelius J. Woelk MD CCFP FCFP

Mrs P. is a 67-year-old woman with severe peripheral arterial disease. Her medical history includes 32 pack-years of smoking, controlled hypertension, and type 2 diabetes mellitus. She had a myocardial infarction about 8 years ago, leading to 2 coronary artery stents. She had an episode consistent with a transient ischemic attack 3 years ago, and the results of a computed tomographic scan at the time showed a number of old lacunar infarcts. Her current medications include the following: 25 mg of metoprolol twice daily, 5 mg of ramipril once daily, 12.5 mg of hydrochlorothiazide once daily, 20 mg of rosuvastatin once daily, 81 mg of acetylsalicylic acid once daily, a 0.2-mg/h nitroglycerin patch daily, 500 mg of metformin 3 times daily, and 80 mg of gliclazide once daily.

Mrs P. presents to the hospital with a deeply erythematous, painful area involving the fourth and fifth toes on her right foot. Over the course of a few days the area becomes very dark. A week later, the tips of all her toes are black and the erythema extends just proximal to her ankle. She is started on 30 mg of long-acting morphine every 12 hours, as well as on antibiotics. After having a discussion with her family and the vascular surgeon, she declines an amputation. Her decision is consistent with how she has felt about amputations for many years, as she witnessed her uncle undergo 2 lower limb amputations in the past.

Now, any movement of the limb causes pain. Mrs P. awakes from her sleep with pain, and overall she finds it very hard to get comfortable. Both elevation and lowering of the leg seem to make her discomfort worse. Although she finds intravenous morphine for breakthrough pain somewhat helpful, it makes her drowsy and does not seem to work fast enough when she needs it.

Chronic critical limb ischemia (CLI) results from chronic poor perfusion of a limb. It is variably defined but usually includes more than 2 weeks of rest pain and ulcers or tissue loss secondary to arterial occlusive disease. Outcomes of this presentation are variable. One year after diagnosis of CLI, 25% of patients have died, 30% are alive with amputations, 20% have ongoing symptoms, and 25% have symptoms resolve.¹

Goals of management of CLI are pain relief and the restoration of skin integrity and function. Key interventions include reducing cardiovascular risk factors and

healing ulcers. Function is best maintained by avoiding amputation.

Quality of life and operative risk are important factors in determining whether limb salvage is possible, whether amputation is required, or whether palliative care might be the better option.² Amputation might be declined or otherwise inappropriate. A number of reviews summarize recommended or possible medical and surgical interventions for CLI^{1,3-6}; however, few of them make specific suggestions regarding pain management, especially in the palliative setting.

Improving circulation

Peripheral artery disease affects mostly the lower limbs and has a substantial effect on quality of life, initially causing intermittent claudication and then progressing to CLI. Management of intermittent claudication remains multifactorial, with an emphasis on smoking cessation, followed by platelet inhibition, control of hypercholesterolemia, exercise, and control of diabetes.

Specific pharmacologic therapy has not demonstrated efficacy in reversing arterial occlusive lesions, or the resulting impaired perfusion seen in patients with CLI.³ Managing pain is a key component of preventing further progression of the disease, in that it allows for ongoing exercise, which promotes and maintains circulation.

Amputation issues

Approximately 10% of patients with intermittent claudication are estimated to deteriorate to CLI within 5 years, and 20% to 30% of patients with CLI require a major amputation.^{1,7,8} Amputation is generally reserved for those who do not respond to medical management and those who are not candidates for angioplasty or vascular reconstruction.

Making the decision whether or not to amputate can be challenging, especially when substantial comorbidities are present. Critical limb ischemia has a high prevalence of concomitant cardiovascular disease, which leads to associated morbidity and mortality. In fact, amputation is associated with 5% to 20% perioperative mortality, and mortality at 2 and 5 years of 25% to 30% and 50% to 75%, respectively.⁷ Above-knee amputations have overall higher mortality rates than those below the knee. Also, amputation itself is associated with the potential for complex pain following the procedure.

What is technically possible is not necessarily wise, depending on the circumstances. Although the chance of survival should not be the only factor determining whether or not to operate, for patients with

unsalvageable ischemia and poor chance of survival or poor quality of life after surgery, the most humane approach might be aggressive palliative care, managing symptoms until the time of death, which would be expected to be in a relatively short time.

Sometimes, for a variety of reasons, patients refuse amputation. If they are unable to play an active role in the decision, family members and caregivers should approach this decision as a team. Making decisions in accordance with a patient's preferences, values, and beliefs is paramount. If patients are unable to contribute to the discussion, the question to be asked is, What would they have wanted if they were able to tell us? A health care directive and an assigned substitute decision maker are very helpful if the patient is unable to actively contribute to the discussion. The decision not to amputate can often be a difficult and emotional one. If the individual is unable to contribute to the discussion, the care team should support the substitute decision maker, so no individual believes that they alone are making the decision not to operate.

Symptom management

Opioids remain the cornerstone of the management of

severe pain. Doses should be those required to keep the patient comfortable without substantial side effects. However, as the case of Mrs P. shows, there are challenges with obtaining pain relief related to a severely ischemic limb.

Positional pain is common in end-stage limb ischemia. Raising the leg might reduce circulation owing to poor arterial pressures. Lowering it might cause pain by increasing venous stasis, thereby increasing tissue edema and reducing arterial flow.

Persistent ulceration might be difficult to heal if circulation to the limb cannot be improved. *Incident pain* is pain that is short-lived, intense, and predictable. A good example of it occurs during dressing changes of ischemic limbs. The challenge is to use an opioid with strong but short-lived characteristics. Fentanyl and sufentanil are examples of such drugs. They have been used successfully sublingually and buccally 5 to 10 minutes before the anticipated incident.

Increasingly, it is realized that inflammation leads to neuropathic pain. At least some of the pain associated with CLI is believed to be neuropathic. As such, there have been a number of small trials evaluating the use of adjuvants that could work alongside opioids to

relieve the pain induced by inflammation caused by the ischemia. Gabapentin, ketamine, and lidocaine have shown some promise in this regard.

In 2005, Heartsill and Brown wrote a case report about a 56-year-old man with rest pain related to marked bilateral femoropopliteal occlusive disease.⁹ Leg pain disrupted his sleep and he became depressed. During the course of his illness he was started on gabapentin; when the dose was increased to 1200 mg 3 times a day, his pain lessened, his mood improved, and he was again able to participate in physical therapy. Heartsill and Brown suggested that CLI might worsen depression, which itself can cause abnormal arterial vasoconstriction and increased platelet aggregation, exacerbating ischemia and reducing the ability of a patient to take part in activities that allow for functional improvement.

A practical approach to palliative symptom management

- Opioids remain the cornerstone of the management of severe pain. Opioid doses should be titrated to effect.
- Consider changing the opioid if there is poor response to pain or if side effects develop.
- Differentiate between breakthrough pain and incident pain. Use adequate breakthrough doses for breakthrough pain, and treat incident-related pain with strong short-acting opioids.
- Add gabapentin early, as it will require a period of titration.
- Consider the addition of an antidepressant (ie, serotonin and norepinephrine reuptake inhibitors or low-dose tricyclic antidepressants) especially if depression is present or suspected.
- Get help. Methadone can only be prescribed in Canada by practitioners with a special licence. Palliative care consultants will likely have more familiarity with other options.

In a 2010 observational pilot study by Morris-Stiff and Lewis, 20 consecutive patients with CLI were experiencing rest pain despite high-dose opiate analgesia.⁷ Gabapentin was added, starting at a 300-mg dose daily and increased to 300 mg 3 times daily over 3 days, and then further increased to 600 mg 3 times daily if needed. Initially, 19 of 20 patients reported considerable night pain; 15 had gangrene or ulceration. Seventeen of 20 patients completed the full observation period of 28 days. Pain scores improved significantly ($P = .0003$) in 15 of 17 patients, falling from a median of 9 to 5. Fifteen of 16 patients had improvement in rest pain with the use of gabapentin.

In 2002 Mitchell and Fallon investigated the effects of a single dose of intravenous ketamine in patients with CLI in a double-blind randomized controlled trial.¹⁰ An infusion of low-dose intravenous ketamine was compared with opioids and placebo in patients with CLI resulting in allodynia, hyperalgesia, and hyperpathia.

The single infusion of 0.6 mg/kg of ketamine delivered over 4 hours and given along with the usual opioids, showed a statistical improvement in pain over the use of placebo and usual opioids.

In 2010, Fröhlich et al studied the effect of intravenous lidocaine in a group of 14 healthy volunteers.¹¹ They hypothesized that lidocaine, administered as a short infusion, would not have an analgesic effect. However, they found that although there was no analgesic effect for thermal pain and normal sensation, there was indeed a sustained decrease in ischemic pain ratings and some analgesic effect for electrical pain. These results suggest that lidocaine might be helpful in treating acute pain.

While no published reports or studies were identified, it might be that other medications typically used for neuropathic pain, including other anticonvulsants, tricyclic antidepressants, and serotonin and norepinephrine reuptake inhibitors, might also be useful in this setting. Methadone could be considered, as it has both opioid and antineuropathic effects.

Nonmedical interventions might also be helpful. Chemical lumbar sympathectomy might be considered to relieve symptoms in those patients not amenable to revascularization.⁴ Spinal cord stimulation, assessed by pain response and a microcirculatory evaluation, has been suggested to be of potential help,¹² but recent recommendations suggest against it, based on insufficient evidence.⁴ In a preliminary study protocol evaluating 32 patients with severe CLI, locally applied shock waves produced objectively detectable positive changes in both microcirculatory perfusion and pain.¹³

Further studies are clearly needed involving all of these drug and non-drug treatments. In the meantime, while one cannot state with certainty that they will help in the palliative setting, these treatments might be worth trying in patients with severe pain despite the ongoing use and appropriate dosing of opioids.

Conclusion

Mrs P.'s long-acting morphine dose is increased. The dose of breakthrough morphine is increased to approximately 10% of her daily scheduled long-acting dose. Fentanyl is used as a short-acting opioid sublingually to treat expected incidents of brief but intense bouts of pain (incident pain). Gabapentin is added, starting at 100 mg 3 times daily for a few days and then titrating up to 300 mg 3 times daily over 10 days.

A balance is struck between comfort and the sedating effects of her medication. She sleeps much of the time, but she arouses with stimuli and awakes occasionally to drink small amounts. She refuses food. About 3 weeks later Mrs P. dies peacefully with her family present.



• **BOTTOM LINE**

- Critical limb ischemia (CLI) is associated with substantial mortality and morbidity, including pain.
- The decision to proceed with a palliative, non-surgical approach is a difficult one that should be made carefully with the patient and the health care team.
- While opioid analgesics remain an important part of pain management in CLI, consideration should be given to incident and neuropathic components of the pain.
- Further study is required to determine evidence-based treatment of pain in CLI.

Dr Woelk is a family physician in Winkler, Man, Medical Director of Palliative Care for the Central Manitoba Regional Health Authority, and Assistant Professor in the Department of Family Medicine at the University of Manitoba.

Competing interests

None declared

References

1. Slovut DP, Sullivan TM. Critical limb ischemia: medical and surgical management. *Vasc Med* 2008;13(3):281-91.
2. Campbell WB, Verfaillie P, Ridler BM, Thompson JF. Non-operative treatment of advanced limb ischaemia: the decision for palliative care. *Eur J Vasc Endovasc Surg* 2000;19(3):246-9.
3. Schanzer A, Conte MS. Critical limb ischemia. *Curr Treat Options Cardiovasc Med* 2010;12(3):214-29. Epub 2010 Apr 14.

4. Setacci C, de Donato G, Teraa M, Moll FL, Ricco JB, Becker F, et al. Chapter IV: treatment of critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2011;42(Suppl 2):S43-59.
5. Lumsden AB, Davies MG, Peden EK. Medical and endovascular management of critical limb ischemia. *J Endovasc Ther* 2009;16(2 Suppl 2):II31-62.
6. Clair D, Shah S, Weber J. Current state of diagnosis and management of critical limb ischemia. *Curr Cardiol Rep* 2012;14(2):160-70. DOI:10.1007/s11886-012-0251-4.
7. Morris-Stiff G, Lewis MH. Gabapentin (Neurontin®) improves pain scores of patients with critical limb ischaemia: an observational study. *Int J Surg* 2010;8(3):212-5. Epub 2010 Jan 11.
8. Creager MA. Medical management of peripheral arterial disease. *Cardiol Rev* 2001;9(4):238-45.
9. Heartsill LG, Brown TM. Use of gabapentin for rest pain in chronic critical limb ischemia. *Ann Pharmacother* 2005;39(6):1136. Epub 2005 May 3.
10. Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. *Pain* 2002;97(3):275-81.
11. Fröhlich MA, McKeown JL, Worrell MJ, Ness TJ. Intravenous lidocaine reduces ischemic pain in healthy volunteers. *Reg Anesth Pain Med* 2010;35(3):249-54.
12. Pedrini L, Magnoni F. Spinal cord stimulation for lower limb ischemic pain treatment. *Interact Cardiovasc Thorac Surg* 2007;6(4):495-500. Epub 2007 Apr 6.
13. Belcaro G, Cesarone MR, Dugall M, Di Renzo A, Errichi BM, Cacchio M, et al. Effects of shock waves on microcirculation, perfusion, and pain management in critical limb ischemia. *Angiology* 2005;56(4):403-7.

Palliative Care Files is a quarterly series in *Canadian Family Physician* written by members of the Palliative Care Committee of the College of Family Physicians of Canada. The series explores common situations experienced by family physicians doing palliative care as part of their primary care practice. Please send any ideas for future articles to palliative_care@cfpc.ca.