Managing pain in peripheral artery disease

WINNIE HONG MB BS, FANZCA, FFPMANZCA

Pain management is an important adjunct in treating peripheral artery disease (PAD), and may help prevent or limit extent of limb loss by facilitating mobilisation and exercise therapy. Pain relief is also important for symptom palliation when surgical revascularisation is not possible or surgery has not relieved pain adequately.

Key points

- **Peripheral artery disease (PAD) is the most common cause of peripheral ischaemia and is associated with severe pain and distress.**
- **Pain management is an important adjunct in treating PAD.**
- **Chronic limb-threatening ischaemia (CLTI) is an advanced stage of PAD.**
- **Revascularisation is the definitive treatment for CLTI to avoid amputation.**
- **Pain relief is also important when revascularisation is precluded.**

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Dr Hong is a Pain Medicine Specialist and Director of the Multidisciplinary Pain Clinic at Concord Repatriation General Hospital, Sydney, NSW.

Peripheral artery disease (PAD) is the most common cause of peripheral ischaemia.[1] It is known to be associated with severe pain and distress.[2] PAD may be asymptomatic, symptoms being dependent on activity levels. Pain is a prominent feature, presenting as either exercise-induced pain associated with intermittent claudication, or the severe rest pain of chronic limb-threatening ischaemia (CLTI) that may be associated with tissue ulceration or necrosis, at an advanced stage of PAD.[3]

Management of PAD

The general goals of management of PAD are:

- managing risk factors to reduce concomitant cardiovascular incidents or complications
- managing limb symptoms including pain, to improve function and quality of life
- preventing or limiting tissue loss which may necessitate amputation.[4]

Pain management is an important adjunct in managing limb symptoms of PAD and may facilitate other aspects of management to help prevent or limit extent of limb loss. With intermittent claudication, pain management facilitates mobilisation and exercise therapy to maintain distal perfusion.[5] Pain relief is also important for symptom palliation when surgical revascularisation is not possible or precluded due to patient comorbidities.

Revascularisation surgery is the recommended definitive treatment for CLTI.[3,6] When successful, it provides pain relief and prevents limb amputation. All patients with CLTI or life-limiting claudication should be referred for consideration of revascularisation. New methods of endovascular surgery allow many high-risk patients to still undergo revascularisation. However, revascularisation may not be possible due to comorbidities, or technical infeasibility.[7] CLTI has a significant impact on quality of life.[2] Uncontrollable pain is an indication that the limb is no longer salvageable and amputation is required. Hence, analgesia is an important part of managing

Table 1. Interpretation of resting ankle-brachial index[13]

Resting ABI	Interpretation	Recommendation For exertional non-joint-related leg pain
1.00 to 1.40	Normal	Consider exercise treadmill ABI to evaluate for PAD
0.91 to 0.99	Borderline	Consider exercise treadmill ABI to evaluate for PAD if highly suspicious
≤ 0.90	Abnormal	Consider referral for vascular surgery
> 1.40	Abnormal	Noncompressible ankle arteries, need alternative evaluation such as toe-brachial index or Doppler waveform study

Abbreviations: ABI = ankle-brachial index; PAD = peripheral artery disease.
Adapted from Aboyans V, Ricco J-B, Bartelink M-L EL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS) 2018; 55: 305-368.[13]

CLTI through facilitating mobilisation, encouraging function and maintaining quality of life.

When the source of pain threatens life or limb, central neural mechanisms cause windup, or sensitisation, with increasing pain amplification. Hence the pain can be extremely difficult to control, especially in CLTI. Prolonged untreated pain is associated with neurodynamic changes leading to increased sensitivity to pain and chronic pain.[8]

Therefore, pain management is important for managing limb symptoms and contributes to limb preservation at all stages of PAD.

Presentation of pain associated with PAD

Symptomatic ischaemia classically presents with intermittent claudication characterised by calf pain that worsens with exertion and is relieved by rest, with a typical claudication distance. However, in some patients, symptoms associated with intermittent claudication may be masked or atypical, resulting in underdiagnosis of the condition.[9,10] Nonspecific symptoms may occur with leg weakness/fatigue, 'ache rather than pain', with or without impaired leg function. Differential diagnoses include peripheral neuropathy and spinal canal stenosis, which may coexist with PAD, making diagnosis difficult. Clinical evaluation including pulse palpation may also be unreliable.[11]

Because of the large proportion of patients with asymptomatic PAD, current guidelines recommend screening with ankle-brachial index for high-risk patients aged over 65 years, or under 65 years but with a history of atherosclerosis in other sites, cardiac failure, abdominal aortic aneurysm or family history of PAD. Resting ankle-brachial indices (ABIs) of less than 0.9 or more than 1.40 are abnormal (Table 1). These values are associated with increased cardiovascular events and mortality.[12,13]

Neuropathic pain may occur in PAD secondary to peripheral neuropathy. Chronic ischaemia is associated with ischaemic peripheral neuropathy.[14] There is evidence of peripheral neuropathy in many patients with claudication and even in asymptomatic patients.[15] Severity of neuropathy progresses with more advanced stages of PAD.[16,17] Neuropathy may also be caused independently by concomitant risk factors such as diabetes mellitus.

Acute or chronic ischaemia (sometimes in previously asymptomatic patients) can be precipitated by acute thrombosis of pre-existing stenosis, loss of a major collateral branch vessel or occlusion of a bypass graft, or aortic dissection.[1] These events are usually accompanied by sudden onset of excruciating pain. When ischaemia becomes critical, tissue anoxia and death ensues.

CLTI is a clinical syndrome defined by recent guidelines as the presence of PAD in combination with rest pain, gangrene or a lower limb ulceration of more than two weeks' duration.[3] This new definition does not require a critical pressure reading. Pain is typically increased when the ischaemic limb is raised. CLTI may be heralded by worsening pain that becomes extreme and very difficult to treat. Consequential peripheral inflammation contributes to pain sensitisation and maintenance.[18] Peripheral tissues become vulnerable to minor trauma with tissue loss and resultant painful ulcerations that heal poorly or become infected. This situation may progress to gangrene with further escalation of pain. Pain relief requires opioid therapy and is important for the management of CLTI while planning for definitive treatment with revascularisation, and improves blood flow by reducing sympathetically mediated vasoconstriction.[19]

Successful revascularisation with reperfusion may relieve pain but some patients continue to experience pain despite reperfusion. This can be caused by neural damage while ischaemic leading to ischaemic neuropathy, or from worsening pre-existing diabetic neuropathy. There is also a significant incidence of neurological damage after lower limb vascular surgery.[20] The incidence is higher with redo exploration, vein harvesting and when an incision extends to below knee level (Table 2). When this occurs, patients may complain of new sensory or motor deficit, or pain in a new area, often with different characteristics to those experienced before. It is important to recognise this phenomenon, as neuropathic pain demands a different treatment approach to nociceptive ischaemic pain.

Pain before amputation is a risk factor for postoperative phantom limb sensations.[21] Phantom pain can be very resistant to treatment once established with most amputees experiencing some phantom sensations in the early postoperative period.[22-24] These may or may not be painful but even nonpainful phantom sensations (such as a feeling that the phantom limb is sticking out at an odd angle) can be very distressing.

Since peripheral inflammation also plays a role in pain generation and maintenance in CLTI, chronic infection in the limb found preoperatively or postoperatively may contribute to persistent pain.[18]

Anxiety and depression are common in patients with PAD,

correlating with the severity of their pain rating.[25] Therefore, clinicians should be aware that symptom reporting in PAD, including pain, is influenced by psychological factors.

Thus, pain associated with PAD is often of mixed nociceptive and neuropathic origin with complex interacting pathophysiological mechanisms.[26] Pain management should be holistic and address specific individual components contributing to pain.

Pharmacological management of pain associated with PAD

In patients with nonreconstructable disease, in addition to antithrombotic therapy (e.g. aspirin and anticoagulants) and vasoactive drugs (e.g. pentoxifylline) to maintain blood flow, prostanoids may improve rest pain, ulcer healing and limb salvage. Intravenous prostanoids such as alprostadil (prostaglandin E1), prostacyclin and iloprost work via vasodilatory and antithrombotic effects.[27] With concurrent definitive therapy, analgesics are important in reducing limb symptoms. Since pain associated with ischaemia is mixed nociceptive and neuropathic with an inflammatory component, NSAIDs, antineuropathic agents and opioid therapy are indicated. Topical agents may also be considered.

NSAIDs

Peripheral inflammation plays an important role in the pathophysiology of pain in PAD.[18] Therefore, NSAIDs are an attractive therapeutic option before starting opioid therapy. However, NSAIDs are associated with renal and cardiac risks. Cardiac risks include stroke and myocardial infarction, especially in the older patient, and the high incidence of comorbid cardiac and renal disease in the predominantly older group of patients with PAD presents a clinical dilemma.

The efficacy of NSAIDs relates to inhibition of COX-1 and COX-2 isoenzymes in the prostaglandin metabolic pathway. There has been considerable controversy regarding the cardiovascular safety of selective COX-2 inhibitors, leading to the withdrawal of rofecoxib. It has been thought that the COX-2 isoenzyme may play a more important role in prostanoid homeostatic balance. Hence, selective COX-2 inhibition may increase risk of thrombotic events and renal toxicity, whereas COX-1 inhibition has been considered to be associated with gastrointestinal risks.[28] Furthermore, there is an increased risk of gastrointestinal bleeding with concomitant use of aspirin and ibuprofen, and there are concerns that competitive COX-1 binders may negate the cardioprotective effects of aspirin by preventing aspirin's access to its acetylation site on platelet COX-1.[29] Because of aspirin's short half-life (15 to 20 minutes), one recommended strategy is to give a single daily dose of ibuprofen two hours after aspirin to avoid interfering with aspirin's efficacy.[29,30]

These considerations have been recently challenged by the PRECISION (Prospective Randomised Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen) trial, which showed that at a moderate dose of 200 mg, celecoxib (COX-2 inhibitor) has lower rates of gastrointestinal, cardiovascular, renal and hypertensive adverse events compared with ibuprofen and naproxen (nonselective COX inhibitors) and does not appear to interfere with the antiplatelet effect of aspirin.[31] Since other NSAIDs were not compared, these results may not be applicable to their COX interactions. Considering these data, for the predominantly older group of patients with PAD who are at risk of gastrointestinal, cardiovascular and renal complications, celecoxib appears to be a safe choice. The lowest effective dose of NSAID should be used for a brief duration if possible. Regular monitoring and clinical follow up after starting therapy are required. Use in patients with uncontrollable hypertension, active congestive cardiac failure or renal failure should be avoided.

Table 2. Incidence of cutaneous nerve injury[20]

Type/Extent of surgery	Percentage incidence
Primary femoral artery only	39%
Redo femoral artery exploration	78%
Superficial femoral vein harvest	76%
Long saphenous vein harvest	82%
Femoral and above knee popliteal	72%
Femoral and below knee popliteal	85%

Adapted from Moawad MR, Masannat YA, Alhamdani A, Gibbons CP. Nerve injury in lower limb vascular surgery 2008; 1: 32-35.[20]

Antineuropathic agents

Chronic peripheral ischaemia is associated with neural damage and peripheral neuropathic pain.[32] More than one mechanism of neurological damage may coexist in a patient (e.g. diabetic peripheral neuropathy).

Nerves are extremely sensitive to hypoxia. Limb paralysis or ischaemic neuropathy may persist after revascularisation and become permanent. The degree of neural damage is related to duration of ischaemia and severity of PAD. With acute ischaemia, axonal degeneration becomes prominent after 24 hours. In chronic ischaemia, focal lesions occur. In diabetic PAD, changes are more profound with diffuse generalised neuronal loss.[33] The pathophysiology of neuropathic pain involves sensitisation of central and peripheral mechanisms.[34]

Treatment should focus on reducing sensitisation associated with neural damage using antineuropathic agents such as antidepressants (especially serotonin and norepinephrine reuptake inhibitors such as duloxetine) and gabapentinoids (gabapentin and pregabalin). Gabapentin can be a useful adjuvant for reducing pain in people with critical ischaemia.[35] Both gabapentin and pregabalin reduce neuropathic pain and decrease opioid consumption and opioid-related adverse effects.[36] However, evidence for the use of gabapentinoids to prevent phantom limb pain is still equivocal.[37]

Opioids

Opioid analgesia may be considered for symptom palliation in the perioperative setting while the patient is being considered for

revascularisation, or amputation if the limb is unsalvageable. However, opioid use for pain associated with intermittent claudication is controversial. Occasionally, some patients may rely on opioid therapy to delay necessary surgery, and relieve stress and anxiety. Patients should be cautioned that pain is a symptom of ischaemia signalling demand in blood flow being exceeded by its supply. Therefore, pain relief may mask ischaemic signals, potentially worsening tissue hypoxia. Furthermore, opioid therapy alone is rarely effective for ischaemic pain without definitive surgery and is associated with side effects including increased sensitivity to pain due to opioid-induced hyperalgesia.

Use of systemic opioid therapy is also limited by comorbidities such as liver and renal diseases affecting drug metabolism and clearance. Cardiac disease is common in patients with PAD. Although opioid therapy usually has no direct effects on cardiac function, methadone and buprenorphine may prolong the QT interval. Cardiac impact is increased if opioid therapy is coadministered with a benzodiazepine.[38] However, with the relatively low dose in a topical buprenorphine patch, cardiac effects are unlikely. Coprescribing of opioids with benzodiazepines should be avoided due to an increased risk of death.[39]

Neuropathic pain may not respond to opioid therapy.[40] The efficacy of opioid therapy is limited by tolerance and counteracted by opioid-induced hyperalgesia. Therefore, systemic opioid therapy should be judiciously prescribed to avoid opioid-induced hyperalgesia in an already sensitised state such as neuropathic pain secondary to ischaemia. Atypical opioids such as buprenorphine, tramadol and tapentadol are generally preferred over conventional opioids because of their efficacy in mixed nociceptive and neuropathic pain states such as ischaemic pain.[41] Buprenorphine and tapentadol are also better tolerated in older people.

Topical agents

The author has had considerable success using topical morphine gel on peripheral vascular ulcers. Our internal audit at Concord Repatriation General Hospital (unpublished) showed that topical morphine on open ulcers has very limited systemic absorption (as expected from poor peripheral circulation), hence excellent patient tolerance. The analgesic effect is likely a peripheral action of morphine on peripheral opioid receptors that have been upregulated in a state of chronic windup associated with peripheral inflammation.[42]

We mix 10 mg of preservative-free morphine with 10 mL of Hydrogel®. This gel is applied to open ulcers with each dressing change using a nonabsorbent dressing. Exudative or infected wounds are contraindications. The analgesic effect may improve with time with the gel application required only with each dressing change.

When the wound is exudative, an absorbent dressing with impregnated ibuprofen can be useful. Ibuprofen is released into the wound when tissue fluid becomes absorbed by the dressing.

If pain is due to localised neuropathy without ulceration, a topical lignocaine 5% patch is helpful for pain relief. Its application is limited by the number of patches required to cover the area (the manufacturer recommends not exceeding three patches per day). However, overdosing is unlikely due to limited absorption. Topical lignocaine gel is similar but less efficacious as it tends to dry up with exposure, thus reducing its usability.

Such topical modalities are well tolerated in the older patient and reduce reliance on morphine analogues, thus lessening the magnitude of opioid-induced hyperalgesia and other systemic opioid side effects.

Other management considerations

Exercise program

Pain relief encourages patients to adhere to exercise programs. Exercise therapy may help reverse pathological events in PAD via exercise-induced vasodilation, which increases distal blood flow, improving mitochondrial function and reducing peripheral inflammation.[43] Therefore, interventions to improve exercise capacity have multiple health benefits including improving vasoresponsiveness, arresting functional decline and increasing longevity.[5]

Supervised exercise programs for intermittent claudication have been shown to improve pain-free walking distance if patients are adherent. Such programs recommend walking until onset of pain. However, adherence is poor, greatly impacting treatment efficacy.[44] The reasons for poor adherence may be multiple.[45] Negative affect, expectation of pain, pain avoidance and pain catastrophising may be contributing factors. Therefore, cognitive behavioural programs addressing these parameters, similar to that for cardiac rehabilitation, may improve adherence to an exercise program and overall coping in the patient with PAD.

Smoking cessation

Tobacco smoking is a highly prevalent risk factor for PAD via multiple mechanisms and is associated with poor outcomes. Smoking reduces tissue oxygenation and attenuates the inflammatory healing response. These effects are reversed by smoking cessation.[46,47] Smoking cessation improves almost all outcomes in cardiovascular disease including overall mortality, surgical complications and secondary surgeries.[48-50]

Furthermore, smokers have higher pain intensity scores and higher rates of disability.[51] Therefore, smoking cessation has potential short- and long-term benefits on outcome and pain control regardless of whether the patient is a candidate for revascularisation surgery.

Nerve blocks

Lumbar sympathetomy can be useful when definitive surgery is not possible or has failed. It is the most important definitive regional technique for ischaemia and is currently underused. The resultant decreased sympathetic tone leads to vasodilation and improved microcirculation.[52] This may be performed with local anaesthetics or neurolysis with phenol or surgery. Symptom improvement includes pain relief, ulcer healing and even avoidance of surgery.[53]

Regional anaesthesia has been reported to improve regional blood flow and may help reduce phantom limb pain after amputations.[54] Regional anaesthesia reduces the patient's systemic opioid requirement and thus opioid-associated adverse effects.[55]

Regional anaesthesia can be performed with continuous infusion of local anaesthetics via a catheter for prolonged use. Subcutaneous tunnelling of the catheter may reduce risk of infection and help stabilise the catheter. Central neuroaxial block via epidural modulates the sympathetic nervous system with associated distal vasodilation while providing pain control. However, frequently patients are on concomitant anticoagulation therapy, which increases the risk of this technique.

Perioperative epidural and peripheral nerve blocks reduce the severity of phantom limb pain.[56] Prolonged analgesia can be achieved with continuous perineural local anaesthetic infusion via an elastomeric external catheter for two months.[54]

Spinal cord stimulation

The use of dorsal column stimulation for PAD is controversial due to the lack of masked studies to evaluate its efficacy. However, evidence is accumulating in support of its use, with improvement in limb survival, pain relief, blood flow and quality of life.[57] Its use is limited by cost and accessibility. Careful selection of patients is required.

Treatment of depression

Persistent pain causes significant suffering.[58] Pain and depression have intricate biological connections.[59] Uncontrolled pain and disability lead to negative affect and higher symptom reporting.[60] Indeed, depressed patients are at greater risk of prospective PAD events and development of PAD.[61] Depression is also associated with poorer function, greater need for revascularisation and poorer overall outcomes.[62-64]

It has been suggested that atherosclerosis-induced peripheral inflammation via neuroimmune pathways may trigger negative mood, which leads to a vicious cycle of further inflammation through sympathetic activation.[25]

Hence, treatment for depression is an important adjunctive modality for pain and independently as a disease modifier for PAD.

Psychological therapy

Due to the high incidence of psychological comorbidities, psychological therapy is imperative in the holistic management of the patient with PAD. Cognitive behavioural therapy addresses anxiety and distress associated with loss of limb or function and may help with adherence to lifestyle changes such as exercise and smoking cessation.

Conclusion

Pain management of the patient with PAD is an important adjunctive treatment affecting outcome. It complements definitive revascularisation and supports palliation in cases where revascularisation is not feasible or has failed. Pain relief for patients with limb ischaemia helps improve function and quality of life, and may assist in limb salvage. It should be approached holistically, addressing mood disorder, exercise capacity and management of risk factors with a multidisciplinary, multimodal approach including advice for lifestyle modification such as smoking cessation and exercise therapy. **PMT**

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A list of references is included in the online version of this article (www.painmanagementtoday.com.au).

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