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Systematic review of pharmacological therapies for the management of ischaemic pain in patients with non-reconstructable critical limb ischaemia

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ABSTRACT

Background Critical limb ischaemia (CLI) is a severe manifestation of peripheral arterial disease, characterised by chronic ischaemic rest pain, ulcers or gangrene. Management of ischaemic pain is challenging in patients with no options for revascularisation and optimal pharmacological therapies have not been established.

Objectives To identify and evaluate the effectiveness of pharmacological therapies to treat ischaemic pain secondary to non-reconstructable CLI.

Methods This systematic review was reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. Comprehensive searches of three electronic databases, a PubMed-related articles link search, grey literature search and hand-searches of the bibliographies of relevant papers and textbooks were performed. Studies recruiting adult patients with CLI of any aetiology were eligible for inclusion. Surgical and revascularisation procedures, and all invasive interventions were excluded.

Results Of 792 studies, six met full inclusion criteria. These studies researched the use of intravenous lidocaine, intravenous ketamine, oral gabapentin and the combination of transdermal buprenorphine and epidural morphine/ropivacaine infusion. All studies showed an improvement in severity of ischaemic pain in CLI but with varying side effect profiles and quality. The extracted studies showed substantial heterogeneity and therefore a meta-analysis was not performed.

Conclusion The pharmacological management of pain secondary to non-reconstructable CLI is a challenging review topic. No recommendations of pharmacological agents can be made following this review but a number of novel approaches to manage pain in this cohort have shown positive results and require further investigation.

BACKGROUND

Definition

The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) defines critical limb ischaemia (CLI) as the following: any patient with chronic ischaemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease.[1] CLI is a chronic condition, distinct from acute limb ischaemia.

CLI is a severe stage of peripheral arterial disease. Patients with CLI can be classified in the grades of the Fontaine classification (stages III–IV) or the Rutherford classification (grades 4–6). Not all patients progress through the predefined stages from claudication to CLI.[2] Progression to CLI is often variable and unpredictable.

Epidemiology

CLI will develop in 500–1000 patients annually in a Western population of 1 million people.[1] It is associated with surgery, hospitalisation and death.[3] Patients with CLI have cardiovascular event rates higher than those in patients with symptomatic coronary artery disease.[4] Thomas *et al* found that in patients with conservatively treated severe CLI, all-cause mortality was 58% with a 2-year survivability rate of 55%.[5] The 5-year mortality exceeds that of colorectal cancer, breast cancer, stroke, acute myocardial infarction and prostate cancer.[6]

Pathophysiology of CLI and ischaemic pain

Most commonly, CLI is caused by atherosclerosis. Other causes include vasculitis, thromboembolic disease, arterial embolic disease, in situ thrombosis, cystic adventitial disease, thromboangiitis obliterans or trauma. Irrespective of the underlying cause, the pathophysiology of CLI is complex. There are three main mechanisms underlying the pathophysiology: haemodynamic abnormalities, oxidative stress and alterations in skeletal muscle metabolism. All compensatory mechanisms to retain skin perfusion become ineffective.

Chronic ischaemic pain has a significant neuropathic component. This is proposed to be secondary to a distal axonopathy affecting nerve fibres of all sizes. Blood flow in the lower limbs of patients with CLI correlates with neurological symptom scores and electrophysiological testing.[7]

Ischaemic pain and impact on quality of life

CLI is primarily characterised by pedal rest pain. It is typically worse at night (when the limb is no longer in a dependent position), often waking patients from their sleep. Pain from ulceration also occurs. Multiple studies have shown that chronic ischaemic pain negatively impacts on multiple dimensions of quality of life.[8–10]

Treatment of CLI

The therapeutic goals in treating CLI include increasing survival, relieving ischaemic pain, healing areas of ulceration, preventing major amputations, improving function and improving quality of life. TASC II recommends that for all patients with CLI, an early referral should be sent to a vascular specialist to plan for revascularisation.[1] Simultaneously, a multidisciplinary approach to control pain, risk factors and comorbidities is recommended.[1] Throughout the disease trajectory, pain control is important to improve quality of life, and to reduce the risk of phantom limb pain in patients who go on to require amputation.[11]

When open or endovascular intervention has failed, or is not possible, pharmacotherapy for CLI is the next step to consider. A 2010 Cochrane review concluded that there is no conclusive evidence for the long-term effectiveness and safety of prostanoids in patients with CLI, despite some positive results regarding rest-pain alleviation, healing of ulcers and amputations.[12] With regard to vasoactive drugs, a Cochrane review found that intravenous naftidrofuryl for CLI was ineffective in reducing the symptoms of CLI.[13]

Palliation and CLI

TASC II reports that ultimately, the majority of care of patients with CLI is palliative in nature.[1] In an ageing comorbid population, preferred revascularisation or surgery is often not an option. There are little data on the outcome of conservative therapy. Most research focuses on physician-reported outcome measures (graft patency, survival, and so on). Research studies including patient-reported outcome measures are limited. Recognising patients in need of palliative care, recording discussions about their management and a high standard of end of life care are all vital.[14]

Ideally, pain control is achieved by reperfusion of the ischaemic limb. When this is not possible or fails due to either the patient or disease status, pain management is challenging. Interventional pain procedures, such as spinal cord stimulation (SCS) and lumbar sympathectomy, may have a role in achieving pain control but evidence to date is inconclusive. Pain management is therefore challenging for multiple reasons: complex pathophysiology resulting in predominantly neuropathic pain, poor tolerance of strong opioids in a cohort with multiple comorbidities often including chronic kidney disease, regional anaesthesia inconsistently effective for ischaemic pain and a limited pool of research specifically targeting ischaemic pain.[15]

Patients with CLI have severe pain, poor quality of life and limited prognosis. If these patients are ultimately being treated in a palliative approach, what evidence do we have for the effectiveness of interventions to treat pain when all other options for limb salvage (revascularisation, surgery, pharmacotherapies) are exhausted? This systematic review was conducted to identify and evaluate the most effective therapies available to treat ischaemic pain in patients with CLI without options for limb salvage.

Objective

To identify and evaluate the effectiveness of pharmacological therapies to treat ischaemic pain secondary to non-reconstructable CLI.

Methods

This systematic review was reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.[16]

IDENTIFICATIONS OF STUDIES (INCLUSION/EXCLUSION CRITERIA)

Types of studies

All study designs were eligible for inclusion apart from single case reports. Single case reports were reviewed but excluded from the data extraction process. Studies that met the inclusion criteria were randomised controlled trials (RCTs), quasiexperimental studies, observational studies with/without control groups and case series.

Types of participants

Studies recruiting adult patients with CLI (as defined by TASC II[1]) were eligible for inclusion. Any underlying cause of CLI was included. Healthy volunteers with experimentally induced ischaemic pain were excluded.

Types of interventions

Any pharmacological interventions to treat ischaemic pain were included. Surgical and revascularisation procedures were excluded. All invasive interventions were excluded, such as SCS and lumbar sympathectomy. Detailed explanation of the roles of these interventions and reasons for exclusion are outlined below.

Spinal cord stimulation

In SCS, a device which stimulates sensory fibres through electrodes is implanted in the epidural space. RCTs conducted to evaluate SCS have limb salvage as their primary outcome with pain relief included in the secondary outcomes. The most recent Cochrane Review (2013) analysed evidence from six RCTs and reported that there was some evidence SCS had a beneficial effect on pain relief in comparison to optimum conservative treatment.[17] A systematic review conducted in 2009 which specifically looked at the role of SCS for pain management reported that trial evidence failed to demonstrate that pain relief in CLI was better for SCS than for conventional medical management.[18] No newer trials were included in the 2013 Cochrane Review. In addition, SCS is a costly and invasive procedure.

Lumbar sympathectomy

The specific role of lumbar sympathectomy in CLI is still unclear. A protocol for a Cochrane review of the role of lumbar sympathectomy in CLI was published last year, therefore further insight into the role of this procedure in CLI will follow.[19] The studies likely to be included did not however meet inclusion criteria for this review (non-pharmacological therapy, invasive, primary outcomes relating mostly to limb salvage).

Types of outcome measures

The primary outcome measure was reduction in pain score, as measured by a visual analogue scale (VAS), Brief Pain Inventory[20] or other scoring methods. Secondary outcome measures included opioid requirements, findings of allodynia, hyperpathia, or hyperalgesia on examination, hours of sleep, and depression and anxiety scores. Side effect profiles of each intervention were included in the data analysis. Only studies with the primary outcome measure related to ischaemic pain relief in CLI were included in the data analysis. This excluded studies with the primary outcome measures relating to limb salvage and secondary outcomes relating to pain management.

Search methods

Searching of three electronic databases was conducted (access via Ovid): MEDLINE (Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to December 2016), EMBASE (1974 to December 2016), Cochrane Library.

For each database, a detailed search strategy was developed (eg, online supplementary appendix 1).

Related article search

A PubMed 'related articles' link search was conducted which has been shown to be useful for reviewing complex evidence.[21]

Language

Only studies published in the English language were eligible for the systematic review.

Date range

Only studies published between 1996 and December 2016 were included (20-year span).

Book search

Two palliative care textbooks were reviewed to identify articles relating to CLI pain management: Oxford Handbook of Palliative Care and Palliative Medicine.[22 23]

Grey literature

To identify relevant unpublished written material or published abstracts or conference proceedings OpenGrey (www.opengrey.ey/) was searched.

Data collection and analysis

Selection of studies

Once the search strategy was completed, a list of titles of studies was reviewed to decide whether they met inclusion criteria. The abstract was read if it was unclear whether the study should be included. If there was still doubt the full paper was reviewed. Following this, a final list of included studies was generated and data were extracted.

Data extraction and management

Predesigned data extraction forms were filled by one reviewer during the data extraction process. To manage citations and tracking of studies throughout the stages of this review, RefWorks software was used.[24]

The following data were extracted: publication details, country origin, study design, study setting, recruitment period, follow-up duration, type of data collected, sample size, gender, age, primary outcome measure, secondary outcome measure(s), intervention details, adverse effects, evidence level.

Assessment of quality of studies

The risk of bias of each study was assessed using the Cochrane Risk of Bias tool for RCTs and the ROBINS-I tool for non-randomised trials.[25 26] The evidence was then graded using SIGN Levels of Evidence and Grading Recommendations.[27]

Data synthesis

Due to heterogeneity among the included studies, meta-analysis could not be performed.

RESULTS

Description of studies

Characteristics of included studies are outlined in table 1.

Search results

Following the initial database search, 1086 studies were listed. Following automatic removal of duplicates by RefWorks, 792 were identified. After reviewing the titles and/or abstracts of 792 studies, nine articles were reviewed and assessed for eligibility. Six were found to be suitable for inclusion in the analysis (online supplementary appendix 2, PRISMA flow diagram).

Included studies

Six studies met inclusion criteria. This included five RCTs as follows: double-blind parallel conventional therapy controlled, double-blind parallel placebo controlled, double-blind crossover, single blind parallel open label, prospective randomised trial. The one remaining study was a prospective observational pilot study.

Interventions used

The following interventions were used in the studies included: intravenous lidocaine, oral gabapentin, intravenous ketamine and transdermal buprenorphine on patients already commenced on epidural morphine/ropivacaine. Studies investigating prostanoids were excluded as the primary outcome measure did not relate to ischaemic pain relief.

Participants

Sample sizes ranged from 8 to 86. Two hundred and thirty-two patients were recruited over the six included studies. All patients had ischaemic pain secondary to CLI and were under the care of a vascular surgery service. One study included participants with CLI still awaiting surgery[28] : this study was deemed appropriate to include as the underlying nature of the pain was no different from patients with CLI not suitable for surgery (in both cases the pain experienced was ischaemic pain secondary to CLI). The other reason to include this study is that the majority of patients in practice suffering from pain secondary to CLI are often left on surgical waiting lists in an attempt for revascularisation, however, never get to surgery due to their deteriorating state.

Settings

Included studies were conducted in UK, Italy, Sweden and Iran. Most participants were outpatients. One study recruited inpatients awaiting surgery.

Excluded studies

List of excluded studies and reasons for exclusion are outlined in table 2.[29–31]

Quality of included studies

The quality assessments of included studies are outlined in tables 3–5.

The double-blind parallel RCT by Vahidi *et al* scores 1++ as it appeared to have very low risk of bias (SIGN grading system[27]). It, however, had a very short follow-up time of 30 min. Persson *et al*'s ketamine RCT contained only eight patients with no sample size calculation, therefore it is likely underpowered and at risk of being influenced by random fluctuations which may overestimate any effects. This was accounted for under the 'other bias' category of the Cochrane tool (Cochrane Risk of Bias Assessment[25]). This study also had a limited follow-up time of 60 min. Mitchell and Fallon's RCT on ketamine was a well-designed double-blind placebo controlled RCT; however, seven withdrew during the study and this resulted in attrition bias. Both trials by Aurilio *et al* were at high risk of bias. They were open-label trials, at risk of both performance and detection bias. The 2005 trial by Aurilio *et al* also did not outline the random sequence generation process or allocation concealment process. The 2010 study by Morris-Stiff *et al* on gabapentin was a prospective observational study without a control group. This study was deemed to have a serious risk of selection bias (ROBINS-I tool[26]). It was graded 3, as per SIGN grading system, reflecting its poor-quality design and high risk of bias.

EFFECTS OF INTERVENTIONS

Results of included studies are outlined in table 6.

Lidocaine

Vahidi and colleagues compared intravenous lidocaine to intravenous morphine in patients with CLI.[32] Prior to the infusion, the mean VAS score in the lidocaine group was 7.50 and in the morphine group was 7.65. After 15 min, the mean VAS score in the group that received lidocaine was lower than in the morphine group (5.75±1.77 vs 7.00±1.83; mean difference 1.25, 95% CI 0.095 to 2.405). At 30 min, the mean VAS score lowered further in the lidocaine group in comparison to the morphine group (4.25±1.48 vs 6.50±1.73; mean difference 2.25, 95% CI 1.218 to 3.282).

Ketamine

Mitchell and Fallon compared ketamine 0.6 mg/kg in 0.9% saline over 4 hours with normal saline over 4 hours on a background of the patient's regular opioid usage.[33] In the ketamine group, percentage pain relief attributed to medication improved from 50% preinfusion to 65% 24 hours postinfusion and 69% 5 days postinfusion. In the placebo group, percentage pain relief attributed to medication went from 58% preinfusion to 56% 24 hours postinfusion and 50% 5 days postinfusion ($p<0.05$ using the t-test and the Wilcoxon rank-sum test). The intervention

Table 1 Characteristics of included studies

Reference	Country	Study design	Study setting	Participants	Intervention	Control	Follow-up duration	Primary outcome measure	Secondary outcome measures
Vahidi *et al*[32]	Iran	Double-blind parallel RCT	Emergency department of tertiary referral centre	n=40 (20 intervention, 20 control)	Lidocaine: lidocaine solution (2 mg/kg) intravenous over 5 min	Morphine solution (0.1 mg/kg) intravenous over 5 min	Assessed before, 15 and 30 min after initiation of infusion	VAS (0–10)	None
Morris-Stiff *et al*[35]	Wales, UK	Prospective observational study (pilot study)	Outpatients under vascular surgery team	n=20 (consecutive patients) 17 completed study	Gabapentin: 300 mg daily, titrated to 300 mg three times a day within 3 days Increased to 600 mg three times a day as indicated	None	Assessed at baseline, 4, 7, 14, 28 days or until surgical intervention or death	VAS (0–10)	Night pain score, opioid requirements
Aurilio *et al*[36]	Italy	Open-label randomised trial	Surgical outpatients in a tertiary referral centre	n=86 (44 intervention, 42 control)	Buprenorphine (35 µg/hour) patch+epidural infusion of ropivacaine/morphine (200 mg+2 mg)	Placebo patch+epidural infusion of ropivacaine/morphine (200 mg+2 mg)	4 weeks with twice weekly contact by researcher	VAS (0–100)	Short-Form McGill Pain Questionnaire, sleep quality, morphine requirements, patient satisfaction, psychobehavioural evaluation (Hamilton Scale)
Aurilio *et al*[28]	Italy	Open-label randomised trial	Patients under vascular surgery awaiting surgery	n=43 (22 intervention, 21 control)	Buprenorphine (35 µg/hour) patch+epidural 100 mL of ropivacaine (2 mg/mL) and 2 mg of morphine at 4 mL/hour	Epidural 100 mL of ropivacaine (2 mg/mL) and 2 mg of morphine at 4 mL/hour rate	30-day observation period	VAS (0–100)	Hours of sleep, adjustment of spinal dose of morphine
Mitchell and Fallon[33]	Scotland, UK	Double-blind placebo controlled RCT	Patients under the care of vascular surgery	n=35 (20 male, 15 female) 7 withdrew so final analysis: 16 intervention, 12 placebo	Ketamine: intravenous ketamine 0.6 mg/kg in 0.9% saline over 4 hours	Intravenous placebo (0.9% saline) over 4 hours	Assessed at entry to study, prior to infusion, 24 hours after infusion and on average 5 days postinfusion	Brief Pain Inventory	Opioid requirements, presence of allodynia/hyperpathia/hyperalgesia
Persson *et al*[34]	Sweden	Crossover, double-blind RCT	All referred from vascular surgery	n=8	Ketamine: racemic ketamine hydrochloride 0.15, 0.3, 0.45 mg/kg intravenous over 5 min	Morphine-hydrochloride 10 mg intravenous over 5 min	VAS scores at 2.5, 5, 10, 20, 30, 40, 50 and 60 min	VAS (0–10)	None

RCT, randomised controlled trial; VAS, visual analogue scale.

Table 2 Excluded studies

Reference	Intervention	Reason for exclusion
Tawfic *et al*[29]	Ketamine	Case report
Heartsill and Brown[30]	Gabapentin	Case report
Fletcher *et al*[31]	Locally applied transdermal nitrate patches	Patients had 'distal limb ischaemia' but the paper did not provide sufficient information to confirm that patients had critical limb ischaemia

Table 4 Risk of bias in non-randomised studies (ROBINS-I tool)

	Morris-Stiff *et al*[35]
Bias due to confounding	+
Bias in selection of participants into the study	–
Bias in classification of interventions	+
Bias due to deviations from intended interventions	+
Bias due to missing data	+
Bias in measurement of outcomes	+
Bias in selection of the reported result	+
Overall bias	Serious risk

Table 5 Quality assessment according to SIGN grading system

Study	1++	1+	1–	2++	2+	2–	3	4
Vahidi *et al*[32]	x							
Morris-Stiff *et al*[35]							x	
Aurilio *et al*[36]			x					
Aurilio *et al*[28]			x					
Mitchell and Fallon[33]		x						
Persson *et al*[34]			x					

group also showed an improvement in effect of pain on general activity ($p<0.03$) and on enjoyment of life ($p<0.004$). No statistically significant difference was seen in opioid requirements between the ketamine and placebo groups.

In the Persson *et al* ketamine trial, racemic ketamine hydrochloride was administered intravenously over 5 min at doses of 0.15, 0.3 and 0.45 mg/kg on respective study days.[34] This was compared with morphine 10 mg intravenously over the same time interval. Ketamine 0.30 mg/kg provided total pain relief in seven of eight patients, whereas ketamine 0.45 mg/kg provided total pain relief in all eight patients. Pain relief lasted up to 10 min and then decreased steadily to a median value to 50% at 60 min. However, there was no statistically significant difference between the analgesic effect of ketamine 0.45 mg/kg and morphine 10 mg at peak effect times (5 and 20 min, respectively) ($p<0.10$, Wilcoxon test).

Gabapentin

In Morris-Stiff *et al*'s paper, the median pain score was 9 at presentation and significantly reduced compared with baseline each of the assessment days (day 4: 7 ($p=0.001$), day 7: 7 ($p=0.0002$), day 14: 6 ($p=0.0004$), day 28: 5 ($p=0.0003$)).[35] Two of the 17 patients failed to show an improvement in pain scores. Fifteen patients reported an improvement in night pain, with secondary better sleep and perceived improvement in quality of life. The median dose was 1271 mg; four were adequately pain controlled on 300 mg three times a day, nine on 1200 mg, and the remainder on 600 mg three times a day. There was no control group to compare effect.

Transdermal buprenorphine + epidural morphine/ropivacaine

In Aurilio *et al*'s 2009 trial, there was a significant difference ($p<0.0001$) at the end point between the intervention group, with a mean VAS score of 10 mm (a reduction of 88%), and the control group, with a mean VAS score of 19 mm (a reduction of 77%).[36] Patients receiving a 35 mg/hour buprenorphine patch demonstrated significantly lower Short-Form McGill Pain Questionnaire scores, mean total score and present pain intensity compared with those receiving the placebo patch ($p<0.0001$). At the end point, the mean score for sleep quality was significantly better in the intervention group ($p<0.0001$). The number of patients requiring rescue morphine was lower in intervention group during each week. There were no significant differences in the neurobehavioural status of the patients ($p<0.165$). In the 2005 trial, mean VAS at baseline was 85 in both groups.[28] At day 15 it reduced to 20 in the intervention and 38 in the control, and

Table 3 Cochrane tool to assess risk of bias for randomised controlled trials

	Vahidi *et al*[32]	Aurilio *et al*[36]	Aurilio *et al*[28]	Mitchell and Fallon[33]	Persson *et al*[34]
Random sequence generation (selection bias)	+	+	?	+	+
Allocation concealment (selection bias)	+	+	?	+	+
Blinding (performance bias and detection bias) All outcomes	+	–	–	+	+
Incomplete outcome data (attrition bias) All outcomes	+	+	+	–	+
Selective reporting (reporting bias)	+	+	+	+	+
Other bias	+	+	+	+	–

Table 6 Results of included studies

Reference	Intervention	Baseline pain scores	Postintervention pain scores	Statistical difference between intervention and control	Secondary outcomes	Adverse effects
Vahidi *et al*[32]	Intravenous lidocaine versus intravenous morphine sulfate	Mean VAS 7.50±1.93	Intervention: 15 min: 5.75±1.77 30 min: 4.25±1.48 Control: 15 min: 7.00±1.83 30 min: 6.50±1.73	15 min: mean difference 1.25 (95% CI 0.095 to 2.405) 30 min: mean difference 2.25 (95% CI 1.218 to 3.282)	None	None
Morris-Stiff *et al*[35]	Gabapentin: median dose 1271 mg/24 hours	Median VAS 9	Day 4: 7 (p=0.001) Day 7: 7 (p=0.0002) Day 14: 6 (p=0.0004) Day 28: 5 (p=0.0003)	No control	Reduction in night pain in 15/16 patients Reduction in opioid requirements in 5/17. No increase in opioid dose required	None
Aurilio *et al*[36]	Buprenorphine transdermal patch+epidural ropivacaine+morphine versus placebo patch+epidural ropivacaine+morphine alone	Mean VAS: Intervention 84.9±3.38 Control 84.8±3.41	At end point: Intervention 10.31±2.13 Control 19.4±1.95	Intervention versus control (p<0.0001 95% CI −10.4 to −8.3)	Statistical significant improvements in intervention vs control in SF-MPQ total, SF-MPQ PPI, Sleepinterference (All p<0.0001) Lower number of patients requiring rescue morphine No significant differences in the neurobehavioural status of the patients (p<0.165)	No side effects in 18 patients in intervention versus 8 in control More SEs (drowsiness, fatigue, constipation, nausea) in control In the control group, two patients (4.7%) suffered significant nausea causing them to withdraw from trial
Aurilio *et al*[28]	Buprenorphine transdermal patch+epidural ropivacaine+morphine versus epidural ropivacaine+morphine alone	Mean VAS: Intervention 85 Control 85	At 15 days: Intervention 20 Control 38 At 30 days: Intervention 10 Control 20	No statistical tests performed	Hours of sleep 3.5 to 5 to 8 hours vs 3.5 to 4.5 to 6 hours in control No patients for additional morphine in intervention, 11 in control	No side effects in 12 patients in intervention versus 6 in control More SEs (drowsiness, fatigue, constipation, nausea) in control 1 withdrawal in control due to nausea
Mitchell and Fallon[33]	Intravenous ketamine versus intravenous normal saline	Pain relief score (mean): Intervention 50 Control 58 Mean 'average pain score': Intervention 5.9 Control 5.8	Pain relief score: Intervention (24 hours post): 65 Control (24 hours post): 56 Mean 'average pain score': Intervention (24 hours post): 5.1 Control (24 hours post): 6.3	17% difference in means of pain relief scores (95% CI 0.2, 33.8) in favour of ketamine versus control. Statistical significance (p<0:05) improvement in the average daily pain scores in the ketamine group	Improvement in effect of pain on general activity (p<0.03) and enjoyment of life (p<0.004) No significant difference in opioid consumption	In ketamine group 33% (n=6) reported feeling more emotional than usual 24 hours after infusion, only 6% (n=1) of placebo group (OR of 7.7, p<0:05) 7 patients withdrew for reasons not related to intervention

Continued

Table 6 Continued

Reference	Intervention	Baseline pain scores	Postintervention pain scores	Statistical difference between intervention and control	Secondary outcomes	Adverse effects
Persson *et al*[34]	Intravenous ketamine versus intravenous morphine	Baseline pain ratings ranged from 0.3 to 10	Ketamine 0.30 mg/kg: total pain relief in 7/8 patients Ketamine 0.45 mg/kg: total pain relief in 8/8 patients Pain relief (median value) of approximately 50% at 60 min	At 5 min: 0.45 mg/kg dose statistical significant difference (p=0.010) and 0.30 mg/kg dose (p=0.05) The 0.15 mg/kg dose was not significant (p>0.05)At 10 min: only 0.45 mg/kg significantly different from morphine (0.05 level) At peak effects 0.45 mg/kg ketamine versus 10 mg morphine (5 and 20 min, respectively): not significantly different (p<0.10, Wilcoxon test)	None	Ketamine: all patients had perceptual disturbances and psychotropic effects (dose dependent) At 0.45 mg/kg dose all had 'unacceptable' SE Highest dose ketamine: mean BP rise ~10% HR changes within the limits of +10 beats/min for all doses

PPI, present pain intensity; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analogue scale.

at day 30 it reduced further to 10 in the intervention and 20 in the control. In the intervention, group mean hours of sleep improved from 3.5 to 5 to 8 and in the control from 3.5 to 4.5 to 6. No patients in the intervention group required additional morphine, in comparison to 11 in the control. No statistical analysis was performed on these results.

Adverse effects

All trials involved close monitoring for adverse effects. No side effects were reported in the intravenous lidocaine trial. In the lidocaine group, there were no reported adverse effects such as nausea, lightheadedness or perioral numbness. Following close monitoring, no serious complications (respiratory arrest, hypotension or cardiac arrhythmia) were observed. ECG readings were unchanged postinfusion. However, patients were only followed up for 30 min postinfusion. In Morris-Stiff *et al*'s trial, patients were followed for 28 days following commencement of gabapentin to monitor for side effects. There were no documented side effects. Both ketamine trials reported significant adverse effects in the intervention groups. In Mitchell and Fallon's trial, despite all patients receiving oral haloperidol 1.5 mg on the evening of the infusion, 33% of patients reported feeling 'more emotional than usual' 24 hours after the ketamine; 6% of the placebo group reported this symptom (OR of 7.7; p=0.05). In Persson *et al*'s trial, side effects were divided into two groups: circulation and psychotropic. There was a marginal effect on systolic blood pressure after varying doses of ketamine (mean blood pressure rises approximately 10% for ketamine dose (0.45 mg/kg)). There was no significant effect on heart rate. All patients in the ketamine group experienced perceptual disturbances and psychotropic effects. These effects were dose dependent; at the highest dose all patients had side effects deemed 'unacceptable' even for a short-term treatment. Unacceptable side effects were effects which involved disturbances of perception, dizziness/vertigo or pronounced sedation. No patients received antipsychotic therapy to limit adverse effects. No patients withdrew because of adverse effects. Both Aurilio *et al*'s trials on the combination of buprenorphine and epidural morphine/ropivacaine found higher incidences of adverse effects in the control group (2009 trial: 59% vs 81%, p<0.001; 2005 trial: 45% vs 71%, no p value reported). All side effects reported were common opioid-induced effects (drowsiness, fatigue, constipation and nausea). Withdrawal from the trials occurred in one patient from the control group in the 2005 trial and two patients from the control group in the 2009 trial. The higher rate of symptoms reported in the control group was felt to be secondary to the increased need for

additional rescue doses of epidural morphine in the control group.

DISCUSSION

Despite TASC II stating that the management of CLI is ultimately palliative in nature, there is a surprisingly limited research base for the use of analgesics to manage ischaemic pain in CLI. This systematic review only identified six studies conducted in CLI with a primary outcome measure assessing ischaemic pain management. The majority of studies focused on limb salvage or include invasive or surgical interventions. In practice, however, the majority of patients referred to palliative or pain management services may be approaching end of life due to non-reconstructable CLI and pain management is challenging. This systematic review has identified a small number of studies but with some promising approaches to manage pain in this frail, elderly, comorbid population.

Two RCTs comparing ketamine with normal saline and morphine sulfate showed significantly reduced pain scores in the intervention groups. Ketamine was found to improve ischaemic pain when compared with normal saline, but when compared with morphine at equivalent peak dose time intervals there was no statistical difference. Both studies had high rates of adverse effects. In the Persson *et al*'s study, all patients receiving the higher dose of ketamine had 'unacceptable' side effects. Mitchell and Fallon pre-empted the known side effects of ketamine by using haloperidol to limit the severity of these symptoms. Despite this, however, in the ketamine group significantly more patients reported feeling more emotional than usual after the infusion. Ketamine is a controversial drug in palliative care. Multiple papers have researched its effectiveness in varying pain syndromes, predominantly with neuropathic components.[37 38] However, the side effect profile continues to be the limiting factor in its use. The overall benefit of ketamine to treat pain secondary to CLI is, therefore, still questionable.

Vahidi *et al*'s trial researching the use of intravenous lidocaine is the first conducted in patients with CLI. Previous research by Frölich *et al* showed that lidocaine had an inhibitory effect on ischaemic pain, producing a sustained analgesic state in ischaemic pain induced by the tourniquet technique in healthy individuals.[39] This is a promising new analgesic approach. This RCT also identified no adverse effects, which is favourable in a frail population with limited prognosis, in which improved quality of life should be the focus of all clinicians treating these patients. However, adverse effects were not monitored for longer than 30 min postinfusion, therefore caution is needed prior to use. The role of lidocaine for more sustained pain relief is also unknown at present.

Two studies conducted by Aurilio *et al* discussed the benefit of a partial opioid antagonist (buprenorphine) in addition to an epidural infusion of morphine and ropivacaine. The additional benefit of buprenorphine is felt to be secondary to the following mechanisms: reduced central hypersensitisation typical of the various forms of chronic pain, different site of action to morphine possibly resulting in a synergic effect by associating the two drugs and possible reduction in the incidence of the side effects.[36] Certainly, in both Aurilio and colleagues' RCTs the intervention group had lower side effect profiles than the control which required higher doses of morphine.

Gabapentin is licensed for the treatment of peripheral and central neuropathic pain in adults at doses up to 3.6 g daily. It is thought to act by binding to calcium channels, modulating calcium influx which results in analgesic, antiepileptic and sedative effects. Gabapentin is a widely used neuropathic agent in both the palliative and pain medicine services. In a prospective observational study of patients with non-reconstructable CLI, gabapentin significantly reduced pain scores, improved sleep, and in some, reduced opioid requirements with no documented side effects. Due to the limitations of the study design and lack of control group, recommendations cannot be made with regard to the use of gabapentin for this cohort of patients on this level of evidence.

LIMITATIONS

This review has a number of limitations. First, the electronic database searching was limited to three databases: Medline, Embase and the Cochrane Library. Further papers may have been identified if a more extensive search strategy was conducted; for example, including databases such as Web of Science and Scopus or conducting a broader search of the grey literature. This review also only included studies published in the English language and within the last 20 years, therefore limiting the scope of papers to analyse and interpret. The search was limited to studies published in the last 20 years due to the fact that the scoping searches showed little earlier evidence. Of those limited number of studies that were available prior to 1996, all were of poor-quality design. Studies were limited to the English language as language resources were not available to perform more in-depth searching. A further weakness of this review is that only one reviewer developed the search terms (which were not validated but developed with a librarian), selected studies for inclusion and conducted the data extraction process. At least two reviewers are recommended to complete this process. This review also restricted itself only to the pharmacological therapies available for management of ischaemic pain in CLI. SCS and lumbar sympathectomy may have a role in a specific subset of patients with non-reconstructable CLI. However, studies relating to these procedures were excluded from this review. For this review, there were no specifications with regard to adequate follow-up periods. Ideally, a follow-up of at least 1 week would be advisable; however, this

was not possible due to lack of evidence. Particular attention needs to be made to the fact that there were two studies included in this review with very short follow-up periods: Vahidi *et al* (30 min) and Persson *et al* (60 min).

CONCLUSION

The pharmacological management of pain secondary to non-reconstructable CLI is a challenging review topic. This is due to the complex pathophysiology of pain in CLI, limited research base, differing pharmacological interventions and varying quality of relevant studies. Synthesis of the included studies to help guide our clinical management of ischaemic pain in non-reconstructable CLI is difficult. Optimising neuropathic pain control appears to be a cornerstone of management. No recommendations of pharmacological agents can be made following this review, but a number of novel approaches to manage pain in this cohort have shown positive results and require further investigation. These include the use of intravenous lidocaine for short-term relief of ischaemic pain in non-reconstructable CLI and the addition of buprenorphine in patients already receiving epidural morphine and local anaesthetic. Gabapentin cannot be recommended on the basis of one positive observational uncontrolled study. The debate surrounding the benefit of ketamine in varying pain states still exists, with our review not supporting its use in CLI on the current level of evidence.

Implications for research

There are a number of research possibilities emerging following this review. Intravenous lidocaine use for ischaemic pain looks promising; however, further research needs to assess its use and safety over a longer duration. With regard to ketamine, further research would be beneficial into alternative dosing regimens and routes of administration (oral, subcutaneous or intravenous) to assess better tolerability and further assess effectiveness. These trials should use conventional therapy as a control, such as morphine sulfate. They should also include prophylactic antipsychotic medication to limit side effects. The use of gabapentin has only been assessed in a prospective observational study; a double-blind controlled RCT compared with conventional therapy should be conducted. The role of other neuropathic agents such as pregabalin, duloxetine and amitriptyline needs to be researched.

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REFERENCES

1 Norgren L, Hiatt WR, Dormandy JA, *et al*. Inter-Society Consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007;45 Suppl S:S5–S67.
2 White JV, Rutherford RB, Ryjewski C. Chronic subcritical limb ischemia: a poorly recognized stage of critical limb ischemia. *Semin Vasc Surg* 2007;20:62–7.
3 Gillum RF. Peripheral arterial occlusive disease of the extremities in the United States: hospitalization and mortality. *Am Heart J* 1990;120(6 Pt 1):1414–8.
4 Caro J, Migliaccio-Walle K, Ishak KJ, *et al*. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord* 2005;5:14.
5 Thomas AR, Raats JW, Lensvelt MM, *et al*. Conservative treatment in selected patients with severe critical limb ischemia. *World J Surg* 2015;39:2090–5.
6 Rogers R, Hiatt W. *Pathophysiology and treatment of critical limb ischemia*.
7 Weinberg DH, Simovic D, Isner J, *et al*. Chronic ischemic monomelic neuropathy from critical limb ischemia. *Neurology* 2001;57:1008–12.
8 Pedrosa DF, Pelegrin AK, Siqueira HB, *et al*. Evaluation of the quality of life of clients with chronic ischemic pain. *Rev Lat Am Enfermagem* 2011;19:67–72. Feb.
9 Sprengers RW, Teraa M, Moll FL, *et al*. Quality of life in patients with no-option critical limb ischemia underlines the need for new effective treatment. *J Vasc Surg* 2010;52:843–9. e1Ot.
10 Balogh O, Péntek M, Gulácsi L, *et al*. [Quality of life and burden of disease in peripheral arterial disease: a study among hungarian patients]. *Orv Hetil* 2013;154:464–70.
11 Nikolajsen L, Ilkjaer S, Krøner K, *et al*. The influence of preamputation pain on postamputation stump and phantom pain. *Pain* 1997;72:393–405.
12 Ruffolo AJ, Romano M, Ciapponi A, *et al*. Prostanoids for critical limb ischaemia. *Cochrane Database of Systematic Reviews* 2010;20:CD006544.
13 Smith FB, Bradbury AW, Fowkes FG, *et al*. Intravenous naftidrofuryl for critical limb ischaemia. *Cochrane Database Syst Rev* 2000;2:CD002070.
14 Campbell WB, Verfaillie P, Ridler BM, *et al*. Non-operative treatment of advanced limb ischaemia: the decision for palliative care. *Eur J Vasc Endovasc Surg* 2000;19:246–9.
15 Kucera TJ, Boezaart AP. Regional anesthesia does not consistently block ischemic pain: two further cases and a review of the literature. *Pain Med* 2014;15:316–9.
16 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
17 Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev* 2013;2:CD004001.

18 Simpson E, Duenas A, Holmes M, *et al*. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess* 2009;13:1–154.
19 Karanth VK, Karanth TK, Karanth L. Lumbar sympathectomy techniques for critical lower limb ischaemia due to non-reconstructable peripheral arterial disease. *Cochrane Database Syst Rev* 2016;12(Issue 12):CD011519.
20 Cleeland CS, Ryan KM. The brief pain inventory, 1994. https://www.mdanderson.org/education-andresearch/departments-programs-and-labs/departments-and-divisions/symptom-research/symptomassessment-tools/BPI_UserGuide.pdf (accessed on 1 March 2016).
21 O'Leary N, Tiernan E, Walsh D, *et al*. The pitfalls of a systematic MEDLINE review in palliative medicine: symptom assessment instruments. *Am J Hosp Palliat Care* 2007:24:181–4. Ju.
22 Watson MS. *Oxford handbook of palliative care*. USA: Oxford University Press, 2005.
23 Walsh D. *Palliative Medicine*. Philadelphia, PA: Saunders/Elsevier, 2009.
24 . RefWorks®.ProQuest https://refworks.proquest.com/ 2016.
25 . "The Cochrane Collaboration Tool For Assessing Risk Of Bias". Handbook.cochrane.org
26 Risk Of Bias In Non-Randomized Studies - Of Interventions | Cochrane Bias. Methods.cochrane.org.
27 Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334–6.
28 Aurilio B, Pace MC, Passavanti MB. Transdermal buprenorphine combined with spinal morphine and naropine for pain relief in chronic peripheral vasculopathy. *Minerva Anestesiol* 2005;71(7-8):445–9. Aug.
29 Tawfic QA, Eipe N, Penning J. Ultra-low-dose ketamine infusion for ischemic limb pain. *Can J Anaesth* 2014;61:86.
30 Heartsill LG, Brown TM. Use of gabapentin for rest pain in chronic critical limb ischemia. *Ann Pharmacother* 2005;39:1136.
31 Fletcher S, Wright M, Wilkinson A, *et al*. Locally applied transdermal nitrate patches for the treatment of ischaemic rest pain. *Int J Clin Pract* 1997;51:324–5.
32 Vahidi E, Shakoor D, Aghaie Meybodi M, *et al*. Comparison of intravenous lidocaine versus morphine in alleviating pain in patients with critical limb ischaemia. *Emerg Med J* 2015;32:516–9.
33 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;97:275–81.
34 Persson J, Hasselström J, Wiklund B, *et al*. The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. *Acta Anaesthesiol Scand* 1998;42:750–8.
35 Morris-Stiff G, Lewis MH, Gabapentin LMH. Gabapentin (Neurontin) improves pain scores of patients with critical limb ischaemia: an observational study. *Int J Surg* 2010;8:212–5.
36 Aurilio C, Pace MC, Passavanti MB, *et al*. Treatment of ischemic pain in patients suffering from peripheral vasculopathy with transdermal buprenorphine plus epidural morphine with ropivacaine vs. epidural morphine with ropivacaine. *Pain Pract* 2009;9:105–14.
37 Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg* 2003;97:1730–9.
38 Azari P, Lindsay DR, Briones D, *et al*. Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. *CNS Drugs* 2012;26:215–28.
39 Frölich MA, McKeown JL, Worrell MJ, *et al*. Intravenous lidocaine reduces ischemic pain in healthy volunteers. *Reg Anesth Pain Med* 2010;35:249–54.