ISCHAEMIC PAIN IN NON-RECONSTRUCTABLE CRITICAL LIMB ISCHAEMIA

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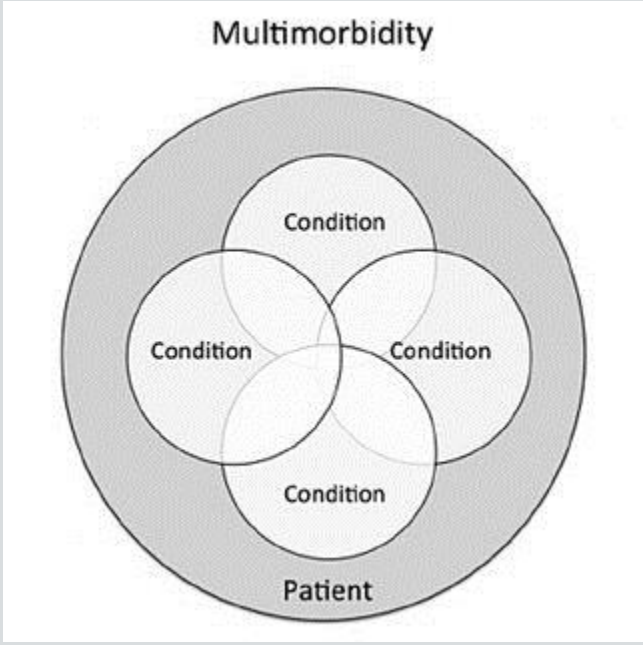
Masterclass in Palliative Care 2019

PRESENTATION OUTLINE

- A Typical Case
- Background
- Why is CLI important?
- Management of CLI
- Systematic Review
- Clinical Application

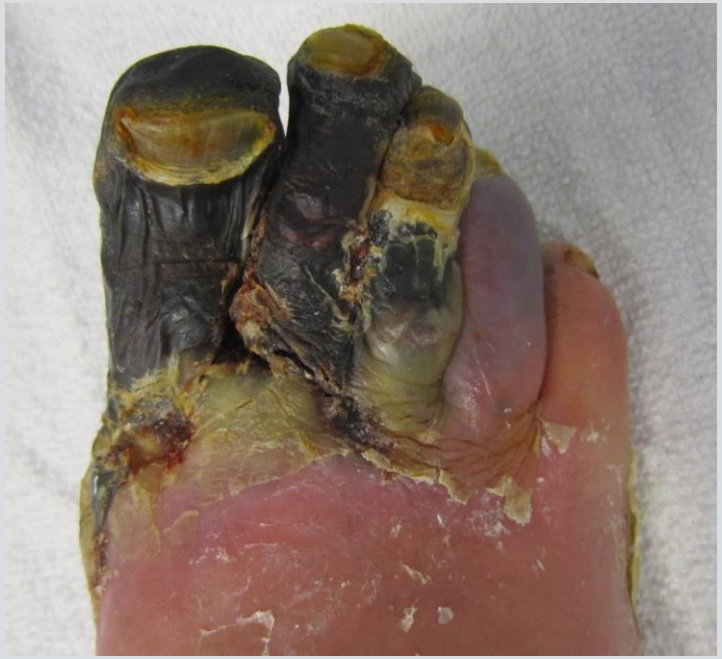
THE CLI PATIENT

- Frail
- Elderly
- Multicomorbid – DM, IHD, CKD, Vascular Dementia
- Hx of polypharmacy
- Hx of multiple surgical interventions
- Now "no option" or "non-reconstructable" CLI



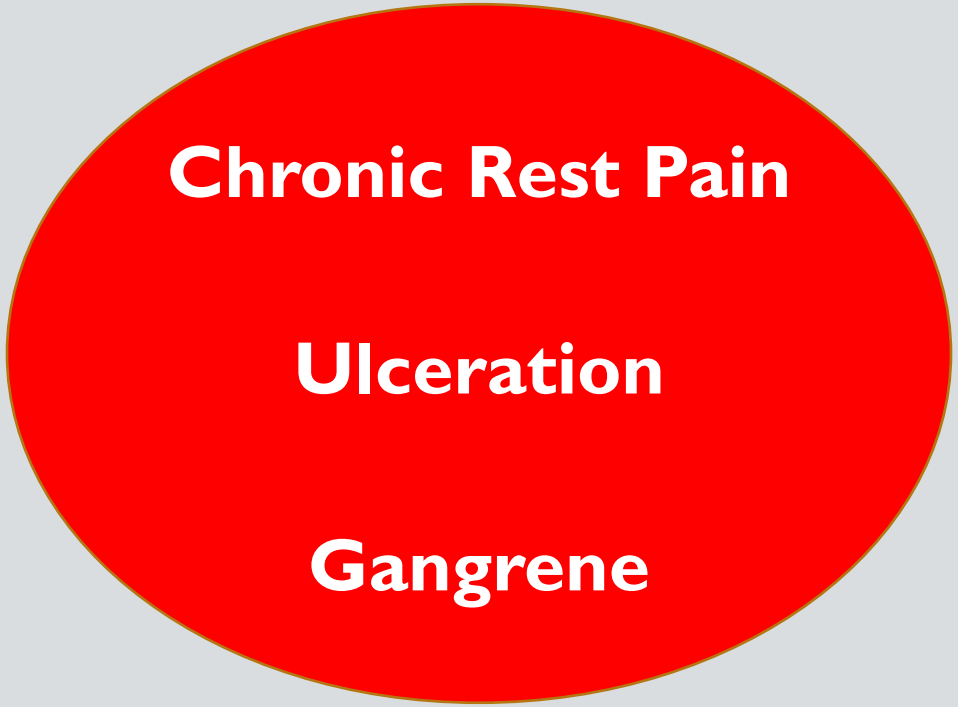
HISTORY

- Constant lower limb pain
- Multiple episodes of opioid toxicity
- Deteriorating renal function
- Fluctuating delirium
- Globally deteriorating



HOW WOULD YOU MANAGE THIS PAIN?

CRITICAL LIMB ISCHAEMIA - DEFINITION



Objectively proven arterial occlusive disease
(TASC II definition)

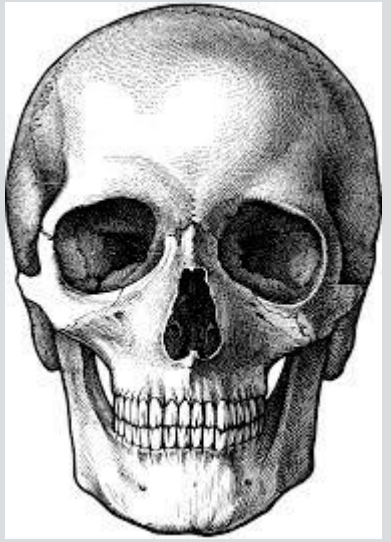
STAGING OF CLI

- A severe stage of peripheral arterial disease
- Fontaine stage III-IV or Rutherford grades 4-6
- Progression is often variable & unpredictable

EPIDEMIOLOGY

- Prevalence increasing with aging population
- Peripheral arterial disease affects ~ 12% of adult population
- Yearly incidence of CLI: 500 to 1000 per million in a Western society (Norgren 2007)

MORTALITY



- Mortality rates of 20% within 6 months from diagnosis of CLI (Adam 2005)
- 2-year survivability rate of 55% in severe CLI treated conservatively (Thomas 2015)
- **5 year mortality > colorectal cancer, breast cancer, stroke, acute myocardial infarction, & prostate cancer** (Nehler 2003)

IMPACT ON QUALITY OF LIFE

- Negatively impacts multiple dimensions of QOL (Pedrosa 2011, Balogh 2013)
- Lower QOL scores in ”no-option” CLI compared with other PAD stages (Sprengers 2010)
- Dimensions affected: physical, psychological, level of independence & pain

ISCHAEMIC PAIN IN CLI

- Chronic rest pain - worse at night, often waking patients
- Significant neuropathic component (Ruger 2008) - ?distal axonopathy affecting nerve fibers of all sizes
- Lower limb blood flow correlates with neurologic symptom scores & electrophysiologic testing (Weinberg 2001)

TREATMENT GOALS OF CLI

- increasing survival
- relieving ischaemic pain
- healing ulceration
- preventing major amputations
- improving quality of life

MANAGEMENT OF CLI

- Revascularisation - endovascular or bypass surgery
- Amputation – avoided if possible
- MDT approach to control pain, risk factors & comorbidities
- Pain control N.B. - improve QOL, reduce risk of phantom limb pain

OTHER MANAGEMENT OPTIONS

- Spinal cord stimulation?
- Lumbar sympathectomy?
- Gene therapy?

"NO-OPTION" CLI

- In an aging comorbid population, preferred revascularisation or surgery is often not an option (Sedighiani 2011)
- Currently no effective pharmacological therapy for revascularisation
- What options are there to manage pain in this cohort?

“Ultimately, much of the care of CLI patients is palliative in nature”

(TASC II)

OUTCOME OF CONSERVATIVELY TREATED CLI?

CONSERVATIVELY TREATED CLI

- Little data - studies involving PROMs do not exist!
- Most research focuses on physician reported outcome measures (graft patency, overall survival, amputation free survival etc.)
- Inclusion of conservatively treated patients not suitable for trial participation needs to occur (Santema et al. 2017)

UNMET PALLIATIVE CARE NEEDS?

- Patients with CLI have
  - severe pain
  - poor quality of life
  - limited prognosis

- Are we meeting their needs?....

PALLIATIVE CARE & VASCULAR SURGERY

Reviews

Embracing the palliative care aspects of peripheral artery disease (PAD): the vascular surgeon's perspective

Erika R. Ketteler & Kathleen O. Maxfield

Pages 237-244 | Published online: 19 Jul 2013

PAIN MANAGEMENT OF LIMB ISCHAEMIA

- Challenging;

  - complex pathophysiology
  - poor tolerance of strong opioids
  - regional anaesthesia inconsistently effective
  - limited pool of research

WHAT IS THE EVIDENCE?

BMJ Supportive & Palliative Care

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

Áine Ní Laoire and Fliss E M Murtagh

BMJ Support Palliat Care published online August 23, 2017

AIM

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

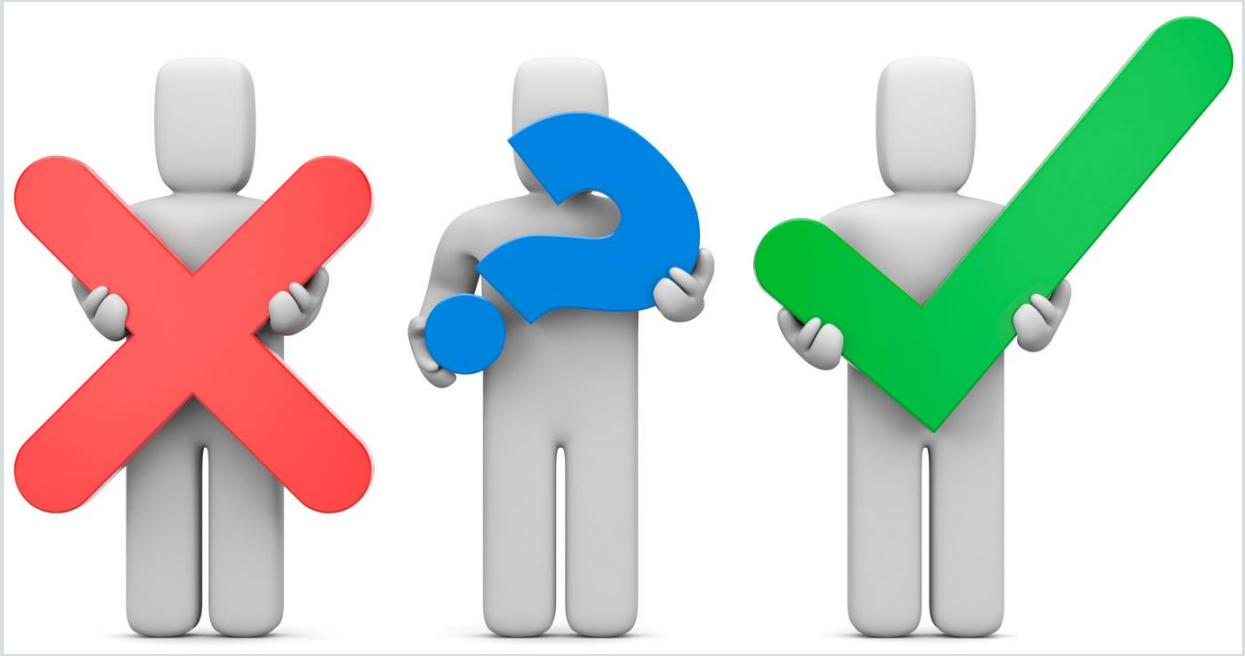
METHOD

Systematic review - in accordance with PRISMA guideline

IDENTIFICATION OF STUDIES

- All study designs apart from single case reports
- CLI from any cause - experimentally induced ischaemic pain excluded
- Surgical, revascularisation & invasive procedures excluded

RESULTS



RESULTS

- From 792 screened, 6 suitable for inclusion; 5 RCTs, 1 observational study

- 4 interventions:
  - **IV Lidocaine**
  - **Oral Gabapentin**
  - **IV Ketamine**
  - **Transdermal buprenorphine + epidural morphine/ropivacaine**

IV LIDOCAINE (VAHIDI 2015)

- Double-blind parallel RCT, N=40
- Lidocaine 2mg/kg IV **Vs** Morphine Sulphate 0.1mg/kg IV
- Effect: At 15 & 30 mins mean VAS pain score lower in intervention group; mean difference 15m 1.25 (CI 0.1-2.4), mean difference 30m 2.25 (CI 1.2-3.3)
- No adverse effects but only monitored for 30 mins post infusion

GABAPENTIN (MORRIS STIFF 2010)

- Prospective observational study (pilot study), N=20
- Gabapentin titrated from 300mg od to max 600mg tds, no control
- Median pain score significantly reduced each of assessment days ($p<.001$)
- 15 patients - improved night pain & perceived QOL
- No adverse effects

KETAMINE (MITCHELL & FALLON 2002)

- Double-blind placebo controlled RCT, N=35
- IV Ketamine 0.6 mg/kg Vs 0.9% Saline over 4 hrs, b/g opioids + haloperidol
- Greater pain relief at 24 hrs & 5 days post ketamine infusion ($p<.05$), improved general activity ($P= 0.03$) & enjoyment of life ($P=0.004$)
- 33% "more emotional than usual" post ketamine, 6% post placebo (odds ratio of 7.7 ($P< 0:05$))

KETAMINE (PERSSON 1998)

- Cross-over double-blind RCT, N=8
- IV Ketamine 0.15, 0.30, 0.45 mg/kg **Vs** IV Morphine 10 mg
- No stat. sign. difference at peak effect times (P<0.10, Wilcoxon's test)
- All had perceptual disturbances & psychotropic effects (at 0.45mg/kg dose all had "unacceptable" SE) **- no prophylactic antipsychotic given**

TRANSDERMAL BUPRENORPHINE + EPIDURAL (AURILIO 2009)

- Open-label randomised trial, N=86
- Buprenorphine 35mcg/hr patch + epidural morphine/ropivacaine **Vs** epidural alone
- Significantly lower pain scores in intervention group ($P < 0.0001$), better sleep quality ($P < 0.0001$)
- More SEs (drowsiness, fatigue, constipation, nausea) in control group

TRANSDERMAL BUPRENORPHINE + EPIDURAL (AURILIO 2005)

- Open-label randomised trial, N=43
- Buprenorphine 35µg/hr patch + epidural morphine/ropivacaine **Vs** epidural
- Intervention: Mean VAS 85 to 20 to 10/ Control: Mean VAS 85 to 38 to 20, mean hrs of sleep from 3.5 to 8 in intervention (3.5 to 6 in control)
- Adverse effects: higher incidences of adverse effects in control group

SIGN GRADING

Quality assessment, according to **SIGN** grading system								
Study	**1++**	**1+**	**1-**	**2++**	**2+**	**2-**	**3**	**4**
Vahidi, 2015 (LIDOCAINE)	X							
Morris Stiff, 2010 (GABAPENTIN)							X	
Aurilio, 2009 (BUPRENORPHINE)			X					
Aurilio, 2005 (BUPRENORPHINE)			X					
Mitchell, 2002 (KETAMINE)		X						
Persson, 1998 (KETAMINE)			X					

DISCUSSION

- Once again…..
- Surprisingly limited research base
- All studies showed benefit in treating ischaemic pain in CLI with varying quality & side effect profiles

SUMMARY OF INTERVENTIONS

- Ketamine - remains controversial!
- Lidocaine - Promising BUT further studies needed
- Buprenorphine + epidural - effective but poor quality studies - ?reproducible effect
- Gabapentin - poor study design, but widely used & well tolerated

CHALLENGES

- Challenging review topic

  - pathophysiology
  - limited research
  - differing pharmacological interventions
  - varying quality of relevant studies

CONCLUSION

- Optimising neuropathic pain control - cornerstone of management
- No single recommendation of a pharmacological agent possible
- Novel approaches need further investigation – lidocaine, partial opioid antagonist & epidural

IMPLICATIONS FOR RESEARCH

- Benefit & safety over a longer duration of IV Lidocaine?
- Alternative dosing/route regimens to assess better tolerability & effectiveness of Ketamine?
- RCT investigating gabapentin? Role of other neuropathic agents?

SPECIAL K - FRIEND OR FOE?

KETAMINE

- General anaesthetic - analgesic in subanaesthetic doses, NMDA antagonist
- No standard regimen in dose, route, frequency of use
- **Multiple undesirable effects**
- Evidence in acute & perioperative pain, complex regional pain syndrome (Consensus Guidelines Regional Anaesthesia & Pain Medicine June 2018)
- "Current evidence is insufficient to assess benefits & harms of ketamine as an adjuvant to opioids for relief of refractory cancer pain" (Cochrane review 2017)
- Evidence to support use in chronic ischaemic pain?.....weak

CLINICAL APPROACH TO ISCHAEMIC PAIN IN CLI

- **Titrate opioids - consider renal friendly opioids (fentanyl/alfentanil)**
- **Add neuropathic agent - gabapentin 1st line**
- **Ketamine – cannot recommend on level of evidence in this review**

FINAL THOUGHT

Are we meeting the needs of patients with CLI?

Talk to your local vascular surgeon!

THANK YOU – QUESTIONS?