



Challenges in

Neuropathic Pain

Welcome to the 19th issue of *Challenges in Neuropathic Pain*, a newsletter from the Multidisciplinary Panel on Neuropathic Pain (MPNP). The feature article in this issue addresses the problem of chronic postsurgical pain, and the series on drugs for the treatment of neuropathic pain concludes with an overview of various miscellaneous agents. The case presentation discusses neurofibromatosis, while the Q&A covers various screening tools for identifying neuropathic pain. Visit www.neuropainhk.org for more resources from the MPNP on neuropathic pain.

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PANEL MEMBERS

Dr Phoon Ping Chen
Consultant and Chief of Service
Department of Anaesthesiology and
Operating Services
Alice Ho Miu Ling Nethersole Hospital and
North District Hospital

Dr Josephine WY Ip
Associate Professor and Chief
Division of Hand and Foot Surgery
Department of Orthopaedic Surgery
Queen Mary Hospital
The University of Hong Kong

Dr Joseph MK Lam
Honorary Consultant and
Honorary Clinical Associate Professor
Division of Neurosurgery
Prince of Wales Hospital
The Chinese University of Hong Kong

Dr Vincent Mok
Associate Professor, Division of Neurology
Department of Medicine and Therapeutics
Prince of Wales Hospital
The Chinese University of Hong Kong

Dr Tak Hong Tsoi
Neurologist and Consultant Physician
Pamela Youde Nethersole Eastern Hospital and
Immediate Past President
The Hong Kong Neurological Society

Dr Chun Por Wong
Chief of Integrated Medical Services
Consultant and Head
Department of Geriatrics
Ruttonjee and Tang Shiu Kin Hospitals

Dr Steven Wong
Consultant Anaesthesiologist
Head of Pain Management Team
Department of Anaesthesiology and Operating
Theatre Services
Queen Elizabeth Hospital

Contact the Panel

Forward any comments
on this newsletter to the
Multidisciplinary Panel
on Neuropathic Pain at
mpnp@asia.cmpmedica.com.

Addressing the Problem of Chronic Postsurgical Pain

Although most patients who have surgery recover uneventfully and return to their normal functioning within weeks, an alarming proportion develops chronic postsurgical pain (CPSP).¹ This article will briefly review the phenomenon of CPSP with reference to its incidence, risk factors, potential methods for prevention, and approach to management of established CPSP.

Acute postsurgical pain

After surgery, patients experience predominately spontaneous resting and breakthrough pain referred to the site of surgery and the surrounding tissues, which are caused by direct activation of nociceptors, inflammation and, in some cases, nerve injury. In addition, movement or touching of the wound, breathing, coughing and gastrointestinal motility can all evoke pain flares.² To ensure adequate management of acute postsurgical pain, many surgical centres have established acute pain services that utilise local anaesthetic agents, opiates and cyclo-oxygenase (COX) inhibitors to control acute postsurgical pain; a recent study has shown also that preoperative pregabalin reduces acute postoperative pain and fentanyl consumption following laparoscopic cholecystectomy.³ Despite this increased focus on pain management there is evidence that postoperative pain control still needs improvement.⁴ One study in 2003 found that about 80% of patients experienced acute pain after surgery; most of these patients described the pain as moderate to extreme.⁵

Procedure-specific postoperative pain management (PROSPECT) is one approach designed to improve management of acute postsurgical pain. As there is growing evidence that the efficacy of analgesic agents differs between surgical procedures,⁶ the PROSPECT Working Group has developed procedure-specific guidelines for various surgical procedures, including thoracotomy, abdominal hysterectomy and non-cosmetic breast surgery. These are freely available at www.postoppain.org.

The transition to CPSP

Although there is no universally agreed definition of CPSP, the working definition proposed by Macrae and Davies is commonly used. A diagnosis of CPSP can be made when the following criteria are met⁷:

- The pain developed after a surgical procedure.
- The pain is of at least 2 months' duration.
- Other causes for the pain should have been excluded (eg, continuing malignancy or chronic infection).
- The possibility that the pain is continuing from a pre-existing problem must be explored and exclusion attempted.

Acute postsurgical pain evolves into CPSP in around 10–50% of patients following common surgeries like breast and thoracic surgery, leg amputation and groin hernia repair.² The incidence varies by surgical procedure (Table) as well as between studies, because of differences in surgical techniques, study design, patient populations and definitions of CPSP.⁸ However, it is clear that it is far from a rare occurrence, and an estimated 2–10% of patients experience severe pain.²

CPSP involves a neuropathic component

The mechanisms of CPSP are widely acknowledged to be highly complex, but are yet to be clearly understood.^{2,8} Kehlet and colleagues suggest that CPSP results from either ongoing inflammation, or more commonly, is a manifestation of neuropathic pain, which results from changes to the peripheral and central nervous system (central sensitization) after surgical injury to major peripheral nerves.^{2,8,9} Although nerve damage during surgery is likely an important cause of CPSP, the issue is obviously more complicated as avoiding sectioning of major nerve trunks does not always prevent CPSP and patients with sectioned nerves do not always develop the condition.⁸ In addition, several postoperative pain syndromes involving different mechanisms can exist after one operation, eg, phantom limb pain, stump pain and back pain after lower limb amputation.⁸

Predictors of CPSP

Since not all surgical patients develop chronic pain, efforts have been made to identify the predictors or correlates of CPSP in the hope that these can be used to recognize patients at risk for CPSP. Briefly, these include^{2,8,10-14}:

- Type and method of surgery (eg, invasive procedures, repeat procedures)
- Younger age
- Female gender
- Genetic susceptibility to chronic pain syndromes/pain sensitivity
- Duration and intensity of preoperative pain
- Severe acute postsurgical pain
- Psychological/psychosocial factors (eg, preoperative anxiety, catastrophizing)

Prevention strategies

CPSP is difficult to treat effectively once established,^{8,9} so interventions to prevent its development are now considered an important component of postoperative management and, if successful, could have a major impact on public health.¹⁵

Severe acute postsurgical pain is consistently associated with a high incidence of CPSP,⁸ making strategies to reduce the intensity of acute postsurgical pain or ensure adequate pain control areas of keen interest. Although adequate postsurgical pain control is mandatory, there is no consistent evidence that it necessarily prevents CPSP.^{8,9} There are also no large prospective studies to confirm that any specific anaesthetic intervention reduces the risk of CPSP.⁹

Studies of pre-emptive or preventive analgesia to prevent chronic pain after breast surgery have shown promising results with venlafaxine, mexiletine with gabapentin, a eutectic mixture of local anaesthetics (EMLA), and EMLA plus gabapentin.² Recent studies also found that perioperative pregabalin reduced the incidence of chronic neuropathic pain at 3 and 6 months after total knee arthroplasty,¹⁶ and improved pain and functional outcomes at 3 months after lumbar discectomy.¹⁷

Kehlet and coworkers believe that the primary focus for CPSP prevention should be the avoidance of intraoperative nerve injury through a greater focus on careful dissection, reduction of inflammatory responses and use of minimally invasive surgical techniques.²

Overall, at the present time, there is limited evidence for effective preventive strategies, and further research in this area is essential.⁸

Management of CPSP

The difficulty of treating established CPSP of neuropathic or inflammatory origin usually necessitates referral to specialist chronic pain management services.⁹ Macrae briefly outlined treatment options for CPSP, emphasizing that the choice of treatment should be driven by the mechanism causing the pain.⁷ Nociceptive pain can be managed with simple analgesics like paracetamol, stronger drugs such as weak opioids or, occasionally, stronger opioids.⁷ Options for neuropathic pain include tricyclic antidepressants (TCA) (eg, amitriptyline), anticonvulsants (eg, gabapentin) or a combination of the two. Macrae advises that although these suggestions are not based on reliable published evidence, "in essence the treatment of [CPSP] is no different from that of other chronic pain syndromes". He also notes that transcutaneous electrical nerve stimulation can be helpful in some cases.⁷

In the 2006 European Federation of Neurological Societies (EFNS) guidelines on pharmacological treatment of neuropathic pain, the authors note that phantom limb pain and postoperative neuropathic pain appear to be similarly responsive to drugs with efficacy in other neuropathic conditions, like TCAs and gabapentin, but also remark that this is based on limited data of relatively poor quality.¹⁸

Table. Estimated incidence of CPSP and disability after selected surgical procedures²

Surgical procedure	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain >5 out of score of 10
Amputation	30–50%	5–10%
Breast surgery (lumpectomy and mastectomy)	20–30%	5–10%
Thoracotomy	30–40%	10%
Inguinal hernia repair	10%	2–4%
Coronary artery bypass surgery	30–50%	5–10%
Caesarean section	10%	4%

However, the efficacy of existing treatments is often limited and many patients remain refractory to currently available therapies.¹⁵ In such cases, a multidisciplinary approach to pain management that incorporates psychology-based pain management approaches becomes particularly important.⁷

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DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

In this issue, we conclude our series on drugs for the treatment of neuropathic pain with discussion of several miscellaneous agents.

Part 10 – Miscellaneous agents

In addition to the first- and second-line agents covered in previous issues of this series, a number of other drugs may provide benefit to some individuals with neuropathic pain.

The N-methyl D-aspartate (NMDA) receptor blockers memantine and dextromethorphan and the sodium channel blocker and anti-arrhythmic drug mexiletine have been investigated in various types of neuropathic pain, including painful polyneuropathies, postherpetic neuralgia (PHN) and spinal cord injury.^{1,2} Some studies showed small benefits while others found no differences compared with placebo.¹ While Dworkin and colleagues consider NMDA receptor blockers and mexiletine potential third-line medications,^{2,3} the 2006 European Federation of Neurological Societies (EFNS) recommendations do not consider there is sufficient support for their use.¹

Recommendations from the Multidisciplinary Panel on Neuropathic Pain (MPNP) suggest that patients refractory to first- and second-line therapies be referred for specialist treatment where alternative agents may be considered. The MPNP recommendations

include NMDA antagonists as third-line agents in PHN or painful diabetic peripheral neuropathy,^{4,5} while mexiletine may be used following failure of anticonvulsants and antidepressants in neuropathic cancer pain.⁶

Botulinum toxin is used clinically in the treatment of spasticity and cervical dystonia, and may also be beneficial in treating neuropathic pain.⁷ While recent preliminary studies have demonstrated a reduction in pain with botulinum toxin in diabetic neuropathic pain⁸ and carpal tunnel syndrome,⁹ another study in PHN showed no benefit.⁷ The authors of the preliminary reports recommend that larger, randomized, controlled trials be performed to further evaluate the effectiveness of botulinum toxin in neuropathic pain.^{8,9}

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Parts 1–9 of this series are available at www.neuropainhk.org in newsletter issues 10–18.

CASE PRESENTATION

In this issue, a case of neurofibromatosis complicated by lower limb (below knee) amputation and neuropathic pain is discussed.

Neurofibromatosis

History

This case discusses a 32-year-old woman with a known history of neurofibromatosis. She was born with congenital pseudoarthrosis of the right tibia; multiple operations were performed in early childhood to treat the pseudoarthrosis. When the patient was aged 6 years, the pseudoarthrosis was successfully healed by vascularized bone graft. Despite the tibia being united, it was markedly deformed and shortened. A below knee amputation (BKA) was subsequently performed when the patient was aged 9 years. Several stump revision procedures were required to fit a prosthesis, which allowed her to walk fairly well.

At the age of 16 years, the patient complained of back pain, and upper and lower limb numbness. Her right BKA stump was frequently affected by cellulitis.

At the age of 24 years, the patient suffered a fall and sustained a fractured right patella which required an internal fixation procedure. She needed to use a wheelchair after this incident. Shortly after the operation, a nodule was found beneath the wound and she experienced significant pain on pressure. Throughout the years, the back pain, and upper and lower limb numbness progressed.

Clinical investigation

Magnetic resonance imaging (MRI) of the right BKA stump revealed a 4.2 x 1.4 x 1.3 cm lesion suggestive of neurofibroma. The mass was excised and the pathologist reported a traumatic neuroma rather than neurofibroma. MRI of the left ulnar nerve did not reveal gross neurofibroma. Neurophysiological study did not reveal a significant focal lesion in the ulnar nerve.

Management

The patient had significant neuropathic pain due to the cut right tibial nerve, and possibly nerve irritation by multiple small neurofibromata in the left ulnar nerve. She complained of ulnar finger numbness; Tinel's sign was positive at multiple sites. She was treated with pregabalin 150 mg bid, amitriptyline 25 mg nocte and dihydrocodeine 30 mg tds prn. The medication stabilized her condition, with the pain being partially controlled. Repeated neurophysiological study did not reveal significant ulnar nerve lesion.

Source: MPNP members

Are there any screening tools to help diagnose neuropathic pain?

Various screening tools are available to help physicians diagnose neuropathic pain. The European Federation of Neurological Societies (EFNS) has recently published updated guidelines that provide an overview of, and recommendations on, the key screening tools.¹ These tools are: the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)²; Neuropathic Pain Questionnaire (NPQ)³; Douler Neuropathique en 4 questions (DN4)⁴; PainDETECT⁵; ID Pain⁶; and the standardized evaluation of pain (StEP)⁷. All these screening tools have been validated in various neuropathic pain populations; the LANSS, DN4 and StEP utilize interview questions and physical examination, while the NPQ, PainDETECT and ID Pain use only interview questions.^{1,8}

Of relevance to the Hong Kong population, one of the screening tools – the ID Pain – has been translated to and validated in Chinese (Table).⁹ The validity of the 6-item patient-completed questionnaire

was assessed in 92 patients with either neuropathic or nociceptive pain. At a score of 3 or more, the questionnaire correctly classified 71% of cases.

While screening tools are useful for identifying patients with possible neuropathic pain, particularly by non-specialist physicians, they do have limitations. As noted in the EFNS guidelines, these tools fail to identify 10–20% of patients with physician-diagnosed neuropathic pain¹; hence, they should be used together with a thorough patient history and physical examination.

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Table. The ID Pain questionnaire⁹

Question	Original English version	Chinese version
1	Did the pain feel like pins and needles?	您的痛楚是否好像被針刺般疼痛?
2	Did the pain feel hot/burning?	您的痛楚是否灼熱或好像被火燒一樣?
3	Did the pain feel numb?	您的痛楚是否帶有麻痺?
4	Did the pain feel like electrical shocks?	您的痛楚是否好像觸電一樣?
5	Is the pain made worse with the touch of clothing or bedsheets?	您的痛楚是否因觸碰衣服或床單而加劇?
6	Is the pain limited to your joints?	您的痛楚是否只限於關節部位?

Scoring: Questions 1–5, Yes = +1 point, No = 0 points; Question 6, Yes = -1 point, No = 0 points. A score of 3 or more indicates probable neuropathic pain.

LITERATURE REVIEW

Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Med 2010;11:456-465.

This cohort study examined the substitution of gabapentin with pregabalin in patients with neuropathic pain due to peripheral neuropathy. Patients treated with gabapentin for neuropathic pain (n = 146) at a single tertiary care neurological clinic were screened for inclusion; 33 gabapentin-responder patients (having received $\geq 30\%$ pain relief with gabapentin monotherapy for at least 4 weeks) and 36 gabapentin–non-responder patients were switched overnight to pregabalin therapy. Of 77 patients unable to switch to pregabalin, 47 were included in the “gabapentin continuous” cohort. Patients were evaluated at baseline and 6 and 12 months. The primary outcome measure was pain severity (visual analogue score [VAS]), while quality of life and occurrence of adverse events were also assessed.

Substitution with pregabalin provided additional neuropathic pain relief of about 25% after 6 and 12 months in both the gabapentin responder and non-responder groups, and also improved pain relief compared with the gabapentin continuous group. Improved quality of life scores were observed in the gabapentin–non-responder group following pregabalin substitution (the gabapentin-responder group had a higher baseline quality of life score). No serious adverse events were reported for either pregabalin or gabapentin; however, 28% of gabapentin–non-responders discontinued pregabalin because of

inefficacy or adverse events.

The author concluded that pregabalin may provide additional pain relief and potentially improved quality of life compared with gabapentin use. However, a switch from gabapentin to pregabalin needs to be considered on an individual basis, as patients with good clinical responses to gabapentin may have little additional benefit with pregabalin. The author suggests that patients who are dissatisfied with gabapentin be considered for pregabalin therapy.



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CMPMedica Pacific Ltd
9th Floor, CNT Tower, 338 Hennessy Road, Wan Chai, Hong Kong
T +852 2559 5888 F +852 2559 6910
enquiry.hk@asia.cmpmedica.com
www.cmpmedica.com