Strategies for prevention of lower limb post-amputation pain: A clinical narrative review

Vanita Ahuja, Deepak Thapa, and Babita Ghai

Abstract

Postamputation limb pain or phantom limb pain (PLP) develops due to the complex interplay of peripheral and central sensitization. The pain mechanisms are different during the initial phase following amputation as compared with the chronic PLP. The literature describes extensively about the management of established PLP, which may not be applicable as a preventive strategy for PLP. The novelty of the current narrative review is that it focuses on the preventive strategies of PLP. The institution of preoperative epidural catheter prior to amputation and its continuation in the immediate postoperative period reduced perioperative opioid consumption (Level II). Optimized preoperative epidural or intravenous patient–controlled analgesia starting 48 hours and continuing for 48 hours postoperatively decreased PLP at 6 months (Level II). Preventive role of epidural LA with ketamine (Level II) reduced persistent pain at 1 year and LA with calcitonin decreased PLP at 12 months (Level II). Peripheral nerve catheters have opioid sparing effect in the immediate postoperative period in postamputation patients (Level I), but evidence is low for the prevention of PLP (Level III). Gabapentin did not reduce the incidence or intensity of postamputation pain (Level II). The review in related context mentions evidence regarding therapeutic role of gabapentanoids, peripheral nerve catheters, and psychological therapy in established PLP. In future, randomized controlled trials with long-term follow-up of patients receiving epidural analgesia, perioperative peripheral nerve catheters, oral gabapentanoids, IV ketamine, or mechanism-based modality for prevention of PLP as primary outcome are required.

Keywords: Analgesia, calcitonin, catheters, epidural, ketamine, phantom limb, prevention

Introduction

At present, approximately 1.6 million people in the United States require limb amputation, which might increase two folds by the year 2050.[1] In 1983, the prevalence of amputees in India were about half a million and it was estimated that 23,500 were added every year. Amputees in India are predominantly male, from rural background, poor, and in working age group. A significant number of these patients have amputation as a result of injuries sustained in railway, road accidents, and due to agricultural equipment.[2] In an epidemiological study done in 155 amputees in Kolkata, India, the most common cause of amputation was trauma (70.3%), followed by peripheral vascular disease. Lower limb amputation accounts for 94.8% of all amputations. The most common age group was 20s and 30s which is a productive population of the country.[3]

Ambroise Paré, a French military surgeon, first described the postamputation phenomenon, which occurs after complete or partial amputation of a limb, during 16th century.[4,5] The reported incidence of phantom limb pain (PLP) was 84% at 8 days after amputation[6] and 67% after 6 months.[7] The factors predisposing for PLP includes pain occurring before surgery,[8,9] upper limb amputations, and bilateral limbs amputation; and it occurs mostly in females.[10] Anxiety and depression affect the development of PLP.[11,12]

The preventive strategies for the PLP pain is difficult to manage and if not addressed adequately may lead to chronic pain. The perioperative role of the anesthesiologist and the acute pain physician is important in the management of somatic and sometimes neuropathic postoperative pain. If the symptoms of hyperalgesia or neuropathic symptoms start developing, then it should be adequately diagnosed and managed.[13] The association between preoperative symptoms and postoperative pain implies that symptoms and not the surgical insult should dictate early intervention when appropriate.[14] Patients who require strong opioids in the preoperative period and are anxious should receive aggressive multimodal and patient-tailored pain management. Perioperative pain should be managed at all levels to prevent the transition of acute to chronic pain and also allow patients to return early to work which would reduce the global economic and social burden.[15]

A search of the existing published literature was carried out from 1990 to 2017 for review articles, randomized controlled trials, observational studies, and case series for preventive strategies in postamputation chronic pain using “phantom limb; analgesia;

epidural; catheters; ketamine; calcitonin; gabapentin" in Pub Med, EMBASE, and Google Scholar, and relevant articles were included. A systematic review was not possible due to heterogeneity of the studies. Hence, we conducted the narrative review, critically evaluating the existing published literature, and have included the level of evidence in related contexts.

Clinical features

The understanding of the phenomena and pathogenesis [Table 1 and Figure 1] following amputations is essential for management. A patient having pain in the amputated part is labeled to have PLP if the pain persists after complete tissue healing and is characterized with symptoms of dysesthesia and pain. PLP is most commonly present in the limbs but may be seen in patients who have amputation of fingers, penis, tooth loss, after mastectomy, and gastrointestinal surgery.[16] Majority of the patients report pain within a day following amputation, and some may not complain at all. After amputation, approximately 70% of the patients suffer from PLP and 50% continue to experience amputation pain 5 to 7 years after surgery.[16,17]

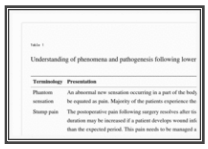

Table 1

Understanding of phenomena and pathogenesis following lower limb amputations

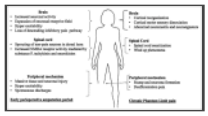

Figure 1

Pathophysiology and mechanism of initial and established phantom limb pain

Factors associated with phantom limb pain

1. The pain following amputation and any ongoing pain due to infection or tissue ischemia
2. Improper fit of the prosthesis can cause pain in the stump of the amputated part
3. Due to improper fit of the prosthesis, there may be excessive pressure or stress on the normal joints and tissue, leading to a pain of new origin. This may sometimes lead to an abnormal gait or movement of the affected part
4. An association has been observed between pain prior to amputation and the development of PLP. The evidence in this regard can be seen in less pain in diabetics and paraplegics, who have reduced peripheral nociceptive inputs and hence less PLP.[18]

Pathophysiology of phantom limb pain

The PLP mechanisms can be broadly divided into four subprocesses such as all pain pathways into transduction, transmission, perception, and modulation.[18] After limb amputation, the motor cortex remains intact and the brain perceives signals as if they are coming from the missing limb. As the limb is no longer present, there is a mismatch between motor commands to and proprioception or somatosensory inputs from the limb. Moreover, there is conflict between the signals coming from the missing limb and the efferent motor signal triggered by the incomplete somatosensory-motor feedback loop. There is an interplay of cortical functions and descending pain inhibitory pathways (thalamus, periaqueductal, nucleus gigantocellularis, and raphe nucleus) leading to reduction in the inhibitory pain pathways and enhanced N-methyl D-aspartate (NMDA) receptor activity at the spinal cord. An early intervention with multimodal acute pain management in these patients can prevent the development of chronic amputation pain or PLP.[17,18]

Preventive Strategies

The current published preventive strategies for the development of PLP has been described in the present clinical review into five

main categories: surgical technique, regional analgesia, pharmacological agents, psychotherapy, and supportive management.

Surgical technique

During an analysis of choice of technique for ligation of large diameter nerves, it is assumed that the ligation of large nerve fibers can cause PLP.[19] Recently, preemptive coaptation and collagen nerve wrapping versus traction neurectomy alone in 17 patients undergoing transfemoral amputations resulted in reduced pain score and reported lower PLP (0% vs 63.6%; $P = 0.01$), neuroma formation (0% vs 54.5%; $P = 0.03$), and better ambulation rate (67% vs 9%; $P = 0.01$) during a follow-up of 6 months.[19] Revised stump surgery was required only if there was a local pathology including bone spur, soft tissue, or bone infection.[16] Recently, use of the targeted nerve implantation or traction neurectomy has been described to prevent or treat neuroma formation. Reliable attachment of muscle to bone allows weight bearing and joint movement in the rehabilitation period.[20] At times, some patients may require revision or staged surgeries secondary to infection, trauma, and so on. These patients require comprehensive and patient-focused pain management.[21] After achieving approximately 80% relief for 40 hours in a patient with ultrasound-guided femoral and sciatic nerve block, the patient received coblation of the femoral and sciatic nerve. This resulted in immediate relief from stump pain and phantom limb pain and 80% relief during 6 months of follow-up.[22] Hence, improved understanding of transected nerves is essential as a preventive strategy for PLP.

Role of the anesthesiologist for preventive strategy in phantom limb pain

Role of the anesthesiologist for perioperative pain management requires a thorough understanding of the level of amputation and the choice of regional analgesia. Availability of round the clock acute pain service allows a preoperative formulation of analgesia plan and its execution. A patient-tailored approach is desired as the patient's pain perception is variable and causes are multifactorial.[23,24] The role of objective pain scores is essential in these patients. Peri-operatively, visual analogue scale, verbal numeric rating scale, and McGill Pain Questionnaire have been used for pain assessment in postamputation patients.[8] Quantitative sensory testing is a reliable objective measure of neuropathic pain, which can improve diagnosis and treatment. It has been used in patients of PLP.[25] Level of evidence for perioperative preventive strategy for PLP is mentioned according to National Health and Medical Research Council (NHRMC)[26] designation in the present review article.

Regional analgesia

Epidural analgesia

In patients undergoing the lower limb amputation, role of epidural analgesia in immediate postoperative pain relief is well established in literature (Level I).[27,28,29,30,31] Epidural analgesia as a preventive strategy of PLP, the published literature of epidural analgesia has shown variable results as shown in Table 2. Use of epidural analgesia as a preventive strategy for long-term PLP was reported by few studies[27,32] and for 6 months by Karanikolas *et al.* (Level II)[33] Jahangiri *et al.*[27] in a nonrandomized trial instituted preoperative epidural analgesia and continued it for at least 3 days postoperatively with an additional on-demand opioid therapy. This study showed reduction in PLP and phantom limb sensation with epidural analgesia over 1 year but there was no difference in stump pain. This suggested the role of preoperative local anaesthetic (LA) blockade in preventing the reorganization of the nervous system and formation of a “nociceptive engram” before amputation.[27] Wilson *et al.*[30] in a randomized double blind trial used epidural local anaesthetic (LA) and ketamine versus LA. The authors reported reduction in persistent pain at 1 year in both groups, with no significant difference between groups for stump and phantom pain (Level II). This study did not have a control group without LA and compared the reduction in PLP with the existing published literature.[30] The authors, in their opinion, also attributed the role of combined spinal epidural anaesthesia during surgery versus general anesthesia to be a preventive strategy, as the former produced a dense sensory analgesia at the time of surgery.[30] Karanikolas *et al.*[33] compared five analgesic regimes in 65 patients. The authors found that the use of perioperative epidural analgesia and patient-controlled morphine analgesia produced similar reduction in PLP during 6 months of follow-up. The follow-up period was only for 6 months. Recently, the perioperative use of epidural LA-fentanyl-calcitonin for 48 hours in 60 diabetic vascular disease patients underwent either major ($n = 21$) or minor ($n = 39$) lower limb amputations under the combined spinal-epidural anesthesia.[32] The authors reported improved grade of phantom pain and reduced the incidence of allodynia and hyperalgesia during 1 year of follow-up (Level II).[32] The authors mentioned several limitations including mixed minor and major amputation patients in this study, follow-up of 1 year, and sample size calculation based

on changes in acute pain (visual analogue scale).

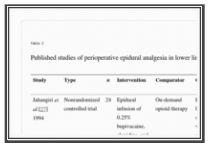

Table 2

Published studies of perioperative epidural analgesia in lower limb amputation patients

On the contrary, Nikolajsen *et al.*[34] reported no difference in the development of PLP in patients receiving perioperative epidural bupivacaine with morphine infusion versus oral/intramuscular morphine group during a follow-up at 1 year. Lambert *et al.*[28] compared preoperative epidural analgesia with intraoperative-placed perineural catheter. Both the infusions were continued in the postoperative period up to 3 days. The authors demonstrated superior pain relief in the immediate postoperative period with epidural analgesia but no differences in PLP at follow-up at 1 year with either preoperative epidural analgesia or intraoperative perineural catheters. Based on the effect of different anaesthetic techniques on reporting of PLP in patients undergoing postamputation lower limb surgery, the published studies found no difference as a preventive strategy for PLP.[29,31] Sahin *et al.*[31] reported superior analgesia in immediate postoperative period with epidural anaesthesia and peripheral nerve blocks as compared with general and spinal anaesthesia in a retrospective study of 65 patients. The results of anaesthetic technique with respect to the development of PLP did not differ during a follow-up of 14 to 17 months.[31] Ong *et al.* in a cross-sectional study reported no difference in stump pain, phantom limb sensation, or phantom limb pain based on the different types of anaesthesia during lower limb amputation.[29]

According to the existing literature, the majority of the studies have not shown the role of epidural analgesia as a long-term preventive strategy of PLP. However, in a few randomized trials, encouraging results of perioperative epidural LA, with/without adjuvants such as opioid,[27] ketamine,[30] and calcitonin,[32] have been reported (Level II).

Due to the heterogeneity in the study designs of the above-mentioned studies and variable results of the literature (Level II), in future, multi-centric randomized controlled trials are required to establish the role of perioperative epidural analgesia with or without adjuvants as a preventive strategy for PLP during long-term follow-up.

Perineural catheters Perineural catheters (PNCs) provide postoperative pain relief after amputation (Level I).[35,36,37] Use of a prolonged postoperative perineural infusion of local anesthetic as a preventive strategy for PLP has shown beneficial results in few studies,[35,36,38,39] while no benefit in few studies,[40,41] as shown in Table 3.

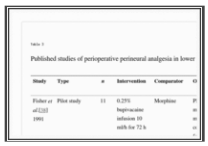

Table 3

Published studies of perioperative perineural analgesia in lower limb amputation patients

In a systematic review, use of perioperative PNCs (3-30 days) reduced opioid consumption by 50% without effecting pain scores, in hospital mortality, PLP, or stump pain.[42] The reported complications were minor when PNCs were kept for the prolonged duration[43] and even when enoxaparin was used in the postoperative period.[44] Literature confirms the role of PNCs in opioid sparing in the immediate postoperative period (Level I)[42] in postamputation patients, but the evidence is low for prevention of PLP (Level III).[35,36,39,45]

Pharmacological agents

Opiate analgesics Use of parenteral opioids for the management of short-term perioperative pain is well established in a systematic review of patients undergoing amputation surgeries (Level I).[37,46] Only one study reported that the role of IV opioid as a perioperative patient–controlled analgesia[33], started 48 hours preoperatively and continuing for 48 hours postoperatively, decreased

PLP at 6 months (Level II). Use of opioid in epidural analgesia[27,34] prevented PLP at 1 year but the studies had limitations as one was a nonrandomized trial[27] and the other included both minor and major amputations.[32]

Use of IV tramadol in postoperative period is well established for acute pain[47,48] relief but not as a preventive strategy for PLP. Tramadol is a weak opioid agonist and acts by inhibiting the reuptake of serotonin and norepinephrine. On comparison, morphine provides superior analgesia as compared with tramadol.[48] The side effects of all opioids are similar including constipation, drowsiness, nausea, and sedation.[49,50]

Further randomized controlled trials are required to evaluate the role of perioperative opioid as an evidence-based preventive strategy for PLP.

N-methyl D-aspartate (NMDA) receptor blockers Ketamine is a noncompetitive blocker of NMDA rectors and its intravenous (IV) use in perioperative period is beneficial for short-term perioperative treatment of PLP.[46] The literature produces conflicting results of use of ketamine for the prevention of PLP. In an observational study, use of IV ketamine (n = 14) for 72 hours compared with controls (n = 14) resulted in reduced PLP during a median follow-up of 557 days (Level III).[51] Hayes *et al.*, in a randomized controlled trial, showed that the PLP was lower in patients receiving IV ketamine but failed to reach statistical significance at 6 months (Level II).[52] Recently, in a retrospective observational study,[54] data collection is going on for patients who received IV ketamine within 30 days of limb amputation. So far, Jaremko *et al.*[53] have reported a trend toward decreased neuropathic and phantom sensations with minimum side effect profile. The collected data were being taken from acute pain medicine service. The authors mentioned that the data could likely be biased due to the factors such as greater uncontrolled pain, potentially in conjunction with other comorbidities limiting medication management.[53] The role of ketamine in epidural infusion has been described above (Level II).[30]

To summarize, the current published literature is conflicting and insufficient regarding the role of perioperative IV ketamine and its long-term effect on PLP.

Gabapentanoids Nikolajsen *et al.* recruited a lower limb postamputation patient on the first day and continued till 30 days. Gabapentin was gradually increased to 2,400 mg/day as compared with placebo. Patients were evaluated at 7 days, 14 days, 30 days, 3 months, and 6 months during the treatment period. Gabapentin did not reduce the incidence or intensity of the postamputation pain (Level II).[54] Although the present narrative review covers the preventive strategies for PLP, the published literature has evidence of gabapentin for established PLP. Bone *et al.* in a cross-over of placebo with gabapentin found gabapentin better in relieving established PLP but no difference in mood, sleep interference, or activities of daily life with mixed success.[55] Here, we would like to mention that the beneficial role of oral gabapentin[56,57] and pregabalin[58,59] in established PLP in adult patients has been reported, but evidence-based studies are required for their role as a preventive strategy in PLP.

Hormonal calcitonin The exact mechanism of calcitonin remains unclear. The various mechanisms that are mentioned in the literature are opioid like action (μ receptors), stimulation of descending serotonergic inhibitory neurons, reduction in production of prostaglandins, pro-inflammatory cytokines, and modulation of voltage-gated Ca^{2+} channels on nociceptive neurons.[60,61] Recently, epidural calcitonin[32] has shown encouraging results as a preventive strategy (Level II) as described above. So far, there is no supportive evidence for use of the parenteral or oral calcitonin as preventive strategy in PLP. Furthermore, studies with larger sample size are required in this regard.

Paracetamol and NSAIDs Role of paracetamol and non-steroidal anti-inflammatory drugs is useful in postoperative pain relief but not specific for prevention of PLP.[46,62,63] The concerns and contraindications regarding the use of these drugs should be followed while using them.

Psychological treatment modalities The aim of psychological therapies is to allow the patient to modify his or her perception and experience of pain. The main aim of multidisciplinary pain management is to allow the patient for early return of work.[64] There is an ever-increasing need of psychological therapies with multidisciplinary approach for reducing pain and the development of chronic pain syndromes. The literature is lacking in preventive role of the psychological interventions for PLP. It is our opinion, early use of cognitive behavior therapy, mindfulness, hypnosis, acceptance and commitment therapy, brief interpersonal therapy, and biofeedback can play a role as a preventive strategy in PLP. The published literature is supportive regarding role of cognitive behavior therapy in

helping patients to overcome dysfunctional thought patterns and behavior patterns.[65]

It would be interesting to observe the results of these psychological interventions when used early in management of patients undergoing amputation surgery and the prevention of PLP.

Supportive management

Supportive management includes stump wrapping, elevation of surgical site, cold therapy, and massage therapy to relieve muscle spasms, group supports, advice regarding stump, and prosthesis care.[10,18] Recently, the use of myoelectric prosthesis has been shown to decrease PLP. The possible mechanism is that behavioral stimulation of the affected amputated part of the body increases the degree of cortical representation and reorganization and use of myoelectric prosthesis reduces PLP and cortical reorganization in these patients.[66]

A templet for multimodal perioperative pain plan as preventive strategy for PLP

1. Identify patients for the prevention of PLP with detailed history taking, assessment of pain, special attention to neuropathic pain, pain questionnaire, anxiety and depression pain questionnaire, and neurological examination
2. Consider a team approach including the surgeon, anesthesiologist, pain physician, physiotherapist, rehabilitation staff, and patient's caregivers
3. Perioperative epidural analgesia with adjuvants (ketamine or calcitonin or opioids) (Level II) or IV opioid PCA (Level II) for optimized postoperative pain relief, starting 48 hours prior to surgery to minimum up to 72 hours postoperatively
4. Include NSAIDs and paracetamol as part of multimodal analgesia
5. Psychological support and rehabilitation
6. Individualization approach regarding use of gabapentanoids as preventive strategy.

Conclusion

The current literature does not support any single technique or drug to be superior over another. However, optimized epidural analgesia and opioid PCA are acceptable as preventive strategies for the prevention of PLP. Use of adjuvants such as calcitonin or ketamine with LA in epidural analgesia shows encouraging results. In future, randomized controlled trials with long-term follow-up of patients receiving epidural analgesia, perioperative peripheral nerve catheters, oral gabapentanoids, IV ketamine, or mechanism-based modality for the prevention of PLP as primary outcome are required.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Article information

J Anaesthesiol Clin Pharmacol. 2018 Oct-Dec; 34(4): 439–449.

doi: 10.4103/joacp.JOACP_126_17

PMCID: PMC6360885

PMID: 30774224

Vanita Ahuja, Deepak Thapa, and Babita Ghai[1]

Department of Anaesthesia and Intensive Care, Government Medical College and Hospital, Chandigarh, India

[1]Department of Anaesthesia and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence: Dr. Babita Ghai, Department of Anaesthesia and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India. E-mail: ghaibabita1@gmail.com

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