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Phantom limb pain- A review of mechanisms, therapy, and prevention

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Abstract

Phantom limb pain is an often-seen sequel to amputation, and one which is increasingly encountered by the perioperative medical team. This article aims to offer a comprehensive review of the literature on the proposed mechanisms leading to phantom limb pain and potential therapies. Furthermore, we will provide a summary of the literature regarding investigation of preventative measures prior and during amputation in an effort to decrease the incidence of phantom limb pain development.

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Introduction

Improvement in the prevention of post-operative pain is a continued global concern, particularly for physicians practicing in the peri-operative setting. The incidence of chronic pain varies between different surgical procedures, ranging from anywhere between 6%-85% [1]. Limb amputations have some of the highest reported incidence of chronic pain, occurring in 50-80% of patients [2,3]. This review article aims to provide a comprehensive review on the etiology and therapy of Phantom Limb Pain (PLP), as well as growing new literature aimed at possible interventions in preventing the development of post surgical PLP.

Post-operative neurological symptoms after surgical amputation can be varied, and are usually categorized as either PLP, Phantom Sensations (PS), or Residual Limb Pain (RLP) - also known as stump pain. Surveys of amputees have shown that nearly all (95%) of patients reported experiencing one or more types of amputation-related pain [4]. PLP is a painful sensation in the distribution of the differenced body area; it can be localized to a specific area or it can be a sensation along the missing limb. It is known to be linked with reorganization in the cortical somatosensory system [5], and is often considered to be a type of neuropathic pain. RLP is distinguished from PLP, as the sensations are felt along and derive from the residual body tissue rather than the amputated limb. This type of pain is often

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reported as a electrical, sharp pain, either centered around the incision site or occasionally deeper within the remaining limb tissue. PLP is more commonly reported as sensations that are distal to the amputation site, and sensations are both nociceptive and neuropathic in nature. Similar to PLP, RLP is highly prevalent after amputation and can last for several years [6]. RLP and PLP often co-exist, with patients reporting both after surgery. RLP is often reported as a stronger sensation after amputation, while PLP develops over time within the first postoperative month or at a later date [7]. PS are non painful stimuli that derive from the site of amputation and over time are seen in up to 90% of post amputation patients [8]. These sensations can be felt as "twisting" of the limb, touch, pressure, vibration, as well as spontaneous movements.

Proposed mechanisms

The pathophysiology underlying PLP is likely multifactorial in nature, and currently both peripheral and central mechanisms are thought to be involved. Risk factors hypothesized to play a role in PLP development include female gender, pre-amputation pain, upper extremity amputation, and residual pain in remaining limb [9]. Peripherally, it is likely that the injury to nerves during amputation play a large role in the development of chronic pain. Following trauma, the nerves undergo a process of deafferentation, and neuromas grow from the proximal portion of the severed nerve. Spontaneous afferent input to the spinal cord is increased due to up regulation of voltage-sensitive sodium channels, change in expression of transduction molecules, and the development of nonfunctional connections between axons called ephapses [10].

Central mechanisms are thought to exist at both the level of the spinal cord and the brain. In the spinal cord, central sensitization is likely a key player in PLP development, as peripheral nerves form connections with the neurons in the spinal cord receptive field and sprout into areas involved in transmission of pain [10,11]. A further up regulation of receptors at the dorsal horn of the spinal cord leads to "wind up phenomenon" [12]. Decreased inhibitory exertion on sensory transmission from the brainstem reticular areas is likely due to the absence of afferent input to the dorsal horn from severed peripheral nerves [13], resulting in autonomous sensory activity from dorsal horn neurons. At the level of the brain it is thought that cortical reorganization is a major cause for PLP. It was hypothesized that somatosensory reorganization -where the cortical areas of the amputated extremity were taken over by adjacent zones- could explain why stimulation of those body parts results in sensations in the phantom limb [14-16]. The intensity of PS's has been found to be correlated to an area of cortical reorganization and size of the de-afferentated site [17]. In a study where forearm Ischemic Nerve Block (INB) was combined with low-frequency repetitive transcranial magnetic stimulation of the deafferented human motor cortex, decreased Intra Cortical Inhibition (ICI) was suppressed by NMDA receptor blockers, while the increase in motor evoked potentials and ICI where abolished by benzodiazepines [18]. INB in healthy volunteers has been shown to induce transient forearm deafferentation in healthy volunteers [19], suggesting that ischemic tissue damage may play a role in the development of PLP, particularly in patients with preexisting vascular disease, a large subgroup of the amputee population.

Pharmacological therapies

A vast number of pharmacological options have been proposed in the treatment of PLP. A recent review of thirty eight treatment modalities concluded that no recommendations for first line management could be made for PLP as the overall evidence of studies was too low [20]. Acetaminophen and NSAIDs are commonly reported as initial therapy for PLP, although few patients report significant levels of benefit [21].

NMDA antagonists

Hyperactivity of the NMDA receptors is thought to be a possible etiology in the maintenance of persistent PLP. Therefore, various studies have evaluated the role of NMDA receptor antagonists, which may halt the sensitization of dorsal horn neurons, as a potential treatment. An early 1996 study of patients with established PLP and stump pain reported an increase in pressure-pain threshold and a decrease in wind-up like pain with an IV bolus and infusion of ketamine (N=11) [22]. A 2008 study reported that an infusion of ketamine at 0.4 mg/kg (n=10) reduced PLP when compared to placebo at the end and 48 hours after infusion [23].

Memantine, another NMDA R antagonist, has also been investigated as a treatment for PLP. An early study in 2000 (n=19) compared memantine to placebo in patients with chronic pain after amputation or surgery, with a dose increasing from 5 to 20 mg/day. This study reported no change in pain between the two groups [24]. Two studies further evaluated the effects of memantine at a dose of 30 mg/day, both reporting no significant clinical benefit of memantine in chronic PLP [25,26]. A recent systematic review in 2016 reported conflicting results, with a case report, two case series, and one prospective study which demonstrated benefit with memantine in the treatment of acute PLP. However in chronic PLP which had been present for over 1 year there were no studies that demonstrated a significant effect for memantine as a therapy [27]. It is possible that the dosage or short run-in period of memantine did not allow the sufficient levels of medication in these patients required to see clinical effect. Further issues raised with the memantine studies include the differential affinity of NMDA receptor antagonists and mechanisms other than NMDA receptor activation that lead to PLP. When comparing efficacy of ketamine vs memantine, it should be noted the administration routes for these two NMDA R antagonists differ as ketamine is given intravenous while in the memantine studies the medication was given PO.

Antidepressants

Antidepressants have long been utilized as a therapy for chronic pain, suppressing pain pathways by a myriad of mechanisms. It appears that the main mechanism of action is the increase in nor epinephrine and serotonin in the synaptic cleft at supraspinal and spinal levels, leading to reinforcement of the descending inhibitory pathways [28]. Overall, reports of the efficacy of various antidepressants on PLP have been mixed. A Randomized Controlled Trial (RCT) of amitriptyline titrated up to 125 mg/d given for 6 weeks found no significant difference in average pain intensity when compared to placebo (n=39) [29]. The low number of patients in the study, short term follows up, and dosage may have contributed to the negative results. A case report of a post-amputation PLP patient treated with doxepin, another TCA, reported relief of both pain and autonomous movements [30]. A case series of PLP patients treated with milnacipran, a Serotonin–Norepinephrine Reuptake Inhibitor (SNRI) approved for the treatment of fibromyalgia, reported rapid and near-total relief from phantom limb pain [31]. Duloxetine -another SNRI-has also been reported to have beneficial effects on PLP in a series of case reports [32,33].

Anticonvulsants

Various trials have investigated the use of gabapentin and pregabalin for various peripheral neuropathic pain syndromes. A RCT in 2006 (n=41) found that gabapentin administration in the first postoperative month after amputation did not decrease either the intensity or incidence of phantom pain when compared to placebo [34]. However, a Cochrane review in 2011 reported that the combined results from 2 placebo-controlled, cross-over trials of six weeks' duration, noting that gabapentin did not improve depression score, function, or sleep quality [35]. One of these studies reported a higher pain intensity difference in patients taking gabapentin at 2.4 g/day at the end of six weeks compared with placebo [36] while the second trial reported no significant difference in average phantom pain intensity [37]. The combination of these two findings for pain intensity change showed a mean difference favoring gabapentin.

Capsaicin

Capsaicin, an active component of chili peppers, is used as an analgesic in various topical ointments and patches. As a member of the vanilloid family it binds to the Vanilloid Receptor Subtype 1 (TRPV1). A prospective 12-week non-interventional study in Germany evaluated the affect of a capsaicin 8% cutaneous patch in 21 patients with post amputation pain and found that a single treatment significantly reduced the average pain intensity over the observational period [38].

Calcitonin

Calcitonin as an analgesic is hypothesized to act through either specific binding sites in the CNS or by impacting descending serotonergic modification on C afferent sensory transmission [39]. A 1992 crossover study in patients who had undergone major amputations and developed severe PLP 0-7 days after surgery reported that a single postoperative infusion of calcitonin led to a reduction in pain intensity in 8 of 13 patients through 1 year follow-up [40]. A more recent randomized, double-blind, crossover trial in 2008 comparing ketamine, placebo, and calcitonin infusions in treating chronic PLP reported no decrease in PLP with calcitonin when compared to placebo [23]. The reason for these contrasting findings is unclear; however the 1992 study investigated patients with acute PLP, while in 2008 patients with a long history of pain were treated.

Opioids

Oral morphine has been shown to affect cortical reorganization in PLP patients, which has been associated with pain intensity [41]. A trial comparing sustained-release morphine to mexiletinein patients with post amputation pain of 6 months or longer reported that morphine led to a decrease in intensity of post amputation pain while mexilitine did not. However, morphine was associated with a higher rate of side effects. Furthermore, there was no improvement in reported levels of overall functional activity between the two groups [42]. Tramadol, an opioid and SNRI has also been reported to lead to improvements in phantom pain intensity after 1 month of treatment [43].

Non-pharmacological therapies

Mirror therapy: Mirror therapy is non pharmacological treatment first reported in 1996 when Ramachandran and Rogers-Ramachandran used a "virtual reality box" with mirrors reflecting the patient's intact limb [44]. In 2007 the first RCT of mirror therapy in patients who had undergone lower limb amputation compared patients in three groups- a reflected mirror, a covered mirror, and trained mental visualization [45]. This study reported reduced phantom limb pain after 4 weeks of the mirror therapy group that was not seen in the other two groups. A 2017 study looking at patients who had upper extremity amputation similarly found a significant decrease in pain scores with mirror therapy when compared to control (covered mirror or mental visualization therapy) [46]. A retrospective analysis of two independent cohorts with unilateral lower limb amputation further reported that the degree of PLP at baseline predicts when mirror therapy relieves pain; patients with reported low PLP experienced a reduction in symptoms more rapidly than those with high baseline PLP [47].

Neuromodulation: Patients with chronic, intractable PLP can be considered as candidates for more aggressive interventions. Various mechanisms of neuromodulation have been utilized in an attempt to address the central neuroplastic changes. Motor Cortex Stimulation (MCS), electrical stimulation of the precentral gyrus, is reported to be effective in treating patients with various forms of chronic pain [48,49]. A 2001 study evaluated 19 patients with PLP and found a dramatic effect on pain in patients treated with MCS [50]. A further case report using functional magnetic resonance imaging in a patient with a hand amputation to guide electrode placement led to reduction in pain and inhibiting effects on both the sensorimotor cortex and the contra lateral primary motor and sensory cortices on fMRI [51].

Spinal Cord Stimulators (SCS), which involves the placement of electrodes in the epidural space with a subsequent application of electric current to area of the spinal cord presumed to be the source of pain, is another form of neuromodulation frequently used in chronic pain [52]. Various case series have been performed evaluating the efficacy of SCS. An early follow-up study in the 1970s looked at dorsal column stimulation in 84 patients, 64 of which were amputees, and found an overall decrease in pain during 5 years of stimulation [53]. A 2010 case series of four patients who underwent SCS placement for intractable PLP showed >80% pain relief in all patients postoperatively [54].

A case series and a case report looking Electroconvulsive Therapy (ECT) both describe pain relief after intervention [55,56]. The case report also hypothesized that the analgesic effect from ECT may be secondary to alterations in cerebral blood flow after noting normalization in blood flow to the anterior cingulated cortex and insula ipsilateral to the patient's pain after ECT which had been increased prior to therapy.

Other therapies

Given the refractory nature of PLP, even in the setting of various medical therapies and interventions, pain providers should be aware of alternative therapies available to their patients. One case series (n=6) by Beaumont et al reported that eight weeks of visual-kinesthetic feedback led to a reduction of pain in four participants, however this result lasted in only one patient at the six month follow-up [57]. A 2002 case review endorsed hypnosis as a useful adjunct for treatment [58], which a RCT of 20 patients with RLP or PLP further corroborated reporting decreased overall pain scores after three sessions [59]. A review of controlled trials in acupuncture literature noted positive effects on PLP symptoms [60], although controversy remains over potential bias in the literature and low methodological quality.

Prevention

Although a high number of amputees report PLP symptoms, some report to be pain free [61], and the risk factors for developing symptoms after amputation remain unclear. It appears that poorly controlled severe pain prior to surgery increases the risk of chronic post surgical pain [62], leading to the idea that good pain control prior to amputation may decrease the risk of developing PLP. A study of 57 patients who underwent lower limb amputation reported that both pre-amputation pain and acute PLP intensity were independent predictors for the development of chronic PLP [63]. Similarly, this study reported that acute RLP was the best overall predictor of chronic RLP. These findings have furthered the role for "preemptive analgesia" in the hope of preventing chronic PLP.

Epidurals

In 1988 Bach et al studied the role of lumbar epidurals to provide 3 pains free days prior to amputation and reported a significant decrease in development of PLP when compared to control [64]. A review by Halbert et al. of various preemptive treatments aimed at reducing incidence of PLP had mixed results for epidurals with two trials, including the aforementioned Bach et al study, showing potential benefit while one trial found that although epidural analgesia was effective in treating acute perioperative pain there was no difference between treatment and control groups in chronic PLP development [65-67]. A recent study by Karanikolas et al. [68] looked at 65 patients with severe lower-limb ischemic pain secondary to peripheral vascular disease that under went amputation and randomized the patients to five different pain control regimens. They concluded that optimum analgesia, be it through preoperative, intraoperative, or postoperative epidural analgesia epidural or systemic opioids drastically reduced the incidence of PLP at six months post operative when compared to nurse driven intramuscular opioid treatment.

Nerve blocks

Given the limited duration of epidural treatment, investigations have also evaluated the ability of infusions of local anesthetics at the peripheral nerve to decrease the incidence of PLP. A study of 71 patients who underwent lower extremity amputation evaluated the effect of a continuous infusion of 0.5% ropivacaine started intra-operatively through a Perineural Catheter (PNC) on PLP intensity [69]. The median duration of infusion was 30 days (95% CI, 25-30 days), and they noted a significant decrease in the reported intensity of severe-to-intolerable pain at the end of the 12 month evaluation. However, a systematic review of seven studies (n=416) comparing the use of a PNC following lower limb amputation with no treatment or placebo reported that although a significant reduction in postoperative opioid use was noted there was no difference in the development of PLP [70]. Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, the quality of evidence for all outcomes was low. The PLACEMENT study has been proposed to explore the feasibility of a trial to assess the impact of a PNC placed at the time of the amputation, hoping to calculate the sample size for an effectiveness trial [71]. Well-performed randomized studies will provide higher quality data to properly assess the utility of this potential preventative therapy.

Medications

Given the possible component of central nervous sensitization following amputation in the development of PLP, it was hypothesized that pre-operative intravenous ketamine infusion might reduce the incidence or severity of chronic PLP. In a randomized trial of 45 patients undergoing above or below the knee amputation, patients were given a ketamine or placebo bolus pre-induction and a continuous infusion for 72 hours postoperatively [72]. Although a difference was noted in the development of PLP at 6 months, it was not statistically significant (47% in the ketamine group vs 71% in the control group, P=0.28). A randomized double blind trial (N=53) evaluating intrathecal or epidural ketamine and bupivicaine vs saline and bupivicaine for lower limb amputation surgery noted post-operative analgesia was significantly better for the group receiving ketamine as a component of their neuraxial analgesia [73], which may be secondary to ketamine's actions on central sensitization. Both groups experienced decreased stump and phantom pain at the amputation site at twelve months than in comparable studies, however no significant difference between the infusions with or without ketamine was noted. The neuraxial technique, with or without ketamine, is thought to reduce ongoing sensitization thereby leading to a positive effect on persistent pain. Notably, neuraxial ketamine was not compared to placebo only in this trial, therefore it is difficult to interpret the potential effect of ketamine on long term PLP. Larger trials of ketamine as a perioperative tool for the prevention of PLP are required. Peri-operative oral ketamine has been shown to be safe in a pilot study of three patients undergoing lower extremity amputation [74], and future studies may involve a PO ketamine regimen in PLP prevention.

Another NMDA R antagonist, memantine, administered with continuous brachial plexus anesthesia in early postoperative stage after acute traumatic amputation of the upper extremity significantly decreased intensity and prevalence of PLP at four weeks and six months. When compared to placebo memantine resulted in a decrease in requested ropivacaine bolus injections [75].

Gabapentin has been evaluated as a treatment for PLP, and a recent study looked at the potential for this drug to be used as a preventative agent in pediatric patients who were diagnosed with osteosarcoma or Ewing's sarcoma around the knee and underwent amputation between 2013 and 2016 [76]. In this double blinded RCT patients were given placebo or gabapentin for 30 days starting 4 days prior to surgery; it reported an overall decrease in both postoperative pain intensity and rate in PLP at the 60 day follow up visit.

Transcutaneous electrical nerve stimulation (TENS) stimulation

Alternative therapies for preventing PLP continue to grow. A RCT looking at 51 patients with lower extremity amputations compared TENS treatment to both sham TENS with chlorpromazine and sham TENS alone [77]. No significant differences in the development of PLP between the groups were noted during the first four weeks or after one year, and although there was a decrease in PLP at 4 months in the TENS group.

Nerve coaptation

Recent research has also been focused on possible surgical techniques to reduce the incidence of PLP. A study of 17 patients who underwent transfemoral amputation reported that preemptive coaptation of the common peroneal nervetotibial and collagen nerve wrapping led to significant reduction in PLP at 2 and 6 months post operative [78]. Furthermore, reductions in Visual Analog Scores (VAS) at both time endpoints and an increase in ambulation rates were reported in the treatment group.

Conclusion

PLP continues to be a challenging condition to manage; prevention and treatment should target multimodal therapies which take into consideration both medication and procedure based interventions. While larger trials with longer follow up are still needed to provide high quality data, ultimately an evidence-based guide for both anesthesiologists and pain physicians will help manage this complex and difficult to treat condition. As further investigations evaluate the potential of peri-operative management on impacting patients who suffer from chronic pain after amputations, it will become increasingly critical for anesthesiologists to be well versed in the benefits they can provide for these patients, both in the operating room and beyond.

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