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Phantom Limb Pain- Mechanism and Evidence Based Management

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Abstract

Phantom limb pain (PLP) is a complex condition resulting in manifestation of pain in the missing body part. PLP is very common in post-amputated individuals and the prevalence rate of as high as 80% has been reported in amputees. PLP leads to a poor quality of life and has a tremendous impact on socioeconomic status of individuals. The mechanism of pain in PLP is still poorly understood despite significant research involving the molecular and neurobiology of the pain. Similarly, various pharmacological and non-pharmacological therapies are described in the literature. This article aims at briefly reviewing the existing literature pertaining to the PLP mechanism and evidence based treatment.

Introduction

Phantom limb pain (PLP) is a complex condition resulting in manifestation of pain in the missing body part. PLP is very common in post-amputated individuals and the prevalence ranges from 60–80% amputees' [1]. PLP leads to a poor quality of life and has a tremendous impact on socioeconomic status with only 43% patients returning to work following amputation [2,3]. Furthermore, psychological distress, anxiety, depression and activity limitation has been reported. In 92% of PLP patients, the pain can occur as early as the first-week post-amputation, and 65% occur in the first six month post-amputation [4].

Various factors may contribute in the manifestation of PLP, such as the site of amputation, time elapsed after amputation, psychological factors, severe pre-amputation pain and high intensity of pain right after amputation [1, 5-7]. It is important to distinguish various elements of post-amputation phenomenon: a) PLP- painful sensations referred to the absent limb, b) Phantom limb sensation- any sensation in the absent limb, except pain; c) Stump pain- pain localized to the stump [2] (Figure 1).

This brief review aims to focus on the mechanism and evidence based treatment of PLP.

Methods

We performed a literature search in Embase, Pubmed and Cochrane central register of controlled trials up to December 2020 using search items "phantom limb pain", "phantom sensation", "analgesics", "anticonvulsants", "antidepressants", "Opioids", "SSRI", "tramadol", "NMDA antagonists", and "mirror therapy".

Mechanism of Pain in PLP

The actual mechanism of pain in phantom limbs is still poorly understood. However, in recent years more and more research has helped us understand the changes that develop in the central and peripheral nervous system that attribute to the sensation of pain.

Initial transection of the peripheral nerves as it happens following surgery leads to an enhanced release of chemical mediators like histamine, bradykinin, Substance P and prostaglandins. Increased sensitivity of

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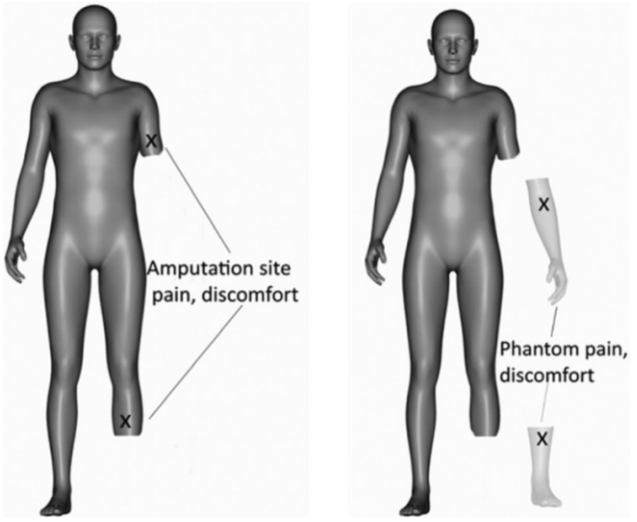

Figure 1: shows graphic representation of phantom limb pain and stump pain.

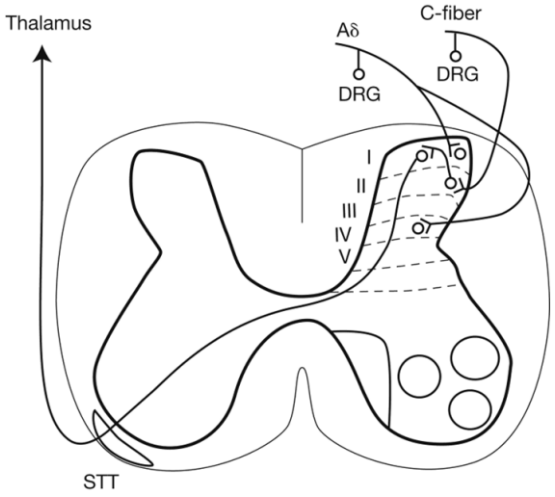

Figure 2: shows the normal termination of first order neurons at various lamellae of the doral horn of the spinal cord.

the nociceptors to these chemicals leads to an increased firing of afferent neurons. In the same time, the sodium channel membrane potential threshold gets lowered [8]. This lowered membrane potential threshold further increases the rate of neuronal impulse transmission. Following transection of peripheral axons, sprouting of new neurons occurs in the ventral terminals of the large myelinated axons. This sprouting permits the sensory axons to terminate in lamina II instead of laminae III or IV (Figure 2). This eventually leads to 'wrong connections' and sensory neurons responsible for touch might connect with the inter-neurons that normally receive input from nociceptors [8]. As a result, even light touch can cause a lot of discomfort. This forms the basis of so-called "peripheral sensitization" of the nervous system following trauma or surgery.

The increased neuronal activity in the peripheral nervous system ultimately leads to "central sensitization" or "Wind-up phenomenon" [9]. The final factor is cortical reorganization. Despite the limb being amputated, the brain still has the old geography wired in. This eventually leads to excessive activity in the neuromatrix due to lack of signals from the limb [10]. The neuromatrix theory of pain states that the perception of painful stimuli does not result from the brain's passive registration of tissue trauma, but from its active generation of subjective experiences through a network of neurons known as the neuromatrix [11]. Recent research has identified the anterior cingulated cortex as a critical part of the neuromatrix.

Treatment of PLP

PLP can be debilitating and a challenge for physicians to treat. A wide range of pharmacological interventional treatments exist; yet little is known about them in respect to PLP. This article will address the effectiveness of both pharmacological, nonpharmacological therapy and surgical therapy.

Pharmacological Treatment

Antidepressants

The most commonly used medications for the treatment of PLP are tricyclic antidepressant. In a randomized controlled study, the authors examined the effect of amitriptyline versus an active placebo over a 6 week period in 39 participants with post-amputation pain [12]. The primary outcome measure was patient-reported average pain intensity. Amitriptyline was started at 10 mg/day and increased to a maximum of 125 mg/day. But the authors did not find any beneficial effects of amitriptyline in the treatment of post amputation pain. Many patients experienced adverse effects with dry moth being the most common side effect. No study has been conducted comparing efficacy of duloxetine or venlafaxine in PLP except 1 case report where combination of pregabalin and duloxetine helped in the management of PLP in acute setting [13].

Anticonvulsants

Anticonvulsants like pregabalin and gabapentin are considered 1st line medications in many neuropathic pain conditions. We found two randomized, double-blind, cross-over studies comparing gabapentin with placebo [14, 15]. Bone et al found that gabapentin statistically reduced pain intensity at 6 weeks. The average VAS reduced from 6.6 (SD 1.8) to 2.9 (SD 2.2) in the gabapentin group, as compared to a reduction from 6.7 (SD 1.9) to 5.1 (SD 2.2) in the placebo group. No statistical difference was found for function. Smith et al did not find any statistical difference in pain intensity between the gabapentin and the placebo group, but participants experienced a statistically significant difference in their pain global improvement scale. The difference from baseline VAS for worst PLP was 1.15 (SD 2.41) in the gabapentin group and 0.58 (SD 2.86) in the placebo group, but the participants considered this to be a meaningful

reduction. Changes in function scores were not significantly altered and a larger percentage of participants believed that the benefits of gabapentin outweighed the side effects (54.2% vs 16.8%). Both the studies involved only small number of participants; hence, it is difficult to draw any meaningful conclusion. However, another randomized study used gabapentin or placebo pre-emptively following day 1 of amputation till day 30 in an incremental dose of gabapentin up to 2400 mg/day and evaluated the pain intensity at 7, 14, 30 days and after 3 and 6 months. They found that gabapentin administered in the first 30 postoperative days after amputation does not reduce the incidence or intensity of postamputation pain [16]. A recent systematic review confirmed that oral gabapentin in patients aged 18 years or older may decrease phantom limb pain. A strong recommendation for the effectiveness of gabapentin in phantom limb pain cannot be ascertained until more methodologically sound studies are executed in this population [17]. Except 1 case report [13], no study has been published comparing the efficacy of pregabalin in PLP. Given the fact that pregabalin has same mechanism to that of gabapentin and also being a 1st line recommended medication in neuropathic pain, it along with duloxetine warrants further clinical research in the setting of PLP.

Another anticonvulsant medication topiramate has been tried in PLP. A pilot prospective, double-blind, randomized, placebo-controlled study examined the effect of topiramate on four PLP patients. A statistically significant reduction of 70–80% VAS was observed between daily doses of 25–800 mg [18]. But, it is impossible to draw any conclusion from such a small cohort of patients. Hence, a more definitive study is needed to explore the potential role of topiramate in PLP.

Calcitonin

Calcitonin therapy in PLP has produced mixed results. A double-blind crossover comparison of Calcitonin 200 IU infusion against a placebo recruited 21 patients out of 161 patients who had undergone major amputations and developed severe PLP up to 7 days postoperatively. Calcitonin infusion reduced pain levels on a numeric analogue scale (NAS) from a median of 7 to 4. Placebo had no effect of pain scores. One week after treatment, 19 patients (90%) had pain relief of more than 50%, 16 (76%) were completely pain free and 15 (71%) never experienced PLP again. One year later 8 out of the 13 surviving patients (62%) still had more than 75% PLP relief. After 2 years PLP exceeded 3 on VAS in 5 individuals (42%), and the remaining 12 patients presented the same PLP as after 1 year. The authors therefore concluded that calcitonin is effective for the prophylaxis of PLP in the early postoperative period (19). The use of calcitonin (200 IE) was examined in chronic PLP against and in combination with ketamine (0.4 mg/kg) infusion in a 20 participant randomized, double-blind trial which was divided into 4 groups. Intensity of phantom pain (VAS) was recorded before, during, at the end and 48 h after each infusion. Ketamine, but not calcitonin, reduced PLP. The authors concluded that ketamine but not calcitonin affects central sensitization occurring in PLP [20].

NMDA receptor antagonists

Hyperactivity of NMDA receptor is hypothesized to cause central sensitization leading to persistent stump pain and PLP [21]. Nikolajsen et al used low-dose ketamine infusion to study its efficacy on PLP. They infused ketamine (bolus at 0.1 mg/ kg/5 min followed by an infusion of 7 μg/kg/min) to 11 patients with established PLP. Ketamine resulted in a reduction in pain in all 11 patients (VAS and McGill Pain Questionnaire). Ketamine increased pressure pain thresholds significantly. Wind-up like pain was also reduced. The authors therefore concluded that NMDA receptor antagonists might be effective in stump and PLP [21]. As ketamine is associated with significant side effects, more studies with large number of participants are needed to examine the benefit and risk in PLP.

Two other NMDA antagonists have been studied in PLP. Oral dextromethorphan (120-270 mg daily) was studied in a pilot double-blind crossover trial of three patients with cancer amputation pain effectively reduced PLP [22]. The other drug memantine did not provide provide any meaningful long-term pain reduction in established PLP [23, 24].

Opioids

Randomized control trials have demonstrated beneficial role of opioids in PLP. It is hypothesized that they may also reduce cortical reorganization. Huse et al. examined the efficacy of oral morphine against placebo in a double-blinded crossover design in 12 patients with PLP. A dose of 70–300 mg/day showed a short-term clinically relevant response to morphine (pain reduction of more than 50% on VAS) was evident in 42%, a partial response (pain reduction of 25–50%) in 8% of the patients. Importantly, neuromagnetic source imaging of three patients showed evidence for reduced cortical reorganization with morphine. The authors therefore concluded that opioids show promise in reducing PLP and may potentially influence cortical reorganization [25].

Wu et al. [26] measured the effects of intravenous lignocaine and morphine administered to post amputation stump and PLP patients over three consecutive days. They infused morphine (0.05 mg/kg bolus + 0.2 mg/kg infusion over 40 min), lidocaine (1 mg/kg bolus + 4 mg/kg infusion) and the

active placebo, diphenhydramine (10 mg bolus + 40 mg infusion). Compared with the placebo, morphine reduced both stump and phantom pains significantly ($P < 0.01$). In comparison lidocaine decreased stump ($P < 0.01$), but not phantom pain. This short-term study with pain scores only measured 30 minutes post infusion is the major drawback. Another RCT also found morphine to reduce PLP when compared with mexiletine but were associated higher adverse effects [27].

Mirror therapy

Mirror therapy (MT) has been extensively studied in PLP and phantom limb movements (PLM). In a recent systematic review [28], twenty studies were selected. Among these 20 studies, 5 were RCTs (163 patients), 6 prospective studies (55 patients), 9 case studies (40 patients) and methodologies were heterogeneous. Seventeen of the 18 studies reported the efficacy of MT on PLP, but with low levels of evidence. One randomized controlled trial did not show any significant effect of MT. As to the effect of MT on PLM, the 8 studies concerned reported effectiveness of MT: 4 with a low level of evidence and 4 with a high level of evidence. But the authors concluded that the overall level of evidence is insufficient to recommend MT as first intention treatment in PLP.

Surgical treatment

Various authors have attempted neurectomy, rhizotomy, sympathectomy, cordotomy and myelotomy as treatments for PLP, but no trials were found for any of these surgical treatments. The only surgery used to treat PLP identified by our literature search is Dorsal-Root Entry Zone lesioning but it is difficult to make any conclusion because of sample size [29].

Non-pharmacological treatment

Many nonpharmacologic treatments have been tested on PLP including acupuncture, biofeedback, hypnosis, reflexology, transcutaneous electrical nerve stimulation, spinal cord stimulation, motor cortex stimulation, deep brain stimulation, transcranial magnetic stimulation and therapeutic touch. The majority found a reduction in pain score; however, these are small case studies or case series, hence no conclusion can be drawn from these studies [29].

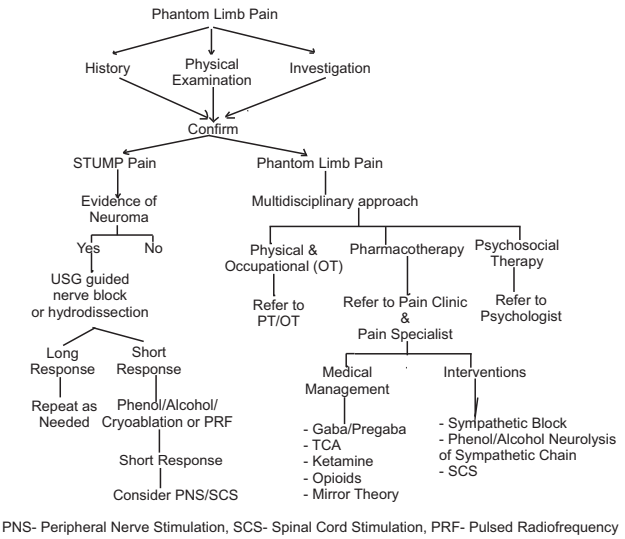

Figure 3: Proposed treatment algorithm for Phantom Limb Pain

Conclusion

PLP is major challenge considering its high prevalence in amputees and is associated significant socioeconomic and psychological burden. The management of PLP is complex and as shown in this review no single pharmacological or non-pharmacological therapy is highly effective [30]. Most studies used small number of patients and provided conflicting results. Only Ketamine, gabapentin and mirror therapy were found to be effective to some extent. However, multiple high quality RCTs involving a large number of patients and even combination therapy (morphine and gabapentin or pregabalin and duloxetine) should be considered in future. Other pharmacological agents with known beneficial role in neuropathic pain like pregabalin, duloxetine and tramadol need to be studied. Finally, potential role of nerve blocks or neuraxial catheters in prevention of PLP should also be studied. Finally, an algorithmic approach for treatment has been proposed from the best available literature (Figure 3).

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.
Conflict of interest: Nil **Source of support:** None

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