Management of Phantom Limb Pain: A Review

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ABSTRACT There are two types of pain after limb amputation, residual limb pain (RLP) that is pain localised on the stump, and pain perceived by the patient on the area of the missing limb which is called phantom limb pain (PLP). The prevalence of phantom limb pain remain high; several studies reported 50%-80% of amputated patients experienced PLP. Phantom limb pain therapy is challenging because its mechanism is not precise yet. In recent years, many therapies are being studied; they are divided into pharmacologic and nonpharmacologic therapy. Pharmacologic treatment such as BoNT/A injection, antidepressants (amitriptyline), anticonvulsants (pregabalin and gabapentin), opioids, NMDA receptor antagonists (memantine and ketamine), and capsaicin 8% patch. Nonpharmacologic therapy such as mirror therapy, transcutaneous electrical stimulation (TENS), spinal cauda equina stimulation, cryoneurolysis, and acupuncture. However, from all those studies, they conclude that there is no first-line treatment. In this review, modalities for PLP treatment over the past few years will be discussed.

KEYWORDS phantom limb pain, management of phantom limb pain, pharmacologic therapy, nonpharmacologic therapy

1.Introduction

The sensation of pain, experienced in the area of the missing body part is called phantom limb pain (PLP) [1,2]. It has to be distinguished from residual limb pain (RLP), formerly known as "stump pain" [3]. PLP first describe by Ambroise Paré in 1552 [4] and named by Silas Weir Mitchell [2,5]. PLP is very frequent in post-amputated patients, and the prevalence may be as high as 50% to 80% [2,6–8]. In 92% of PLP patients, the pain occurs in the first-week post-amputation, and 65% occur in the first six-month post-amputation [3,9]. Phantom limb pain is classified as neuropathic pain and associated with differentiation and cortical reorganisation mechanism in the somatosensory system. From all those treatments that are being studied, no one shows significant effectiveness [7].

Several factors may contribute in PLP, such as the site of amputation, concomitant nonpainful sensation on stump organ, time elapsed after amputation, psychologic factors, and high intensity of pain right after amputation [10].

Not only a limb, but also other body parts can experience PLP, such as tongue, teeth, breasts, eyes, testicles, penis, rectum, or bladder. However, the most common site is upper and lower extremities [11].

Higher prevalence of adverse effects of PLP was reported in several studies such as low quality of life, psychologic distress, lack of treatment responses, activity limitation, anxiety and depression [3,6,10].

Lack of treatment response makes PLP a challenge condition up to this day, as the mechanism of PLP is not apparently known yet. Therefore, a review of all available literature is warranted as there are no standard guidelines in the management of PLP [9].

2.Pathophysiology

As the mechanism of PLP still not clearly defined yet, it is considered as neuropathic pain because there are changes in peripheral and central nervous system [1,2,9,11,12].

a. Peripheral Nervous System

Amputation including axotomy result in complete disconnection of peripheral motor and sensory nerve structure, that can lead to hyperexcitation of sensory neuron resulted from inflammatory

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mediators released by macrophages, Schwann cells, mast cells, as well as changes in sodium channels and gene expression [2]. In PLP there are several changes along the neuronal axis. The peripheral mechanism was related to neuroma formation and ectopic discharge. Noxious stimuli result from trauma on neuron can cause central sensitisation, long-term potentiation, and expansion of sensitive area in central neurons [5].

b. Central Nervous System

Phantom limb pain mechanism in the central nervous system is related to reorganisation disturbance in the primary sensorimotor cortex, including changes in motor cortex excitability and peripheral factor such as nociceptive inputs from residual limb [6,7,13]. Based on cortical reorganisation, there is an alteration of neuroplasticity in cortex fields which project the amputated limb. Cortical fields which receive no input from periphery will shrink and become smaller. The common adjacent cortical area of body parts then take over the cortical fields [1,5,10]. This mechanism is shown in functional neuroimaging. Central nervous system changes not only occur in the cortex but also in another area of the brain including spinal cord, such as increased synaptic responsiveness in dorsal horn [2].

3.Clinical manifestation

Clinical manifestation can be different among PLP patients [1]. PLP should be distinguished from post-operative pain, residual limb pain and nonpainful phantom sensation (the feeling that the limb is still there) [2]. Clinical characteristics of PLP commonly describe as burning, sharp, shooting, shocking, throbbing, cramping, heat and cold, needles sensation, stabbing, tingling, itching, and electric shock-like feeling [1,2,9,14]. Duration of episode range from few minutes to continuous. Onset may vary from hours to decades following amputation, and the frequency may range from every few days to several times each day [14]. Risk of phantom limb pain is an increase in a patient who experience pain before amputation, acute pain after amputation and the patient who suffers from residual limb pain [2].

4.Treatment

Phantom limb pain therapy is complicated because its mechanism is not clear yet [12]. Many therapies are considered useful, divided into pharmacologic and nonpharmacologic. Pharmacologic therapy : beta-blockers, calcitonin, anticonvulsants, antidepressants, topical capsaicin, selective serotonin-reuptake inhibitors (SSRIs), anaesthetics, opioids, tramadol, analgesics, N-Methyl D-aspartate (NMDA) receptor antagonists, muscle relaxants, non-steroidal anti-inflammatory drugs (NSAIDs), synthetic cannabinoids, botulinum neurotoxin (BoNTs) [1,3,4,7,9]. Nonpharmacologic therapy includes mirror therapy, transcutaneous electrical stimulation (TENs), transcranial magnetic stimulation, acupuncture, spinal cord stimulation, spinal cauda equina stimulation, cryoneurolysis, and many more [1,3,7].

a. Pharmacologic therapy

- **Botulinum neurotoxins (BoNT/A)**
  Botulinum neurotoxins (BoNT), extracted from Clostridium botulinum, has been used globally for cosmetic purposes. In medicine, BoNT has been used for the neurologic disorder, especially in spasticity disorder. Food and Drug Administration (FDA) has approved BoNT as a medication for dystonia or spasticity, such as blepharospasm, strabismus, focal dystonia, hemifacial spasm, or other spasticity disorder [12,15]. There are several types of botulinum toxin (A-G). Botulinum toxin type A (BoNT/A) inhibit acetylcholine (ACh) release from cholinergic presynaptic neurons. It inhibits vesicle docking of acetylcholine inside the presynaptic neuron. There are two mechanisms of BoNT/A on PLP, but the primary mechanism associated with a peripheral nerve. Kollewe et al. study three patients with PLP and fasciculation on stump organ, after injection of BoNT/A, fasciculation and PLP are disappeared and the effect of injection last for 8-11 weeks for every injection. This result showed the cholinergic effect on the peripheral nerve and considered as a secondary factor from muscle relaxation because of decreasing ACh release [12]. Wu et al., study 14 patients with PLP and RLP and randomised into two groups, the first group received BoNT/A injection and second group received lidocaine/methylprednisolone. At the end of the study, PLP intensity stays the same on both group [16].
- **Antidepressants**
  One of the most commonly used medications for neuropathic pain is Tricyclic antidepressants (TCAs). TCAs, such as amitriptyline acts as the inhibitor of serotonin-norepinephrine uptake blockade, NMDA receptor antagonist, and sodium channel inhibitor where it can produce analgesic effect [17]. Robinson studied the effectivity of amitriptyline on PLP compare to placebo. In his study, 39 participants are divided into two groups and followed for six weeks. There are no significant differences between the two groups in managing PLP [18]. In the other hand, a recent study reported 55 mg of amitriptyline has a significant response in controlling PLP [8].
- **Opioid**
  Opioid binds to its receptors in both peripheral and central nervous system. It provides the only analgesia without loss other sensation such as proprioception and touch. It disrupts one of the mechanisms of PLP in the central nervous system, as it diminishes cortical reorganisation [17]. In the recent study, 94 patients were followed for one month that randomly assigned to receive an individually titrated dose of tramadol. The result shows tramadol provided significant relieve of PLP and RLP without any significant side effects [8].
- **N-methyl-d-aspartate (NMDA) receptor antagonist**
  N-methyl-d-aspartate (NMDA) receptors have an essential function in central and peripheral sensitisation. It is considered NMDA receptors stimulation can result in activation of glutamate receptors. This activation starts when the neuron is traumatised and continues as the patient experienced pain. Because of this mechanism, memantine, as an NMDA receptor antagonists can help to modulate pain on the peripheral receptors after injury or amputation [19].
- **Anticonvulsants**
  Pregabalin is designed as lipophilic gamma-aminobutyric acid (GABA) analogue that facilitates diffusion across the blood-brain barrier. Pregabalin and gabapentin show improvement in neuropathic pain [21]. Gabapentin 3-alkylated analogue and pregabalin (S-[+]-isoutylgaba) bind to α 2- δ subunit and modulate calcium influx on the nerve terminal, as a result, lower several neurotransmitter exocytoses, including glutamate, noradrenaline, serotonin,

dopamine [21,22]. Rusy et al., study 7 participants treated with gabapentin, PLP resolve on 6 participants in two months treatment. One patient still experienced pain to a lesser intensity. Gabapentin can be an adjunctive therapy in PLP treatment [23]. Compare to gabapentin; pregabalin is more favourable in pharmacokinetic profile. It shows pain reduction in lower doses than gabapentin. Pregabalin may be effective for a patient that failed in gabapentin therapy [21].

- **Capsaicin 8% patch**
  There are several studies report higher efficacy, safety, and tolerability of a single application of capsaicin 8% patch in neuropathic pain. Capsaicin is a natural selective agonist of the vanilloid receptor TRPV1. It is composed of a pungent ingredient from the chilli pepper. It released rapidly from the patch, overstimulated of the skin TRPV1 nociceptors and made it no longer able to respond to pain stimuli. Study of 14 patients with capsaicin 8% patch was assessed after four weeks application. The result shows spontaneous decrease of PLP and RLP (-1.007 [p=0.028] and -1.414 [p=0.018]) [10].

b. Nonpharmacologic Therapy

- **Mirror Therapy**
  In the last two decades, mirror therapy has frequently been chosen in managing PLP. Vilayanur Ramachandran introduced this method, it is effortless and can be done by the patients alone [1]. Yildrim and Kanan [1] investigate 15 patients with PLP. Training of this method took 40 minutes. The Mirror Therapy Practice Follow-Up Booklet and the mirror were given to the participants when the trainer thought they were capable doing this method alone. The result shows there is a significant improvement in PLP score every week and total score after one month ($p<0.01$) [1]. Barbin et al., did a systematic review to mirror therapy. They found 20 studies from Medline, Cochrane Database and Embase. From those studies, they conclude that mirror therapy needs more evidence to be recommended as the first choice of treatment [3].
- **Transcutaneous Electrical Stimulation (TENS)**
  Transcutaneous Electrical Stimulation (TENS) is a technique that uses the portable battery-powered device to deliver electrical currents to the intact skin surface. There are electrodes attached to the skin surface to stimulate the peripheral nerves. TENS is contraindicated in the patient with a pacemaker or other implanted devices. TENS can be used as a single therapy or combine with other treatment with chronic pain, including PLP and RLP [24].
- **Repetitive Transcranial Magnetic Stimulation (rTMS)**
  Repetitive transcranial magnetic stimulation (rTMS) is recently studied as PLP treatment. It disrupts central maladaptive plasticity. Post-stroke pain and spinal cord injury pain reduced after daily rTMS. Malavera et al. did a randomised controlled trial on 54 participants to receive rTMS. They used real rTMS for treatment group and sham coil rTMS for the control group. The result shows high-frequencies of rTMS induced clinically significant reduction of PLP patient, 15 days after treatment compared to control group [6].
- **Spinal Cauda Equina Stimulation**
  In several treatment modalities, spinal cauda equina stimulation was used to manage pain in intractable post-amputation pain. Lee et al. did spinal cord stimulation on 46 years old male. He experiences PLP since three years ago on the ankle and foot following above-the-knee amputation surgery. The spinal cord stimulation failed to show the satisfactory result. They tried another treatment and reported an excellent pain reduction following spinal cauda equina stimulation [11].
- **Cryoneurolysis**
  Cryoneurolysis, also known as cryoablation or cryoanalgesia, is a specific intervention that inhibits nerves conduction after cold application. Pain relief is achieved by freezing the nerve, as the ice crystals damage the vasa nervorum, leading to endoneurial injury and Wallerian degeneration of the nerve. Freezing inhibits nerve conduction but spares the basal lamina of Schwann cell. This is the reason why cryoneurolysis can produce complete regeneration and restoration without neuroma formation [2]. Moesker et al. studied five patients with PLP; they exclude patients with RLP. On stump organ, the peripheral nerve was located with a nerve stimulator. Complete resolution of the phantom pain confirmed the precise location. They reported patients had long-term relief of PLP for several years [2].
- **Acupuncture**
  Acupuncture had been used to treat pain, but the efficacy of neuropathic pain was not apparent yet, especially on PLP treatment [4]. Trevelyan et al., study 15 patients with PLP, they try to evaluate the efficacy of acupuncture treatment. They reported, acupuncture may be beneficial and useful in PLP treatment, but it needs further studies with more sample [25].

5.Conclusion

Until now, from all treatment modalities, no one gives optimum-long term result, so now we concern to the prevention of PLP such as reducing pre-amputation pain and acute pain following amputation. Prevalence of PLP is very high to the amputated patients, so we need further randomised, double-blind, controlled trial study with more adequate samples.

6. Competing Interests

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