Abstract

Phantom limb pain treatment and management has no clear direction as of yet, but research into the issue is uncovering different approaches that show promise of discovering a solution to this issue. Mechanism of phantom limb pain is poorly understood, but it is clear multiple factors are at play. Peripheral, spinal as well as supraspinal level of the nervous system is involved in the production of the painful sensation. Treatment approaches primarily include pharmacological agents and non-invasive treatments, but there are a few invasive treatment options available as a last resort. Although concrete guidelines are not set, available treatment approaches offer various options for management of pain. It is important to remember that different factors can be dominant in producing painful stimuli in specific patients. These facts demand an individualised approach with regard to patient’s history, symptoms and preferences.

Keywords: chronic pain, intractable pain, pain management, phantom limb

INTRODUCTION

Phantom limb pain was first described in 1551 by French military surgeon Ambroise Paré who reported that patients long after the amputation is made feel pain in the amputated part. Silas Weir Mitchell, a famous Civil War surgeon got inspired on the field and said: “Thousands of spirit limbs were haunting as many good soldiers, every now and then tormenting them.” That’s how the term “phantom limb pain” was coined.

Phantom limb pain are the sensations perceived by the region of the body that is no longer present, mostly due to amputation, congenital malformation, vascular incident or trauma. However, it can also occur following nerve avulsion or spinal cord injury. Risk factors are: upper extremity amputation, presence of preamputation pain, residual pain in remaining limb and time after amputation. The pain sensation varies from individual to individual, but is more common among females than males. The onset of pain can happen immediately or years after the amputation. There are reports of two peak periods of onset, the first one within a month and the second a year after amputation. Also, stress, anxiety and depression can trigger and contribute to the exacerbation or persistence of phantom limb pain. Phantom limb pain treatment and management has no clear direction as of yet, but research into the issue is uncovering different approaches some of which show promise of solving the puzzle.

MECHANISMS OF PHANTOM LIMB PAIN

The etiology of phantom limb pain is at present not completely understood. Studies have shown that multiple mechanisms on all levels of the neural axis (peripheral, spinal and supraspinal) have an important role in pain development.

1. PERIPHERAL MECHANISMS

Limb amputation causes severe tissue and neuronal injury. The proximal portions of the transected nerves form a proliferative mass of disorganized tissue called neuroma that contains endings of nociceptive C fibres and demyelinated A fibres. They show an increased rate of spontaneous activity. This hyperexcitability is thought to be a result of upregulation of voltage-sensitive sodium channels, downregulation of potassium channels and development of new nonfunctional connections between axons. The neuroma formation occurs in residual limb and is thought to be the cause of residual-limb pain that has moderately high correlation with phantom limb pain. This theory is supported by findings that lidocaine, an unspecific sodium channel blocker, blocks phantom limb pain when injected into the neuroma. Downsides of this theory is the fact that phantom limb pain occurs in many cases immediately after amputation before a neuroma could have formed and that it can not explain the pain in people with congenital absence of limbs.
Another site of ectopic and increased activity after neuronal transection is dorsal root ganglion. The cell bodies in ganglion show similar hyperexcitability as neuroma fibres. The ganglion cells can amplify impulses from the residual limb or can lead to cross-excitation and induce depolarisation of surrounding neurons.3

2. SPINAL MECHANISMS

Gate control theory asserts that activation of non-nociceptive fibers can interfere with nociceptive (C and Aδ fibers) and thereby inhibit pain. Firing of the Aβ fibers activates the inhibitory interneuron, reducing the chances that the projection neuron will fire, even in the presence of a firing nociceptive fibres.5

In a process called central sensitization, an increased activity of peripheral nociceptors leads to a change in the synaptic structure of a dorsal horn.5 After nerve injury, there is an increase in excitability of spinal cord neurons, and C fibres and Aδ afferents gain access to secondary pain signalling neurons. Sensitization of dorsal horn neurons is mediated by release of glutamate and neurokinins. It may manifest itself as mechanical hyperalgesia and an expansion of peripheral receptive fields.4

Pressure can provoke phantom pain. The pharmacology of spinal sensitization involves increased activity in NMDA receptor operated systems and many aspects of the central sensitization can be reduced by NMDA receptor antagonists. In human amputees, for example, the stump or phantom pain evoked by repetitive stimulation of the stump ('wind-up' like pain) can be reduced by the NMDA antagonist ketamine.4

Neurons in lamina II normally receive Aδ and C fibres input and respond best to noxious stimulation. Peripheral nerve damage may result in a substantial degeneration of C fibres terminals in lamina II and loss of its synaptic contacts with pain signalling neurons. Consequently, central terminals of Aβ mechanoreceptive afferents, which normally terminate in deeper laminae (III and IV), sprout into laminae I and II. The incoming Aβ signal might be interpreted as allodynia (experience of pain from a non-painful stimulation).1

3. SUPRASPINAL MECHANISMS

In recent years the research into phantom limb pain focused on cortical reorganisation in the primary cortex. During the process of reorganisation, the adjacent representational zones in somatosensory and motor cortex take over the areas that represent the amputated extremity.4 Several imaging studies have noted this phenomenon. This theory partly explains why the nociceptive stimulation of the remaining limb part or surrounding area causes the sensation in the amputated limb.

Another interesting mechanism of phantom limb pain proposed Melzak in his ‘neuromatrix and neurosignature’ hypothesis. The neuromatrix is a network of neurons in the brain that integrates inputs from thalamus, somatosensory cortex, reticular formation, limbic system and the posterior parietal cortex into a perception of the body and self. The deprivation of inputs to the neuromatrix that follows limb amputation causes an abnormal neurosignature. This altered neurosignature could be the cause of the phantom limb pain sensation.5

TREATMENT APPROACHES

PHARMACOLOGICAL APPROACH:

1. ANTICONVULSANTS

Gabapentin is currently the most commonly used anticonvulsant. Gabapentin interacts with a high-affinity binding site in brain membranes which has recently been identified as an auxiliary subunit of voltage-sensitive Ca++ channel, α and δ subunits.6 It reduces the brief stabbing and lancinating pain. Side-effects are rare, except for sedation and tolerance.

2. ANTIDEPRESSANTS

Tricyclic antidepressants are among the most commonly used. Amitriptyline acts primarily as a serotonin-norepinephrine reuptake inhibitor, but shows effects on serotonin and norepinephrine transport as well. It is metabolised to nortriptyline, more potent and selective norepinephrine reuptake inhibitor. Nortriptyline has been found equally effective as amitriptyline, but with lesser incidence of orthostatic hypotension, dry mouth, nausea and vomiting as a side-effect.2

3. PREEMPTIVE ANESTHESIA AND ANALGESIA

Use of analgesics and anesthetics during the preoperative period should not only prevent the amputated side of the nerve from triggering hyperplastic changes, but also decrease the amplification of central neural sensitization. It has been shown that perioperative epidural anesthesia of ropivakain does not completely abolish phantom limb pain, but increases the number of patients with the mild form of it.7 On the other hand, ketamine was not found effective in reduction of acute central neural sensitization.7

4. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), enzymes responsible for prostaglandin synthesis and thereby decrease the nociception peripherally and centrally.

NON-INVASIVE TREATMENT APPROACHES:

1. TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

TENS is a non-invasive analgesic technique that uses pulsed electrical currents and delivers them to the intact surface of the skin through electrodes. As the pulse intensity gets higher and its frequency lower, efficiency increases.2 Studies show a 66% pain reduction lasting ten hours.7
2. TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS affects brain structures with electrical current induced by a powerful magnetic field which is delivered to the scalp. Magnetic field can be delivered as a single pulse or as sets of pulses. Several studies have shown that it can only transiently relieve pain.¹

3. MIRROR BOX THERAPY (VISUAL FEEDBACK THERAPY)

Mirror box therapy is an alternative treatment strategy that has been proven successful in managing phantom limb pain. Mirror box is a box with two compartments devided with parasygitaly placed mirror between arms or legs of the patient. The patient places an unaffected limb into one side of the mirror box and the affected limb into the other. Then they perform movements using the unaffected limb while watching its mirror reflection superimposed over the unseen affected limb. Our brain has mirror neurons which fire both at times when we perform an action or just observe it. Imagined movements share the same cortical pathway as executed motor tasks. Furthermore, the visual feedback dominates somatosensory feedback and sensory experiences can be evoked by visual information alone.¹ The presence of mirror neurons generates tactile sensations in the affected limb elicited by touching the virtual image of the limb in the mirror. The visual illusion of movement modulates somatosensory input and its activation remodulates cortical mechanisms of pain perception in the phantom limb.² This can allow patients to relax from potentially painful position.

INVASIVE TREATMENT APPROACHES:

1. SURGICAL DESTRUCTIVE INTERVENTION

Destructive procedures like thermal nerve root destruction, rhizotomy and spinal ganglionectomy led to unerestorable damage of nerve tissue. Initial pain relief was accompanied with high rate of recurrant pain. The indication for surgical destructive intervention nowadays is limited to refractory pain in patients with short life expectancy. Dorsal root entry zone lesion can be used for patients with brachial plexus avulsion or cervical nerve root injury. Dorsal root entry zone lesion is a neurosurgical procedure in which we use laminectomy to access the dorsal nerve root, microscopic probe is then injected into nerve cells that can trigger pain signals and those cells are destroyed using radiofrequency current.¹

2. NERVE BLOCKS

For upper extremity phantom pain interscalene or stellate ganglion blocks are used and for lower extremity lumbar sympathetic block. Nerve blocks are often combined with physical therapy.¹

3. INVASIVE NEUROMODULATION

This treatment approach is reserved for patients who failed various trials of non-invasive treatments and consists of either deep brain stimulation, motor cortex stimulation or spinal cord stimulation.

a) Deep brain stimulation (DBS) is an electrical stimulation of subcortical areas such as the thalamus or basal ganglia after the thin stick leads are stereotactically implanted. Evidence up to date suggest that DBS has decreased the pain more than 25% in long term and improved quality of life.¹

b) Motor cortex stimulation (MCS) is an electrical stimulation of the precentral gyrus using epidural surgical leads. Due to the representation of the upper limb on the convex part of the precentral gyrus and the lower limb interhemispheral, this treatment is favourable for upper extremity phantom pain. A study revealed that more than half of patients show pain relief when this method was used.¹

c) Spinal cord stimulation (SCS) is an electrical stimulation in which electrodes are placed in the epidural space near the spinal area presumed to be the source of pain. Electric current has sympatholytic effect.¹

The treatment has two phases. In the first phase electrical stimulator is implanted temporarily and patients are monitored. Only the patients who show significant pain relief are considered for the second phase of treatment, permanent implantation.¹
DISCUSSION

Even though there are many different approaches to managing phantom limb pain, there is no safe and sure path to treat patients who experience it. That is why it is important to emphasise a multidisciplinary approach when treating this condition. Different pharmacological treatments can be successful in managing the painful stimuli, but are not efficient enough to be used as the only treatment. Pain relief can actually be almost insignificant, it can be more important that the agents enable patients to be more active in the other parts of their treatment. That is why non-invasive treatment approaches as well as physical therapy and psychosocial support have to be a part of first line management of phantom limb pain. Unfortunately, none of the specific treatments that belong to these treatment groups show significantly better results in comparison with others, so there is no clear guideline on which one to choose for a particular patient. That decision should be made individually for each patient taking into account their history, symptoms and preferences, as well as resources available. It is becoming increasingly accepted that clinically significant cortical reorganisation is associated with continuing chronic phantom limb pain. To prevent chronic pain, treatment has to eliminate the painful stimuli and restore normal input to the cortical zone of amputation. Central, peripheral and psychological factors can all have a role in causing the pain, which is why it is important to detect which of these factors is dominant in a specific patient, so treatment can be focused on it. Invasive treatment approaches should only be used as a last resort, as there are serious risks involved, and their efficacy is often not sufficient to justify the risk.

CONCLUSION

Studies dealing with phantom limb pain have been unable to account for the exact mechanism responsible for the production of pain. That is the reason why treatment approaches are so numerous, and results few and far apart. This is most probably due to the fact that there are complex multifactorial drivers behind the sensation of pain in phantom limb pain. However, it is becoming clear that cortical reorganisation plays a key role in phantom limb pain and preventing it might be the solution to the management of phantom limb pain. This requires multidisciplinary approach and individualized treatment plans, with regard to the number of different treatments available. Sadly with their efficacy still unreliable, there are as of yet no clear guidelines for treatment and management of phantom limb pain. Although some of the approaches available show promise in small clinical trials, there are still not enough large trials to clearly differentiate between treatment options and single out the optimal approach, if this is even possible for this condition where multiple elements are at play. It is important to remember that different factors can be dominant in producing painful stimuli in specific patients, which is why therapy should be based on individual needs of each patient with this condition.
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Sažetak

Liječenje fantomske boli još uvijek nema jasno definiran smjer, ali istraživanja o toj temi otkrivaju različite pristupe koji obećavaju. Mehanizam nastanka fantomske boli nakon amputacije još uvijek je nejasan, iako je poznato da su mnogobrojni faktori uključeni. Periferna, spinalna i supraspinalna razina živčanog sustava igraju ulogu u izazivanju bolnog osjeta. Terapijski pristup primarno uključuje farmakološku terapiju i neinvazivne metode, ali postoji nekoliko invazivnih terapijskih metoda koje su dostupne ukoliko ostale ne postignu uspjeh. Iako ne postoje konkretno smjernice, dostupni terapijski pristupi nude široku paletu mogućnosti za liječenje fantomske boli. Bitno je imati na umu da različiti faktori mogu biti dominantni u stvaranju bolnih podražaja kod svakog pojedinog pacijenta. Ove činjenice zahtijevaju individualizirani pristup pacijentu uz obraćanje pažnje na anamnesu, simptome i želje pacijenta.

Ključne riječi: fantomska bol, kronična bol, liječenje boli, refraktorna bol