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Phantom Limb Pain

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ABSTRACT
Amputation is often causing chronic postoperative pain with an incidence of 85%. Phantom limb pain or PLP is one of the post-amputation phenomena characterized by pain in the limb that has been removed, including the amputation. Neuropathic pain occurs due to hyperexcitability of damaged nerves and other functional nerves around them, causing changes in neuroma sensitivity, decreased potassium channel expression, and increased voltage-gate of sodium channel (VGSC) activity. VGSC buildup triggers cell membrane hyperexcitability, becomes an ectopic initiator of pain, and causes central and peripheral sensitization. Neuromas in the stump respond more to stimuli because they are sensitive to cytokines and amines, causes the massive process of nociceptive impulses and resulting in pain. Neural plasticity allows the nervous system to compensate for the damage after amputation, the brain undergoes a somatotopic map adjustment due to missing limbs. Plasticity is the brain's response to pain that causes the increase of pain signal transmission in the spinal cord. This is known as central sensitization and causes hyperalgesia and allodynia. The plasticity of nerve damage leads to ectopic discharge, it leads to spontaneous pain in the area innervated by the damaged nerve or the nerves surrounding the damaged nerve. Plasticity is the brain's response to pain that causes the transmission of pain signals in the spinal cord to increase. This mechanism is known as central sensitization, which causes hyperalgesia and allodynia. The plasticity of nerve damage leads to ectopic discharge, which can lead to spontaneous pain in the area innervated by the damaged nerve or the nerves surrounding the damaged nerve.

Key Words: phantom limb pain, neurology, physiology

1. INTRODUCTION

Amputation is one type of surgery that most often causes postoperative chronic pain with an incidence of up to 85%. Postoperative chronic pain has an impact on the onset of mental health problems and significantly decreases the quality of life (Torrance et al, 2014). Most of the post-amputation patients report limb pain with mild intensity and rarely complain of severe pain **(Nikolajsen et al, 2013).**
After a person has undergone an amputation, a condition called the post-amputation phenomenon can occur. Phantom limb pain or PLP is one of three components in this post-amputation phenomenon, occurs in almost all post-amputation patients and is characterized

by pain in the leg that has been removed during the amputation procedure. Another component in this phenomenon is phantom limb sensation, which is a sensation other than the pain in the limb that has been lost, this complaint can exacerbate PLP **(Abd-Elsayed et al, 2019)**, but will usually decrease over time after amputation; and pain in the remaining limb (stump), this occurs only in 5-10% of amputated patients **(Nikolajsen et al, 2001)**.

Pain in the stump is caused by the surgical wound that triggers an inflammatory response, thus inhibiting the nociceptive stimulus. Impulses that pass through the nociceptive receptors will be sent to the spinal cord after transduction in the primary aδ-fiber and c-fiber primary afferents.

Primary afferent neurons synapse with secondary afferent neurons in the dorsal horn of the spinal cord and are transmitted to the central nervous system, namely the cerebral cortex and other higher centers through contralateral spinothalamic and spinoreticularis pathways **(Dubin et al, 2010)**. These impulses are processed by the center with a complex mechanism and interpreted as pain **(Garland et al, 2012)**.

The wound initiates the release of inflammatory mediators, includes cytokines, bradykinin, and prostaglandins, and causes the patient to feel nociceptive pain. To promote wound healing, peripheral sensitization regulation will raise the pain threshold. As the wound heals, the inflammatory mediators stop being released and the pain sensitization disappears.

The central nervous system also experiences plasticity in response to pain which increases the transmission of pain signals in the spinal cord. This plasticity increases the excitability of neurons in the central nervous system. This mechanism is known as central sensitization. Clinically, this causes the increase of pain response to nociceptive stimuli (hyperalgesia) and pain arising with non-nociceptive stimuli (allodynia) **(Coderre et al, 1993)**.

Phantom limb pain occurs in the absence of nociception and nociceptors. Both the central nervous system and the peripheral nervous system are known to be involved in the occurrence of PLP **(Flor, 2002)**. Hill et al and Sherman et al stated that although psychological factors are not directly involved in PLP, they can exacerbate the intensity of the pain **(Hill, 1999; Sherman et al, 1987)**.

PLP is felt by 60-80% of patients after undergoing the amputation procedure **(Bekrater-Bodmann et al., 2015; Ephraim et al., 2005; Kern et al., 2009)**. In addition to physical changes, PLP also occurs due to disintegration and tension in other body parts and stumps. As many as 20% of post-amputation patients complained of secondary pain felt in the residual limb and other areas such as the shoulders, neck, and upper back with severe pain intensity **(Hanley et al., 2009; Ostlie et al., 2011)**.

Various studies have shown risk factors that increase the incidence of PLP, includes the psychological state when a person experiences stress, the presence of pain in the stump, traumatic amputation, and amputation of the upper limb. Besides, studies have shown that older children experience PLP more frequently **(Krane et al. 1995; Wilkins et al. 1998)**. Other studies by Flor et al showed that female patients experience PLP more frequently than men (Flor et al, 2002).

The presence of pain that is felt before amputation also increases the incidence of PLP **(Ephraim et al., 2005; Bosmans et al., 2010; Davidson et al., 2010; Desmon et al. 2010)**. Patients who had pain since before amputation had a higher incidence of PLP **(Hall et al, 2017)**. A study by Redrobe et al showed 72% of 58 patients with pain before amputation had PLP for 8 days. However, PLP complaints disappeared with time, only 58% of patients still complained of PLP up to 2 years after amputation **(Redrobe et al., 1998)**.

PLP occurs rapidly after amputation **(Jensen et al, 1983)**, and in most amputees, PLP becomes chronic with great variability in intensity, frequency, and quality **(Jensen et al., 1983; Desmond et al., 2010)**. PLP causes personal suffering, reduces the quality of life, and disrupts sleep **(Kern et al., 2009).**

2. DISCUSSION

After the amputation, there will be re-regulation of the motor and sensory cortex systems. A consequence of this complication is phantom limb pain **(Montoya et al, 1998)**. That is a condition in which a person feels pain in a limb that is no longer, for example, because it has been amputated **(Jensen et al., 1985)**. Although it usually occurs in the early post-amputation phase, this can last a long time **(Sherman, 1989).** Phantom pain arises from dendrite stimulation that is heavier than usual receptor stimulation, causes the person to feel pain in the area that has been removed.

The sensory stimulus in the former amputation is sent to the motor regulation center and causes an interpretation of the movement sensation. A study by Mitchell e al tried to provide electrical stimulation at the stump, the results showed that patients can feel the finger's movement sensation even though it has been removed **(Mitchell, 1871).** Stimulation in the form of vibration and touch in the area around the amputated region or parts of the body with nerves damaged by amputation causing pain. This is indicated by the Tinel sign, which is a condition of a mechanical stimulus to a damaged nerve or a neuroma in the stump interprets as pain **(Nikolajsen et al, 2005).**

Hughling Jackson's research showed that phantom pain often occurs in the legs, both upper and lower, in patients who know that they have lost a limb **(Baloh, 2021)**. Phantom pain occurs most often after a person loses a limb, therefore it is called phantom limb pain. Phantom pain can also occur in other areas of the body, for example, the eyes, nose, tongue, teeth, breasts. In a study by Jensen et al and Katz et al, the pain that felt due to PLP was the same as pain before amputation **(Jensen et al, 1985; Katz et al, 1990)**.

PLP is classified as neuropathic pain due to damage peripheral nervous system damage. Unlike pain caused by direct trauma to the limb, phantom pain is caused by a combination of pain signal transmission from the brain or spinal cord problems. Even though the limb has been removed, the nerve endings at the location of the stump end continue to send pain signals to the brain that make the brain think the limb is still there. Sometimes, the brain's memory of pain is maintained and interpreted as real pain, even though the signal comes from the injured nerve. The somatosensory cortex is an area of the brain that stores somatotopic map data, the center for storing all kinds of information about the part of the body that is responsible for our sense of touch.

It is well known that phantom limb pain is neuropathic pain due to the hyperexcitability of damaged nerves and other functional nerves around them **(Gold et al., 2003).** This damaged part of the nerve is overexcited and causes inappropriate conditions, includes changes in neuroma sensitivity to temperature, decreased potassium channel expression, and increased voltage-gate of sodium channel activity **(Devor, 2006; Gorodetskaya et al, 2003)**. VGSC is a transmembrane protein that acts to initiate action potentials and conduct nerve impulses, is also involved in regulating the dynamic excitability of nerve cells. The abnormal VGSC condition affects the quality of nerve excitability **(Persson, 2009; Krafte et al., 2006; Catterall et al., 2005; Gold et al., 2003).**

Peripheral nerve damage due to amputation causes retrograde degeneration of axotomy afferent neurons **(Janig et al., 1984)**, and the formation of action potentials from outside the nociceptive system, called ectopic discharge. As previously explained, damaged peripheral and/or central nerve fibers trigger VGSC accumulation and cell membrane hyperexcitability. This condition becomes an ectopic initiator in the process of pain that can occur continuously and cause central and peripheral sensitization **(Baron, 2009; Decosterd and Berta, 2009; Ossipov and Porreca, 2009; McMahon et al, 2004; Meliala & Barus, 2003)**.

At the end of the stump or the end of the nerve fibers from the remaining organs of the amputation will grow new shoots (sprouting) that reach the target organ. New shoots that do

not reach the target organs will form neuromas, to be a site of VGSC and other ion channel accumulation that is also found in the dorsal root ganglion lesion area (GRD). Ectopic activity is found in neuroma and DRG after nerve injury occurs. Neuromas respond more strongly to stimuli **(Fried et al, 1991)** because they are sensitive to cytokines and amines so that nociceptive impulses are processed massively causing the patient feels pain **(Devor, 2005)**. It also causes the afferent impulses that form from the neuroma and send to the spinal cord to be excessive and the pain response to be abnormal **(Wall et al., 1974)**. The C-fiber sends impulses irregularly and slowly, whereas myelinated axons impulses are delivered faster **(Devor, 2005)**.

The steps of electrical impulses formation in the nervous system is called electrogenesis. The part of the nerve that is affected and the GRD are the site of this process. Electrogenesis consists of two phases: the formation of a depolarization generator, and its translation into nerve impulses that are ready to be delivered **(Devor, 2009).**

Tang et al in their journal said that adult human neurons can plasticize which is a form of nervous system adaptation, this makes nervous structures can dynamically modulate by forming white matter and gray matter **(Tang et al., 2012)**. A research by Klein et al showed that this ability of plasticity allows the nervous system to compensate for the neural damage, where nerves that are damaged and do not function normally are supported by other healthy and well-functioning nerve cells, and new axon innervation pathways will be formed **(Klein et al., 2015)**. This mechanism also occurs in post-amputation patients according to the Penfield map **(Ramchandran et al, 1992)**. After the amputation, the brain undergoes a somatotopic map adjustment due to a missing limb. For example, the facial somatosensory cortex will support an amputated upper limb somatosensory cortex. The brain's perception of these limbs will not disappear and can be brought back to the surface. This happens by reconnecting the neural circuits that no longer receive stimulation from the amputated part of the body. This brain response is thought to cause phantom stimulation that is considered real by the body.

The study of 17 patients who had undergone a right lower leg amputation showed that the premotor cortex of the left temporal lobe was thinning. Whereas in the white matter of the right superior corona radiata in the right temporal lobe, left PMC, and right fronto-occipital inferior fasciculus there was a decrease in fractional anisotropy. This finding was absent in 18 other healthy study subjects **(Jiang et al., 2015)**.

Neural sensitization can occur with changes in the synaptic response in the dorsal horn of the spinal cord due to increased activity of peripheral nociceptors in inflammatory pain **(Woolf et al, 2005)**. Amputation causes excessive central excitation due to nerve damage. And plasticity is a response to pain that causes the increase of pain signals transmission in the spinal cord. This mechanism is known as central sensitization.

Clinically, this results in increased pain response to nociceptive stimuli (hyperalgesia) and pain arising with non-nociceptive stimuli (allodynia) **(Coderre et al., 1993)**. Besides, wind-ups, long-term potentiation, and secondary hyperalgesia are also associated with central sensitization. Wind-up occurs as a result of repeated c-fiber activation of NMDA receptor activation. NMDA receptors become active due to the presence of nociceptive stimuli, which prevents the receptors from being inhibited by magnesium ions. This causes amplification of the secondary afferent neuron's response to pain and the response of secondary afferent neurons be lasts longer which is called long-term potentiation. Long-term potentiation has a role in the development of hyperalgesia outside the area of inflammation, it is known as secondary hyperalgesia **(Ikeda et al, 2003; Schaible, 2007).**

Nerve damage also plays a role in postoperative chronic pain. The plasticity of nerve damage leads to ectopic discharge, which can lead to spontaneous pain in the area innervated by the damaged nerve or the nerves around the damaged nerve **(Schaible, 2007; Devor, 2009)**. This

causes an increase in nociceptive input to the dorsal horn of the spinal cord which results in central sensitization **(Schaible, 2007; Bird et al, 2016).**

3. CONCLUSION

PLP is a neuropathic pain that occurs without nociception and nociceptors. The hyperexcitability of damaged nerves and other nerves around them that are still functioning properly causes changes in neuroma sensitivity to temperature, decreased potassium channel expression, and increased VGSC that triggers cell membrane hyperexcitability, initiate central and peripheral sensitization, and causes pain. The plasticity of nerve damage also leads to ectopic discharge which triggers spontaneous pain in the area innervated by the damaged nerve or the nerves surrounding the damaged nerve.

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