REVIEW ARTICLE

Pain Management after Amputation of Lower Limb

Manjaree Mishra[1], Vivek K. Katiyar[2], Sumit Sharma[2], Ram N. Meena[2], Rahul Khanna[2], Shashi P. Mishra[2*]

[1]*Department of Anesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttra Pradesh, India.*
[2]*Department of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttra Pradesh, India.*

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ABSTRACT

Pain remains a very important issue that needs to be addressed after amputation of the lower limb. There are may pharmacological agents available and many procedures which can be used to give pain relief to these patients but with varying degree of acceptability and success.

The current review article discusses about the challenges related to the management of pain after amputation of lower limb and recent trends in this field.

Keywords: Trauma, Amputation, Pain, Limb

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INTRODUCTION

There are several different conditions that can necessitate lower limb amputation (LLA), including trauma and disease.[1,2] There are many different outcomes from lower limb amputation (LLA). Compared to population norms, amputation usually negatively affects physical function, physical role performance, social function, vitality, overall health, and pain levels.[3] Following lower limb amputation, daily competence tends to decline with age for both sexes, but men often have better physical function than women.[3] Additionally, patients who have high anatomical levels, dementia, or who were homebound and ambulatory prior to surgery are less likely to be able to live independently in their homes after amputation.[4]

Postoperative persistent pain and non-painful sensations that originate from tissue trauma, nerve injury, and other variables are experienced by patients who have had limbs amputated. A secondary condition known as post-amputation pain, persistent pain associated with amputation is a painful condition. The presence of pre-amputation pain has been acknowledged as a risk factor in the emergence of amputee pain,[5] and it is gradually becoming acknowledged that the condition is multifaceted. Both Phantom pain and residual limb pain, commonly known as Stump Agony, are the effects of post-amputation pain. Phantom pain is frequently defined as pain that originates in the body part that is absent and is felt as a stabbing, throbbing, scorching, or cramping form of pain. Physical elements like pressure changes and changing weather can make phantom pain worse, as can psychological factors like emotional stress.[6] After surgery, the "phantom limb" is claimed to resemble the amputated limb in terms of size and shape. The phenomenon known as telescoping is the steady decrease in phantom size over time and its restriction to the residual limb, leaving just the foot, hand, or digits on the stump.[7] In contrast, residual limb pain affects the part of the body that is still there and is felt in the distal residual section. Along with the pain, individuals occasionally report itching, tingling, or cramping.

HISTORY

Ambroise Paré, a surgeon, enlisted in the French army in 1536. He rose to prominence as a surgical pioneer, particularly in amputation.[8] In the middle of the sixteenth century, gangrene would develop in serious bullet wounds. Amputation was required as a result. The most popular technique to halt the bleeding was cauterizing the wound, but Paré sought quicker, less painful solutions. Paré was the first to write about amputee troops who were still aware of their lost limb during his tenure as a military surgeon.[9]

The nervous system of the human body was a monograph written by Charles Bell that was released in 1830. This monograph is the first to describe a variety of neurological conditions. Bell defines an amputee who still experiences pain from a missing limb and the sensation of motion in it. Bell proposes that "muscular sensation," a term he had already created, is the cause of this phantom limb.[10] The descriptions

**Author for Correspondence: spmishra.gs@bhu.ac.in*

of phantom limbs by Magendie (1833), Rhone (1842), and Gueniot (1862) were also in-depth.[11]

The Atlantic Monthly featured an article written by Civil War surgeon Silas Weir Mitchell in 1866. The name "phantom" was first applied by him to these sensations, which he discusses in "The Case of George Dedlow".[9]

Amputations suffered during World Wars I, II, the Vietnam War, and the Israeli War led to reports of this suffering lasting into the current era.[12-14] The investigation of additional causes of amputation, such as peripheral vascular disease (often brought on by arteriosclerosis and neoplasms, either benign or malignant growths), continued.[11] At the time, early study indicated that 4% of people experienced phantom limb discomfort, which was thought to affect a limited fraction of people.[15] The fact that later research has discovered a greater percentage for the instances of pain is most likely due to the fact that at the time, phantom limb pain was measured by whether a patient requested pain medicine or not.[11]

Post-amputation Pain Mechanism

The brain, spinal cord, and peripheral nerve systems are thought to interact to generate post-amputation pain, although the exact mechanisms by which this occurs appear to be complex and yet little understood.

Physiological Mechanisms

It is well-known that after amputation, the nerve fibre axons become injured and then regenerate as a disordered lump termed a neuroma in the remaining limb. The nerve terminals of demyelinated A fibres and nociceptive C fibres, which exhibit greater rates of spontaneous activity, are larger and disordered in the neuromas.[16] Although neuromas may operate as "pain generators" in about 30% of cases, the aberrant discharges are known to produce post-amputation discomfort.[6,17] According to Burchiel and Russell 18, the neuromas often do not become painful on their own, but mechanical (such as pressure) or chemical stimulation can speed up their ectopic discharges by upregulating the expression of sodium channels.[19,20] Even harmless stimuli like pressure or a temperature change might increase neuroma discharges, making them seem painful. The fact that administering a local anesthetic injection into a stump neuroma can momentarily alleviate both phantom and stump pain in some patients, if not all, supports it further.[16]

Apoptosis of GABA and glycine-expressing interneurons occurs as a result of aberrant increase in excitatory input at the dorsal horn as a result of nerve injury, which removes inhibition on the nociceptive pain signals and causes post-amputation pain.[16] When nerves are severed due to amputation, there is a considerable increase in ectopic discharge from the dorsal root ganglion (DRG) neurons, which mostly causes persistent pain.[21] Because of nerve damage, brain derived neurotrophic factor (BDNF) is released from DRG neurons, which switches inhibitory interneurons into excitatory nociceptive interneurons and encourages the release of pain-signaling neurotransmitters like glutamate.[16]

Etiology

Variable rates of lower limb amputation (LLA) are caused by diabetic complications, including neuropathic foot and ischemic foot, peripheral vascular disease (PVD), trauma, infection, malignancy, and congenital lower limb defects.[1,2,22] Lower limb amputation may be required due to cellulitis, sepsis, rhabdomyolysis, and burns.[23] The following conditions increase the risk of lower limb amputation: hypertension, coronary artery disease, smoking, and end-stage renal disease.[24] According to the Global LEA study from 2000, less than 10% of major lower limb amputations in men are due to trauma. Lower limb amputation is more common in people with high systolic (135-221), high diastolic (86-117), high pulse (53-125), severe retinopathy, and high pack-years smoked (more than or equivalent to 15).[25]

Over 80% of seniors who are retired, 5% who are jobless, and 2% who are employed have non-traumatic LLA.[26] A high incidence of LLA is linked to low income, being single (whether divorced, widowed, or never married), having a history of foot ulcers, and having both diabetes and cardiovascular disease.[27] The most common cause of LLA is diabetes, while trauma only causes a small percentage of cases. Trauma is the primary contributor of LLA in various regions of other nations where there is conflict and violence.[27]

Prevalence and Incidence

According to the amputee Coalition of America, the number of amputees in the US was estimated to be 1.7 million in 2007. This number is predicted to increase to 1.8 million in 2010 and 2.2 million in 2020.

In a research, 95% of the 914 individuals with limb loss who were questioned reported experiencing post-amputation pain. Approximately 70% of amputees reported having residual limb pain, compared to 80% of all patients who reported having phantom pain. While a comparable amount (60%) of patients with residual limb pain indicated moderate to severe pain, 65% of patients with phantom pain considered their suffering moderate to severe intensity. In patients who had an amputation during the previous two years and those who had undergone an amputation for more than ten years, phantom pain prevalence ranged from 73 to 82%. For the same amount of time since amputation, the range of amputees with residual limb discomfort was 65 to 75%. Additionally, the discomfort was experienced by the amputee regardless of their age or gender.[28]

In research on amputees with upper-limb amputations, 90% of those surveyed reported experiencing pain, with 76% describing multiple types of pain. Phantom and residual limb pain were reported by 79% and 71% of all amputees in the study. 45% of amputees with phantom limb pain were found to have moderate to severe pain, whereas 35% of those with residual limb pain had moderate to severe pain.[29] In a study of patients who underwent lower limb amputations, 79% of amputees reported having phantom feelings, whereas 72% of amputees reported having phantom pain, and 74% of those

assessed reported having pain in the residual limb. Patients with residual limb pain reported it to be severe in severity in 38% of cases and patients with phantom pain in about 30% of cases.[30]

It is known that phantom limb pain can start in an amputee as soon as one week after the amputation or even 40 years afterwards.[31] A study conducted in Denmark on 58 patients who underwent amputation indicated a drop in the prevalence rate of phantom pain from 72 to 59% at 2 years following the amputation, according to certain reports.[32] In a different poll of 590 British soldiers who had long-standing amputations, phantom pain was experienced by 55% of participants while residual limb discomfort was recorded by 56%.[33]

Need Assessment

A problem that requires attention is chronic pain brought on by amputation. Despite the availability of a wide range of treatments, amputee pain patients frequently experience chronic pain that is challenging to cure. Pharmacological and electrical stimulation techniques are frequently used to treat phantom and stump pain, however they are not always effective in considerably reducing pain. The current treatment options are ineffective, have drawbacks, and increase the chance of addiction. A limb loss patient's quality of life is negatively impacted by a number of issues in addition to the pain, such as unemployment, disability, rage, frustration, and depression. Effective medicines to adequately control post-amputation pain are still greatly needed and unmet. Due to such problems, it is even more crucial to create and sell newer technologies and solutions that can supply this area's unmet need.

Treatments

There are numerous ways to address post-amputation pain, but none of them appear to be targeted and efficient. Antidepressants, anticonvulsants, opioid and non-opioid analgesics, NMDA blockers, neural blockade, transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), and behavioral studies are all alternatives for treating this pain condition. While some clinical studies have shown that certain therapy strategies successfully reduce pain significantly, other clinical investigations have concluded that they are not.

Opioids

Opioids are administered for a number of chronic pain syndromes, including phantom limb pain, for this reason. Opioids have been discovered to be a successful remedy for treating the symptoms of phantom limb pain.[34] Opioids can effectively relieve moderate to severe post-amputation pain, but if they are administered before to surgery to manage chronic amputation pain, their postoperative intake increases.[35,36] Studies that advocate spinal opioid infusion to lessen post-amputation pain have conflicting findings and do not support its long-term benefit.[37] Despite their usefulness, they are challenging to manage because to the danger of addiction and major side effects include nausea, vomiting, hallucinations, drowsiness, headaches, and insomnia.

NMDA Receptor Antagonist

Oral NMDA receptor antagonists have shown to be useless in clinical trials, although showing promise in animal investigations.[38] Ketamine administered intravenously has been demonstrated in studies to be somewhat beneficial in lowering amputation pain just after surgery, but the outcomes from controlled trials are mixed.[39,40] Although it is known that ketamine treatment raises pressure-pain thresholds, heat sensitivity has not been affected.[41] Calcitonin therapy may reduce pain after surgery but is ineffective for persistent post-amputation pain issues.[42] Using the NMDA receptor antagonist Memantine to treat phantom limb pain also had ineffective results.[43]

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

After opioids and acetaminophen, NSAIDs are the drugs that are most frequently used to treat phantom limb pain.[44] NSAIDs typically function as nonselective inhibitors of the COX enzyme.[45] A neurotransmitter that conveys pain, prostaglandins, are typically made by COX. In a poll of people who had lower limb amputations, more than 20% of those who responded said they took NSAIDs to relieve their phantom limb discomfort.[44] Despite their frequent use, little study has been done on the effectiveness of treating both acetaminophen and NSAIDs. In the same study, more over half of the participants who used NSAIDs gave the medication a 1 or a 2 on a scale of 1 to 5, indicating that it provided only marginal pain relief.[44] NSAIDs function by blocking the enzymes required for the synthesis of prostaglandin, a neurotransmitter that amplifies pain. Acetaminophen is reportedly just as effective as NSAIDs.[44] Although the precise mechanism of action of acetaminophen is unknown, it is thought to be a mild inhibitor of prostaglandins (like NSAIDs), but with a distinct mechanism of action.[46] Although acetaminophen and NSAIDs are frequently administered, there is little evidence on their efficacy in treating phantom limb pain beyond self-report data.

Antidepressants

Only a small number of controlled trials have demonstrated the effectiveness of tricyclic antidepressants (TCA), despite the fact that they constitute the first line of treatment for post-amputation pain.[35,47,48] TCAs are also favored because to the added antidepressant effects that may be advantageous given that many amputees (35–50%) experience depression despite the fact that the dose for pain management (100 mg/day) is lower than the antidepressant dose.[38,49] Although secondary amine TCAs like desipramine and nortriptyline are more tolerable than tertiary amine TCAs like amitriptyline and are as efficacious, many patients may find them to be intolerable 50. These drugs frequently have dose-dependent side effects such urine retention, drowsiness, dry mouth, and constipation. TCAs are not advised due to an increased risk of sudden cardiac death because many amputees are at risk of developing coronary illnesses or have already had peripheral arterial disease.[51] More trials are necessary to demonstrate the effectiveness of TCAs since there have been too few well-controlled studies

conducted and because a trial that failed to identify any value of antidepressants in the treatment of post-amputation pain.[52]

Antiepileptic Drugs

According to Flor *et al.*,[53] anticonvulsants like gabapentin do not significantly enhance depression, life satisfaction, or functionality. They also do not significantly reduce phantom pain or residual limb discomfort. Even when gabapentin successfully reduces pain, there are no appreciable changes in mood, sleep disruption, or everyday activity.[54] Carbamazepine taken orally is helpful at reducing shock-like pain but has no effect on other aspects of post-amputation pain.[55]

Mirror Therapy

Mirror therapy is a less invasive therapeutic approach that has shown potential in reducing pain from phantom limbs. Mirror box therapy, commonly referred to as mirror therapy or virtual reality box therapy, was developed in the 1990s by Vilayanur S. Ramachandran.[56] Amputations of the upper and lower limbs can both benefit from mirror treatment. Mirror treatment has been demonstrated to be useful for patients with Parkinson's disease and stroke in addition to those who experience phantom limb pain.[57,58] Pain from phantom limbs can be effectively treated with mirror treatment.[59] Mirror treatment has been demonstrated to lessen the discomfort's duration and intensity.[60,61] The pain reduction was demonstrated to last throughout the treatment, in contrast to some prior treatments.[61] A variety of external factors can influence the outcome of the treatment; for example, it appears that treatment works best for those who do not wear a prosthesis.[62] Additionally, it appears that the therapy works best for people whose phantom limb pain is being relieved by distorted views of it.[62] The patient will experience a distortional vision of the phantom limb, which will make them feel as though their limb is twisted unnaturally, such as backward or deformed. It should be mentioned that mirror treatment has certain negative effects, such as a hazy feeling of psychological annoyance and confusion.[63] It is challenging to comprehend the system's complete involvement in mirror treatment because the mirror neuron system is little known and was just recently identified.

Neural Blockade

For the treatment of post-amputation pain, various neural blockades have been used, such as sympathetic blocks, stump injections, peripheral nerve blocks, epidural and subarachnoid blocks, but only a small percentage of patients (14%) experience a significant temporary change, and even fewer experience a significant prolonged change (5% patients).[64] Although there are no set inclusion criteria for their usage, neural blockades may be beneficial if used right after surgery.[65,66]

Surgical Intervention

It is challenging to treat post-amputation pain surgically, and this involves removing neuromas that form at the severed ends of peripheral nerves after surgery. An amputee may get some pain relief following surgery but not total pain relief.[67] The cut nerve ends continue to grow back to generate new neuromas and cause pain even after the neuroma has been removed.[68] In order to reduce phantom limb pain, procedures like anterolateral cordotomy and dorsal root entry zone (DREZ) to induce lesions (to block pain signals) have been tried. However, any significance of these procedures will need to be supported by large multicenter studies because they also carry risks of significant morbidity and mortality.[16]

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is a portable, low-cost, safe gadget that produces electric currents that travel through the skin and stimulate underlying nerves. People with chronic pain can get temporary relief with TENS, a treatment technology. In comparison to other phantom limb pain therapies such pharmaceutical interventions, there are just modest adverse effects. TENS devices use an electrical current to stimulate or excite sensory nerves. In doing so, the device triggers the body's own pain-relieving systems. The pain gate mechanism and the endogenous opioid system are thought to be the two naturally occurring systems that TENS units target. It is unclear how the stimulation's ideal pain-relieving characteristics relate to its frequency, intensity, and the systems it interacts with.[69] TENS has been discovered to be a successful method of treating stump pain.[70] The same study demonstrated that the right electrode location could induce TENS feelings in the missing limb, which reduced its discomfort.[70]. TENS has also been proven to be a successful painkiller for people with phantom limb pain, according to study.[71] However, it should be emphasized that TENS therapy does not reduce pain over the long term. To determine if TENS is useful for or against treating chronic pain, multicenter RCTs must be conducted because the long-term efficacy of TENS for pain alleviation is unknown.[72] Patients frequently stop using it over time because to its external system, cords, and disruption of daily routines.

Spinal Cord Stimulation (SCS)

Spinal cord stimulation and injections are examples of less invasive therapies for phantom limb discomfort. Through surgery, a spinal cord stimulator is attached to the spinal cord and a wire transmits a modest electrical current to the spinal cord.[73] In the dorsal epidural space, electrodes are inserted. This area is found below the vertebral bone and above the spinal cord's dura. The spinal cord's surrounding fibres are stimulated when the gadget is turned on, which causes the pain to be felt there to be felt there. Although the exact process of spinal cord stimulation is unknown, it is hypothesized that it either modifies the chemical transmission of the spinal cord's dorsal root or activates dorsal column nuclei.[74] There are conflicting findings about spinal cord stimulation and phantom limb pain.[75,76] Although patients initially experienced pain alleviation with the device's placement, the improvement was less significant one and two years later.[75] Infection at the surgical site and allergic dermatitis to the generator were among the side effects observed in individuals with phantom

limbs after the spinal cord stimulator was implanted.[76] Because both of these studies had limited sample sizes, more research is required to determine whether this medication should be given to patients who are experiencing pain from phantom limbs.

Invasive Treatment

Deep brain stimulation and stump repair are invasive treatments for pain from phantom limbs. These operations are time-consuming and may have a variety of negative side effects.

Stump Revision Therapy

Stump revision therapy is typically used to aid prosthesis fitting and/or neuroma treatment.[77] A prosthesis may require a stump revision if skin scarring, the form of the bone(s), or persistent ulcers prevent the prosthesis from fitting properly. A neuroma, on the other hand, is a benign growth of nervous system tissue that develops as a result of irritation or damage (amputation in this case). Generally speaking, neuromas are painful no matter where they are. While neuromas can be uncomfortable, they are not the primary cause of pain in the stump, and phantom limb discomfort can happen whether or not there is a neuroma.[78] Typically, stump modification is not done only to alleviate phantom limb pain. Because the success rate for stump revision is quite poor when there is no known source of the pain (which is commonly stump pain), it is not usually done simply for phantom limb discomfort.[77] Any procedure carries the possibility of complications like infection. These factors account for the paucity of studies on the impact of stump revision on phantom limb discomfort.

Deep Brain Stimulation

Electrodes are inserted deep inside the brain during deep brain stimulation. These electrodes target specific cells to cause the release of particular neurotransmitters, or they regulate aberrant activity (much like a pacemaker) by delivering an electrical stimulus to specified regions of the brain.[79] Parkinson's disease, Tourette syndrome, and chronic pain are among the neurological illnesses that are treated using deep brain stimulation.[79-81] Deep brain stimulation is effective when previous treatments, such as drugs and other more conservative techniques, have failed to cure chronic pain.[82] Deep brain stimulation in the periventricular grey matter and the somatosensory thalamus, in particular, has demonstrated up to a 60% reduction of the pain while studying phantom limb discomfort.[83,84] These studies' modest sample sizes, like those of other therapies for phantom limb pain, call for more investigation. Having said that, the success of deep brain stimulation in treating generalized chronic pain and in these tiny phantom limb investigations shows its potential.

As was mentioned, invasive techniques have a higher risk than more cautious ones. Deep brain stimulation may be viewed as a potential treatment while stump revision surgery appears ineffective in the cure of phantom limb pain (but effective for residual stump discomfort). Particularly when a more conservative course of action has failed.

Affect on Patient's Quality of Life

Pain from an amputation can impair a patient's functional potential and have physical and mental effects. When compared to the general population, amputees experience clinical depression 3 to 5 times more frequently, and depressed mood and depression after amputation are more common, with prevalence rates ranging from 35 to 51.4%.[49] Poor psychological health after limb loss in such patients has been expected to be caused by limited exercise, age, and time since amputation. It is typically the pain after amputation rather than the loss of a limb that has the greatest influence on daily activities, limits completion of simple tasks, and negatively correlates with return to employment among amputees with moderate to severe post-amputation pain.[85,86] According to reports, amputees with chronic pain are more impaired than those who don't.[87]

Economic Burden on Society

The average annual cost of pain and depression medications for someone with post-amputation discomfort can surpass $3,000, and the average annual cost of a pain management center's treatment plan is over $6,000 per year. In the United States, it is anticipated that treating severe phantom and stump pain will cost over $1.4 billion in drug costs and over $2.7 billion in pain centre treatment programs each year. When all expenses for pain treatment, including doctor and emergency room visits, hospital stays, radiography, nerve blocks, and other surgical procedures, are taken into account, the cost per patient might approach $30,000 annually, costing the US over $13 billion to treat amputees with severe pain.[88,89]

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