"EFFECT OF INTRATHECAL KETAMINE IN PREVENTION OF PHANTOM LIMB PAIN FOLLOWING LOWER EXTREMITY AMPUTATION SURGERIES: A RANDOMIZED CLINICAL TRAIL."

By

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ABBREVATIONS

PLP- Phantom limb pain

SP- Stump pain

PLS- Phantom limb sensation

CVS- Cardiovascular system

CNS- Central nervous system

PNS- Peripheral nervous system

NMDA- N-methyl-D-Aspartate

ASA- American Society of Anaesthesiologists

EEG- Electroencephalogram

IV- Intravascular

IM-Intramuscular

RCT- Randomized clinical trail

NRS- Numeric Rating Scale

HR- Heart Rate

BP- Blood Pressure

RR- Respiratory Rate

SpO2- Arterial oxygen saturation

MW- Mann Whitney U test

C *- Chi square test

M- Mean

Mdn- Median

SD- Standard Deviation

LT/RT- Left/Right

AKA/BKA- Above knee amputation/ below knee amputation

FFA- Forefoot amputation

ABSTRACT

Background and objectives

Phantom limb pain is a common complication seen after extremity amputation. It is a chronic neuropathic pain syndrome where individuals experience pain in an amputated limb, even though the limb is no longer physically present. PLP is a common condition after limb amputation, with 60-80% incidence rate in who had a limb amputation. Various studies and literatures shown NMDA receptor antagonist, Ketamine has been effective against phantom limb pain. Ketamine offers enhanced pain relief, if it is administered as continuous epidural infusion in immediate post operative period. But pre-emptive intrathecal ketamine uses & its efficacy for preventing phantom limb pain in this context has not been studied previously. Henceforth, this study aimed to assess the effectiveness of pre-emptive intrathecal ketamine in prevention of phantom limb sensation and pain.

Methodology

We conducted a randomized clinical trial to assess the efficacy of pre-emptively administered intrathecal ketamine in prevention of phantom limb pain in extremity amputation surgeries. This study was conducted in 70 patients aged between 18-65 years with ASA grade 1 & 2. Patients were assigned to ketamine group (n=35) and control group (n=35) using a sealed envelope computerized randomization method. The study drug was administered with injection Bupivacaine in spinal anaesthesia.

Stump pain, phantom limb sensation and phantom limb pain were assessed at 6hours, 12 hours, 24 hours, 48 hours, 72 hours, 5 days, 7 days, 15 days, followed by 30^{th} day of every

month for a period of 6 months postoperatively. Post patient discharge, telephonic conversations were made to follow up the patients.

Results

There was a significant difference noted between ketamine and control group in terms of stump pain, phantom limb sensation and phantom limb pain. Ketamine group showed reduction in phantom limb pain occurrence and severity of phantom limb pain than the control group. Ketamine group showed better tolerance for stump pain and reduction in severity of stump pain. Ketamine group elicited almost nil phantom limb sensation in contrast to control group. Quality of life improvement seen in ketamine group. The majority of participant in ketamine group required minimum pain killers in immediate post operative period when compared to control group. Both the groups did not experience any side effects perioperatively.

Conclusion

Pre-emptively administered intrathecal Ketamine in prevention of post operative phantom limb pain in patients underwent lower extremity amputation surgery under subarachnoid block showed reduction in the incidence of phantom limb pain and improvement in quality of life in comparison with control group.

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INTRODUCTION

Limb salvage is an important part of podiatry, with goal of preserving the function & length of lower extremity, controlling co-morbidities and infections. In certain situations, lower extremity amputation is unavoidable, as decided by both the patient and physician. Major reasons for lower extremity amputation are vascular disease, injury, infection and carcinoma. Interestingly, vascular conditions are major cause of lower extremity amputations, especially in adults 65 years and older. Pain may result from several sources, such as infection, trauma, stump pain, phantom pain and postoperative complications.

PLP is the occurrence of painful sensation in missing limb parts and it has been defined as neuropathic pain syndrome [1-3]. The earliest medical account of post amputation sensation was provided in 1552 by Ambroise Pare, a French war surgeon, who observed that, patients reported violent pain in the missing limb after amputation [4]. Phantom limb pain and sensations can have an onset immediate postoperatively or years following amputation. Two peak phases of onset have been reported, within a month and a year following limb salvage [5]. Pain tends to decrease in frequence & span in the first 6 months following limb salvage [6]. While 80% of patients might develop PLP post amputation of a lower limb [4, 7], reported incidence is wide-ranging because either there is no standard definition for phantom limb pain or because, fearing stigmatisation as having a mental disorder, many patients do not report their pain.

The pathophysiological mechanisms of development of phantom limb pain are not clear, but drastic alterations in CNS & PNS to peripheral nerve damage and the ensuing changes in peripheral sensory input are hypothesized in the development of phantom sensations. Central sensitization at the level of spinal cord is most probably going to contribute significant chronic pain [8-10]. Peripheral nerve injury models in animal models have illustrated that N-methyl D-aspartate (NMDA) receptor activation is central to central sensitization, especially for nerve injury models [11,12]. Experimental studies incriminate sensory stimulation from noxious stimuli at the moment of nerve damage with immediate central neural plasticity in provoking neuropathic pain lasting. NMDA antagonists given to animals prior to nerve impairment significantly lessened behavioural indicators of neuropathic pain and attendant neuronal chemical modification [13,14].

Its mechanism of action is supposed to be the blocking of sensitization of the spinal cord. Hence, there is a need for further study in understanding the diverse mechanisms involved in phantom limb pain. With identification of such mechanisms by researchers and clinicians, specific therapies could be more effectively formulated. Ultimately, this would translate to enhanced care and enhanced results for the patient in the long run. Our research, we evaluated the impact of pre-emptively used intrathecal NMDA antagonist, Ketamine along with local anaesthetic on attenuation of spinal sensory relay provoking hyperplasic changes, acute central sensitization & evolving into persistent phantom limb pain.

OBJECTIVES OF THE STUDY

Primary Objective:

- To study the effect of intrathecal ketamine in prevention of phantom limb pain following lower extremity amputation surgeries.

Secondary Objective:

- To assess the incidence and severity of post amputation phantom limb pain.

REVIEW OF LITERATURE

The knowledge landscape in the last few decades has shown a real explosion, comprising the information on reasons that bring about the phantom limb pain and ways of curing them. Meanwhile, several factors have been identified, such as the site of the amputation, pre-existing pain, both have showed favorable circumstances for the occurrence of PLP. The proposed process and mechanisms evolved from psychogenic theory to the peripheral & central neuronal interchange that are about cortical reorganization. A wide range of treatment methods has been used, but therapy specific guidelines have yet to be formulated [15]. Following peripheral nerve injury, there is documentation of central sensitization in the neurons of dorsal horn of spinal cord.

This activity is defined by "chronic potentiation when short lasting stimuli generate increased post-synaptic potentials. Hyperexcitability, down-regulation of inhibitory processes, structural alterations in main centers of central sensory neuronal endings, and inter neurons and nerve projections are the other elements that have been identified as the process" [16]. Thus, during the process, there also higher action at NMDA receptors that is conveyed by neurotransmitters like substance P, tachykinins and neurokinins at the dorsal horn of spinal cord, then preceded by 'windup phenomenon' with upregulation of these receptors in this area.

Finally, it leads to changes in firing matrix of central nociceptive neurons [17]. Despite the progressive reasoning of mechanistic basis for post excise pain and publication of clinical trials, avoidance of both PLP and stump pain still leaves huge hurdle. A number of previous articles on animal models have been described on the role of the pre-emptive administration of NMDA antagonists in the prevention of neuronal hyperexcitability and the development of neuropathic pain [12-14].

Bill Y. Ong and co-workers analyzed the effects of different anesthetic methods in 150 patients on recovery of post-amputation pain. Their findings concluded that subarachnoid block and epidural anesthesia as neuraxial anesthetic procedures were better options for pain relief than general anesthesia in the initial week of post-amputation. Nevertheless, anesthetic treatments produced no feelings of stump pain or PLS around 14 months past lower limb removal [18].

Nikolajsen and authors analyzed the efficacy of intravenous ketamine in a double blinded controlled trial on treatment of SP & PLP. All 11 individuals showed, reduction in rating of SP and PLP scores, also difference in pressure pain thresholds. Ketamine significantly reduced pain that was like a wind-up. On the other hand, pain due to the thermal stimulations did not subside from the use of the drug. This experiment showed that the blocking of NMDA receptors minimizes the pain.

Using a randomized study that compared the pre-emptive modulation of afferent input with epidural ketamine on post-amputation pain and sensory processing as main outcomes, Wilsons and others were able to prove the use of this drug. Thus, it was observed that Stump pain was not much onset of one year. However, the postoperative analgesia was really effective in the ketamine Vs placebo group, subjects experienced less stump sensitivity. The involvement of NMDA receptors in induction of pain after amputation was the point this research covered, but it demands, follow-up exam to get the final result.

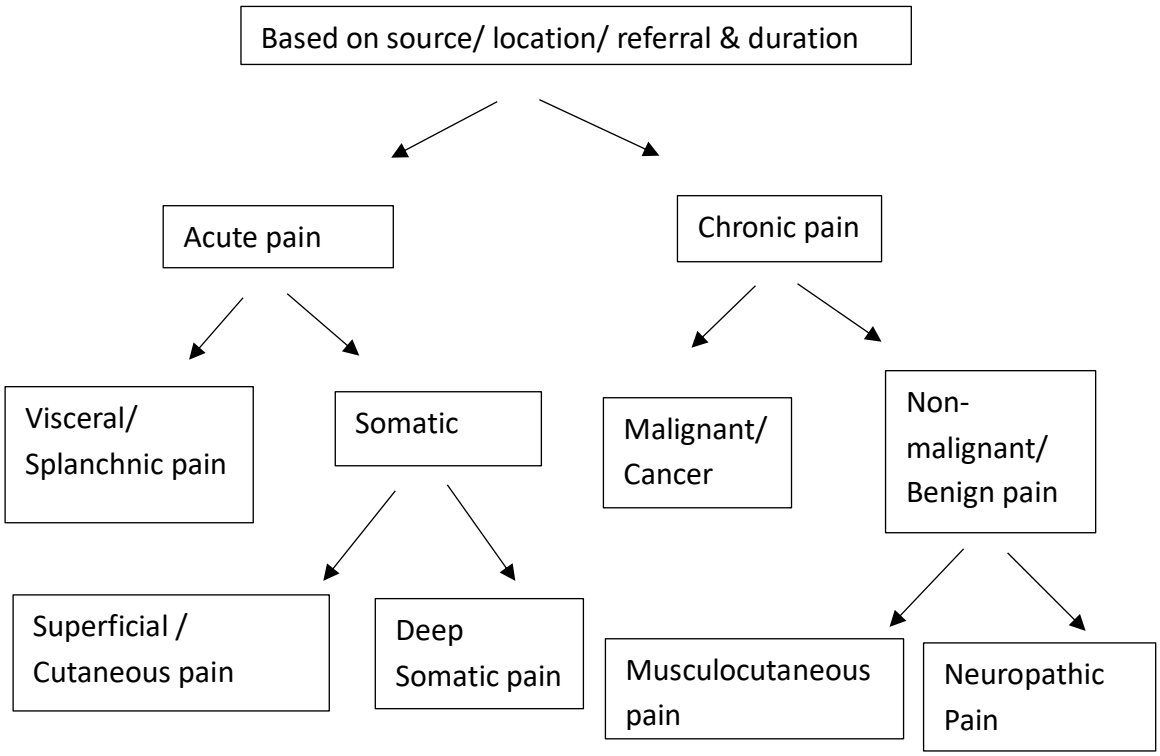
However, there is still no consensus on the efficacy of NMDA receptor antagonist ketamine intrathecally on phantom limb pain and therefore the present study was undertaken.

BASIC SCIENCE

PAIN

The word Pain is derived from the Latin word Peone and the Greek word Poine meaning Penalty or Punishment. Pain is defined by "**The International Association for the Study of Pain** as an unpleasant sensory and emotional experience associated with actual or potential tissue damage". Pain is an unpleasant subjective experience that is the net effect of a complex interaction of the ascending and descending nervous systems involving biochemical, physiologic, psychological and neocortical processes.

Classification of Pain:



Acute Pain:

Sudden onset, characterized typically by sharp, localized sensations and linked to a specific injury or illness. It usually resolves once the underlying cause is treated. It lasts > 30 days and occurs after muscle strains and tissue injury such as trauma or surgery and is described as a linear process. A poorly treated pain can cause psychological stress and compromise the immune system due to the release of endogenous corticosteroids.

Chronic Pain:

Chronic pain is defined as pain that persists for more than three to six months, continuing beyond the initial injury or illness has been healed. Unlike acute pain, which serves as a warning signal for injury or illness, chronic pain often persists even after the original cause has been resolved. This condition can significantly impact an individual's quality of life, leading to physical limitations, emotional distress, and social isolation. It may be nociceptive, inflammatory, neuropathic or functional in origin.

Common Causes of Chronic Pain:

- **Medical Conditions:** Diseases such as arthritis, diabetes, and fibromyalgia are frequently associated with chronic pain.
- **Injuries:** Past injuries, even those that have healed, can lead to ongoing pain.
- **Nerve Damage:** Neuropathic pain arises from nerve injuries or malfunctions.
- **Unknown Causes:** In some cases, no clear cause for the pain can be identified.

Impact on Daily Life:

Chronic pain can interfere with daily activities, work, and personal relationships. It is often linked with mental health issues such as depression and anxiety. The persistent nature of the pain can lead to frustration and a sense of helplessness.

CONSEQUENCES OF CHRONIC PAIN

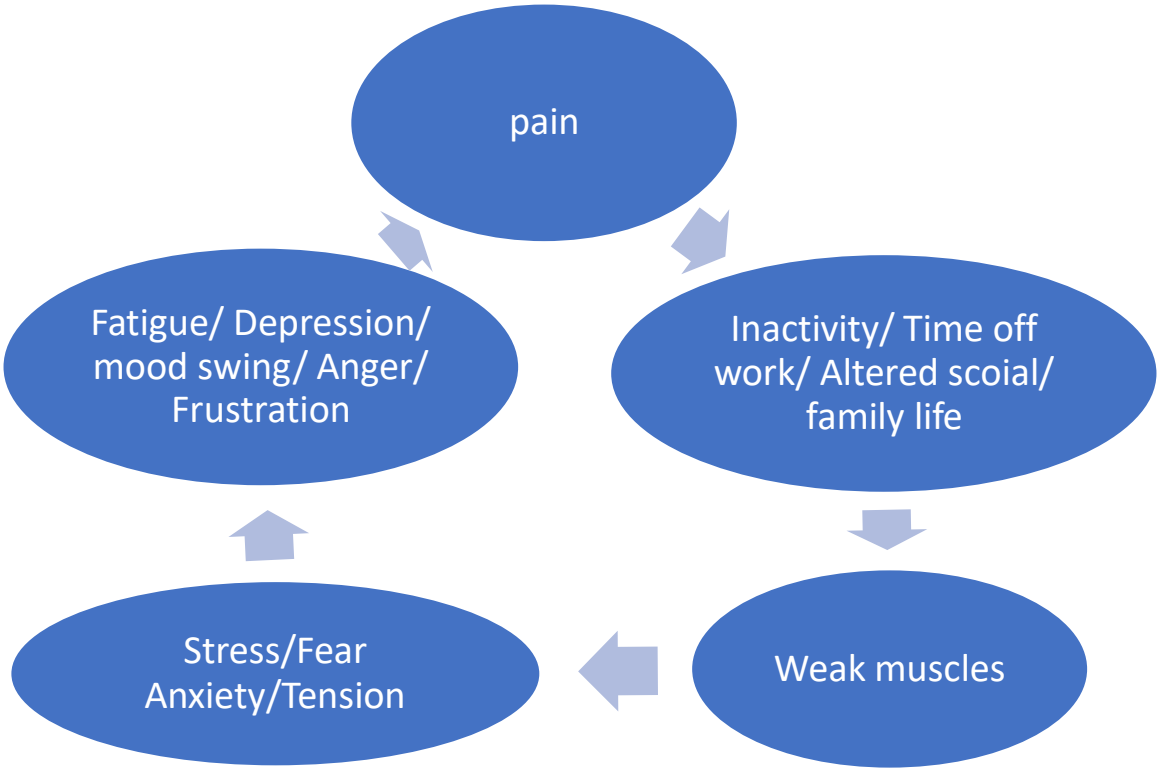


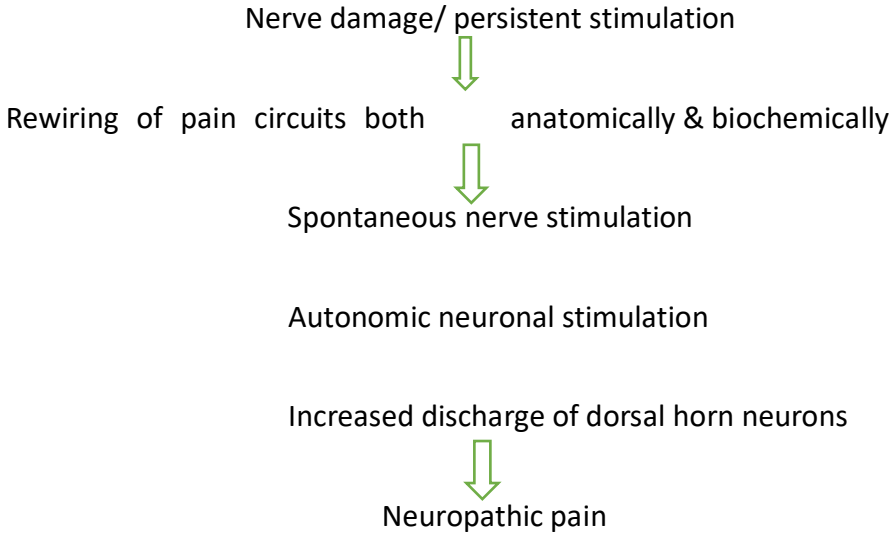
Table: 1- Contributing Biological factors.

PERIPHERAL MECHANISMS	**Results from peripheral stimulation of nociceptors. They contribute to pain associated with chronic musculoskeletal, visceral, vascular disorders.**
CENTRAL MECHANISMS	**Associated with disease or injury of the CNS.** **Characterized by burning, aching, hyperalgesia, dysesthesia.** **It is associated with thalamic lesions, spinal cord injury, surgical interruption of pain pathways and multiple sclerosis.**
PERIPHERAL-CENTRAL MECHANISMS	**These mechanisms involve abnormal function of the peripheral and central portions of the somatosensory system.** **Associated with abnormal functions of the peripheral and peripheral portions of Site Specific nucleases & loss of descending inhibitory pathways.**

NEUROPATHIC PAIN:

Neuropathic pain is a result of an injury or malfunction of the nervous system. It is described as aching, throbbing, burning, shooting, stinging, tenderness or sensitive to skin. Neuropathic pain is divided into peripheral and central neuropathic pain. Examples of peripheral neuropathic pain are Acute herpetic neuralgia, Acute shingles outbreak, Distal polyneuropathies, diabetes, Human Immunodeficiency Virus or Chemotherapeutic agents. Examples of central neuropathic pain are Central stroke pain, Trigeminal neuralgia, Complex regional pain syndrome with causalgia & reflex sympathetic dystrophy.

MECHANISM OF NEUROPATHIC PAIN:



MECHANISM OF PAIN: The pain pathway comprises several interlinked processes, beginning in the periphery with specialized receptors (PNS) and culminating in complex processing within the brain (CNS). Sensation of pain is composed of 4 basic processes includes: **Transduction, Transmission, Modulation and Perception.**

1.Transduction: Detecting Noxious Stimuli

Nociceptors or Pain Receptors are specialized sensory nerve endings distributed throughout the body tissues, that are activated by noxious insults to peripheral tissues. The receptive endings of the peripheral pain fibres are free nerve endings. These receptive endings are widely distributed in the skin, dental pulp, periosteum and meninges. Skin receptors for pain are high threshold mechanoreceptors which detects local deformation, eg: Touch and Polymodal receptors which detects a variety of stimuli causing injury, eg: Heat or noxious stimuli.

NERVE FIBERS:

Primary afferent fibres are once activated, nociceptors convert the stimulus into an electrical signal. These signals are carried by two main types of fibres. Nerve fibres involved in pain transmission are A fibres (A- Beta and A- Delta) and C fibres. A- Beta fibres are large, myelinated, fast conducting, low stimulation threshold fibres, responds to light touch. A- Delta fibres are small, lightly myelinated, slow conducting fibres, responds to heat, pressure, cooling & chemicals, produces sharp sensation of pain. C fibres are small, unmyelinated, very slow conducting fibres. It responds to all types of stimuli and transmit prolonged dull pain. It requires high intensity stimuli to trigger a response and are often polymodal.

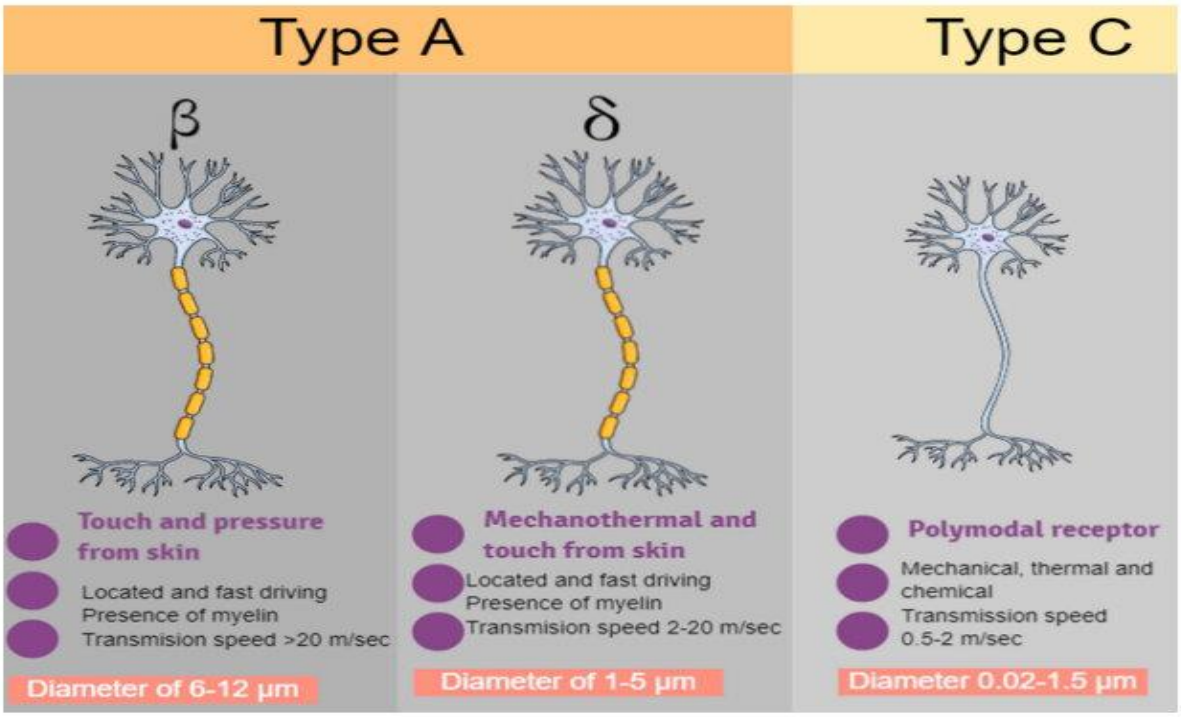


Figure 1: TYPES OF PAIN CONDUCTING NERVE FIBRES

NEUROTRANSMITTERS:

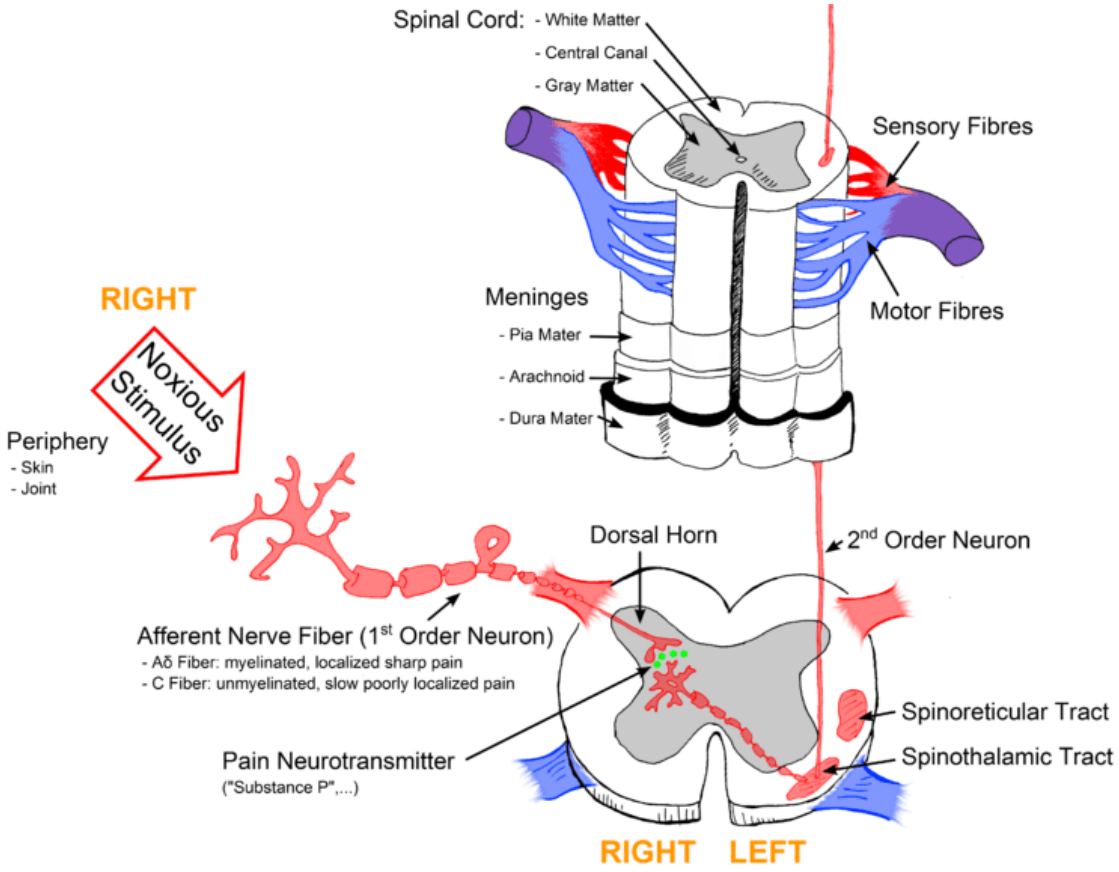
Pain sensation is modulated by excitatory and inhibitory Neurotransmitters released in response to stimuli. The neurotransmitters involved in pain:

- Bradykinin - stimulates the nociceptors,
- Histamine, Potassium, Adenosine triphosphate - exiting the nociceptors
- Prostaglandins I2, Leukotrienes – activation of nociceptors by interacting with other chemical mediators.
- Substance P, Glutamate – discharge of pain releasing substances by nociceptors.
- Prostaglandins E2, Prostaglandins I2- sensitization of nociceptors.

NEURONS:

FIRST ORDER NEURONS	•These are the cells in the posterior nerve root ganglia, receive impulses from pain receptors through dentrites. •These impulses are transmitted through the axons to spinal cord. •Impulses are transmitted by A- delta fibre or C fibres.
SECOND ORDER NEURON	•The neurons of marginal nucleus & substantia gelatinosa form the second order neurons. •Fibres from these neurons ascends in the form of the lateral spinothalamic tract. •Fibres of fast pain arise from neurons of the marginal neucleus and slow pain arise from neurons of substantia gelatinosa.
THIRD ORDER NEURON	•The neurons of pain pathway are the neurons in Thalamic nucleus, reticular formation, tectum, gray matter around the aqueduct of sylvius. •Axons from these neurons reach the sensory area of cerebral cortex or hypothalamus.

Figure 2: ORDERS OF NEURONS



2.Transmission: Sending the Signal to the Central Nervous System.

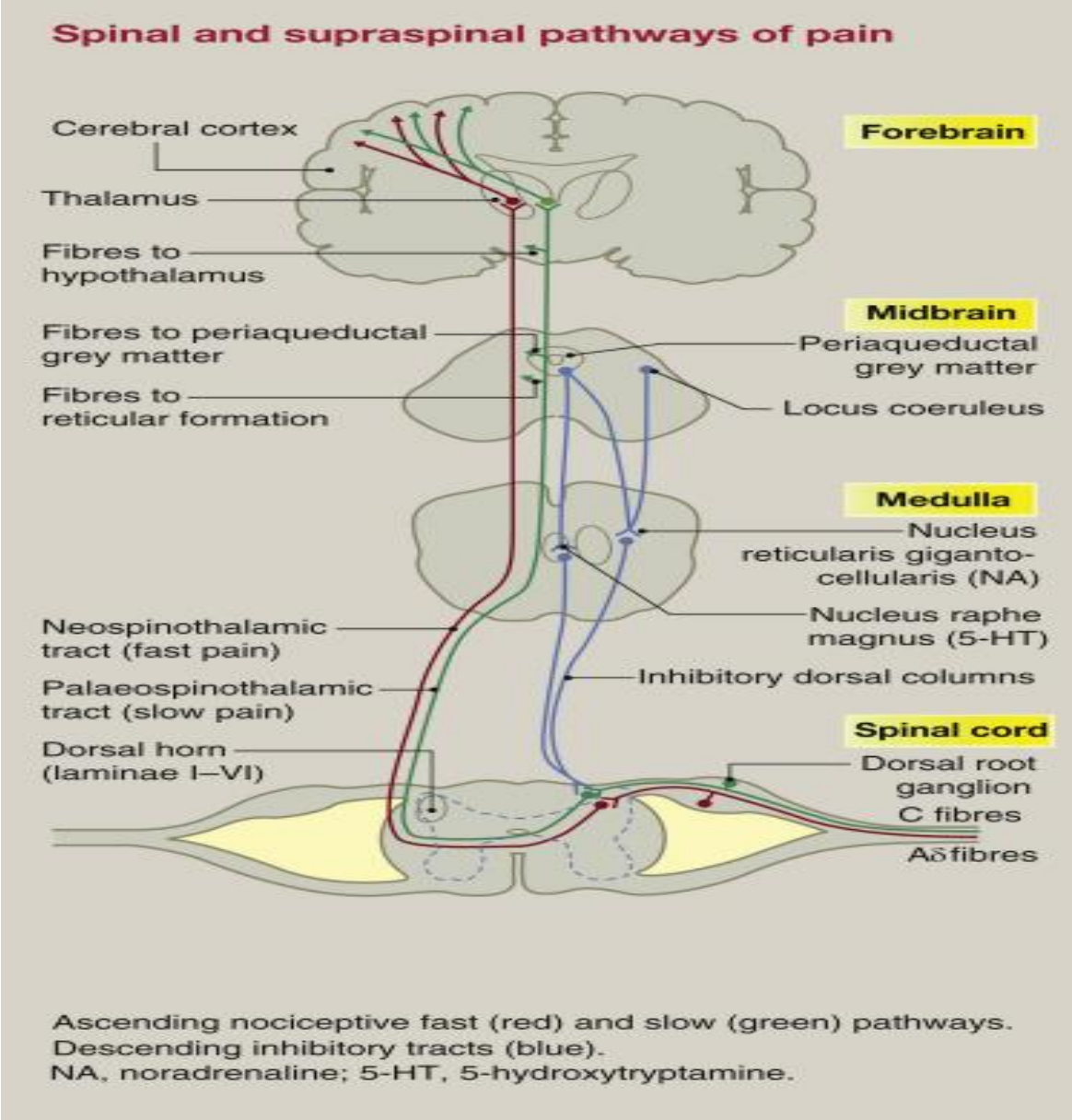
Spinal cord Entry: The axons of primary afferent fibres enter the spinal cord via the dorsal roots and synapse in the dorsal horn. The dorsal horn is organized into layers (Rexed laminae) where: A-δ fibres primarily synapse in laminae I and V, C fibres synapse mainly in lamina II (the substantia gelatinosa).

Ascending Pathways: Second-order neurons in the dorsal horn decussate (cross over) via the anterior white commissure. Their axons then ascend contralaterally in several pathways:

1. **Spinothalamic Tract:** This is the principal pathway for transmitting pain and temperature information to the thalamus.

2. **Spino-reticular and Spino- mesencephalic Tracts:** These contribute to the affective and arousal components of pain by projecting to brainstem regions.

Figure 3: ASCENDING AND DESCENDING PAIN PATHWAYS



3.Perception: The Brain's Processing of Pain:

Thalamic Relay: In the thalamus, specifically within the ventroposterolateral nucleus, pain signals are further processed before being sent to cortical regions.

Cortical Processing: The signals reach the primary somatosensory cortex, which localizes the pain (i.e., where it is coming from). In addition, other brain regions such as the insular cortex, anterior cingulate cortex, and prefrontal cortex contribute to the emotional, cognitive, and motivational dimensions of pain.

4.Modulation: Modifying Pain Signals

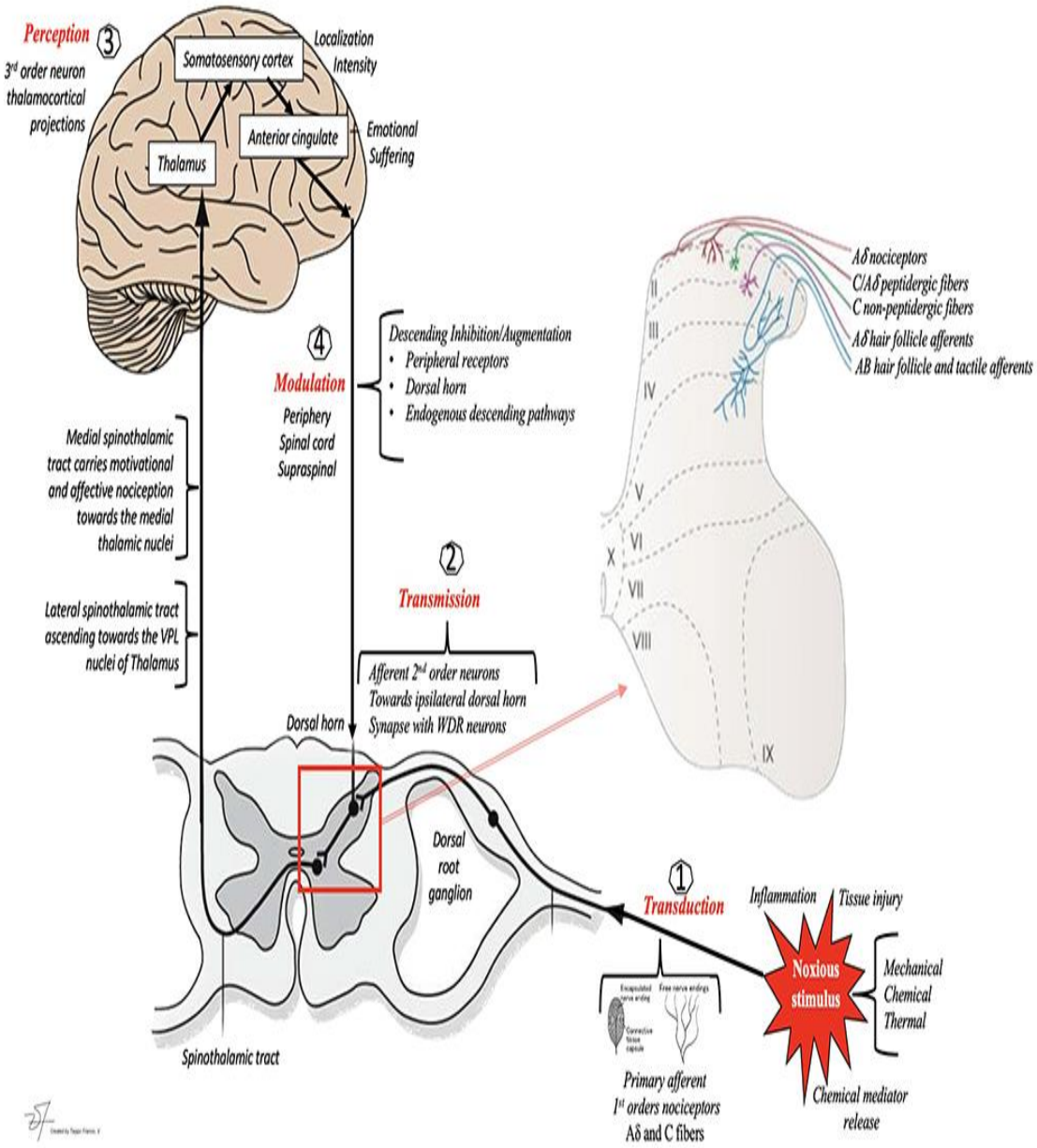
1. Descending Inhibitory Pathways: The brain can modulate incoming pain signals via descending pathways. Key areas include:

- **Periaqueductal Gray:** Located in the midbrain, the PAG is central to initiating analgesia.

- **Rostral Ventromedial Medulla:** Receives input from the Periaqueductal gray and sends inhibitory signals down to the dorsal horn.

Neurochemical Mediators: Neurotransmitters and neuromodulators, such as serotonin, norepinephrine, and endogenous opioids (endorphins, enkephalins) play critical roles in dampening the transmission of pain at both spinal and supraspinal levels.

Figure 4: MECHANISM OF PAIN



PAIN THEORIES

Pain theories are proposed to offer the possible physiologic mechanisms involved in pain. They are as follows:

- **Specificity theory**
- **Pattern theory**
- **Neuro-matrix**
- **Gate control theory**

SPECIFICITY THEORY:

This theory states pain as separate modality evoked by specific receptors that transmit information to pain centres or regions in the forebrain where pain is experienced.

PATTERN THEORY:

Pain receptors share endings or pathways with other sensory modalities but different patterns of activity of the same neurons can be used to signal painful and nonpainful stimuli. Eg. Light touch applied to skin would produce the sensation of touch and intense pain pressure would produce pain through high frequency firing of the same receptor.

NEUROMATRIX THEORY:

This theory was put forward by MELZACK. This theory explains the role of brain in pain as well as the multiple dimensions and determinants of pain. According to this theory the brain contains a widely distributed neural network called the body self Neuromatrix that contains

somatosensory, limbic & Thalamocortical components. The body self Neuromatrix involves multiple input sources such as

- Somatosensory inputs.
- Other impulses/ inputs affecting the interpretation of the situation.
- Various components of stress regulation systems.
- Intrinsic neural inhibitory modulatory circuits.

GATE CONTROL THEORY:

It was proposed by MELZACK & WALL in 1965. According to this theory, the pain stimuli transmitted by afferent pain fibres are blocked by Gate Mechanism located at the posterior gray horn of the spinal cord. If the gate is open, pain is felt and if the gate is closed pain is supressed. Impulses in A delta and C fibres can be blocked by modulated by A beta activity that can selectively block impulses from being transmitted to the transmission cells in the spinal cord and then to CNS resulting in no pain.

PHANTOM LIMB PAIN

Phantom limb pain (PLP) is the perplexing and often debilitating phenomenon in which amputees experience pain in a limb that is no longer present. Despite the absence of the physical structure, the brain continues to “feel” sensations from the missing limb. Phantom limb pain is the sensation of pain or discomfort perceived in a limb that has been amputated. Despite the physical absence of the limb, individuals may experience feelings ranging from tingling and itching to severe pain. This phenomenon is distinct from residual limb pain, which

originates from the actual site of amputation and typically diminishes as the surgical site heals. PLP affects up to 60–80% of amputees.

MECHANISM OF PHANTOM LIMB PAIN

1. **Peripheral Mechanisms:**

Nerve Injury and Neuroma Formation:

At the time of amputation, the peripheral nerves are severed, which leads to the formation of neuromas (tangled masses of regenerating nerve fibres). These neuromas are often hyperexcitable, showing increased expression of sodium channels and spontaneous activity. Such aberrant peripheral inputs can send continuous pain signals toward the central nervous system even after the limb is gone.

Dorsal Root Ganglion Changes:

The cell bodies of sensory neurons reside in the dorsal root ganglia. After amputation, these neurons may undergo phenotypic changes, upregulating pain-related ion channels and other molecules, that contribute to the generation of spontaneous discharges. Although blocking peripheral nerve conduction may sometimes reduce PLP, it does not always eliminate the pain, suggesting that peripheral changes modulate, but do not solely cause phantom limb pain.

2. **Central Mechanisms:**

Cortical Reorganization and the Neuro-matrix:

The CNS plays a critical role in phantom limb pain through mechanisms of neuroplasticity. When a limb is amputated, the corresponding region in the primary somatosensory and motor cortices is deprived of its usual input. In response, adjacent cortical areas may “invade” the

deafferented zone, a process known as cortical remapping. This maladaptive plasticity is thought to generate abnormal pain perceptions by creating a mismatch between the brain's internal representation (or neuro-matrix) and the actual body state.

The brain maintains a network of neurons that continuously produces a "body-self" image. After limb loss, the persistence of the neuro-matrix, even in the absence of sensory input, can lead to the perception of a phantom limb. Conflicts between expected sensory feedback and actual inputs may trigger chronic pain.

Central Sensitization:

In addition to cortical reorganization, central sensitization, an increased responsiveness of central neurons to normal or subthreshold afferent input, also contributes to PLP. Changes at the level of the spinal cord, such as enhanced activity at NMDA receptors and reduced inhibitory GABAergic tone, can amplify pain signals. This hyperexcitability ensures that even minimal peripheral input, or in some cases no input at all, is perceived as painful.

Interplay Between Peripheral and Central Factors:

The development of phantom limb pain is not solely a "central" or "peripheral" phenomenon; rather, it is the result of an intricate interplay between the two. Peripheral nerve injury initiates aberrant signalling that can trigger central changes, while the CNS's response, in terms of cortical remapping and sensitization, further amplifies the pain experience. Moreover, factors such as pre-amputation pain and psychosocial stress can predispose individuals to developing more severe PLP. Understanding these mechanisms has important clinical implications. For example, mirror therapy is based on the principle that visual feedback can help "retrain" the brain's representation of the limb, potentially reversing maladaptive

cortical reorganization and alleviating pain. Similarly, interventions targeting peripheral nerve activity (e.g., local anaesthetics or neuroma treatments) aim to reduce the aberrant inputs that fuel central sensitization.

CONSEQUENCES OF PHANTOM LIMB PAIN:

- **Psychological impact:**

Phantom limb pain is often associated with high levels of anxiety and depression, particularly in the early stages after amputation, due to the constant pain and the difficulty of adapting to the missing limb.

- **Functional impairment:**

The pain can interfere with daily activities, making it difficult to perform tasks that require fine motor skills or mobility, depending on the affected limb.

- **Sleep disruption:**

The pain can disrupt sleep patterns, leading to fatigue and further impacting daily functioning.

- **Social withdrawal:**

Some individuals may withdraw from social interactions due to discomfort or embarrassment about their condition.

- **Prosthetic use challenges:**

Phantom pain can make it difficult to wear and use a prosthetic limb effectively, further limiting mobility and independence.

- **Impact on quality of life:**

Overall, phantom limb pain can significantly reduce a person's quality of life, affecting their physical, emotional, and social well-being.

PAIN ASSESSMENT TOOLS

Pain may be accompanied by physiologic signs & symptoms and there are no reliable objective markers of pain. The severity of pain can be assessed by rating scales and multidimensional scales. Rating scales provide the simple way to classify the intensity of pain and should be selected based on the patient's ability to communicate. Multidimensional scales are helpful in obtaining information about the pain and impact on quality of life, but are more often time consuming to complete.

Figure 5: NUMERIC RATING SCALE:

A numeric pain scale is a tool used to measure pain intensity on a scale of 0 to 10, where 0 means no pain and 10 means the worst pain. It's a common way to assess pain severity. Patients are asked to circle the number that best describes their pain. The score is recorded in the patient's electronic health record. This allows clinicians to track pain intensity over time.

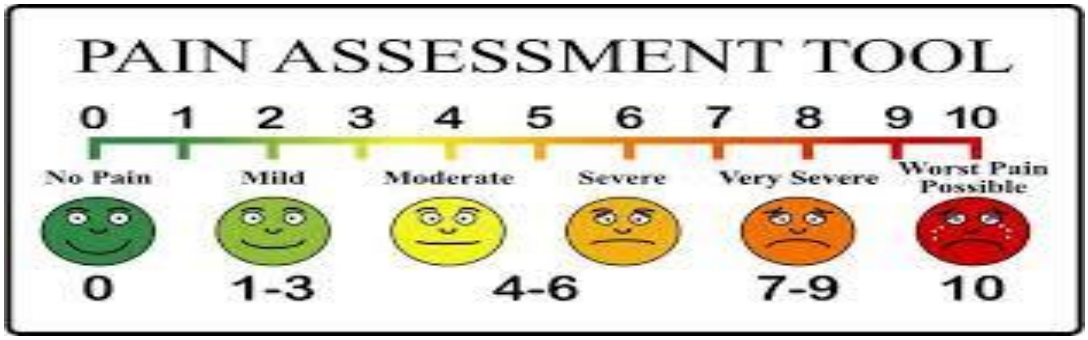
BENEFITS:

- The numeric pain scale is quick and easy to use.
- It's well validated and has shown high correlations with other pain-assessment tools.

LIMITATIONS:

- It's difficult to interpret the clinical importance of changes from baseline on this scale.
- If a value of “10” is chosen and the pain worsens, the patient has no way to express this change.

Figure 6: PAIN ASSESSMENT TOOL

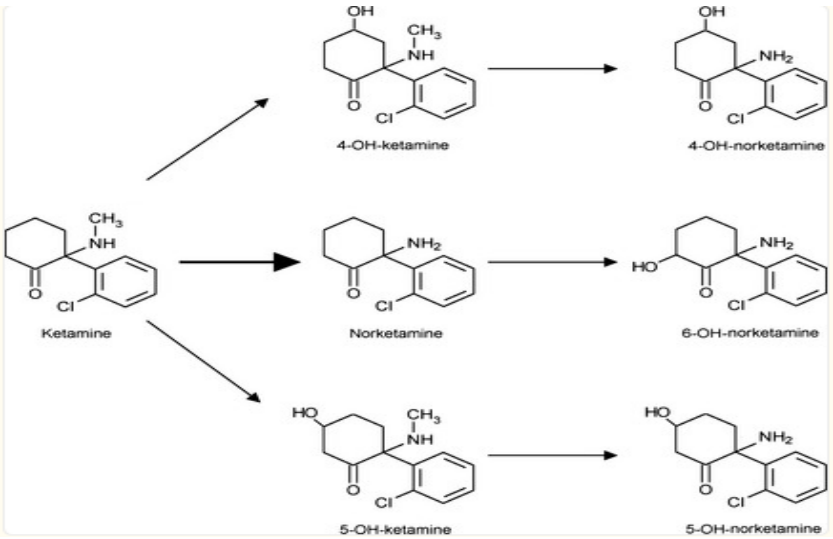


KETAMINE

Ketamine is a hydro soluble aryl-cyclo-alkylamine (phencyclidine derivative) with a molecular mass of 238g/mol and pKa 7.5. that produces dissociative anaesthesia characterized by evidence on the EEG of dissociation between the thalamocortical and limbic system. Ketamine is frequently described as a "unique drug" because it has hypnotic, analgesic, amnesic effects. It was first used clinically in 1970 and because of these combined effects, it was though that it might be the perfect anaesthetic agent.

Ketamine is a racemic mixture of two enantiomers of equal quantity, both (*R*)- and (*S*)-enantiomers, *S* (+) enantiomer is an active enantiomer, two times stronger than the racemic form and four times than the R (-) ketamine isomer.

Chemical Structure of Ketamine:



Mechanism of Action:

Ketamine hydrochloride is a nonbarbiturate dissociative anaesthetic. As a cyclohexanone derivative, the drug rapidly acts and produces profound anaesthesia and analgesia. Its chemical name is 2-O-chloro-phenyl-2-methylamino cyclohexanone hydrochloride; the structural formula is CHC1NO. Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) and glutamate receptor antagonist that blocks hyperpolarization activated cyclic nucleotide gated receptors. The unique dissociative action and partial agonism of opiate mu-receptors permit painful procedures in a consistent state of sedation and comfort. Ketamine can elevate the levels of glutamate in the brain, stimulating synaptogenesis and elevated levels of brain-derived neurotrophic factor. Ketamine may interact with the sigma receptors. It works by decreasing central sensitization, wind-up phenomenon (development of ongoing, worsening, or chronic pain), and pain memory. Cholinergic, monoaminergic, and opioid systems seem to play both a positive and negative modulatory function in both analgesia and sedation. Ketamine reverses tolerance to opioids.

Routes of Administration: Ketamine injection can be administered as intravenous, intramuscular, subcutaneous, intra-arterial and intrathecal. Ketamine is available in tablets, capsules and syrups form for oral administration, intra nasal sprays and drops, rectal/ vaginal suppositories, inhalational dry powders and aerosols are also available.

Pharmacokinetics:

Absorption: Ketamine administered IV exhibits a rapid onset of action, achieving peak plasma concentrations quickly. The IM route of administration provides a high bioavailability of 93% and results in peak plasma levels within 5 to 30 minutes. However, oral ketamine has a significantly lower bioavailability of around 16% to 29% due to extensive first-pass hepatic

metabolism. In contrast, intranasal and intrarectal administration of ketamine has demonstrated better bioavailability at 45% to 50% and 25% to 30%, respectively.

Metabolism: Ketamine is primarily metabolized by the enzymes Cytochrome P450 3A4 and, secondarily, the enzymes Cytochrome P450 2B6 and Cytochrome P450 2C9. It undergoes N-dealkylation, hydroxylation, conjugation, and dehydration.

Distribution: Ketamine quickly enters the brain. It has a plasma protein binding from 10% to 50%. The steady-state volume of distribution is 3 to 5 L/kg.

Elimination: Following IV administration, ketamine redistributes from the CNS to peripheral tissues. Its elimination half-life is typically 2 to 4 hours. After administration, most ketamine and metabolites are excreted through urine, with 91% of administered radioactivity appearing over 5 days. Only about 20% occur as the parent drug or major metabolites. Additionally, hydroxylated metabolites of ketamine and nor-ketamine are eliminated in urine and bile.

Pharmacodynamics:

1. **Central Nervous System:** After IV injection, the effects of Ketamine on the CNS begins slowly than other anaesthetic induction agents**.** The anaesthetic state produced is frequently called **"dissociative anaesthesia"** which implies that the patient is detached from the environment and self. In contrast to the smooth induction of anaesthesia, the patient may be agitated on recovery from ketamine, often called emergence delirium, patient may be disoriented, restless and crying. Ketamine is potent cerebral vasodilator & capable of increasing cerebral blood flow

by 60% in normal individual and causes a rise in intracranial pressure, should not be used in patients who have sustained a recent head injury.

2. **Cardiovascular System:** Ketamine causes mild stimulation of the CVS. The systolic BP rises about 20-40 mmHg & small increase in diastolic. The heart rate increases by about 20%, overall increases the workload of the heart.
3. **Respiratory System:** If Ketamine is administered slowly by IV induction, breathing is well maintained and may even increase slightly. Ketamine preserves pharyngeal and laryngeal reflexes. Ketamine produces bronchodilation.
4. **Skeletal Muscle:** Muscle tone is often increased.
5. **Placenta:** Ketamine crosses the placenta.
6. **Secretions:** Salivation is increased.
7. **Eyes:** The intra ocular pressure rises for a short period of time following administration. Pupils moderately dilate. Eye movements may continue throughout the surgery.

USES OF KETAMINE:

- **Induction of Anaesthesia:** Ketamine is widely used as an anaesthetic induction agent in paediatric and acute hypovolemic patients. Because of its rapid onset of action, it has been used as an IM induction agent in children and extensively for burns patient debridement and skin grafting procedures.
- **Analgesia:** Intense analgesia can be achieved with sub- anaesthetic doses. Analgesia is greater for somatic pain than visceral pain. Ketamine is useful as an analgesic adjuvant in patients with pre-existing **chronic pain syndromes**.

- **Reversal of Opioids:** Sub anaesthetic dose of administration of Ketamine reduces the opioid tolerance in patients.
- **Improvement of Psychiatric Disorders**: Ketamine in small doses improves the post operative depressive state in patients with mental depression. Intermittent treatment with low dose ketamine also results in long term suppression of obsessions & compulsions in patients with obsessive compulsive disorder & for depression in bipolar disorders.
- **Ketamine** is useful in de-addiction of alcoholism and drug addiction.
- **Ketamine** is administrated as a treatment for bronchospasm.

ADVERSE SIDE EFFECTS:

The most common adverse drug reactions associated with ketamine are nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, and confusion. Reports of the emergence phenomenon exist for approximately 6% to 12% of patients. The common adverse drug reactions of ketamine are listed below.

- **Allergic:** anaphylaxis and angioedema**.**
- **Cardiovascular:** Transient increases in blood pressure, bradycardia, left ventricular dysfunction in patients with heart failure, respiratory and cardiac arrest, and arrhythmias**.**
- **Gastrointestinal:** Anorexia, nausea, and vomiting.
- **Muscular:** Muscle stiffness and spasms or tonic-clonic movements resembling seizures and enhanced skeletal muscle tone.

- **Ophthalmologic:** Diplopia, nystagmus, and increased intraocular pressure.
- **Psychiatric:** Amnesia, anxiety, confusion, depression, disorientation, dysphoria, dissociative state, hallucinations, flashbacks, unusual thoughts, extreme fear, excitement, irrational behaviour, and insomnia.
- **Respiratory:** Apnoea, increased laryngeal and tracheal secretions, laryngospasm, airway obstruction in infants (may not be drug-related), and respiratory depression.
- **Skin:** Injection site reactions (infrequent), local pain, erythema, and morbilliform rash.
- **Neurologic:** Confusion, emergence, delirium, seizures, and hallucinations.

Drug-Drug Interactions

- **Central nervous system depressants:** Co-administration of ketamine with opioid analgesics, benzodiazepines, or CNS depressants, including alcohol, may induce profound sedation, respiratory depression, coma.
- **Sympathomimetic medications:** Vasopressin and sympathomimetic medications may increase ketamine's sympathomimetic effects. Simultaneous use of Monoamine oxidase inhibitors with ketamine is contraindicated.
- **Theophylline:** Concurrent use of ketamine with theophylline or aminophylline could potentially reduce the seizure threshold.

MATERIALS AND METHODS

After procuring institute ethical committee clearance, this prospective, RCT (double blinded study) was carried out among 70 Patient's aged betwixt 18 & 65 years belongs to American Society of Anaesthesiologists [ASA] class I and II underwent elective lower extremity amputation procedure under subarachnoid block at "KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehru Nagar, Belagavi, Karnataka" for a span of one year, (November 2023 to October 2024).

SAMPLE SIZE AND RANDOMIZATION:

Based on mean and SD, lowest sampling size formula was

$$n = \frac{(z_\alpha + z_\beta)^2(s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Parameter considered in calculation was the level of VAS in phantom limb pain. "X1 is the mean of the first group and X2 is the mean of the second group. s1 is the standard deviation of the first group and s2 is the standard deviation of the second group where z_α is linked with the level of significance and z_β is linked with the power of the test. For 5% level of the significance z_α = 1.96 and z_β = 0.84 for 80% power of the test".

Patients were allocated in a randomized manner using computer randomization software and "by opening a sealed envelope method" into ketamine and control groups.

a) Group Ketamine, number=35

b) Group Control (Normal saline), number=35

Inclusion Criteria

- Patient underwent elective lower extremity amputation operation under Subarachnoid Block.
- Patients above 18 and below 65 years old.
- Belonged to American Society of Anesthesiologists class I & II.

Exclusion Criteria:

- Patients known allergic to experimental medicines.
- Patients with neuro-behavioral changes, severe diabetic /autonomic neuropathy.
- Patients under long term analgesics and contraindicated for subarachnoid block.
- Patients failed follow ups for pain evaluation.
- Patients experienced further limb salvage procedures in the course of follow up were eliminated from evaluation.

An informed written consent was procured from the patients while pre-anaesthetic checkup, one day earlier to the procedure. On operation day, patient's nil by mouth status was verified & all patients were secured with intravenous access and provided aspiration prophylaxis. Anaesthesia assistants were allocated to prepare drug trial and recorded the group. Neither patients nor anaesthesiologists were known about trial preparations given, to warrant unbiased outcome.

Group K received intrathecal preservative free ketamine 25mg added to 10mg of hyperbaric bupivacaine made a total of 2.5ml, while Group C received 0.5ml of sterile normal saline added to 10mg of hyperbaric bupivacaine made a total of 2.5ml intrathecally

for subarachnoid block. Inside operation theatre, standard anaesthesia monitors were applied including electrocardiogram, arterial saturation probe and non-invasive blood pressure.

Under strict aseptic precautions, using 27G Whitacre spinal needle, subarachnoid block was administered using trial drug preparation between L3 & L4 intervertebral space by midline approach in sitting or lateral position of patient. The attending anaesthesiologist administered the drug preparation based on group allocation of patients. After the confirmation of effective neuraxial blockade, surgical procedure was performed on the patients. Patients did not receive any sedative or hypnotic or general anaesthesia during the procedure.

Throughout the peri-operative period, patients vitals such as HR, BP, RR and SPO2 were monitored. Intra-operative hypotension was managed with IV & Mephentermine boluses. Blood loss was replaced with colloid or blood transfusion whenever required. Post-operative pain was treated with IV non-steroidal anti-inflammatory drugs like injection Paracetamol 1 gm IV, injection diclofenac 75mg IV/IM and IV tramadol 100mg IV/IM, if the patient requested or pain score above or equal to 4 NRS (numeric rating scale) Post operatively. Persistent pain was treated with oral pregabalin 75mg, Gabapentin 100 to 300mg and up to 150mg of Amitriptyline at night. Alternate or complementary therapies was preferred in case of failed response to medical management of pain whenever possible. The investigator and patients were blinded to the study drug used intra-operatively. SP, PLS and PLP assessment were done using Numeric pain rating scale (NRS) post operatively.

Evaluation methods:

Standard assessment with NRS for pain was obtained by patient interview. Pain severity was evaluated using NRS range of 0-10 (0 -no pain; 10- worst pain imaginable). SP was explained as "a pain perceived from the stump or the remaining part of the leg, whereas PLS is referred as a non-painful sensation from the removed part of the leg. Phantom limb pain was defined as a painful feeling from the removed part of the leg".

Mean NRS estimation of pain severity assessed preoperatively and initial 15 days of operation were assessed from patient interview. Pain assessment elicited at postoperative 6 hrs, 12 hrs, 24 hrs, 48 hrs, 72 hrs, 5^{th} day, 7^{th} day, 15^{th} day followed by 30^{th} day of every month for 6 months of post-surgery. Post-discharge from the hospital, pain evaluation was done via telephonic conversation with the patients. Participators were enquired for the number of days per month with pain, prior to evaluation month. Rescue pain therapy used by patients including dosage, frequency and compliance to treatment were recorded. All participators were enquired, whether pain affects their abilities to focus, to carry out everyday activities and ability to sleep at night.

RESULTS

STATISTICAL ANALYSIS:

Data was scrutinized utilizing statistical software **R version 4.4.2** and **Microsoft Excel. Categorical variables** specified in the **frequency tables**. **Continuous variables** stated in **Mean ± SD /Median (Min, Max)** form. **Chi square test** was utilized to look over interrelation of categorical variables. **Normality of variable** was surveyed by **Shapiro Wilk test** and **QQ plot**. If data showed normal distribution, **parametric tests** were utilized. Or else, **non-parametric tests** were utilized. **MW U test** was employed to differentiate the distribution of variables among groups.

P value $\leq$ 0.05 indicates statistically notable.

The dataset includes quantification from **70 participators**, evenly split into two batches: 35 in **control group and 35 in ketamine group**. Subsequent table provides the differentiation of demographic variables between two groups.

Table 2: Differentiation of demographic data among groups.

Variables	Sub-Category	Control	Ketamine	Total	P value
Age in years	**M ± SD** **Mdn (Min, Max)**	**49.23 ± 13.02** **52 (24, 65)**	**50.89 ± 13.8** **55 (19, 65)**	**50.06 ± 13.34** **53 (19, 65)**	**0.5801^{MW}**
Gender	**Female**	**7 (20%)**	**6 (17.14%)**	**13 (18.57%)**	**0.7586^{C}**
	Male	**28 (80%)**	**29 (82.86%)**	**57 (81.43%)**	

The control Batch had a **mean age of 49.23 ± 13.02 years**, with a **median of 52 years** (range: 24–65), while the ketamine batch had a **mean age of 50.89 ± 13.8 years**, with a **median of 55**

years (range: 19–65). However, differentiation was not statistically notable (P value = 0.5801). Regarding gender distribution, the control group contained **7 (20%)females** and 28 **(80%)males**, whereas ketamine group had **6 (17.14%) females** and **29 (82.86%)males. Nil notable variance** was found in gender distribution among the batches **(P value = 0.7586)**.

The below table depicts the comparison of surgery proposed between groups.

Table 3: Comparison of surgery proposed between groups.

Surgery Proposed	Control	Ketamine	Total	p-value
LT AKA	**8 (22.86%)**	**3 (8.57%)**	**11 (15.71%)**	**0.2424^{MC}**
LT BKA	**4 (11.43%)**	**12 (34.29%)**	**16 (22.86%)**	
LT FFA	**6 (17.14%)**	**5 (14.29%)**	**11 (15.71%)**	
RT AKA	**6 (17.14%)**	**4 (11.43%)**	**10 (14.29%)**	
RT BKA	**8 (22.86%)**	**7 (20%)**	**15 (21.43%)**	
RT FFA	**3 (8.57%)**	**4 (11.43%)**	**7 (10%)**	

From **Chi square test**, there is no **notable dissimilarity** seen in the proposed surgery between the groups **(P value = 0.2424)**.

The below table shows the resemblance of preoperative assessments in between the groups.

Table 4: Resemblance of preoperative assessments between groups.

Variables	Sub Category	Control	Ketamine	Total	P value
Pre operative Pain assessment (NRS)	**M ± SD** **Mdn (Min, Max)**	**4 ± 2.74** **5 (0, 8)**	**3.11 ± 2.73** **4 (0, 8)**	**3.56 ± 2.75** **5 (0, 8)**	**0.1362^{MW}**
Number of Days with Pain Symptoms	**M ± SD** **Mdn (Min, Max)**	**2.89 ± 2.75** **2 (0, 10)**	**3.8 ± 4.52** **2 (0, 15)**	**3.34 ± 3.75** **2 (0, 15)**	**0.8760^{MW}**

The mean preoperative pain score (NRS) in control group was 4 ± 2.74, with a median of 5 (range: 0–8), while in the ketamine group, the mean score was 3.11 ± 2.73, with a median of 4 (range: 0–8). Out MW test, it is noticed that there is no similarity in the dispersal of preoperative pain score between groups (p-value = 0.1362). The number of days with pain symptoms was also similar between the groups, control group showed a **mean of 2.89 ± 2.75 days** (median: 2, range: 0–10) and the ketamine group having a **mean of 3.8 ± 4.52 days** (median: 2, range: 0–15) **(P value = 0.8760)**.

Table 5: Resemblance of stump pain (NRS) among groups at different time points.

Time point	Sub Category	Control	Ketamine	Total	p-value
6 hours	M ± SD Mdn (Min, Max)	7.46 ± 0.66 8 (6, 8)	6.86 ± 0.69 7 (6, 8)	7.16 ± 0.73 7 (6, 8)	< 0.001^{MW*}
12 hours	M ± SD Mdn (Min, Max)	7.6 ± 0.65 8 (6, 9)	7.09 ± 0.51 7 (6, 8)	7.34 ± 0.63 7 (6, 9)	< 0.001^{MW*}
24 hours	M ± SD Mdn (Min, Max)	7.31 ± 0.68 7 (6, 8)	6.8 ± 0.68 7 (5, 8)	7.06 ± 0.72 7 (5, 8)	0.0024^{MW*}
48 hours	M ± SD Mdn (Min, Max)	6.6 ± 0.69 7 (5, 8)	6.03 ± 0.92 6 (4, 7)	6.31 ± 0.86 6 (4, 8)	0.0090^{MW*}
72 hours	M ± SD Mdn (Min, Max)	5.74 ± 0.85 6 (4, 7)	4.94 ± 1.19 5 (2, 6)	5.34 ± 1.1 6 (2, 7)	0.0033^{MW*}
5 days	M ± SD Mdn (Min, Max)	3.86 ± 1.33 4 (0, 6)	3.09 ± 1.52 4 (0, 5)	3.47 ± 1.47 4 (0, 6)	0.0174^{MW*}
7 days	M ± SD Mdn (Min, Max)	2.14 ± 1.72 3 (0, 5)	1.46 ± 1.29 2 (0, 4)	1.8 ± 1.55 2 (0, 5)	0.0452^{MW*}
15 days	M ± SD Mdn (Min, Max)	0.46 ± 0.95 0 (0, 3)	0 ± 0 0 (0, 0)	0.23 ± 0.71 0 (0, 3)	0.0057^{MW*}
1 month	M ± SD Mdn (Min, Max)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	1^{MW}
2 months	M ± SD Mdn (Min, Max)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	1^{MW}
3 months	M ± SD Mdn (Min, Max)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	1^{MW}
4 months	M ± SD Mdn (Min, Max)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	1^{MW}
5 months	M ± SD Mdn (Min, Max)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	1^{MW}
6 months	M ± SD Mdn (Min, Max)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	1^{MW}

Around **6 hrs postoperatively**, control group reported, **increased mean pain score** contrast to ketamine group, with a **statistically notable differentiation (P value< 0.001)**. This trend continued at **12 hrs (p-value< 0.001)**. **Notable differences** persisted at 24 hours (p-value = 0.0024), 48 hrs (P value = 0.0090), **72 hrs (P value = 0.0033), 5 days (P value = 0.0174),** and **7 days (P value = 0.0452)**, with ketamine group consistently reporting **lower pain scores**. By **15 days**, pain was minimal in both groups, but control group still had a slightly **elevated mean score** in contrast to ketamine group, showing significant differentiation **(P value = 0.0057)**. From 1 month onwards, both groups reported **no stump pain (NRS = 0)**, with **no significant differences (p-value = 1).** These findings suggest that **ketamine effectively reduced postoperative stump pain in the early recovery period**, but by one month, both groups had complete pain resolution.

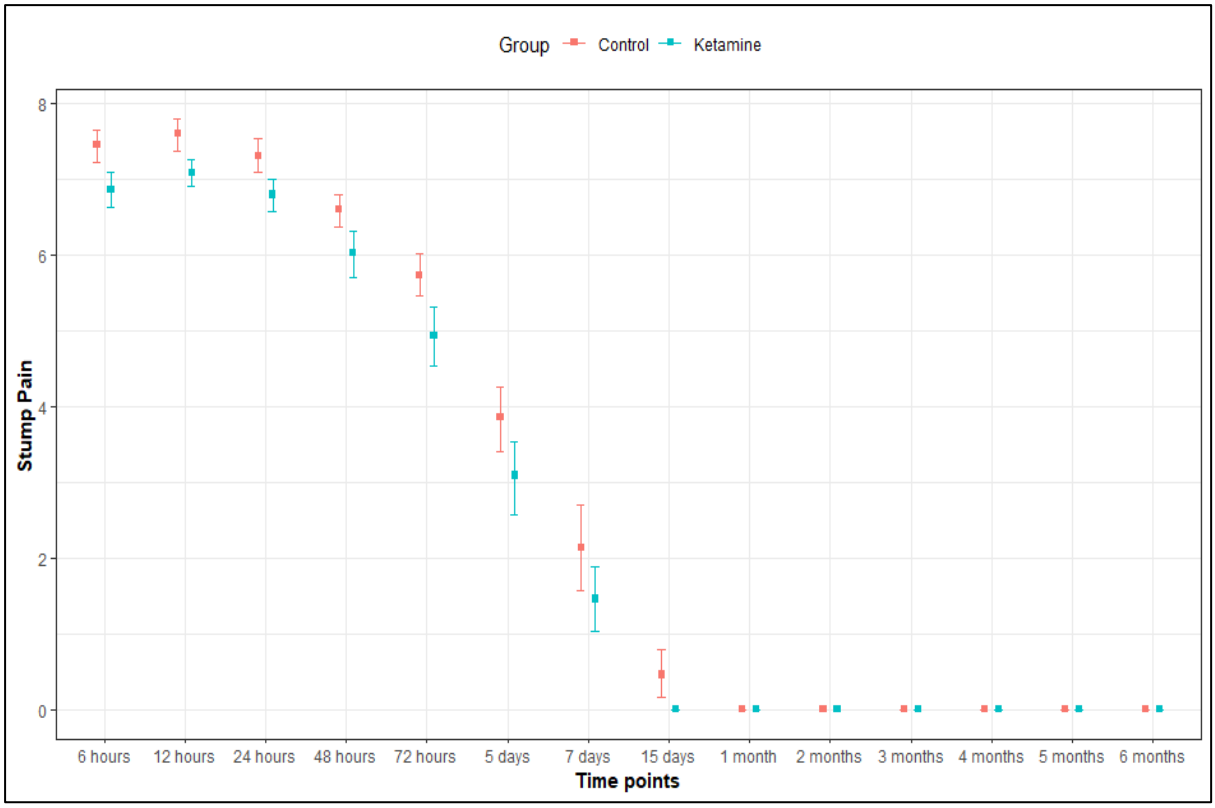


Figure 7: Mean diagram of Stump pain over time and group.

Table 6: Comparison of Phantom sensation betwixt classes at different periods.

Time point	Sub Class	Control	Ketamine	Total	p-value
6 hours	Absent	6 (17.14%)	35 (100%)	41 (58.57%)	< 0.001[C*]
	Present	29 (82.86%)	0	29 (41.43%)	
12 hours	Absent	3 (8.57%)	35 (100%)	38 (54.29%)	< 0.001[C*]
	Present	32 (91.43%)	0	32 (45.71%)	
24 hours	Absent	2 (5.71%)	35 (100%)	37 (52.86%)	< 0.001[C*]
	Present	33 (94.29%)	0	33 (47.14%)	
48 hours	Absent	0	34 (97.14%)	34 (48.57%)	< 0.001[C*]
	Present	35 (100%)	1 (2.86%)	36 (51.43%)	
72 hours	Absent	0	35 (100%)	35 (50%)	< 0.001[C*]
	Present	35 (100%)	0	35 (50%)	
5 days	Absent	4 (11.43%)	32 (91.43%)	36 (51.43%)	< 0.001[C*]
	Present	31 (88.57%)	3 (8.57%)	34 (48.57%)	
7 days	Absent	6 (17.14%)	29 (82.86%)	35 (50%)	< 0.001[C*]
	Present	29 (82.86%)	6 (17.14%)	35 (50%)	
15 days	Absent	11 (31.43%)	31 (88.57%)	42 (60%)	< 0.001[C*]
	Present	24 (68.57%)	4 (11.43%)	28 (40%)	
1month	Absent	13 (37.14%)	33 (94.29%)	46 (65.71%)	< 0.001[C*]
	Present	22 (62.86%)	2 (5.71%)	24 (34.29%)	
2 months	Absent	9 (25.71%)	34 (97.14%)	43 (61.43%)	< 0.001[C*]
	Present	26 (74.29%)	1 (2.86%)	27 (38.57%)	
3 months	Absent	4 (11.43%)	32 (91.43%)	36 (51.43%)	< 0.001[C*]
	Present	31 (88.57%)	3 (8.57%)	34 (48.57%)	
4 months	Absent	12 (34.29%)	28 (80%)	40 (57.14%)	< 0.001[C*]
	Present	23 (65.71%)	7 (20%)	30 (42.86%)	
5 months	Absent	21 (60%)	30 (85.71%)	51 (72.86%)	0.0156[C*]
	Present	14 (40%)	5 (14.29%)	19 (27.14%)	
6 months	Absent	29 (82.86%)	34 (97.14%)	63 (90%)	0.1229[MC]
	Present	6 (17.14%)	1 (2.86%)	7 (10%)	

At **6 hours**, majority of participators in the control group **(82.86%) reported present phantom sensations**, while **none of the subjects in the ketamine group (100%) had phantom sensations (p-value < 0.001)**. Similar results were seen at **12, 24, and 48 hours**, where most of the control group still experienced phantom sensations, while the ketamine group showed a higher rate of absence of phantom sensations. By **72 hours, all subjects in the ketamine group (100%) no longer experienced phantom sensations,** whereas the control group still had **100%** reporting phantom sensations. This trend continued up to 5 days, with the ketamine group showing significantly fewer instances of phantom sensation. By **6 months**, however, the difference between the two groups became less pronounced, with only a slight difference **(p-value = 0.1229)**, and the majority of subjects in both groups did not report phantom sensations. These findings suggest that ketamine effectively reduced the occurrence of phantom sensations in the early postoperative period, but over time, both groups showed a decrease in phantom sensations.

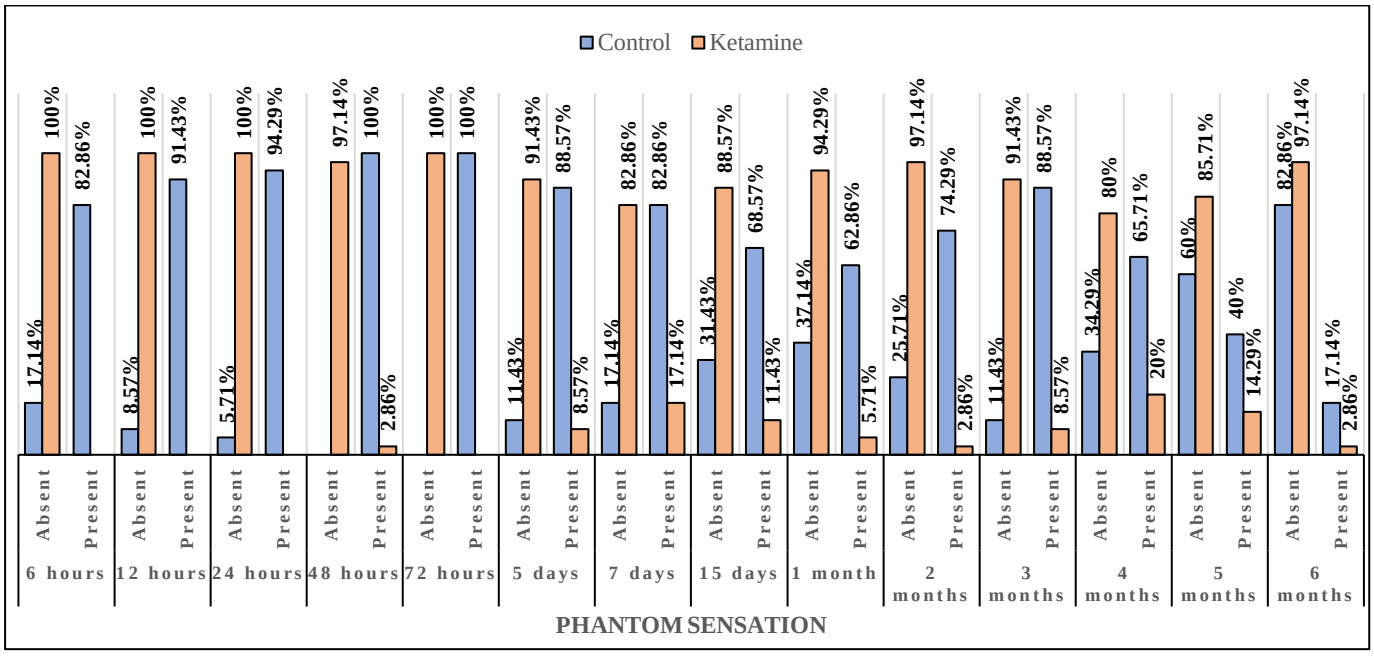


Figure 8: Distribution of phantom sensation over groups at different time points.

Table 7: Comparison of Phantom limb pain (NRS) over groups at different time points.

Time point	Sub Category	Control	Ketamine	Total	p-value
6 hours	M ± SD Mdn (Min, Max)	5.46 ± 2.68 6 (0, 8)	0 ± 0 0 (0, 0)	2.73 ± 3.33 0 (0, 8)	< 0.001^{MW*}
12 hours	M ± SD Mdn (Min, Max)	6.06 ± 2.1 7 (0, 8)	0 ± 0 0 (0, 0)	3.03 ± 3.39 0 (0, 8)	< 0.001^{MW*}
24 hours	M ± SD Mdn (Min, Max)	5.97 ± 2.11 7 (0, 8)	0 ± 0 0 (0, 0)	2.99 ± 3.35 0 (0, 8)	< 0.001^{MW*}
48 hours	M ± SD Mdn (Min, Max)	5.57 ± 1.63 6 (0, 7)	0.09 ± 0.51 0 (0, 3)	2.83 ± 3.01 1 (0, 7)	< 0.001^{MW*}
72 hours	M ± SD Mdn (Min, Max)	4.71 ± 1.72 5 (0, 7)	0 ± 0 0 (0, 0)	2.36 ± 2.67 0 (0, 7)	< 0.001^{MW*}
5 days	M ± SD Mdn (Min, Max)	2.6 ± 1.72 3 (0, 5)	0.14 ± 0.6 0 (0, 3)	1.37 ± 1.78 0 (0, 5)	< 0.001^{MW*}
7 days	M ± SD Mdn (Min, Max)	1.49 ± 1.54 2 (0, 5)	0.31 ± 0.9 0 (0, 3)	0.9 ± 1.38 0 (0, 5)	< 0.001^{MW*}
15 days	M ± SD Mdn (Min, Max)	0.49 ± 1.01 0 (0, 3)	0.17 ± 0.57 0 (0, 2)	0.33 ± 0.83 0 (0, 3)	0.1498^{MW}
1 month	M ± SD Mdn (Min, Max)	1.11 ± 1.43 0 (0, 4)	0.06 ± 0.34 0 (0, 2)	0.59 ± 1.16 0 (0, 4)	< 0.001^{MW*}
2 months	M ± SD Mdn (Min, Max)	0.97 ± 1.48 0 (0, 4)	0.11 ± 0.68 0 (0, 4)	0.54 ± 1.22 0 (0, 4)	0.0011^{MW*}
3 months	M ± SD Mdn (Min, Max)	1.71 ± 1.86 2 (0, 6)	0.14 ± 0.6 0 (0, 3)	0.93 ± 1.58 0 (0, 6)	< 0.001^{MW*}
4 months	M ± SD Mdn (Min, Max)	1.14 ± 1.67 0 (0, 5)	0.06 ± 0.34 0 (0, 2)	0.6 ± 1.31 0 (0, 5)	< 0.001^{MW*}
5 months	M ± SD Mdn (Min, Max)	0.43 ± 1.09 0 (0, 4)	0 ± 0 0 (0, 0)	0.21 ± 0.8 0 (0, 4)	0.0213^{MW*}
6 months	M ± SD Mdn (Min, Max)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	0 ± 0 0 (0, 0)	1^{MW}

Around 6 hours, the control group had a **higher phantom limb pain score** whereas the ketamine group had no pain, with a **statistically notable similarity (P value< 0.001**). Similar results, observed at **12, 24, 48**, **and 72 hours**, where control group had notably elevated pain scores contrast to ketamine group. By **5 days**, while the control group still reported some pain, the ketamine group's pain was **significantly lower**. However, by 15 days, the pain scores were similar between two groups **(P value = 0.1498).** At later time points, such as **1 month, 2 months, and 3 months**, the ketamine group continued to report significantly lower pain levels in contrast to control group. By 6 months, **no pain was reported in either group (P value = 1)**. These results suggest that ketamine significantly reduced phantom limb pain in the early postoperative period, with a persistent benefit for several months.

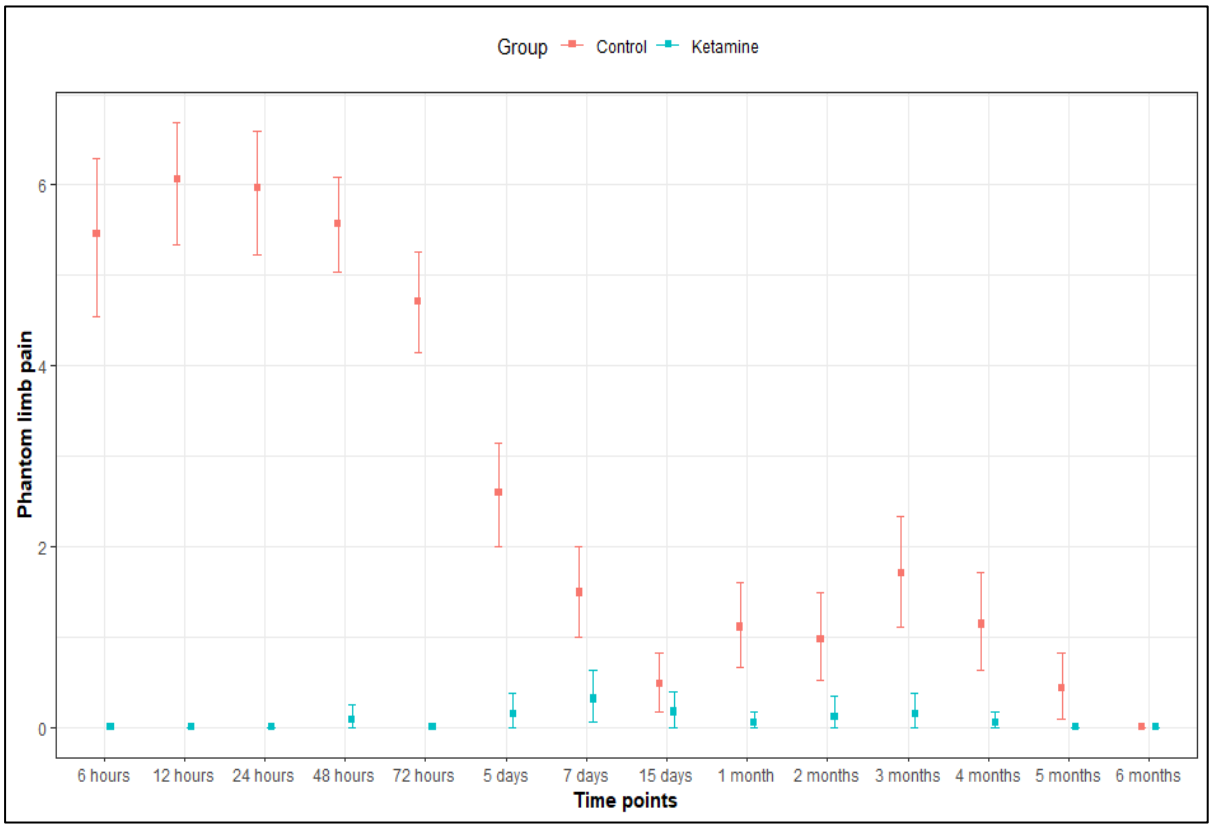


Figure 9: Mean diagram of Phantom limb pain over a period and group.

The subsequent table shows the comparison of number of days of pain symptoms during the month of interview over groups at different time points.

Table 8: Comparison of number of days of pain symptoms during the month of interview over groups at different time points.

Time point	Sub Category	Control	Ketamine	Total	p-value
1 month	**M ± SD** **Mdn (Min, Max)**	**2.34 ± 3.19** **0 (0, 10)**	**0.11 ± 0.68** **0 (0, 4)**	**1.23 ± 2.55** **0 (0, 10)**	**< 0.001^{MW*}**
2 months	**M ± SD** **Mdn (Min, Max)**	**1.71 ± 2.84** **0 (0, 10)**	**0.09 ± 0.51** **0 (0, 3)**	**0.9 ± 2.19** **0 (0, 10)**	**0.0014^{MW*}**
3 months	**M ± SD** **Mdn (Min, Max)**	**2.29 ± 2.64** **2 (0, 9)**	**0.14 ± 0.6** **0 (0, 3)**	**1.21 ± 2.19** **0 (0, 9)**	**< 0.001^{MW*}**
4 months	**M ± SD** **Mdn (Min, Max)**	**1.54 ± 2.37** **0 (0, 7)**	**0.06 ± 0.34** **0 (0, 2)**	**0.8 ± 1.84** **0 (0, 7)**	**< 0.001^{MW*}**
5 months	**M ± SD** **Mdn (Min, Max)**	**0.51 ± 1.34** **0 (0, 5)**	**0 ± 0** **0 (0, 0)**	**0.26 ± 0.97** **0 (0, 5)**	**0.0213^{MW*}**
6 months	**M ± SD** **Mdn (Min, Max)**	**0 ± 0** **0 (0, 0)**	**0 ± 0** **0 (0, 0)**	**0 ± 0** **0 (0, 0)**	**1^{MW}**

The total days with pain manifestation throughout the month of evaluation at various time points between the control and ketamine groups shows **significant differences** at each point except for **6-month** follow-up. At **1 month**, the control group experienced significantly more pain contrast to ketamine group, with a **P value of < 0.001**. This trend continued through 2, 3, and 4 months, with the ketamine group reporting significantly fewer pain days. By 5 months, the control group still had some pain, while the ketamine group reported none, with **statistically notable significance (P value = 0.0213)**. Around **6 months**, both groups reported no pain, and no remarkable similarity among them **(P value = 1)**. Overall, use of ketamine

significantly reduced amount of days with pain manifestations throughout follow-up period, especially in the early months.

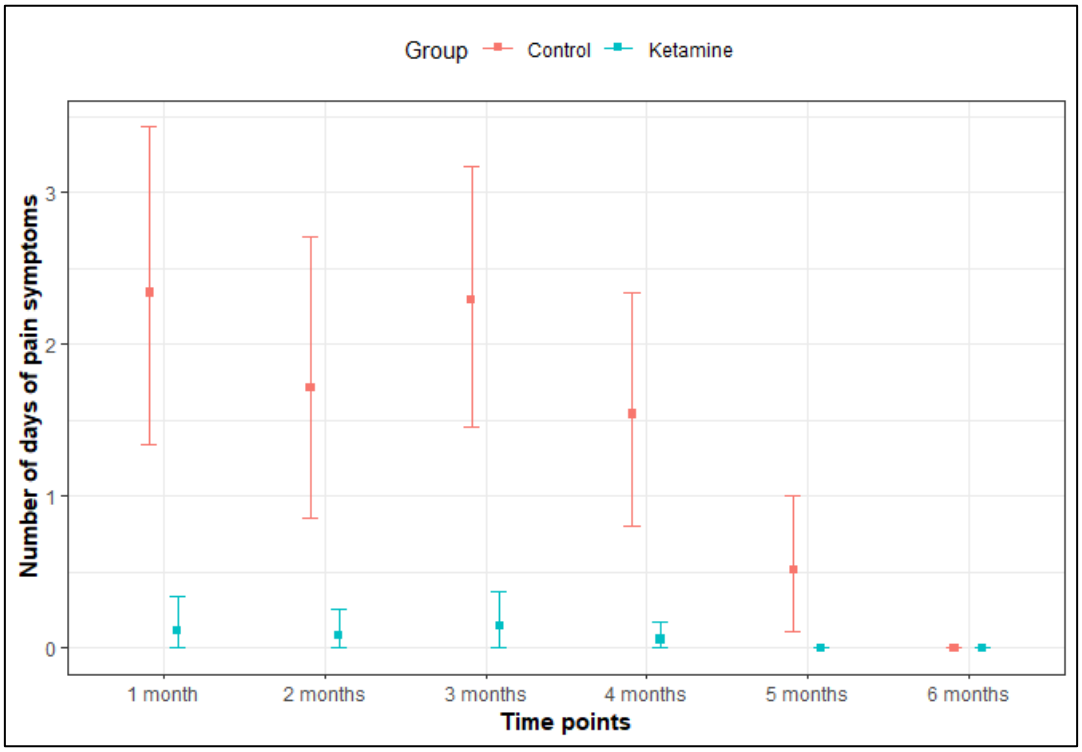


Figure 10: Mean plot of number of days of pain symptoms over time and group.

The below table depicts the comparison of Effect on Quality of life among groups.

Table 9: Comparison of Effect on Quality of life over groups.

Time point	Sub Category	Control	Ketamine	Total	p-value
1month	No	27 (77.14%)	1 (2.86%)	28 (40%)	< 0.001[C]*
	Yes	8 (22.86%)	34 (97.14%)	42 (60%)	
2months	No	27 (77.14%)	1 (2.86%)	28 (40%)	< 0.001[C]*
	Yes	8 (22.86%)	34 (97.14%)	42 (60%)	
3months	No	32 (91.43%)	3 (8.57%)	35 (50%)	< 0.001[C]*
	Yes	3 (8.57%)	32 (91.43%)	35 (50%)	
4 months	No	29 (82.86%)	3 (8.57%)	32 (45.71%)	< 0.001[C]*
	Yes	6 (17.14%)	32 (91.43%)	38 (54.29%)	
5months	No	16 (45.71%)	0	16 (22.86%)	< 0.001[C]*
	Yes	19 (54.29%)	35 (100%)	54 (77.14%)	
6months	No	6 (17.14%)	0	6 (8.57%)	0.0295[MC]*
	Yes	29 (82.86%)	35 (100%)	64 (91.43%)	

Around **1 and 2 months**, a large proportion of the control group reported **no effect on their quality of life (77.14%),** while almost **all individuals in the ketamine group reported a positive effect (97.14%)**. This trend continued at **3 and 4 months**, where 91.43% and 82.86% of the control group reported no improvement, compared to **91.43%** and **91.43%** in the ketamine group reporting **positive effects**. By **5 months**, towering percentage in control group (54.29%) reported upgraded quality of life, but ketamine group had 100% improvement. By 6 months, the difference remained **statistically significant**, with 82.86% of the control group reporting **no effect** and **100%** in the ketamine group experiencing an improvement in quality of life. The results suggest that **ketamine significantly improves the quality of life over time.**

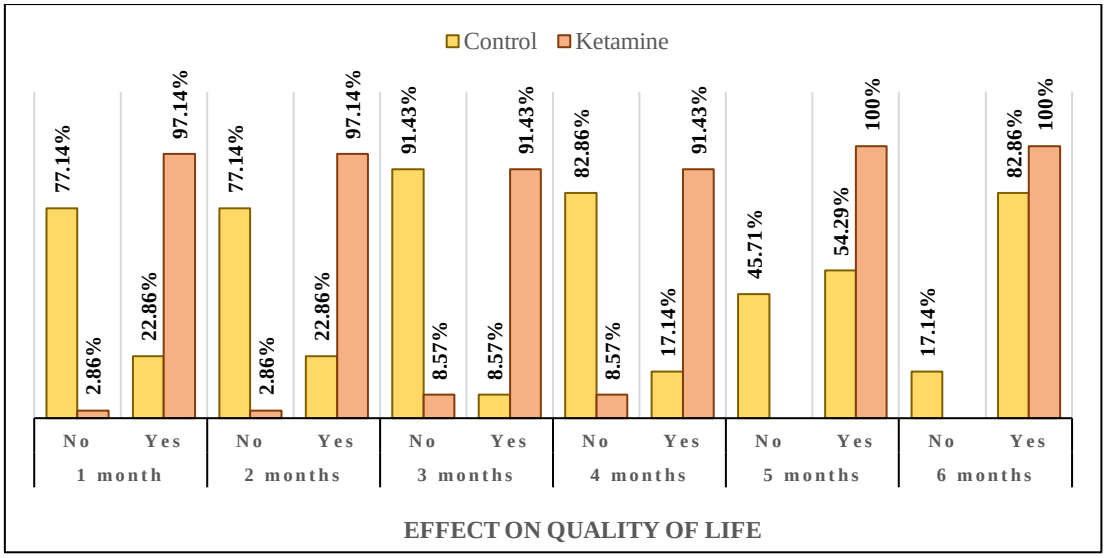


Figure 11: Distribution of effect on quality of life over groups at different time periods.

DISCUSSION

The incidences of phantom limb pain as presented from historical times to the recent periods have shown diverse figures that go from around only 2% in the earlier records to the higher rates seen currently. Then again, differences in these statistics might have been due to the fact that patients in the past hardly complained of pain. Sherman and co-authors found, only 17% of phantom pain cases were taken care of [20]. Thus, it is essential to uniformly define phantom limb pain to make sure that the treatment is effective.

Phantom pain means the feeling of pain in such a portion of the body as the limb, the organ, and another tissue. This happens after an amputation or a nerve injury. In podiatry, the main cause of PLP is amputation of limb which is in an untreatable condition. Stump neuromas, prosthetics, fibrosis, or even some residually populant local tissue inflammation, can be confused with PLP are the after effects of postoperative pain.

A non-typical array of feelings makes it difficult for patients to describe PLP, such as burning, stinging, aching, or piercing pain, mixed with the sensation of warmth and cold in phantom region. Besides these, the sensations are sometimes brought on by the environment, emotional state, or physical condition of the patient, and some of the time they will increase/decrease [21].

The chief method to diagnose phantom limb pain is through exclusion and mostly is based on the patient's background. Therefore, the majority of the laboratory determinations are superfluous. However, a complete blood count can facilitate determining whether a patient is infected or not. Another test like ultrasound can discover neuromas which are likely pain sources. In addition to this, if a psychological examination confirms that

the triggers the patient is exposed to are significantly contributing to his pain symptoms, a psychological test should be performed [22].

Phantom limb pains seem to be more present in those that report longer minutes of stump pain and usually do so at a slow pace. Medical research reveals that the dorsal root ganglion cells undergo changes when a nerve is totally disconnected, such that they change from being active to hyper excitable which makes them more sensitive to chemicals and mechanical stimuli. This intensified activity can be responsible for new connections in the dorsal horn and other parts of the brain.

On the molecular level, greater amounts of glutamate and NMDA (N-methyl D-aspartate) are affiliate to higher sensitivity of the feeling, which causes both allodynia and hyperalgesia. One of the reasons, maladaptive plasticity, is known for the persistence of PLP problem, that is loss of GABAergic inhibition, glutamate-induced chronic potentiation and structural changes such as myelination & axonal sprouting [23,24].

The N-methyl-D-aspartate receptor antagonist action against PLP has not been clear yet. These drugs, especially ketamine and dextromethorphan, have been able to deal with chronic pain syndromes, while memantine has brought about certain results. As a Cochrane review contained in six different studies on memantine to placebo, stated that, there was no findable significance in pain [25,26]. On the other hand, ketamine infusions have shown better treatment outcomes. Their similar mechanisms aside, the difference in efficacy between ketamine and memantine is not clear. Evidence exists at Level 2 more so in support of the use of ketamine infusions with phantom limb pain.

Shanthanna & co- worker's, case report successfully demonstrated that an early & efficient utilization of potent NMDA antagonist ketamine continuous IV infusion led to the complete remission of PLP. This study also says, pre-amputation pain levels play a significant role along with quantity & quality of sensory input at the time of nerve injury, in occurrence of post amputation PLP. Animal studies had demonstrated the central role played by the NMDA receptor activation in nerve injury models & also modifications of these changes when it was pre-empted by NMDA antagonist ketamine. Ketamine a potent NMDA antagonist decreases the C fibre sensitization & sensory input, as well prevention of supraspinal and cortical reorganization changes if it is pre-emptively administered to patients [27].

Animal research has confirmed the NMDA receptor activation plays in development of nerve injury in models, and also has proved that those changes can be moderated when it was pre-empted by NMDA antagonists [28,29]. That analysis of reducing sensory input and decreasing C fibber sensitization brings in the suggestion for regional blockade which is actually pre-emptive analgesia.

One of the studied (in cancer) and phantom limb pain relief routes for Ketamine is the use of various routes has been in cancer and phantom limb pain. The analgesic effects of occur at plasma concentrations above 100-150 ng/ml, anaesthesia occurs at high dose. However, a low dose ketamine is unlikely to induce anaesthesia but may provide pain relief, based on the studies made in the past. Apparently, this concludes "that ketamine works for phantom limb pain", where often opioids fail. Studies decide that administration of low-dose intravenous ketamine might be an appropriate approach in the healing process for acute phantom limb pain [30,31].

Wilson & colleges assessed the efficacy of pre-emptively utilized epidural racemic ketamine with bupivacaine on modulation of sensory input of post amputation pain & sensory processing. They assessed 53 subjects for a year who underwent lower extremity amputation whoever experienced combination of subarachnoid block & epidural bolus preceding infusion with racemic ketamine & bupivacaine and pain evaluation was done at 8 days, 6 weeks, 3 months, 6 months & 12 months post procedure. They proved acute effects of ketamine on ongoing sensitization, peri-operative sensory attenuation, ketamine group had significant reduction in stump mechanical sensitivity, alteration in pain processing, reduced requirement and significant improvement with post operative analgesia and overall incidence of phantom limb pain. This study also proved short & long term effects on pain perception is due to modulation of sensory input at the time of amputation, the effects of massive glutamate release & excitotoxic discharge at the time of nerve injury & which can be modified with adequate amount of sensory blockade with NMDA receptor antagonist Ketamine. Henceforth, this study led to conduction our research where pre-emptive dense blockade with intrathecal Bupivacaine with preservative free racemic ketamine proved efficiency of intrathecal ketamine on acute analgesic strategy with acute sensory response, additionally reduced incidence of phantom limb pain, stump sensitivity, reduced post operative analgesia and improvement of quality of life [31].

A meta-analysis included 28 studies with PubMed, EMBASE and CENTRAL search by Susan et al, collectively proposed efficiency of N-methyl-D-Aspartate receptor antagonist as primary treatment for chronic neuropathic pain. Treatment with ketamine decreases pain in post amputation pain with overall efficient size: -1.8 [confidence interval 95%- 1.98, -0.37, P= 0.21] [32].

IV infusion of ketamine at anaesthetic & subanaesthetic doses enhances significant pain relief in patients suffering from refractory complex regional pain syndrome. Intranasal administration of low-dose ketamine also decreases pain scores in patients with neuropathic pain of various origins. Several researches have proven that IV ketamine infusion sufficiently reduces pain scores in patients with complex regional pain syndrome. *N*-methyl-D-aspartate receptors have been an attractive target for treatment of chronic neuropathic pain for two decades.

Ketamine & dextromethorphan remains the most studied NMDAR antagonists in clinical setting for treatment of patients with neuropathic pain. NMDAR antagonists are very effective in reducing hyperalgesia and allodynia caused by nerve injury in animal models. However, clinical studies suggest that the therapeutic effects of this class of drugs are mostly limited to patients with complex regional pain syndrome & painful diabetic neuropathy. An ideal treatment for neuropathic pain would be to reduce the increased activity of NMDARs while maintaining their physiological function [33].

According to previous literatures, we decided to run this research employing Ketamine, a NMDA receptor antagonist as a pre-emptive analgesia intrathecally in a sub arachnoid block as an addictive with local anaesthetic injection Bupivacaine among the patients who underwent lower limb amputation. The trial was developed to evaluate the patient's overall quality of life.

Almost all patients reported no phantom limb sensation or pain in immediate post operative period, while very few patients had only phantom limb sensation after few months of post amputation with only rare, if at all, phantom pain. This study clearly demonstrated that pre-emptive Ketamine treatment lessens Phantom limb sensation.

In our research, ketamine, as an NMDA receptor antagonist, depicted a notable reduction in stump pain as opposed to the normal saline group. The members in ketamine group indicated a remarkable reduction in PLP & pain in immediate post-surgery phase in contrast to normal saline group, while they experienced improved pain. On the other hand, the ketamine group did not have a lot of days of ghost leg pain with only a few.

LIMITATIONS

As Phantom Limb Pain is a purely sensory experience, it can only be described by the patient, making it difficult to objectively quantify and compare across individuals. Each person's phantom limb sensation can vary significantly in terms of quality, location, intensity, and frequency, making it challenging to develop universal assessment tools. While some scales exist to measure PLP, there is no single, widely accepted gold standard for evaluating its severity and characteristics. Patients may be influenced by their own expectations, the clinician's questions, or social factors when describing their phantom pain, potentially introducing bias in reporting. Differentiating between pain arising from the phantom limb and pain originating from the residual limb stump can be challenging, further complicating evaluation. Due to the subjective nature of PLP, conducting rigorous research studies is often difficult, requiring careful consideration of study design, control groups, and outcome measures. Psychological factors like anxiety and depression can influence the perception and reporting of phantom pain, making it important to consider mental health aspects in evaluation.

CONCLUSION

Phantom limb pain is a widely recognized issue among amputees and has been the focal point of attention of researchers across the globe. The precise triggers or mechanisms of the phantom limb phenomenon are still unknown, but the studies found out that the acquired NMDA and glutamate together with the amplification of the sensitivity which leads to allodynia, hyperalgesia, and origin of PLP is the molecular basis of it. Intrathecal ketamine proved to be effective in cutting down postoperative stump pain, and the phantom limb sensation, the phantom limb pain in the early recovery period while increased the quality of the patient's life through the benefits which remained for several months. This method puts intrathecal ketamine out there as a useful strategy for treating post amputation pain.

SUMMARY

In this research we compared the efficacy of ketamine in prevention of PLP by intrathecal administration of ketamine and normal saline as an adjuvant to bupivacaine in a spinal anaesthesia for patients, subjected to elective lower limb amputation. This experiment was conducted in 70 patients of ASA grade 1 & 2 undergoing lower limb amputation on an elective basis under spinal anaesthesia. The patients were randomly distributed by “opening a sealed envelope method" into two groups, Group K (Ketamine, number= 35) and Group C (Control, number= 35). Demographic analysis was similar in relation among the groups. With proper aseptic precautions, subarachnoid block was done using injection Bupivacaine heavy (0.5%) 2ml along with 0.5ml of either of the investigational drug on the basis of randomly allocated method. HR, non-invasive BP, RR and SPO2 were all observed during preoperative period. Post operatively on NRS pain scale SP, PLS, PLP were evaluated from 6 hrs, 12 hrs, 24 hrs, 48 hrs, 72 hrs, 5 days, 7 days & 15 days, 30th day of each month for 6 months post operatively, until the patient get discharge.

After the patient gets discharge, telephonic conversation was utilized to note the post operative pain.

Rescue post operative pain medications were recorded. Ketamine group illustrated the reduction significance of SP, PLS & PLP during early & late post operative phase when compared with control group. Improvement in the quality of life was significant in ketamine group contrast to control group. So, ketamine as an antagonist of NMDA receptor efficiently sensitized the onset of phantom limb pain.

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ANNEXURE-I

INFORMED CONSENT FORM

KAHER's J N M C Belagavi

"EFFECT OF INTRATHECAL KETAMINE IN PREVENTION OF PHANTOM LIMB PAIN FOLLOWING LOWER EXTREMITY AMPUTATION SURGERIES: A RANDOMIZED CONTROLLED TRIAL".

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

OBJECTIVES:

PRIMARY OBJECTIVE: To study the effect of intrathecal ketamine in prevention of phantom limb pain following lower extremity amputation surgeries.

SECONDARY OBJECTIVE: To assess the incidence and severity of post amputation phantom limb pain.

INTRODUCTION: MR/MRS/MS _____ we are requesting you to enroll yourself in study titled "Effect of intrathecal ketamine in prevention of phantom limb pain following lower extremity amputation surgeries: A randomized controlled trial" conducted by DR.__Post Graduate in MD Anaesthesiology under the guidance of DR._____, MD, Associate Professor, Department of Anaesthesiology, J.N. Medical College, Belagavi under KAHER, Belagavi.

Explanation of procedure: On the day of surgery, after being shifted to the operating room, the standard monitors consisting of pulse oximetry, non-invasive blood pressure and electrocardiogram will be attached, you will be allocated in a randomized manner by sealed envelope method in two groups and the study drugs, Group K {ketamine 25mg + Bupivacaine 10mg} or Group C {Sterile normal saline 0.5ml + Bupivacaine 10mg} will be administered intrathecally for subarchanoid block for undergoing elective lower extremity

amputation surgery.

Withdrawal from participation in the study: Participation in this study in voluntary.You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/ will not get any benefits by participating in this study. The data gathered will help population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study**.**

Privacy and confidentiality: The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you,will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact:

"Name of the student/ PI, mobile number, email ID". If you have any question or complaints with regardto your right as study participant you may contact **Dr. Harsha Hegde**, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study **"Effect of intrathecal ketamine in prevention of phantom limb pain following lower extremity amputation surgeries: A randomized controlled trial".** My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature/ left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II- PROFORMA

"EFFECT OF INTRATHECAL KETAMINE IN PREVENTION OF PHANTOM LIMB PAIN FOLLOWING LOWER EXTREMITY AMPUTATION SURGERIES: A RANDOMIZED CLINICAL TRIAL".

Patient's Name: I.P No:

Age: Date:

Gender: Anaesthesiologist:

Address: Contact no:

Pre- anaesthetic evaluation:

Chief complaints:

Past History:

H/o co-morbidities and drug intake:

H/o previous surgeries:

Previous anaesthetic experience:

General physical examination:

Height (cms): Weight (Kgs): BMI:

Pallor: Icterus: Cyanosis: Clubbing: Lymphadenopathy:

BP: PR: RR: SpO2:

Systemic examination:

RS: **CVS:**

CNS: **GIT:**

Airway Assessment:

Teeth: Jaw movements: MPG:

Investigations:

Hb (gm/dl): TLC: Platelet count:

Serum Creatinine**:** FBS: Chest x-ray: ECG:

Preoperative physical status: ASA Grade I/ II

Diagnosis:

Proposed surgery:

Data collection:

1. Preoperative pain assessment of affected limb

Pain assessment (NRS):

Number of days per month with pain symptoms in the previous month:

Preoperative pain medication:

2. Postoperative assessment by patient interview

Duration	6 hours	12 hours	24 hours	48 hours	72 hours	5 days	7 days	15 days
Stump pain (mean NRS)								
Phantom sensation (present/absent)								
Phantom limb pain (mean NRS)								
Rescue pain therapy Dosage, frequency and compliance								

3. **Postoperative assessment by telephonic conversation with study participants:**

Duration	1 month	2months	3months	4 months	5 months	6 months
Stump pain (mean NRS)						
Phantom sensation (present/absent)						
Phantom limb pain (mean NRS)						
Number of days in a month with pain symptoms during the month of interview						
Rescue pain therapy Dosage, frequency and compliance						
Effect on quality of life/daily routine(yes/no)						

If any alternate pain therapy used with details:

Signature of the anaesthesiologist:

Signature of the principal investigator:

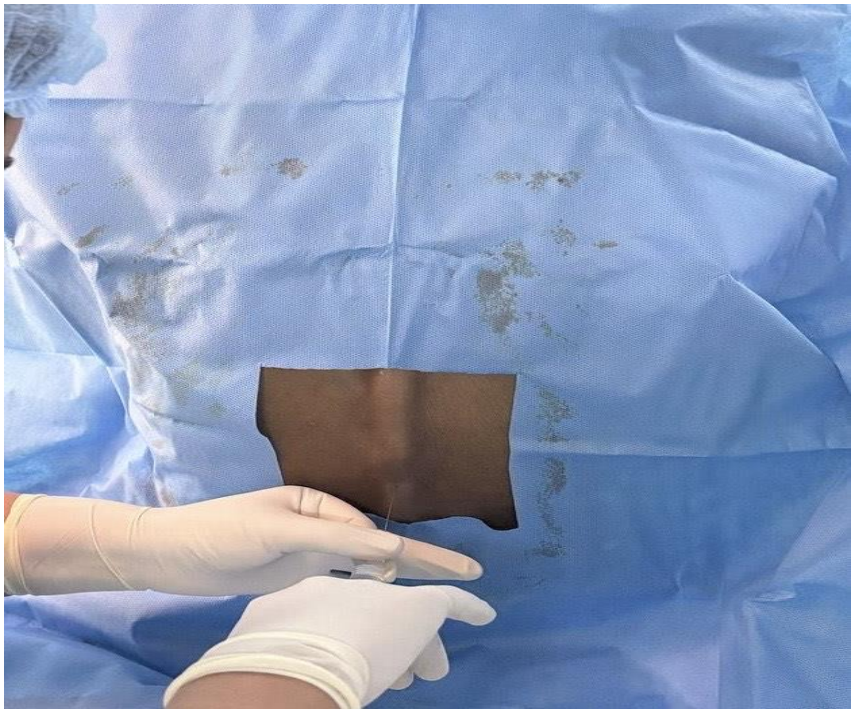
ANNEXURE III- PHOTOGRAPHS

PHOTOGRAPH 1- KETAMINE AMPOULE

PHOTOGRAPH 2- BUPIVACAINE AMPOULE

PHOTOGRAPH 3- 27 GAUGE WHITACRE SPINAL NEEDLE WITH INTRODUCER

PHOTOGRAPH 4- ADMINISTRATION OF SPINAL



ANNEXURE IV- MASTER CHART