Pain - Mechanism, Types, Pathways, And Management: A Comprehensive Review

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ABSTRACT

Pain is the most common symptom which brings a patient to the hospital. It is an unpleasant sensory or emotional experience that may or may not involve tissue damage. Understanding the mechanisms of pain is vital for the proper management of pain. Pain can be divided into acute and chronic pain on the basis of duration. Pain mechanisms are Nociceptive, Neuropathic, Nociplastic, and Psychogenic. Simple medications like Acetaminophen can manage pain. However, uncontrolled pain may require opioids. Chronic and persistent pain may require pain management as per the WHO Ladder.

KEYWORDS: Pain, Pathways, Mechanism, WHO Ladder, Opioids.

ABBREVIATIONS

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, WHO: World Health Organization, VAS: Visual Analogue Scales, NRS: Numerical Rating Scales, SGR: Substantia Gelatinosa Rolandi

1.0 INTRODUCTION

Pain is defined as "an unpleasant sensory and emotional experience associated with or resembling that is associated with actual or potential tissue damage [1]. The pain came from the word Peine (French), which in turn derived from the Latin word poena, meaning “punishment, penalty.” Pain is also derived from the Greek ποινή (poine), generally meaning "price paid, penalty, punishment [2,3].” Pain is a protective mechanism that stimulates individuals to withdraw from harmful stimuli, helps prevent further damage, and helps resolve damage that occurs. Pain is resolved when a noxious stimulus is removed but may persist sometimes.

Pain is presenting complaint in patients visiting emergency services in more than 50% of cases [4]. Chronic pain prevalence ranges from 12-80% of the population in various epidemiological studies [5]. Pain is described by the region of the body (upper limbs, back and others.), organ system (urinary, cardiac, respiratory, and others.), duration, ratio and periodicity, severity, and underlying cause of pain. Pain is acute; however, when it lasts more than 3 months, it is called chronic pain. Causes of chronic pain are such as cancer, arthritis, peripheral neuropathy, chronic pelvic pain, fibromyalgia, and idiopathic pain.

2.0 MECHANISMS

Nociceptive pain is caused by noxious stimuli to sensory nerve-ending fibers exceeding thresholds. It can be classified into somatic, deep somatic and visceral. It can also be classified according to the type of noxious stimuli into mechanical, thermal and chemical [6].

Neuropathic pain is perceived because of damage or trauma to nerve fibers or nervous tissue. It can be classified into Central, Peripheral, and mixed neuropathic pain. Neuropathic pain includes Diabetic neuropathies (painful), post-Herpetic neuralgia, entrapment neuropathy, and traumatic neuropathies. [7].

Nociplastic pain is perceived due to altered sensory processing and modulation in the central and peripheral nervous systems. This severe pain is multifocal and widespread compared to minimizing inflammation and nerve damage. Associated symptoms like insomnia, fatigue, memory loss and mood problems are seen. This pain includes fibromyalgia, chronic pelvic pain syndrome, irritable bowel syndrome, and others. [8].

Psychogenic pain is perceived without evidence of trauma, inflammation, or illness. It is associated with people having emotional, mental, or behavioral factors. This pain is frequently associated with grief, regret, emotional trauma, broken heart and others. Examples of these types of pain are headaches, back pain, and others [9].

3.0 IMPORTANCE OF PAIN

Though an unpleasant sensation, as has already been said, it is a protective mechanism. So we get conscious whenever there is the presence of any nociceptive stimulus, and thus we look out for its removal, hence useful. Pain receptors are free nerve endings and bare nerve terminals. These are non-adapting in nature or adapt very little in relation to other sensory receptors in the body, so the pain proceeds as long as the receptors remain stimulated. The intensity of pain is directly proportional to the rate of tissue damage.

4.0 TYPES OF PAIN STIMULI

4.1 THERMAL STIMULUS

Often people begin to recognize pain when the skin receives heat above 45° C. At this temperature, tissue harm commences. By and by, tissue destruction follows increasing temperature. Therefore, it is evident that pain ensuing from thermal injury is due to the rate at which tissue damage is taking place and not with the entire damage so far that occurred.

4.2 CHEMICAL STIMULUS

Damage to tissues (particularly skin) releases some chemicals/Algogenic substances (pain-producing). These chemicals are Bradykinin, Serotonin, K+ ions, Histamine, Acids, Acetylcholine and Proteolytic enzymes. Prostaglandins and Substance P are not directly responsible for producing pain, but they do increase the sensitivity of free nerve endings and potentiate the power of other Algogenic substances.

4.3. MECHANICAL PAIN

Either due to stimulation of pain receptors or muscle contraction resulting in compression of blood vessels, hence ischemia. Also, spasms increase muscle metabolism and release pain-producing substances. But in the case of muscle spasms around the fractured bone or spasms of abdominal muscles, peritonitis is beneficial, as it does immobilization of harmed part, which is requisite in healing.

4.4. ISCHEMIC PAIN

In this pain, the more the rate of metabolism, the more quickly pain impresses. Reduced blood flow leads to a decreased oxygen supply, resulting in anaerobic respiration and the production of lactic acid and its accumulation in the tissues. Tissue damage due to lack of oxygen results in allogenic substances releasing the free nerve endings.

5.0 TYPES OF PAIN

5.1 FAST PAIN

Synonyms: sharp/pricking/acute/electric pain.
Type of stimulus: mechanical and thermal.
Usually felt within 0.1 seconds when a nociceptive stimulus is given.
Localization: well localized.
Afferent fiber: A-delta
For example, burns, pricks with a needle, and superficial pain.

5.2 SLOW PAIN

Synonyms: aching/throbbing/chronic/dull/visceral pain.
Type of stimulus: mechanical, thermal.
Localization: poorly localized diffuse kind of pain.
Afferent fiber: C fiber
Usually felt after a second and develops slowly over seconds or minutes as the damage continues.

6.0 AFFERENTS FOR PAIN

Peripheral nerves are divided based on varying degrees of myelination into three types of fibers, i.e., A (A-alpha, A-beta, A-gamma, A-delta), B, C (A fibers are heavily myelinated, and C fibers are unmyelinated). Afferents for pain are of two varieties,

A-delta and C fibers. A-delta fibers are myelinated (hence conduct faster with the velocity of 30 to 12 m/s), thicker (diameter of 2 to 5 µm) and are responsible for sharp localized pain. C fibers are unmyelinated (conduct with a velocity of 0.5 to 2 m/s), thin (0.3 to 1.5 µm diameter), and responsible for slow, poorly recognized pain. Both fibers have a high threshold for pain response, but C fibers have an even higher one. More the threshold means more resistance to stimulus.

7.0 COMPONENTS OF PAIN

Nociceptive: denotes the actual injurious component.

Affective: denotes the psychological component associated with fear /anxiety and others. So, our perception of pain is the sum of these two components.

8.0 PAIN TEMPERATURE PATHWAY / ANTEROLATERAL ASCENDING TRACT SYSTEM

The anterior ascending tract carries crude touch sensation, and the lateral ascending tract carries pain and temperature sensation. They move together hence called an Anterolateral ascending tract system.

Injury, tissue damage, or muscle spasms release algogenic substances that stimulate pain receptors or free nerve endings. First-order Neurons (A-delta / C Fiber) have their cell bodies in the dorsal root ganglion, their peripheral process towards the receptors (free nerve endings), and their central process in the dorsal horn of the spinal cord (particularly at SGR (Figure 1).

The peripheral process of first-order neurons, i.e., A-delta / C fiber, receives pain stimulus and thus transmits it. The central process of first-order neurons in the dorsal horn of the spinal cord gives off few ascending and descending branches throughout, forming a local tract there which is known as the dorsolateral tract of Lissauer (dorsal, because it gets formed in the dorsal horn and lateral because the second-order neurons synapse with the first-order neurons at the dorsal column and then move to contralateral lateral column of the spinal cord).

Second-order Neurons, as mentioned earlier that they synapse with first-order neurons at the dorsal column (Neurotransmitter between A-delta Fiber and Second-order neuron is Glutamate and between C fiber and the second-order neuron is Substance P), then they move to the contralateral Lateral column of the spinal cord. The first-order neurons are being added medially from the upper body, i.e., the lower body fibers are most lateral in the tract, and that from the upper body is most medial.

Second-order neurons traverse to the contralateral lateral column of the spinal cord after synapsing with first-order neurons at SGR and travel up to the thalamus, known as the lateral spinothalamic tract. Lateral spinothalamic tract, along with the Anterior Spinothalamic tract (carrying crude touch) and Spinotectal pathway (carrying Spinovisual reflexes), these three fuses together at the medulla oblongata and are called Spinal lemniscus / lateral lemniscus till the termination of spinotectal tract.

Now, especially the fast pain-carrying second-order neurons connect to the Ventro-posterolateral nuclei of the thalamus and slow pain-carrying second-order neurons, these are differently distributed, some of these are connected to ventroposterolateral nuclei, and many of them get connected to Intra-Laminar nuclei of the thalamus. Slow pain fibers on their way to the thalamus stimulate the Reticular formation (a set of interconnects best known for their role in promoting arousal and consciousness, known as the switch of the cerebral cortex, extending throughout the brainstem).

If the slow pain-carrying fibers carry a strong, painful stimulus, it irritates the reticular formation. The patient remains alert and awake, unable to sleep in severe pain. Third-order neurons begin from the thalamus, travel through the posterior limb of the Internal Capsule then transmit information to Somatosensory areas of the Cerebral Cortex (Post central gyrus): Quality / nature / intensity / location / comparison and recognition of pain. Limbic cortex (Cingulate gyrus) evokes emotional response (an affective component of pain) and insular cortex generates autonomic response on stimulation in the pain pathways [10,11].

8.1 LOCALIZATION OF PAIN

Fast pain is well localized rather than slow pain because C fibers are diffusely and multi-synaptically connected to their second-order neurons, whereas A-delta fibers have direct connections with their corresponding second-order neurons.

9.0 QUANTIFICATION OF PAIN

Various pain scales are developed to quantify and stratify the degree of pain. The pain scales improve communication about pain. Pain is an individual feeling experienced differently by different people so these scales are used to standardize pain severity. Pain scales can help in helps with the diagnostic process, tracking the progression of a condition, and determining how effective a treatment is in managing pain. Different pain scales are in use, each with its benefits and disadvantages. The pain scales fall under three main categories:

- **NRS**: Numbers are used to grade pain.

- **VAS:** Pictures of pain scales that best match pain level.
- **Categorical scales:** Words, numbers, colors, or locations are used to grade pain [12].

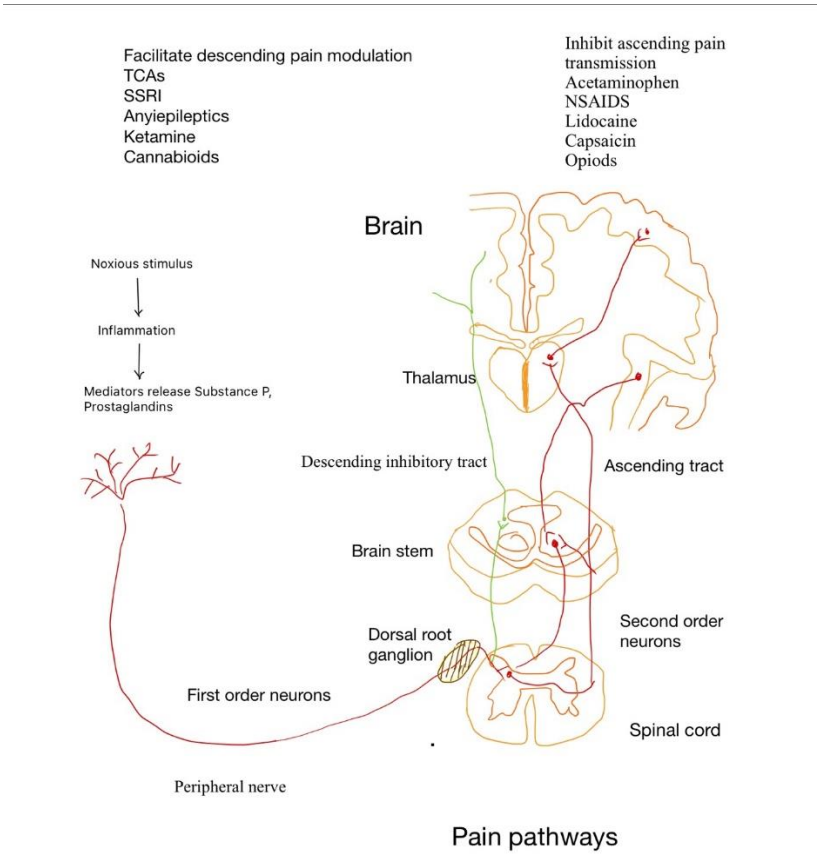

Figure 1. Pain pathways and mechanisms.

10.0 MANAGEMENT OF PAIN

Pain is a symptom of disease, so prompt and correct diagnosis and symptomatic relief are key to pain management. Timely relief of pain is mandatory, and simultaneous investigations can be done. Simple pain medications like Acetaminophen and NSAIDS are useful in 20% to 70% of cases [13]. Pain intensity can vary according to psychological factors like social support, cognitive behavioral therapy, excitement, or distraction [14]. Relief from acute and chronic pain should be recognized as a human right, and chronic pain is differentiated into different pain syndromes. Pain medicine has been developed as a separate medical specialty for proper management [15]. The WHO analgesic ladder was a strategy the WHO proposed in 1986 to provide adequate pain relief for cancer patients [16]. The key concept of the ladder is that it is essential to have adequate knowledge about pain, to assess its degree in a patient through proper evaluation, and to prescribe appropriate medications [17].

WHO ladder of pain mainly consisted of three steps [4]:

1. **First step**. Mild pain: Non-steroidal anti-inflammatory drugs (NSAIDs) (non-opioid analgesics) or Acetaminophen with or without adjuvants.
2. **Second step**. Moderate pain: weak opioids (hydrocodone, codeine, tramadol) with or without non-opioid analgesics and with or without adjuvants.
3. **Third step**. Severe and persistent pain: potent opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with or without non-opioid analgesics, and with or without adjuvants.

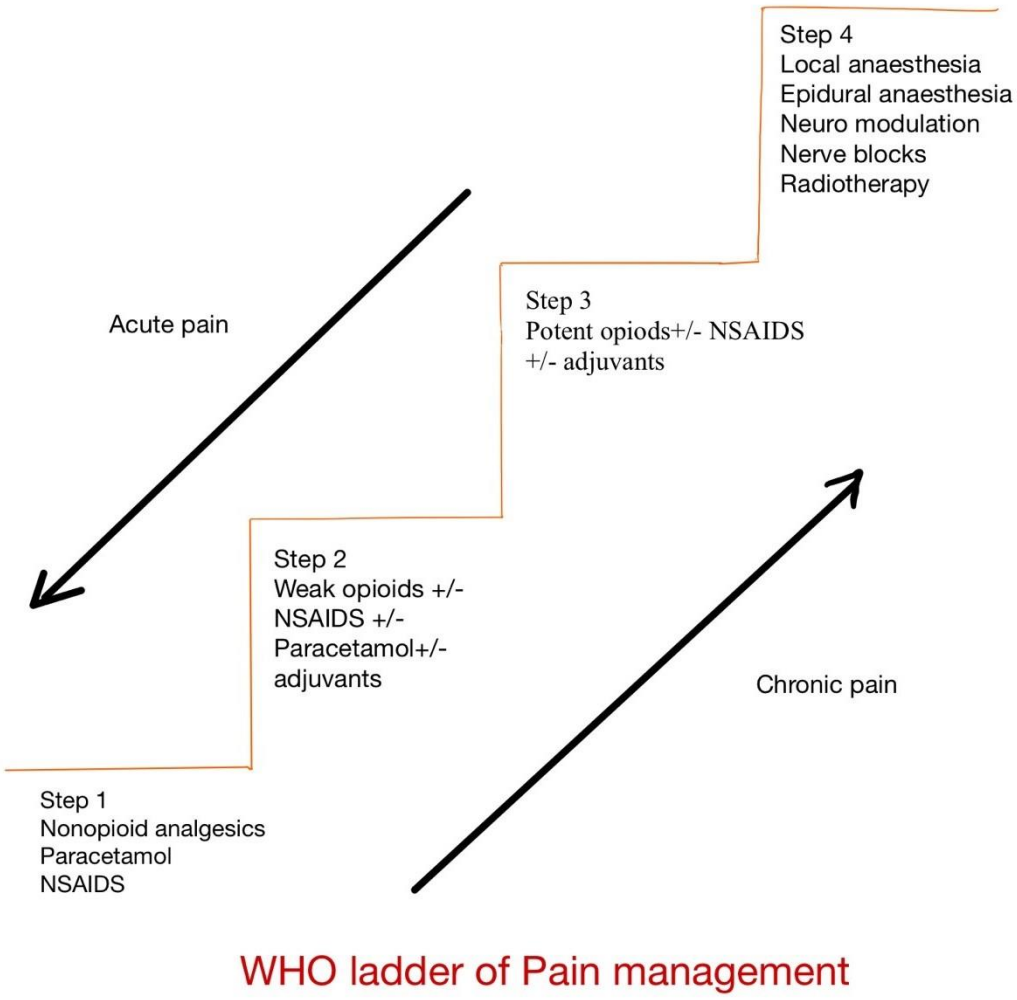

Figure 2

There are interventions (non-pharmacological) for treating pain refractory to opioids, NSAIDs, Acetaminophen or adjuvants. This includes procedures such as nerve blocks, epidural analgesia, intrathecal instillation of local anesthetic and analgesic drugs with or without infusion pumps, neuromodulation with spinal cord stimulators, brain stimulators, ablative procedures (e.g., radiofrequency, microwave, cryoablation ablations; laser-induced thermotherapy, irreversible electroporation, electrochemotherapy), cementoplasty as well as palliation radiotherapy [18,19]. Pain relief is also attempted with various herbal medicines and procedures, e.g., Acupuncture. A study of herbal medicines involving 2050 participants found that *Capsicum frutescens* is effective in reducing pain compared to a placebo. Other herbal medicines like Devil's claw (*Harpagophytum procumbens* subsp. *procumbens*), Comfrey roots and leaves (*Symphytum officinale*), lavender essential oil, Willow bark extract (*Salix alba)*, common comfrey (*Symphytum officinale) and others.*, are also used commonly to and found to be more effective than placebo for the reduction in pain [20]. In a meta-analysis of 13 studies regarding chronic pain, pain relief with Acupuncture was minimal as compared to placebo [21]. Chronic pain is difficult to manage, so it requires a multidisciplinary team including physicians, psychologists, the specialty concerned (neurology, cardiology, urology and others.), physiotherapist, nurse and others [22]. Patients with social and family support require fewer analgesics, experience less pain, and improve faster than those without [14].

AUTHOR CONTRIBUTIONS

SS – Conceived and designed the analysis; wrote this article.
SKS, PA, VT, AD – Conceived and designed the analysis.
MK – Drafted the article; Critically revised the article.

CONFLICT OF INTEREST

None.

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