

Review Article

A Systematic Review of Pain

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Abstract: The management of pain is challenging despite it being the recent focus of extensive research. A number of clinical practice guidelines for the management of pain have been published worldwide over the past 2 decades. Pain is most appropriately treated with the use of opiates, and careful consideration should be given to the pharmacokinetic and pharmacodynamic properties of various analgesics to determine the optimal agent for each individual patient. This review will discuss chronic pain, including epidemiology, diagnostic tools, the multitude of co-morbidities, and common treatment modalities currently available to physicians.

Keywords: review, systematic, pain

A SYSTEMATIC REVIEW OF PAIN

Pain is a concept difficult to define and derived from “poena” in Latin (punishment, revenge, torture. According to the definition of International Association for the Study of Pain (IASP), “ pain is a sensorial unpleasant feeling and behavior that originates from a certain region of the body, that is can be dependent on tissue damage or not, and is accociated with previous experiences of the person ” . Pain is complex sensation with neurophysiological, biochemical, psychological, ethnic, cultural, religious, cognitive and environmental dimensions [1].

Neuropathic pain is defined by IASP as pain initiated or caused by primary lesion or dysfunction of nervous system. Patients with neuropathic pain account for 30-50% of subjects presenting to pain clinics [2]. Pain is always subjective. Each individual gains this experience as a consequence of painful conditions he/she has encountered throughout life. Many people state that they experience pain without tissue damage and physiopathological changes. This pain is perceived as a sensation deriving from any place in the body.; it also has emotional components. It is impossible to discriminate this sensation from that associated with tissue damage. If a patient defines a sensation as pain, physican should accept is as pain.

Nociception , is activity formed via receptors called nociceptors against painful stimulants and stimulants that will cause pain if they are prolonged. Pain is a nociception sensation and like other

perceptions, it is determined by the interaction between neurosensorial activity and organic and psychological factors [5].

Classification of pain

It is possible to classify pain according to various parameters.

- a) Physiological-clinical
- b) According to duration ,
- c) According to point of origin,
- d) According to its mechanisms.

Physiological- clinical pain classification

Physiological pain is a response to intensive painful stimulant. For example, escape reaction starts with the stimulation of nociceptors in order to escape pro stimulants that will harm the body, for example fire. Therefore, physiological pain in both a protection and alerting system for the body. In clinical pain, many physiological processes participate in the event.

Classification of pain according to its duration

Acute pain

It is pain that starts suddenly and is closely related to the causative lesion in time, place and severity starting with tissue damage and decreases gradually during recovery process until disappearing completely. It is almost always nosiceptive. Its function is to protect organism, localize and limit the damage. It may be associated with findings such as tachycardia and hypertension according to activation of autonomous nervous sytstem. Postoperative pain, renal colic,

myocard infarction and pancreatitis are acute pain pictures [4-6]. Acute pain is not syndrome or disease but a symptom.

Chronic pain

Chronic pain occurs with the continuation of pain after an acute disease picture or reasonable process of recovery. This process varies between 1-6 months. However, recently this concept has changed and pain lasting longer than expected is accepted as chronic pain irrespective of its duration.

Chronic pain is a complex picture that involves both nociceptive and neuropathic components, changes the quality of life after its stimulant function is over and in which psychological factors play role both in clinical picture and efficacy of treatment. In chronic pain, nociceptive, neuropathic components or both may be present. In many patients with chronic pain, autonomic responses are not as high as those in acute pain. However, irregularity of sleep and affective disorders are striking. Personal and environmental factors play part in chronic pain.

It exerts serious emotional, physical and economic burden on the person, his/ her family and the society [3]. Most common types of chronic pain are seen in musculoskeletal disorders, chronic visceral diseases, peripheral nerve, nerve roots, or posterior root ganglion lesions (causalgia, phantom extremity pain, postherpetic neuralgia) cranial nervous system (CNS) lesions (stroke, spinal cord injury, multiple sclerosis) and cancer [4-6]. While acute pain is evaluated as a symptom, chronic pain is a syndrome.

Classification of pain according to the regions it is derived from

Somatic pain

It is pain transmitted with somatic nerve fibers. It develops through stimulation of nerve endings with mechanical or chemical stimulants, pathological events leading to chronic stretching in connective tissue and inflammation of innervated structures [6]. It may be classified as superficial or deep. Superficial somatic pain develops with stimulants from skin, subcutaneous tissues, and mucous membranes. It is well localized and has the characteristics of sharp, stabbing, pulsating or burning pain, while deep somatic pain originates from muscles, tendons, joints and bones. It is dull and not localized well [4, 5].

Visceral pain

It is acute pain that develops related to abnormal function or disorder of visceral organs or their membranes (parietal pleura, pericardium, peritoneum). It starts slowly and is dull and aching. Its localization is difficult. It may emerge as pain reflected to other regions. The reflection of cardiac pain to left arm and

the reflection of diaphragmatic pain to left shoulder are its classical examples [4,5].

Sympathetic pain

Sympathetic pain emerges with the activation of sympathetic nervous system and its examples are vessel origin pain, reflex sympathetic dystrophy, and causalgias. The patient complains of feeling cold in painful region. There are dystrophic changes [3].

The classification of pain according to mechanism of development

Nociceptive pain

It may be defined as proper physiological response to painful stimulant [4]. It arises via the stimulation of special pain receptors termed as nociceptors found commonly in skin, muscle, connective tissue and visceral organs by physiopathologic events. It is associated with somatic or visceral organ injury [3, 7]. It is usually believed that nociceptive pain is proportional to estimated tissue damage. Somatic and visceral pains are examples of this type of pain. The main difference between somatic and visceral pain is that somatic pain is transmitted by sensory fibers while visceral pain is transmitted by sympathetic fibers. The examples of nociceptive pain are muscular and joint pains, cancer pain and tension type headache. In the treatment of nociceptive pain, good response is obtained to opioid analgesics, non steroid antiinflammatory drugs (NSAIDs) and peripheral nerve denervation [4, 6].

Neuropathic pain (Neurogenic pain)

It arises as a result of peripheral nerve trauma or metabolic diseases. Unlike inflammatory pain, it emerges long after nerve injury as a consequence of nervous system dysfunction or its primary lesion. In contrast to physiological pain, it is characterized by increased spontaneous pain without external stimulant or against a normally harmless stimulant. Somatosensory system is abnormally stimulated [4, 5, 8]. Neuropathic pain should be kept in mind when autonomic dysfunction accompanied with a different neurological lesion or paresthesia dysesthesia develops in motor and sensory regions. Pain may appear spontaneously. As pain threshold becomes lower, stimulants which are normally painless may lead to pain (allodynia). Response to stimulation may be both continuous and may have exaggerated amplitude (hyperalgesia). The sensation of pain may be reflected to healthy regions [3, 7, 8]. Generally, neuropathic pain responds less than nociceptive pain to opioid drugs and neurolytic procedures. In treatment, adjuvant analgesic drugs should always be used [9]. Mononeuropathy associated with nerve compression or inflammation, neuralgias like lightning, diabetic polyneuropathies and deafferentation pain can be considered among neuropathic pain models [8].

Deafferentation pain

This pain arises with the cessation of transmission of sensorial stimulants associated with lesions in peripheral or central nervous system to central nervous system [4].

Reactive pain

It arises in association with the stimulation of nociceptors as a consequence of reflex activation of motor or sympathetic afferents.

Psychomatic pain (Psychogenic pain)

These are feeling described as pain in conditions when psychic and psychosocial problems such as anxiety and depression increase. Somatization and hypochondriasis are among its examples. Although a painful condition may really exist, the actual problem is psychological and an unimportant tissue problem is felt excessively with the increase in the neurophysiological sensitivity of the patient [3].

Neuroanatomy and neurophysiology of pain

Medical treatment of pain has become easier with the understanding of physiology and neuroanatomy of pain event. Nociceptor term is used in reference to pain sensitive. Nociceptive system is composed of neurons receiving pain information (noxious stimulant) and transmitting it to cortex. Pain is a perception event within the framework of nociception [10].

Regions and systems playing role in the transmission of pain

The transmission of painful stimulants from periphery to central takes place in four stages. i.e. transduction, transmission, modulation and perception. Transduction and transmission function in the periphery, modulation in medulla spinalis and perception in the transmission of pain to central nervous system and perception of pain [11,12].

The transmission regions and systems of pain can be divided into four headings;

1. Nociceptors and surrounding regions
2. Medulla spinalis dorsal horn neuronal system
3. Afferent systems
4. Antinociceptive systems

Nociceptor and surrounding regions

The starting point of nociceptive processes are primary afferent nociceptors. Under normal conditions, painful stimulus is transmitted to spinal cord via nociceptor fibers.

Receptors termed nociceptors and responding to harmful (thermal, mechanic, chemical) stimulants play part in the perception of pain. Nociceptor cell bodies are found in spinal and trigeminal ganglions. These nerve ends consist of distal extensions of

demyelinated C fibers and myelinated delta fibers. Delta fibers are the thinnest of myelinated sensory afferent nerves, their diameter of axon vary between 2-7 μm and speed of transmission between 10-30 m/second. C fibers are demyelinated. Their diameter varies between 1-5 μm and speed of transmission is under a 2.5 m/second. The ends of A-delta fibers are called as thermal or mechanic nociceptors according to the type of stimulation. The activation of these nociceptors produces a sharp and well localized pain.

Nociceptors at the end of C fibers are termed as polymodal nociceptors. They are activated by severe mechanic, chemical or thermal stimulants [13, 14].

Peripheral nociception event following harmful stimulation to the skin can be outlined as follows [10]:

- a) Mechanical stimulant stimulates nociceptor directly. This stimulation is transmitted rapidly by A-delta fibers and enables prompt and early pain perception.
- b) Harmful mechanical stimulant disrupts the cell membrane permeability and integrity of tissues in that region, as a consequence of local cellular degradation, and precursors of bradykinin are released into extracellular space.
- c) Rapid chain biochemical reactions of these substances result in the bradykinin. Bradykinin directly activates nociceptor and leads to vasodilatation in peripheral vessels. In addition, bradykinin contributes to the formation of prostaglandins by influencing cellular membranes.
- d) Serotonin released from thrombocytes directly activates nociceptor as well as helping the release of prostaglandins by acting on cellular membranes.
- e) Outflux of potassium ions by cellular degradation activates nociceptors.
- f) Both due to direct tissue trauma and to the impact of serotonin and bradykinin on phospholipids in cellular membranes prostaglandins and leukotriens are released. Precursor substance is arachidonic acid. Prostaglandins develop from arachidonic acid, via cyclooxygenase enzyme. Prostaglandins both increase nociceptor sensitivity and lead to accumulation of more algescic substances by increasing vasodilatation in local circulation. From nociceptor endings which have become sensitive with an axon reflex mechanism, neuropeptides are released to surrounding tissues especially tachykinins (Substance-P), neurokinin and CGRP (calcitonin gene related peptide) initiate the events of edema and burning in the region. P-substance gives rise to release of histamin from mast cells.

Tachykinins are potent vasodilators. Thus, both nociceptor activation increases and edema and burning in that region is enhanced [10].

Spinal Cord Dorsal Horn Neurons

Medulla spinalis (MS) dorsal horn is the region where central endings of, primary afferent neurons synapse with spinal nociceptive neurons. Afferent pain fibers, after passing through Lissauer tractus, terminate in gray matter of posterior horn, mostly in marginal zone. Most of the fibers extend to one or two rostral or caudal segments, while some pass to contralateral posterior horn via anterior commissura.

Nociceptive ascending systems

There are five tracts in nociceptive output system. There are five tracts in nociceptive ascending system. Projections neurons of these tracts are cross each other. In anterior commissura and are present in anteriolateral column of spinal cord white matter [10, 15].

Spinothalamic tract: Spinothalamic tract originates from Lamina I, V, VII and VIII neurons and is classically considered the most important tract transmitting pain [4, 5]. In addition, it produces cortical and subcortical attention to pain [10, 15].

Spinoreticular tract : Spinoreticular system serves to create a general condition of alertness to harmful stimulant and to keep cortex and subcortical structures aware (limbic system and diencephalon) rather than being associated with localization and specificity of painful impulses [10, 15].

Spinomezencephalic tract : It plays an important role in the activation of antinociceptive descending tract [4-6, 8].

Spinopontoamygdal System : This system is associated with pain fear and memory involving behavioural and autonomic reactions to pain such as shouting, running away, mydriasis and cardiovascular-respiratory responses [4-6, 8].

Postsynaptic Dorsal Column: Collateral axons of thick fibers ascend at posterior root and form the large part of this pathway. It is thought that this pathway is important especially the transmission of visceral pain [4-6, 8].

Antinociceptive tract: An antinociceptive activity arises in dorsal horn and brain stem against painful stimulant. Especially with the discovery of endogenous opioid peptides, the presence of enkephalinergic and monoaminergic inhibition to painful impulses at spinal and supraspinal levels have been demonstrated [10, 15]. They can be examined in three groups:

- a) Enkephalinergic neurons in mesencephalic periaqueductal gray matter. These are in connection

with cerebral cortex and hypothalamus. It is thought that neurons of hypothalamic origin harbor endorphine [10].

- b) More laterally placed nucleus are present on bulbous and pons. Their main neurotransmitter is noradrenalin [10].
- c) Antinociceptive spinal segmental mechanism accounts for another important analgesia group in which spinally located enkephalinergic neurons play an important role. Neurons carrying dimorphine are dense in this region [10]. The antinociceptive effects of these descending tracts are mediated by α_2 adrenergic, serotonergic and opioid receptor mechanisms. As a result of the stimulation of these receptors, secondary intracellular messengers are activated and K^+ channels are opened and increase in intracellular Ca^{+2} concentration is inhibited. Inhibitory adrenergic tracts basically originate from periaqueductal gray matter and reticular formation. Main neurotransmitter of this tract is noradrenalin [4, 5, 8, 11]. In addition, it is thought that GABA, as a general inhibitory substance, participate in antinociceptive mechanisms. In addition to these, peripheral such as somatostatin and bombesin are neuronal neuropeptides have been shown to exert inhibitory effects. Fast and short lasting inhibition on projection neurons is mediated mostly by monoaminergic transmitters GABA and partly by enkephalin. Longer inhibition is carried out via endorphin and partly by enkephalin and somatostatin [10].

Cerebrum and pain

In cerebral cortex, regions associated with pain are 1 and 2. Sensory areas, frontal lobe, especially 9 and 12. Areas and posterior regions and association fibers connecting these regions of brain to each other. Postcentral gyrus is the place where rapid perception is represented. In the lesions of this region, hypoalgesia may arise with impairment in other sensory types [10].

Control Mechanisms on Dorsal Horn

The pain arising when a tissue is injured does not always have the same quality and localization. At first injury, pain lasting for a very short time is felt. It is followed by a second pain less localized and lasting longer and hyperalgesia. This occurs especially following deep tissue injuries. If condition causing pain is continuing and a pathological pain has arisen, this may last for days and months. In both cases, the variability of pain response is mediated by partly peripheral and partly dorsal horn cells in nociceptive and antinociceptive mechanisms. In the 3. period, that is when pathological pain emerges, the event has no longer any relation within periphery and it continues with mechanisms between dorsal horn cells and other

cells of central nervous system. This occurs typically in deafferentation pain. In this event, there are three different time stages and accordingly three different dorsal horn mechanism [10, 15].

1. Speed gate control
2. Slow sensitivity control
3. Prolonged connection control

Gate control :

Substantia gelatinosa cells influence the transmission of afferent stimulus to T cells by blocking the transmission of afferent stimulus to T cells or presynaptically blocking the impulse in a delta and C fiber axons or postsynaptically by inhibiting chemical neurotransmitter release and modifying the perception level of incoming excitator stimulant. These cells inhibit thin and thick nerve endings. Gate mechanism is basically controlled by the activity of thick alpha and beta fibers. They stimulate gate cells (gate is closed) and prevent transmission to T cells .Thin fibers inhibit gate cells, and increase the opening of gate and transmission of stimulus to T cells. When stimulation is prolonged, thick fibers become adapted and thin fibers become dominant [9].

Accordingly, gate in spinal cord is opened and painful stimulant is transmitted to upper centers via ascending tract [11]. In this condition, after being informed of peripheric painful event, pain is also controlled by release of supraspinal decending inhibitor and rapidly acting aminoacid transmitters. Mostly, inhibitor transmitters such as serotonin, noradrenalin and GABA are effective [10, 15].

Sensitivity control: Following acute tissue injury, in the dorsal horn projection neurons, nociceptive excitability increase, which appears later and lasts longer, occurs. Another important characteristics of this process is that dorsal horn nociceptive cells respond also to painful stimulants far from the injured site.

Afferent input dominant in this period are from central endings of C fibers. And slow acting neuropeptide transmitters continously excite central passage cells. Among these substance P, neurokinin A and cholecystokinin (CCK) can be mentioned [10,15].

Connection control: If peripheral nerves or dorsal roots are severed, neuronal excitability and neuronal metabolic changes occur slowly starting from the cut to dorsal horn. These effects are observed mostly in cells where afferents end mostly inter neuron. [10, 15].

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