Introduction

Multimodal analgesia (MMA) is achieved by using combinations of analgesics (e.g., opioids, non-steroidal anti-inflammatory drugs, and local anaesthetics), which act simultaneously by different mechanisms, resulting in additive or synergistic analgesia with fewer adverse effects ***(Dorr et al, 2008).***

MMA is a multidisciplinary approach to pain management with a goal to maximize the analgesic effect and minimize the side effects of the medications. It takes advantage of the additive or synergistic effects of various analgesics, permitting the use of smaller doses with a concomitant reduction in side effects. Many of the negative effects of analgesic therapy are related to parenteral opioids, limiting its use is the major principle of MMA ***(Wheeler et al, 2002).***

Postoperative pain remains poorly controlled despite recent advances in the development of new drugs and techniques. One approach to improving postoperative pain control is to use a multi-modal analgesic regimen which capitalizes on the combined actions of multiple agents in

reducing perioperative nociceptive input and central sensitization ***(Joel et al, 2006).***

Pain involves multiple mechanisms that ideally require treatment using a multimodal (or 'balanced') analgesic technique with the aim of improving analgesia by combining analgesics with additive or synergistic effects ***(White et al, 2010).***

Combinations of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated and may offer enhanced effects. A systematic review of this subject determined that when used as a combination, NSAIDs and paracetamol offer superior analgesia and studies included had positive results with regard to lowering visual analogue scale (VAS) ***(Ong et al, 2010).***

Other non-opioid analgesics including ketamine, dexmedetomidine, dextromethorphan, alpha- 2 agonists, beta-blockers, local anaesthetics, and acetaminophen can help to improve the pain management and perioperative outcome ***(Suzuki et al, 2009).***

Aim of the work

This study aims to compare between the effect of MMA and single mode analgesia in lumbar spine surgery on intraoperative and early postoperative analgesia, the consumption of morphine in both types and incidence of side effects.

Physiology of Pain

Definition of Pain:

The International Association for the Study of Pain (IASP) has proposed the following definition: "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" ***(Bonica, 1990).*** Pain causes a reflexive withdrawal response accompanied by a reaction, most frequently a feeling of unpleasantness. The sensory process of detecting the "actual or potential tissue damage" is called **nociception** ***(Kyranou & Puntillo, 2012).***

The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus ***(Mersky & Bogduk, 1994).***

Pain threshold is the least experience of pain that a subject can recognize as suggested in 1994, whereas a new definition is now being discussed by IASP that pain threshold is the minimal intensity of a stimulus that is perceived as painful. **Pain tolerance level** is the greatest level of pain that a subject can recognize as suggested in 1994, whereas a new definition is now being discussed by IASP that pain tolerance level is the maximum intensity of a stimulus that evokes pain and that a subject is willing to tolerate in a given situation. Thus, even though traditionally viewed as an entirely sensory phenomenon, pain differs fundamentally from other conventional sensory modalities in that numerous and diverse types of stimuli that are capable of initiating a complex multifaceted pain response ***(Loeser & Treede, 2008)***.

Classification of Pain:

Acute Pain:

Acute clinical pain typically arises from soft tissue trauma or inflammation, with the most common example being postoperative surgical pain. Although it does not serve a protective function in the sense that physiologic pain does, acute pain does play a biologically adaptive role by facilitating tissue repair and healing. This is achieved by

hyper-sensitizing the injured area (primary hyperalgesia) as well as the surrounding tissues (secondary hyperalgesia) to all types of stimuli such that contact with any external stimulus is avoided and the reparative process can proceed undisturbed. This realization is not, however, a license to allow patients to suffer needlessly in the postoperative period. By having an appreciation of the underlying functional basis of such pain, the practitioner is able to initiate appropriate pain management strategies while taking steps to optimize wound healing ***(Woolf, 1995).***

Two types of acute (nociceptive) pain; somatic and visceral are differentiated based on origin and features:

- **Somatic pain** can be further classified as superficial or deep. Superficial somatic pain is due to nociceptive input arising from skin, subcutaneous tissues, and mucous membranes. It is characteristically well localized and described as a sharp, pricking, throbbing, or burning sensation. Deep somatic pain arises from muscles, tendons, joints, or bones. In contrast to superficial somatic pain, it usually has a dull, aching quality and is less well-localized. An additional feature is that both the intensity and duration of the stimulus affect the degree of

localization. For example, pain following brief minor trauma to the elbow joint is localized to the elbow, but severe or sustained trauma often causes pain in the whole arm ***(Morgan et al, 2006)***.

- **Visceral pain** is due to a disease process or abnormal function of an internal organ or its covering e.g., parietal pleura, pericardium, or peritoneum. Four subtypes are described: (1) true localized visceral pain, (2) localized parietal pain, (3) referred visceral pain, and (4) referred parietal pain. True visceral pain is dull, diffuse, and usually midline. It is frequently associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating, and changes in blood pressure and heart rate. Parietal pain is typically sharp and often described as a stabbing sensation that is either localized to the area around the organ or referred to a distant site (The phenomenon of visceral or parietal pain referred to cutaneous areas results from patterns of embryological development and migration of tissues, and the convergence of visceral and somatic afferent input into the central nervous system) ***(Morgan et al, 2006)***.

Chronic Pain:

Chronic pain persists beyond the expected time frame for a given disease process or injury and has been arbitrarily defined as having a duration greater than 3 to 6 months. Such pain may arise as a result of sustained noxious input as ongoing inflammation, or it may be autonomous, with no temporal relation to the inciting cause. Chronic pain may manifest itself spontaneously, or it may be provoked by various external stimuli. The response is typically exaggerated in duration or amplitude, or both. In recognition of the multifactorial nature of this type of pain, the IASP has incorporated more than 200 clinical syndromes in their classification of chronic pain, with cancer pain, osteoarthritic pain, and post-amputation phantom limb pain among the most relevant. In all cases, chronic pain is maladaptive and offers no useful biologic function or survival advantage, with the nervous system itself actually becoming the focus of the pathology and contributing to patient morbidity. Therefore, chronic pain implies more than just duration-it is a debilitating affliction that has a significant impact on a patient's quality of life and is often characterized by a dismal response to conventional analgesic treatments. In the future, an understanding of the altered neuromechanisms underlying

this state of heightened neural sensitivity may pave the way to more effective chronic pain management strategies ***(Merskey et al, 1994)***.

During the past 4 decades, major advances have been made in pain science. Chronic pain is now understood to involve a neural response to tissue injury where peripheral and central events related to disease or injury can trigger long-lasting changes that result in sensitization. In this way, the nerves become stuck in the on position, such that, after injury, the neurons are capable of firing spontaneously or in response to stimuli that normally would not cause pain. With this information, we now understand such clinical observations as allodynia (pain evoked by a stimulus that normally does not cause pain, such as light touch), hyperalgesia (increased pain response to stimuli that are painful), or phantom pain (pain referred to an area of the body that has been amputated or has lost its sensory innervation) ***(Mary, 2015)***.

Transmission of Pain:

The complex pain-pathway can be briefly summarized as transduction, transmission, modulation and perception.

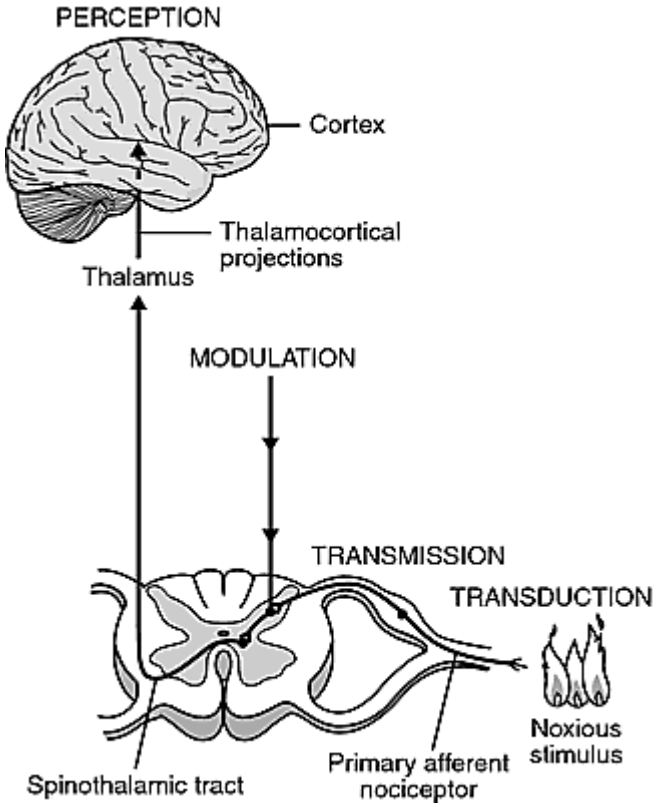

Figure (1): The four processes that make up nociception: transduction, transmission, modulation, and perception ***(Ferrante and VadeBoncouer, 1993)***.

A-Transduction

Noxious stimuli translated into electrical activities at the sensory nerve endings. Surgical incision is the starting point which affects potassium, serotonin and histamine release from damaged cells, bradykinin (BK) from injured vessels and prostaglandin (PG) from nerve endings (nociceptors). These mediators induce further recruitment of

other inflammatory agents like IL-1, IL-6, TNF-alpha, Substance-P, Acetylcholine (Ach). Substance-P, a vasoactive neuropeptides is responsible for further release of BK, histamine from mast cells and serotonin from platelets all together then stimulates additional nociceptors. Stimulation of nociceptors results in depolarization of nerve endings which is carried to the spinal cord via A-delta and C fibers. Neural depolarization reduces excitatory threshold of nociceptors of both the injured area (primary hyperalgesia) and that of non-injured area (secondary hyperalgesia) and this phenomenon is known as peripheral sensitization ***(Basbaum et al, 2009)***.

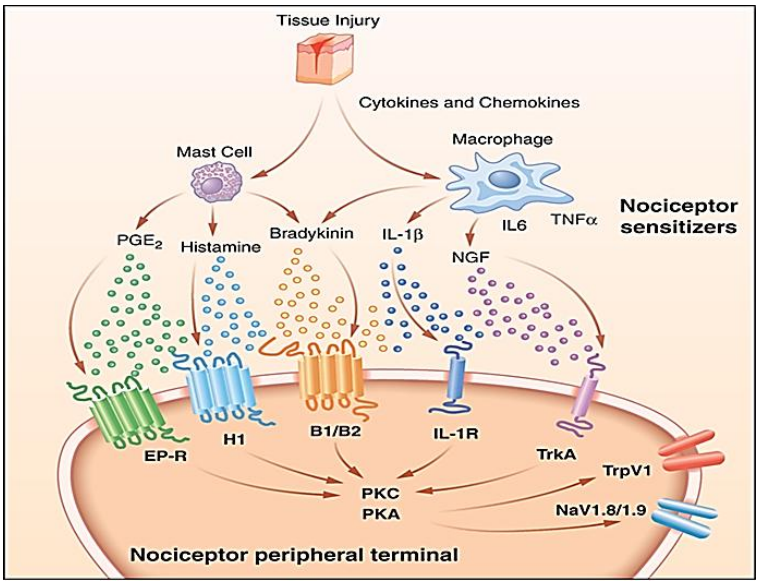

Figure (2): Peripheral sensitization ***(Longnecker et al, 2012)***

A-delta is myelinated fibers responsible for quickly conducting pain perception and accurately localizes pain producing area. C-fibers are unmyelinated and slower in conducting pain information from a diffuse area. These fibers mainly terminate at secondary afferent neurons of Rexed laminae 1 and 2 in the dorsal horn of spinal cord. Adjacent interneuron circuits, descending inputs from higher spinal cord, mid brain areas (periaqueductal areas, raphe nucleus, locus ceruli, and reticulo-spinal) and cerebral centers significantly modulates information carried by afferent fibers ***(Murinson et al, 2004)***.

B-Transmission

Synaptic transfer of generated electrical activities from one neuron to another from periphery to higher centers through spinal tracts. Neurotransmitters of majority of the interneurons are gamma amino butyric acid (GABA) and glycine both of which are inhibitory in action. Main excitatory amino acid is alpha amino-3-hydroxy-5- methyl-4-isozole propionic acid (AMPA/Kinate receptor) located at the post-synaptic to primary afferent fibers. It is important to note that N-methyl-D-aspartate (NMDA) receptors are post-synaptic to interneurons and the AMPA/Kinate and

substance-P must be activated prior to NMDA receptor activation ***(Phillips and Currier, 2004)***.

It has been speculated that peripheral NMDA receptors may also play a role in cutaneous and deep tissue pain as it has been recognized found in deep tissues in association with the terminal endings of nerve fibers ***(Alfredson and Lorentzon, 2002)***. The first event at molecular level in the dorsal horn is release of excitatory amino acid like glutamate and aspartate from primary afferent fiber nerve endings. They bind to AMP/kinate receptors leading to opening of ion channels and depolarization of second order neurons. These voltage sensitive events remove magnesium plug responsible for keeping NMDA receptors in inactive state. Glycine binding also takes place to finally activate NMDA receptors. Now a complex cascade of events occur which include marked release of intracellular calcium which then activates phospholipase-A2, enhances PG production and increases production of substance-P. NMDA activation also causes release of nitric oxide (NO). Both PG and NO diffuses extracellular to induce primary afferent neurons to release excitatory neurotransmitters. It is believed that once the cascade of events is initiated, blockade of peripheral nociceptor inputs fails to completely stop dorsal horn

neurons from firing. This wind up phenomenon leads to clinical sequel of hyperalgesia, muscle spasm, allodynia, increase sympathetic tone and subsequent decrease blood flow ***(Kawasaki et al, 2008)***.

Higher doses of analgesics such as opiates are required to suppress the pain and hence NMDA receptors are implicated in the development of opiate tolerance. This also explains why long standing pain syndrome fail to improve even after surgical intervention and correction of primary anatomic abnormality. NMDA receptors are also held responsible for the complex phenomenon of central sensitization (ability of benign and low threshold stimuli to activate second order neurons) if afferent nerve stimulation is intense and of sufficient duration ***(Basbaum et al, 2009)***.

C-Modulation

Release of chemical messengers from higher center and brain stem that modulates the painful stimuli. After the extensive modulation at dorsal horn, the second degree afferent from the dorsal spinal cord ascends one-two level before crossing to other side and ascends as crossed spinothalamic tract. These tracts ends in the thalamus and third order neurons start from here to end in the cerebral

cortex and here second degree of modulation takes place also known as central nociceptive processing ***(Kawasaki et al, 2008)***.

On the way there are projections to periaqueductal gray matter (PAG) which is specialized for pain localization. The spinoreticular tract is another ascending tract which synapses at the brainstem reticular formation, before terminating in thalamus and hypothalamus. This tract is particularly responsible for emotional aspect of pain. Descending tracts through PAG and rostral ventromedial medulla inhibit pain transmission due to presence of high concentration of opioid receptors and endogenous opioids ***(Azam et al, 2016)***.

D-Perception

Complex interaction in thalamus, cortex, limbic system and reticular system leading to recognition and reaction to primary stimuli. A large area of cerebral cortex known as "pain matrix" is activated during acute pain activation which includes somato-sensory area (S1 & S2), insular, anterior cingulate cortex as well as thalamus. Thalamus modulation is responsible for sensory discriminative processing whereas cerebral cortex produces