# INTRODUCTION

Regional anaesthesia is frequently and successfully used in several surgical procedures. During surgery, the most important advantages of regional anaesthesia are that the patient is conscious; breathing spontaneously has intact reflexes such as cough and swallowing. In addition to, sympathetic blockade in the lower extremities thereby reducing blood loss during the perioperative period, and post operative analgesia facilitating mobilization of the patient and therefore, reducing the risk of thromboembolism ***(Coskuner et al., 2007)***.

Bupivacaine, a drug with long lasting local anaesthetic effect, in epidural anaesthesia, provides an effective and safe anaesthesia ***(Coskuner et al., 2007)***.

Recently, Alpha 2-adrenoceptor agonists are being increasingly used in anaesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anaesthesia and surgery; but also cause sedation and analgesia; they are also used as adjuvants during regional anaesthesia. Clonidine, which was initially introduced as antihypertensive, is the most commonly used alpha 2 agonist by anesthesiologist, Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in human for analgesia and sedation ***(Bhatia, 2002)***.

Clonidine has proven to be a clinically useful adjunct in clinical anaesthesia practice as well as in chronic pain therapy

because it has both anaesthetic and analgesic-sparing activity ***(Khan et al., 1999)***.It has been also used as an adjunct in regional anaesthesia in various settings including post operative epidural analgesia ***(Sites et al., 2003).***

Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in human for analgesia and sedation. Dexmedetomidine has an eight-fold greater affinity for alpha-2 adrenergic receptors than clonidine and much less alpha-1 effects. A major advantage of dexmedetomidine is its higher selectivity compared with clonidine for alpha-2A receptors, responsible for the hypnotic and analgesic effects of such drugs. Recent data has shown that the addition of dexmedetomidine to anaesthetic mixture for continuous extradural analgesia; to be satisfactory in the first 24 hours of the postoperative period ***(Maguey et al., 2006)***.

# AIM OF THE WORK

The study was designed to evaluate the efficacy of dexmedetomidine and clonidine when added to bupivacaine for post operative epidural analgesia in patients undergoing orthopaedic surgery of the lower extremity.

# ANATOMY AND PHYSIOLOGY OF PAIN

Pain is **defined** by the ***International Association for the Study of Pain*** (IASP) as an unpleasant sensory and emotional experience that is primarily associated with tissue damage. It is a protective mechanism that occurs whenever tissues are being damaged, and it causes the individual to react to remove the pain stimulus **(Tenti and Hauri, 2004).**

## Pain pathway

Specificity theory states that there is a specific pain system that transfers information about potential or actual tissue damage to the place of perception (the brain). Nociceptive energy is transduced into electrophysiological signals that are transmitted to perceptive apparatus. However, the pain pathway is not 'hard wired', but undergoes profound functional changes and modulation under certain conditions, such as tissue damage and inflammation (e.g. postoperative pain). This plasticity is mediated by many mechanisms, including peripheral/primary and central/secondary sensitization. The substrate for these changes is a plethora of chemical mediators peripherally and spinally, comparable in complexity to neurotransmitters in the brain ***(Smith, 2007).***

## *I*-Primary afferent neurons:

There are three classes of primary afferent fibers in skin that may be activated by a given cutaneous stimulus. The fibers

that are largest and have the fastest conduction velocity are the large-diameter myelinated (Aβ) fibers. These fibers, when activated, do not normally result in a sensation of pain, but rather of light touch, pressure, or hair movement. The axons of the nociceptive neurons are generally unmyelinated (C fibers) or thinly myelinated (Aδ fibers) ***(Dubner, 1994).***

Unmyelinated C polymodal nociceptors are activated by many potentially tissue-damaging modalities, are associated with prolonged 'burning' pain, and are slowly conducting (0.5–2.0 m/s). Some may have a differential sensitivity to heat or mechanical stimuli ***(Smith, 2007).***

The Aδ is thinly myelinated, mechano-heat receptors that thought to mediate a briefer 'sharp' pain. These larger fibers are more rapidly conducting (5–20 m/s). Aδ fibers are also delineated into two types, depending on their differential responsiveness to intense heat. A final group of nociceptors do not appear to exhibit sensitivity to noxious stimuli. These 'silent' nociceptors develop novel sensitivity usually after tissue injury or inflammation. Silent nociceptors have been well characterized in the visceral domain, although there is some evidence to support the existence of somatic counterparts ***(Smith, 2007).***

**II-Spinal cord to brain:**

Secondary afferents decussate and pass up the spinal cord to the midbrain via the spinothalamic, spinoreticular and spinomesencephalic tracts to the thalamus and to sensory cortex,

but also have many other links, such as to reticular formations, limbic and hippocampus areas, figure (1). The different pathways may have functional correlates involving memory, cognition and emotion, which contribute to the neural network of overall pain perception. Moreover, neurons that project from these areas of the brain provide descending modulation of spinal cord processing. ***(Brooks and Tracey, 2005)***

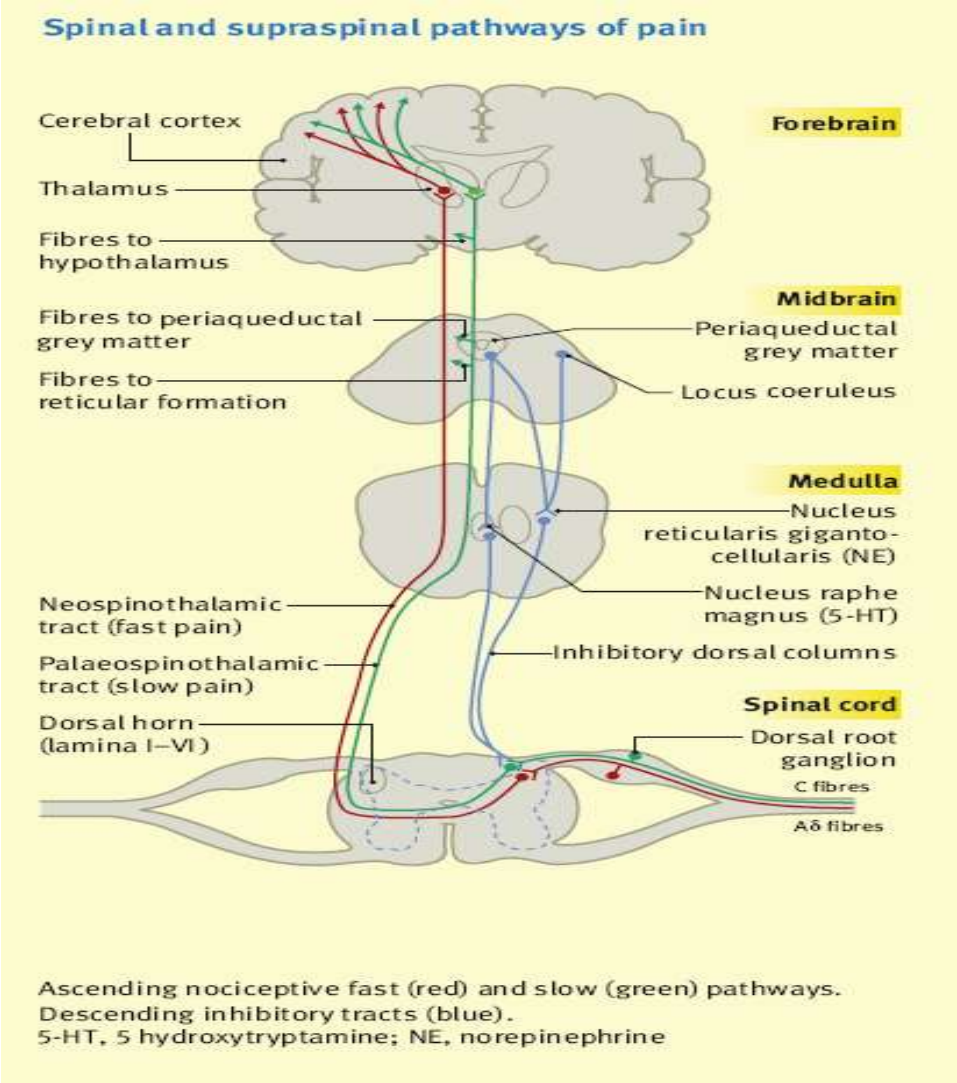


**Figure (1):** Spinal and supraspinal pathways of pain.*(Smith, 2007)*

The first synapse in somatosensory signaling occurs either at the spinal dorsal horn or in the dorsal column nuclei at the spinal cord-brain stem junction. Evidence has accumulated to indicate that both nociceptive and non nociceptive fibers provide input to both of these initial targets. However, under normal circumstances, the dorsal column nuclei can be considered to selectively process inputs from the large myelinated fiber classes related to light touch, whereas the spinal dorsal horn primarily processes inputs of the nociceptive primary afferent fibers ***(Pockett, 1995).***

At the spinal level, nociceptive afferent fibers from the periphery terminate in a highly ordered way in the dorsal horn of the spinal cord on the same side of the body as the dorsal root ganglion (DRG), where the primary sensory neurons are located. The dorsal horn is anatomically organized in the form of lamina (Rexed's) (figure 2).

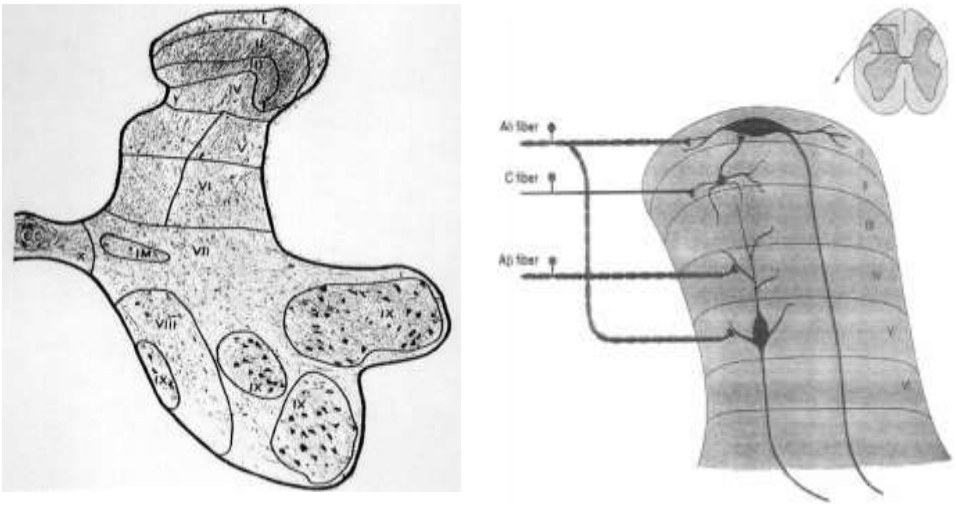


**Figure (2):** Location of Rexed's laminae at the L5 level of the spinal cord ***(Dubner, 1994).***

The unmyelinated C fibers terminate primarily in lamina II, whereas the thinly myelinated Aδ fibers end in lamina I and in laminae III to V. The collaterals of the large myelinated fibers (Aβ) that terminate in the dorsal horn do so in laminae III to V ***(Dubner, 1994).***

Two predominant types of second-order nociceptive spinal projection neurons have been identified in the spinal cord: wide dynamic range (WDR) neurons and nociceptive specific (NS) neurons. WDR cells are especially concentrated in the deeper laminae of the dorsal horn (laminae III to V) where they receive input from both low-threshold (Aβ) and nociceptive afferent fibers, and, hence, are activated by both non-noxious and noxious stimuli. However, the responses of WDR cells to these stimuli are graded so that noxious stimuli evoke a greater response than non-noxious stimuli ***(Dubner, 1994)***.

In contrast to WDR cells, NS projection cells respond only to noxious stimuli under physiologic conditions. The majority of NS cells are found in the superficial laminae of the dorsal horn (I and outer II). These cells have a lower rate of spontaneous activity than WDR cells, averaging about 3 to 5 Hz. The discharge rates to the noxious stimuli of NS cells are comparable to those of WDR cells, averaging about 50 Hz. ***(McMahon, 1992).***

The axons of both WDR neurons and NS second-order neurons cross the midline near the spinal level of the cell body,

gather into a bundle of ascending fibers in the contralateral anterolateral spinal region, and then ascend toward targets in the brain stem and diencephalon. The conduction velocity of the WDR cells is usually faster than that of the NS cells (approximately 30m/second versus. 12 m/second. Additionally, the axons of the NS cells, which largely arise from lamina I of the dorsal horn, and those of the WDR cells, which primarily arise from laminae III to V, tend to run in slightly different positions in the anterolateral spinal funiculus. In the anterolateral spinal column the NS cell axons are found in the dorsal medial region, whereas axons of WDR cells are more concentrated in the ventrolateral region ***(McMahon, 1992).***

## III- The pain matrix:

Usually pain experience is described along 2 main axes: the sensory discriminative dimension, comprising spatial, temporal, and intensity properties, and the affective-motivational dimension related to the unpleasantness of pain. Consistent with the multidimensional concept of pain, multiple brain regions, which composite the pain matrix, have been demonstrated to be involved in representing both the discriminative and emotional components of acute (experimental) ***(Derbyshire and Jones, 1991; Paulson et al., 1998)*** and chronic pain ***(Mountz et al., 1998; Mackey & Maeda, 2004).***

Anatomically, the pain system is divided into lateral and medial systems. The lateral system consists of spinothalamic

tract neurons projecting to the ventrobasal nucleus of the thalamus, which projects to the primary and secondary somatosensory cortex, and parietal operculum. In contrast the medial pain system consists primarily of spinothalamic tract neurons that project to the intralaminar and medial thalamic nuclei, which subsequently project to the anterior cingulate cortex (ACC), amygdala, hippocampus, and hypothalamus. Whereas the lateral pain system is mainly associated with the sensory-discriminative aspects of pain processing, the medial pain system plays a crucial role in the motivational-affective and cognitive evaluative aspects of pain processing, memory for pain, and autonomic neuroendocrine responses ***(Jones et al,. 1991 and Davis et al., 1997).***

The insula, however, encodes both the intensity and the laterality of painful and non-painful thermal stimuli ***(Craig et al., 2000 and Bingel et al., 2003)***, but may also have a role in affective pain processing ***(Critchley et al., 2004).*** Thus, the insula probably occupies a space between the medial and lateral systems, facilitating integration of information from both ***(Peyron et al., 2002)***.

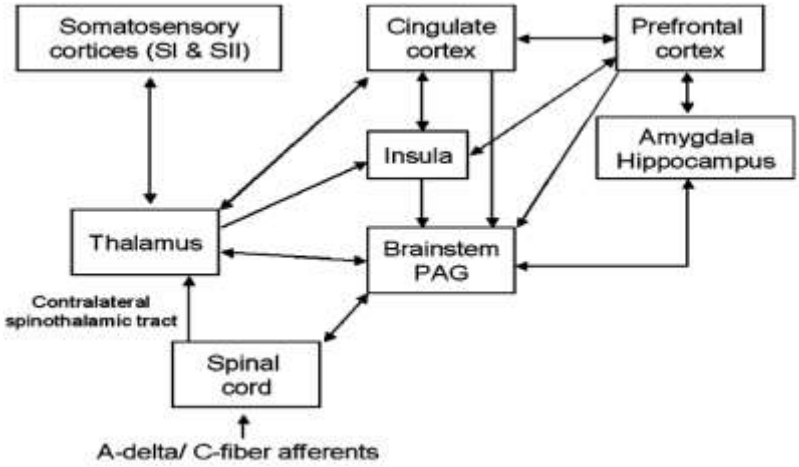


**Figure (3):** The ‘‘pain matrix’’. Main anatomic components of the ‘‘pain matrix’’ and their possible functional connections ***(Treede et al., 1999)***(ACC, anterior cingulate cortex; Pf, parafascicular nucleus; SI, primary somatosensory cortex; SII, secondary somatosensory cortex).

Relatively a wider distribution and highly consistent set of brain areas have been described that are activated on various types of experimental pain conditions like those evoked by mechanical, thermal, and chemical nociceptive stimuli that elicit tonic and/or phasic pain. Activated brain areas include primary and secondary somatosensory cortices (SI and SII), ACC, insular cortex, primary motor and premotor cortices, prefrontal cortex (PFC), and thalamus in addition to posterior parietal cortices, amygdala, basal ganglia, midbrain (periaqueductal grey matter), and cerebellum ***(Peyron et al., 2000 and Apkarian et al., 2005)*** Together, this set of brain areas is referred to as the ‘‘pain matrix’ **(Figure 3)** ***(Lorenz et al., 2005).***

## Pathophysiologic Consequences of Untreated Pain

Untreated pain can lead to the following consequences:

1) Impaired breathing: segmental reflex arches directly hamper the muscles involved in breathing by increasing their tone. Furthermore abdominal pain inhibits deep inspiration resulting in a reduced respiratory capacity predisposing to atelectasis and pneumonia which in turn may cause respiratory insufficiency.

2) Impaired gastrointestinal and urological smooth muscle activity, also caused by segmental reflex arches and sympathetic over activity lead to hypomotility and eventually ileus and urinary retention ***(Francesca et al., 2003).***

3) Stimulation of the sympathoadrenal axis and the **neuroendocrinal stress response**. Direct stimulation of the sympathetic nervous system plus release of catecholamines results in positive inotropic and chronotropic heart function and increased systolic blood pressure causing an increased myocardial O2 consumption, a risk for myocardial ischemia. The vasoconstriction also induced diminishes the microcirculation and is one factor of impaired wound healing. In this context the risk of cerebrovascular accidents (of hemorrhagic or ischemic insult) is also increased. Besides noradrenaline augments free fatty acids in the blood adding another cardiovascular risk factor in the long term. Increased level of stress-induced catabolic hormones like ACTH, cortisol,

glucagon, and reduced anabolics like insulin, testosterone, and growth factors results in a catabolic state. In addition, cortisol brings on immunosuppression. Together with the induced hyperglycemia, there is an increased risk of wound healing disorders or infections. Increased secretion of aldosterone and ADH leads to a reduced diuresis, potassium loss and sodium retention, and therefore fluid retention with all its potential harm such as hypertension and pulmonary edema ***(Tenti and Hauri, 2004).***

4) Prolonged pain impairs mobilization and leads to a specific morbidity associated with long bed confinement such as pulmonary atelectasis, and infections, thromboembolic manifestations, urinary tract infections and decubitus ulcers.

5) Pain leads to anxiety and insomnia sustaining the neuroendocrinal response.

6) Prolonged pain leads to sensitization (physiological amplification) and therefore to a greater susceptibility and possible chronification of pain.

7) For all of the above untreated pain leads socioeconomically to a more expensive and longer hospital stay with delayed work integration ***(VanLaecke and Oosterlinck, 1994).***

## Gate Theory for Control of Pain

The gate control theory of pain refers to the mechanism(s) which diminish conduction of painful stimuli from the first to the second order neuron. According to the gate control theory there is a gating mechanism within the **dorsal horn of the spinal cord** which controls the entry of pain signals into the pain pathway ***(George, 2006)***.It is controlled by nerve cells in the substantia gelatinosa of Rolandi **(*Koga et al., 2005).***

The gating mechanism acts as a modulating system that controls the transmission of nerve impulses from afferent fibres to transmission cells (T cells) in laminae V and VI in the dorsal horn. Myelinated and unmyelinated fibres control the gating mechanism. Activation of large myelinated A-δ fibres (not pain signaling) tends to block transmission of impulses to neurons concerned with pain (*close the gate*). Therefore stimulation of large sensory fibres from the peripheral tactile receptors tends to depress the transmission of pain. Whereas activation of small C fibres tends to facilitate transmission (*open the gate*). Descending signals from the brain also affect the gating mechanism in the spinal cord ***(Costigan and Woolf, 2002).***

Opiate receptors also play a powerful role in the gate control mechanism. Opioid receptors are found at all levels of pain transduction (nerve endings, dorsal horn of spinal cord, thalamus, and sensory cortex) and are stimulated by endogenous opioids (encephalins) as well as exogenous

opioids. In the dorsal horn encephalins are released by A-δ fibres. They decrease impulse frequency of the second order neuron. Opioids have both presynaptic and postsynaptic effects in the dorsal horn and affect the modulation of nociceptive input. **(*De Leon and Lema, 1996)***

**Evaluation of Pain**

By its definition, pain is an internal, subjective experience that cannot be directly observed by others or by the use of physiological makers or bioassays. The assessment of pain, therefore, relies largely upon the use of self-report. Although the self-report of pain or any other construct is subject to a number of biases, a good deal of effort has been invested in testing and refining self-report methodology within the field of human pain research ***(Benzon et al., 2005)***.

Assessing pain requires measurement tools that are valid and reliable, as well as an ability to communicate (using language, movements, etc.).In addition, pain is a multidimensional experience incorporating sensory and affective components which may be assessed separately ***(Haythornthwaite and Fauerbach, 2001)***.

Valid and reliable assessment of pain is essential for both clinical trials and effective pain management. The nature of pain makes objective measurement impossible. Acute pain can be reliably assessed, both at rest (important for comfort) and during movement (important for function and risk of postoperative complications), with one-dimensional tools such