INTRODUCTION

Interest in combining regional and general anesthesia to offer the possibility of a pain-free post-operative period has increased in recent years. Caudal block is the most commonly used regional anesthesia method in lower abdominal and urological surgery in children. It provides excellent intra- and post-operative analgesia, and reduces the need for additional analgesics ***(Akbas et al., 2005).***

The main disadvantage of caudal anesthesia is the short duration of action after a single injection of local anesthetic solution. Prolongation of single-shot caudal analgesia has been achieved by the addition of various adjuvants ***(De Beer and Thomas, 2003).***

Bupivacaine has been in clinical use for more than 30 years. It is widely used for caudal epidural analgesia in children but it is associated with a number of side effects, including motor weakness, cardiovascular and central nervous system toxicity. This has resulted in the continuing search for new and safer local anesthetic agents ***(De Beer and Thomas, 2003).***

Ropivacaine is a long-acting aminoamide local anesthetic and was the 1st to be formulated as a pure S-enantiomer. It is reported to have a better safety profile than bupivacaine, with less risk for CNS and cardiac toxicity. The greater degree of block in nerve fibers of pain transmission than of motor

function for a given concentration would be of further benefit ***(Bosenberg et al., 2005).***

Ketamine, a phencyclidine derivative, has structural similarities to bupivacaine and has some local anesthetic effects. The primary mechanism of action is through the blockade of *N*-methyl-D-aspartate receptors situated in the substantia gelatinosa of the spinal cord. Ketamine also binds to the opioid receptors, with a preference for the μ receptors ***(De Beer and Thomas, 2003).***

Neostigmine, a cholinesterase inhibitor has been found to provide analgesia by both intrathecal as well as epidural routes. It inhibits the breakdown of endogenous acetylcholine and thus indirectly stimulates both muscarinic and nicotinic receptors to produce analgesia. This effect is mediated via spinal M_1 muscarinic receptors and supraspinl M_1 and M_2 muscarinic and nicotinic cholinergic receptors ***(Bhardwaj et al., 2007).***

AIM OF THE WORK

The aim of the present study is to compare the analgesic efficacy of caudal administration of: Plain Bupivacaine 0.25% (1 ml/kg), Plain Ropivacaine 0.2% (1 ml/kg), Plain Bupivacaine 0.25% (1 ml/kg) mixed with Ketamine (0.5 mg/Kg), Plain Ropivacaine 0.2% (1 ml/kg) mixed with Ketamine (0.5 mg/Kg), Plain Bupivacaine 0.25% (1 ml/kg) mixed with Neostigmine (2 ug/kg), and Plain Ropivacaine 0.2% (1 ml/kg) mixed with Neostigmine (2 ug/kg) in the relief of pain after elective subumbilcial surgical procedures in children.

ANATOMY

The performance of caudal anesthesia calls for an expanded understanding of the epidural and sacral anatomy.

Typically, the sacrum is formed by five fused sacral vertebrae. Occasionally the fifth lumbar vertebra is incorporated, wholly or partially, into the mass (sacralization of L5), or S1 is wholly or partially separate (lumbarization of S1).Commonly, the coccyx is fused to the sacral lower extremity ***(Ellis, 2006).***

The sacrum is wedge shaped and presents a markedly concave anterior and convex posterior surface (Figure 1). The anterior surface comprises a central mass, formed by the fused vertebral bodies, which ends on each side as four anterior sacral foramina – these transmit the anterior primary rami of S1–S4. Lateral to the foramina lays the lateral mass, which rapidly diminishes in size from above downwards, giving the sacrum its triangular shape ***(Sethna and Berde, 2000).***

The posterior aspect is made up of fused vertebral arches, which roof the sacral canal. This is open inferiorly as the sacral hiatus, guarded on either side by a sacral cornu. The four posterior sacral foramina lie exactly opposite their corresponding anterior foramina, and transmit the posterior rami or nerves S1–S4; S5 passes between the termination of the

sacrum and the coccyx. The lateral aspect of the sacrum bears the large articular surface, which articulates with the corresponding surface on the ilium to form the synovial sacroiliac joint. Behind this surface is a roughened area, which marks the attachment of the powerful posterior sacroiliac ligament ***(Ellis, 2006).***

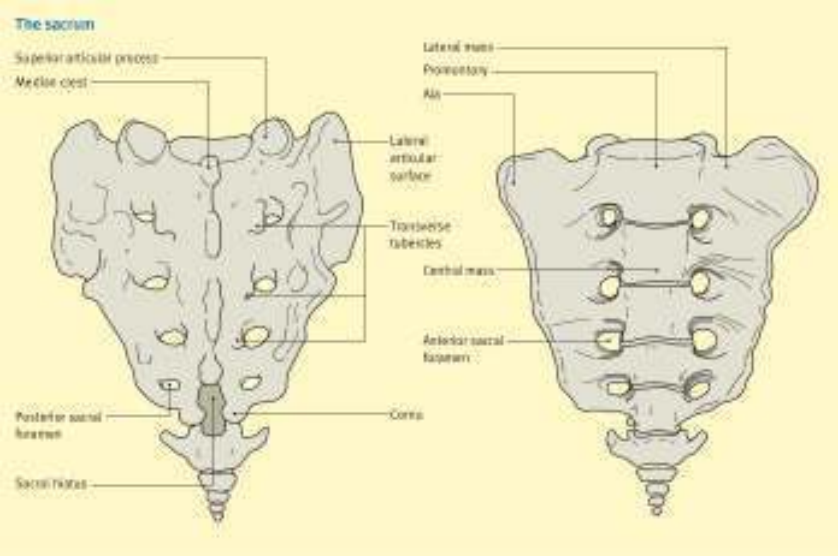

Figure (1): The sacrum in posterior (left) and anterior (right) views ***(Ellis, 2006)*.**

The upper surface of the sacrum presents the body, which is oval in section, and its anterior edge forms the sacral promontory. The sacral canal is triangular in section. The upper surface of the lateral mass forms a wing on either side, termed the ala, which is crossed, and lightly grooved, by the lumbosacral cord, bearing the roots of L4 and L5 to join the sacral plexus ***(Ellis, 2006).***

The sacral hiatus, a triangular gap on the posterior aspect of the lower end of the sacrum, is of clinical importance. It is formed by failure of fusion of the laminae of the fifth sacral segment. The defect may be greater than this in many cases, representing a spina bifida occulta. Lateral to the hiatus lie the margins of the deficient lamina of S5, which bear the sacral cornua inferiorly. Anterior to the hiatus lies the body of S5. The hiatus is roofed by the posterior sacro-coccygeal ligament, passing from the cornua to the coccyx, and is about 1–3 mm thick. This ligament is covered by subcutaneous fat and skin only.

In a thin patient the hiatus can easily be located by identifying the cornua as two adjacent knobs, which can be felt about 5 cm above the tip of the coccyx at the upper end of the natal cleft. ***(Ellis, 2006)*** Since the dural sac terminates at the level of the junction of the first and second sacral vertebrae, the extradural space continues below this level. Here, it contains loose extradural fat, the lower part of the vertebral plexus of veins, the lower sacral nerve roots and the filum terminale. Local anesthetic injected into the extradural space via the sacral hiatus will primarily affect the sacral nerve roots and will provide anesthesia for surgery (Figure 2) below the level of the umbilicus and the perineum ***(Dalens, 2000).***

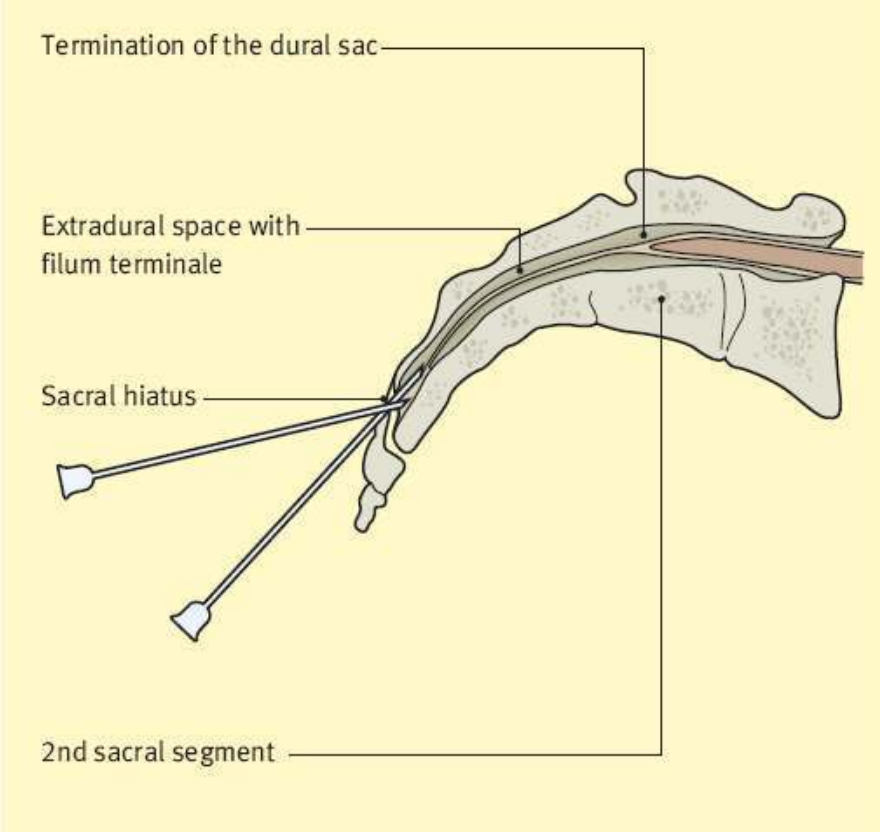

Figure (2): Longitudinal section through the sacrum to show the termination of the dural sac and the anatomy of a caudal block ***(Ellis, 2006)***

PHYSIOLOGY OF PAIN

The Biology of Pain Sensation

The International Association for the Study of Pain (IASP) define pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage', which indicates that, in the conventional sense, pain is caused by noxious stimuli, but may also be experienced in the absence of such stimuli ***(Brooks and Tracey, 2005)***.

Hyperalgesia refers to an exaggerated response to a stimulus that is normally painful (essentially an amplification of the pain signal).

Primary hyperalgesia refers to the nociceptor sensitization, the increase in frequency and amplitude of the action potential.

Secondary hyperalgesia, also known as central hyperexcitability, is an increase in the perception of the painful stimulus that results from an alteration in the neuroregulatory proteins associated with pain perception.

Allodynia is a Pain due to a stimulus that does not normally provoke pain, it often occurs after repetitive tissue injury ***(Jones, 2001).***

Dysaesthesia is an unpleasant abnormal sensation, whether spontaneous or evoked. Hyperalgesia and allodynia are specific cases of dysaesthesia.

Hyperaesthesia refers to increased sensitivity to stimulation, excluding the special senses. Hyperalgesia and allodynia are specific cases of hyperaesthesia.

Several classes of nerve fiber responsible for conduction of pain signals have been described ***(Raja et al. 1999).*** For example, thinly myelinated A δ fibers respond to changes in temperature and to mechanical stimuli; however, one may further classify A δ nociceptors to reflect whether they are fast or slowly adapting, and whether they have a high or low threshold for activity (so-called type I or II A-fiber nociceptors) ***(Brooks and Tracey, 2005).***

The other major class of nociceptors is C-fibers, or C mechano-heat receptors; these are unmyelinated, and thus are relatively slowly conducting, and convey a sensation of burning. To be noted that there is large overlap in the types of stimuli that will activate given nociceptors, and hence many are termed polymodal ***(Brooks and Tracey, 2005).***

In addition to these receptors, there are different afferent fibers that while normally unresponsive, become active during inflammation, and are called silent or sleeping nociceptors. Activation of these neurones occurs following tissue damage, making the nociceptor membrane more permeable to sodium

ions, leading to the generation of an impulse (action potential). These action potentials are propagated from the PNS (peripheral nervous system) to the CNS and synapse in the dorsal horn of the spinal cord, and depending on the intensity of stimulation, and hence frequency of firing, this may be sufficient to produce a postsynaptic output ***(Jones, 2001).***

The processing of acute and prolonged painful stimulation in the dorsal horn is depicted, and provides the physiological basis for two major characteristics of clinical pain: hyperalgesia and allodynia (fig. 3). An acute stimulus will trigger a series of events leading to excitatory pain signals reaching the brain via the spinal cord; as the stimulus is short lived, so is the neuronal response. However, given a longer, more chronic stimulus, sensitization may occur at either the peripheral and/or the central level ***(Brooks and Tracey, 2005).***

Localized inflammation in the tissues leads to hyperexcitability of peripheral nociceptors, and may cause exaggerated responses to normally painful mechanical or thermal stimuli – this is termed primary hyperalgesia. Alternatively, sensitization may occur at the level of the dorsal horn neuron following, for example, a burn or cut injury (so-called central sensitisation).

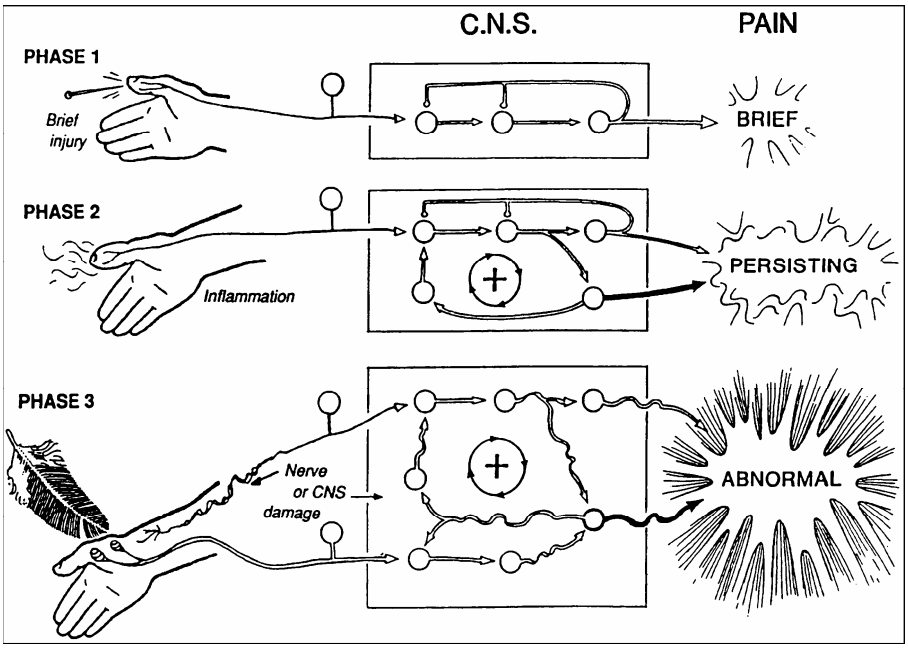

Figure (3): Schematic representation of the three phases of pain ***(Cervero and Laird, 1991)***.

Amplification mechanisms, which are still not fully understood, then enable peripheral neurons not normally associated with pain to evoke painful sensations. Such centrally mediated sensitization is thought to explain the phenomenon of secondary hyperalgesia, whereby mechanical stimulation around the initial injury site (i.e. in normal skin) produces pain. Another related symptom of peripheral nerve injury is depicted in phase 3 of Fig. 3. Similar to secondary hyperalgesia, damage to the peripheral nerve induces plastic changes in the CNS (i.e. central sensitization), which are maintained by continuing discharge from the damaged afferent, and enables recruitment

of low-threshold mechanoreceptors (e.g. Aβ fibres), which, when brushed, evoke pain. Here, because pain is produced following a normally nonpainful stimulus (e.g. light brush), the pain evoked is referred to as allodynia.

The nociceptive afferents terminating in the dorsal horn release numerous transmitters, of which some act directly, while some serve as modulators. Under normal conditions, high levels of the excitatory amino acids glutamate and aspartate, substance P (SP) and calcitonin gene-related peptide (CGRP) have been found in the superficial dorsal horn and are, therefore, considered as the main nociceptive transmitters under physiological conditions ***(Riedel and Neeck, 2001).*** But also vasoactive intestinal peptide (VIP), cholecystokinin (CCK) and neurotensin have been identiefied in enhancing nociceptive nervous traffic ***(Jones, 2001).***

To the contrary, inhibitory interneurons importantly counteract the flow of nociceptive signals. Gamma aminobutyric acid (GABA), a major inhibitory transmitter in the CNS, is localized in high concentration in interneurons of laminae I–III of the spinal cord gray matter, and has been implicated in the inhibition of acute and persistent pain ***(Schadrack and Zieglgänsberger, 1998).*** In addition, an antinociceptive role has been attributed to cholinergic interneurons, acting via muscarinic and nicotinic receptors, and to opioidergic interneurons containing enkephalins or

dynorphin, which exert their actions via δ, κ and μ opioid receptors ***(Coggeshall and Carlton 1997).***

Beyond the peripheral nociceptor and dorsal horn, depending on the type of nociceptor activated, pain related information ascends in the contralateral spinothalamic tract (STT), but there are also direct connections to the medulla and brain stem via the spinoreticular (SRT) and spinomesencephalic (SMT) tracts and to the hypothalamus via the spinohypothalamic tract (SHT) ***(Brooks and Tracey, 2005).***

Numerous animal studies have been performed using anatomical tracers, and indicate that functionally differentiated nociceptors form synaptic connections within eight distinct laminae of the dorsal horn. Generally, cells within these laminae send their ascending axonal projections across the dorsal or ventral commissure of the spinal cord and form white matter bundles or funiculae, which connect to the brainstem and thalamus. A brief summary of the projections involved from the periphery to the CNS is shown in fig. 4.

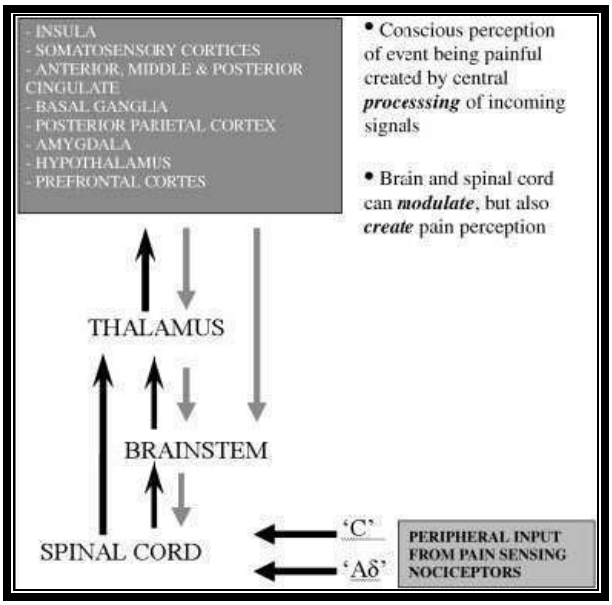

Figure (4): Simple schematic of nociceptive pathways from the periphery to supraspinal regions. Black arrows represent transmission of pain signals supraspinally, which is integrated at several levels along the neuroaxis, and at almost every level influenced by descending fibers (grey arrows) ***(Tracey and Dunckley, 2004).***

The Pain Matrix

Recent studies have revealed that the somatosensory area (S1) is only one among many other circumscribed cortical areas which are implicated in the global experience of pain ***(Price, 2000; Tracey et al., 2000).*** The cortical and subcortical brain regions found to be commonly activated by nociceptive stimulation included: anterior cingulate cortex(ACC), insula, frontal cortices, S1, second somatosensory cortex (S2) and amygdale and are often referred to as the 'pain matrix' ***(Ingvar, 1999)***. A summary of the pain matrix is given in fig.5.

In fig. 5, the pain matrix is subdivided into a medial and a lateral pain system; this distinction, which is based on the projection sites from medial or lateral thalamic structures to the cortex, is probably an oversimplification of the networks involved, but is a useful means for grouping brain regions that appear to have similar roles in pain perception. For instance, the lateral pain system (S1, S2) is primarily thought to have a role in discriminating the location and intensity of painful stimuli ***(Kanda et al. 2000),*** whereas the ACC is involved in the affective (cognitive–evaluative) component of pain ***(Vogt et al., 2003).***

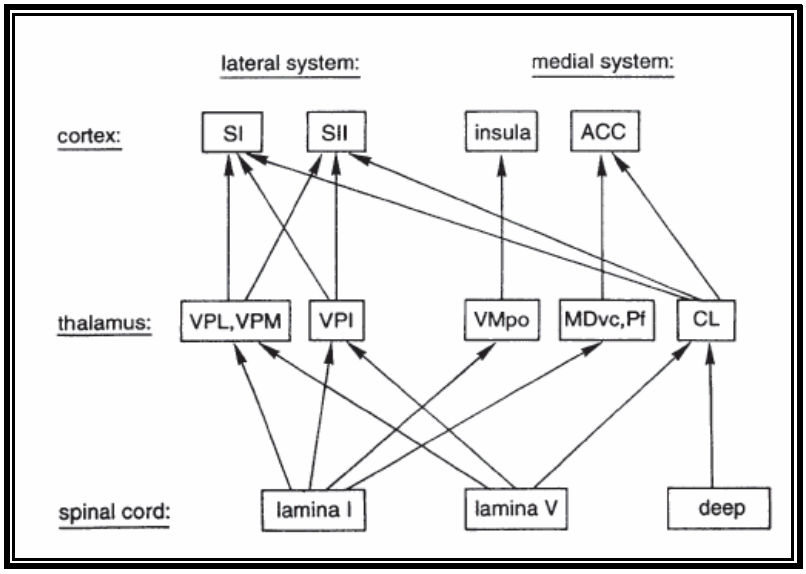

Figure (5): Cortical areas that receive information from the spinothalamic tract ***(Treede et al., 1999).*** (ACC, anterior cingulate cortex; CL, centrolateral nucleus; MDvc, ventrocaudal part of medial dorsal nucleus; Pf, parafascicular nucleus; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; VMpo, posterior part of ventromedial nucleus; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.)