INTRODUCTION

Magnesium (Mg), a non-competitive antagonist at N-methyl-D aspartate (NMDA) receptors, has the potential to prevent central sensitization from peripheral nociceptive stimulation ***(Jiehao et al., 2012).*** As for neurotoxicity, magnesium has been shown to provide analgesia without complication when administered into the epidural space in combination with bupivacaine ***(Tanmoy et al., 2010)***. In patients undergoing cesarean section, Mg has been shown to improve analgesia when combined with epidural fentanyl ***(Yousef and Amr, 2010).*** However, little information is available regarding the analgesic effect of epidural magnesium as a solo adjunct to spinal anesthesia.

Epidural anesthesia has been popular over recent decades as there is evidence for reduced blood loss and fewer thromboembolic complications using neuraxial techniques in orthopedic surgery ***(Marces et al., 2013).***

AIM OF THE WORK

The aim of this study is to compare between intravenous magnesium and epidural magnesium as adjuvant to spinal anaesthesia during elective caesarian section as regard post-operative analgesia, including comparison of analgesic efficacy, side-effects, and complications.

Chapter One

PAIN

First attested in English in 1297, the word pain comes from the Old French peine, in turn from Latin poena, "punishment, and penalty". The pain can significantly interfere with a person's quality of life and general functioning ***(Turk and Dworkin, 2004)***.

1) Definition of pain:

The International Association for the Study of Pain defines pain as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage.” This definition recognizes the interplay between the objective physiologic sensory aspects of pain and its subjective emotional and psychological components ***(Carr and Goudas, 1999).***

Pain is clinically divided into: acute pain which is primarily due to nociception, and chronic pain which may also be due to nociception, but in which psychological and behavioral factors often play a major role ***(Butterworth et al., 2013).***

Postoperative pain is one of the types of acute pain and can be further differentiated based on the origin and feature into somatic and visceral pain. Somatic pain is due to nociceptive input arising from skin, subcutaneous tissues and mucous

membranes. It is characterized by being well-localized and described as sharp, pricking, throbbing or burning sensation ***(Grubb, 1998).***

Visceral pain - on the other hand - is due to nociceptive input arising from internal organ or one of its coverings. It is usually dull diffuse pain which is frequently associated with abnormal sympathetic or parasympathetic activity causing nausea, vomiting, sweating and /or changes in blood pressure or heart rate ***(Grubb, 1998).***

Chronic post-surgical pain is more common than realized. So, in order to achieve good quality of postoperative analgesia, careful history should be taken from the patients about any coexisting medical conditions such as substance abuse or withdrawal, anxiety disorder, affective disorder, hepatic or renal impairment and any past history of poor pain management. In addition, preoperative patient education should be done to the patients to improve expectations, compliance and ability to effectively interact with pain management techniques ***(Chris, 2003).***

2) Neuro-physiology of pain:

In 1955, Sinclair DC and Weddell G developed "peripheral pattern theory", based on a 1934 suggestion by John Paul Nafe. They proposed that all skin fiber endings (with the exception of those innervating hair cells) are identical, and that

pain is produced by intense stimulation of these fibers ***(Bonica, 1990).***

Another 20th-century theory was "gate control" theory, introduced by Ronald and Patrick in the 1965 Science article "Pain Mechanisms: A New Theory"***(Melzack and Wall, 1965)***, The authors proposed that both thin (pain) and large diameter (touch, pressure, vibration) nerve fibers carry information from the site of injury to two destinations in the dorsal horn of the spinal cord, and that the more large fiber activity relative to thin fiber activity at the inhibitory cell, the less pain is felt (***Moayedi and Davis, 2012)).***

Some sensory fibers do not differentiate between noxious and non-noxious stimuli, while others, nociceptors, respond only to noxious, high intensity stimuli ***(Moayedi and Davis, 2012).***

- ***Stimulus:***

Surgery produces tissue injury with consequent release of histamine and inflammatory mediators such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor). Release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation in which release of

neurotransmitters (i.e., substance P and calcitonin gene–related peptide) in the periphery induces vasodilatation and plasma extravasation Noxious stimuli are transduced by peripheral nociceptors ***(Julius and Basbaum, 2001)***.

- ***Nociceptors:***

Sensation is often described as either protopathic (noxious) or epicritic (non-noxious). Epicritic sensation (light touch, pressure, proprioception and temperature discrimination) is received by low-threshold receptors (specialized endorgans on the afferent neurons) and conducted by large myelinated nerve fibers, while protopathic sensation (pain) is subserved by high-threshold receptors (free nerve endings) and conducted by small unmylinated nerve fibers ***(Carr and Goudas, 1999).***

At the peripheral end of the nociceptor, noxious stimuli are transduced into currents that, above a given threshold, begin to generate action potentials that travel along the nerve fiber to the spinal cord. This protopathic pain is transmitted mainly by free nerve endings that sense mechanical or chemical tissue damage. The "specificity" (whether it responds to thermal, chemical or mechanical features of its environment) of a nociceptor is determined by which ion channels it expresses at its peripheral end ***(Woolf and Ma, 2007)***.

Several types of these pain receptors includes:

(1) Mechano-nociceptors, which respond to pinprick.

(2) Silent nociceptors, which respond only in the presence of inflammation.

(3) Polymodal mechano-heat receptors which are more prevalent and respond to excessive pressure, extreme of temperature and pain producing substance ***(Richardson and Mustard, 2009).***

The pain signal travels from the periphery to the spinal cord along an A-delta or C fiber. Because the A-delta fiber is thicker than the C fiber, and is thinly sheathed in an electrically insulating material (myelin), it carries its signal faster (5–30 m/s) than the unmyelinated C fiber (0.5–2 m/s) (figure 1) ***(Macres et al., 2013).***

Pain evoked by the (faster) A-delta fibers is described as sharp and is felt first. This is followed by a duller pain, often described as burning, carried by the C fibers**,** thus Noxious sensations can often be broken down into two components: a fast, sharp, and well-localized sensation “first pain” which is conducted by A- delta fibers; and a duller, slower onset, and poorly localized sensation “second pain” which is conducted by C fibers (figure 2) ***(Julius and Basbaum, 2001).***

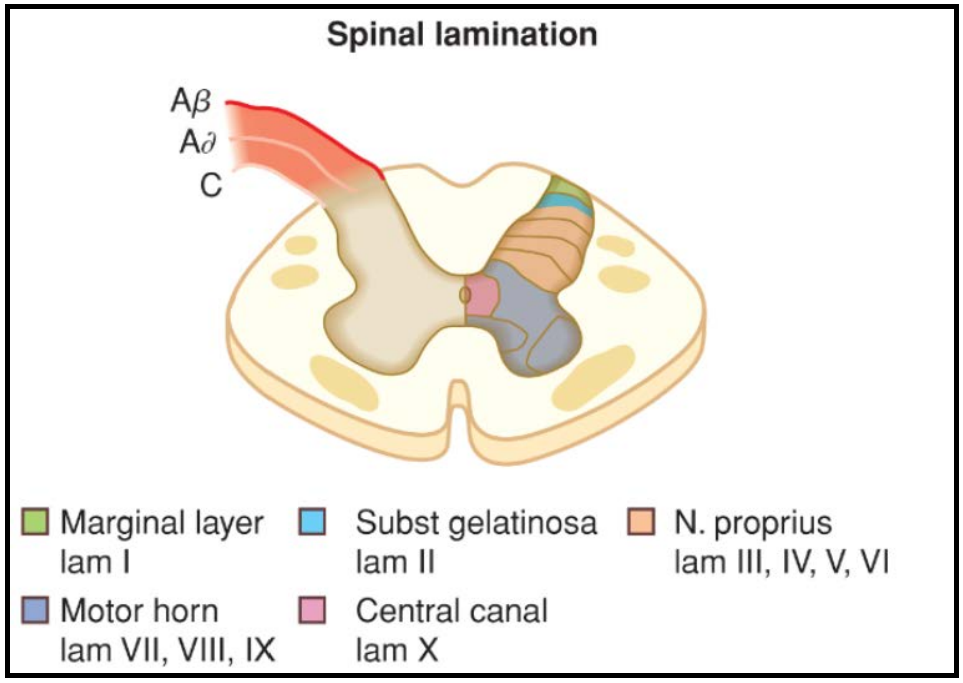

Figure (1): Different types of nerve fibers quoted from ***(Marcas et al., 2013).***

These first order neurons enter the spinal cord via Lissauer's tract. A-delta and C fibers synapse on second order neurons in substantia gelatinosa (laminae II and III of the dorsal horns). These second order fibers then cross the cord via the anterior white commissure and ascend in the spinothalamic tract. Before reaching the brain, the spinothalamic tract splits into the lateral neospinothalamic tract and the medial paleospinothalamic tract (figure 3) ***(Macres et al., 2013).***

Second order neospinothalamic tract neurons carry information from A-delta fibers and terminate at the ventral posterolateral nucleus of the thalamus, where they synapse on third order neurons (dendrites of the somatosensory cortex).

Paleospinothalamic neurons carry information from C fibers and terminate throughout the brain stem, a tenth of them in the thalamus and the rest in the medulla, pons and periaqueductal gray matter ***(Macres et al., 2013)***.

Pain-related activity in the thalamus spreads to the insular cortex (thought to embody, among other things, the feeling that distinguishes pain from other homeostatic emotions such as itch and nausea) and anterior cingulate cortex (thought to embody, among other things, the motivational element of pain) and pain that is distinctly located also activates the primary and secondary somatosensory cortices ***(Romanelli and Esposito, 2004).***

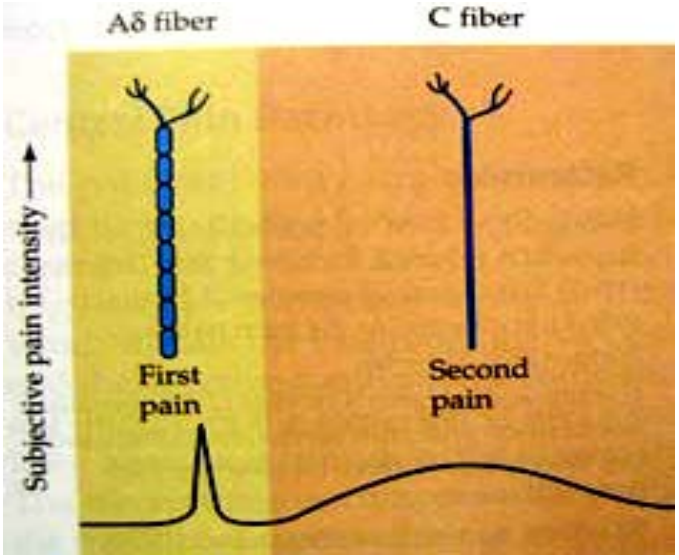

Figure (2): A- delta and C fibers quoted from ***(Julius and Basbaum, 2001).***

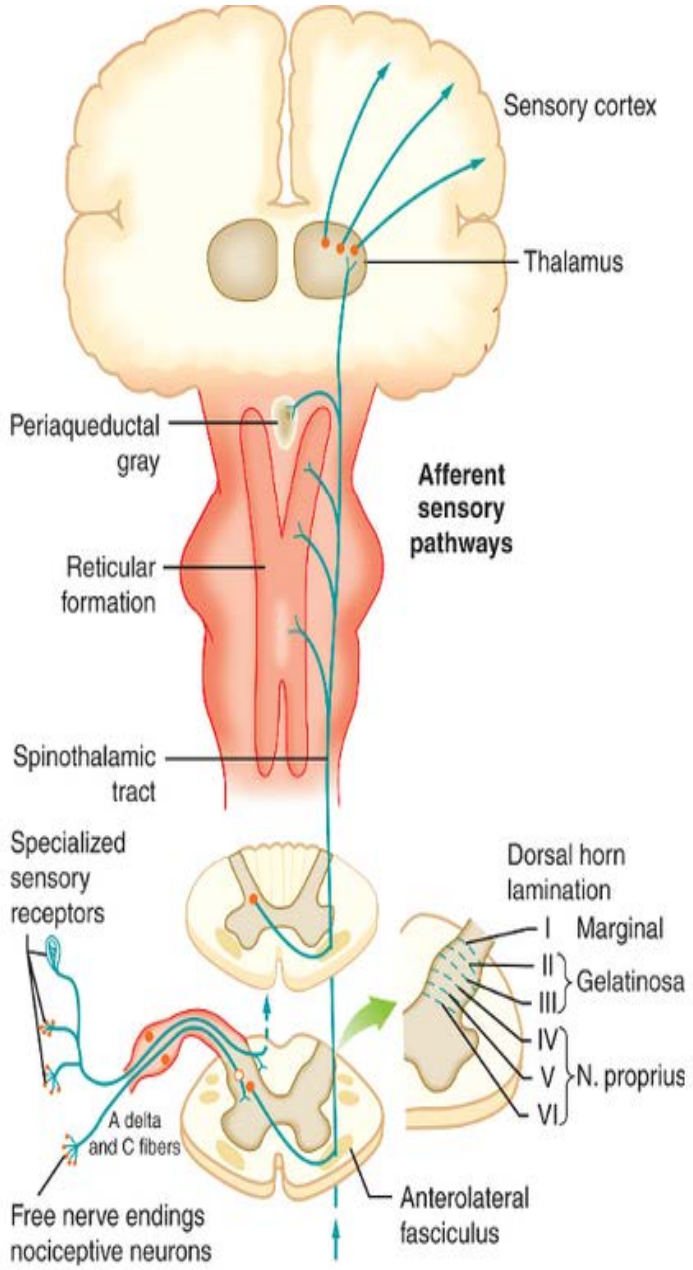

Figure (3): Peripheral nerve fibers and pain pathway quoted from ***(Macres et al., 2013)***.

3) Complications of postoperative pain:

Moderate to severe acute pain, regardless of its site, can affect nearly every organ function and may adversely influence postoperative morbidity and mortality. Acute pain is typically associated with neuro-endocrinal stress response that is proportional to pain intensity and it has been hypothesized that a reduction in surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby to an improved outcome ***(Richardson and Mustard, 2009).***

- ***Postoperative pain effect on different organs;***

  (A) Cardiovascular effects.

  (B) Pulmonary effects.

  (C) Gastrointestinal effects.

  (D) Endocrinal effects.

  (E) Hematological effects.

  (F) Immunological effects.

  (G) Psychogenic effects.

  (F) Development of chronic pain.

(A) Cardiovascular effects:

Cardiac morbidity is a major cause of perioperative death. Catecholamine-induced tachycardia, enhanced contractility, increased afterload and increased preload from hypervolemia (caused by enhanced release of arginine vasopressin and aldosterone) are well characterized determinants of increased oxygen demand. Increased oxygen demand, with hypervolemia, may precipitate ischemia and acute cardiac failure, especially in patients with poorly compensated coronary artery or valvular heart disease ***(Warltier et al., 2000).***

(B) Pulmonary effects:

Pain increases total body oxygen consumption and carbon dioxide production which necessitates an increase in the work of breathing. Patients with poor pain control have inadequate cough, leads to further reduction in the tidal volume and functional residual capacity which in turn can cause atelectasis, intrapulmonary shunting and hypoxemia ***(Kehlet and Holte, 2001).***

(C) Gastrointesinal effects:

Sympathetic hyperactivity induced by pain increases sphincter tone and decrease motility of intestine, causing ileus. Pain also increases stress ulceration due to increase in gastric acid secretion ***(Holte and Kehlet, 2000).***

(D) Endocrinal effects:

The dominant neuro-endocrinal responses to pain involve hypothalamic-pitutary-adrenocortical interactions. Those interactions result in increased catecholamine and catabolic hormone release. These effects cause sodium and water retention and increased levels of blood glucose, free fatty acids and lactate ***(Desborough, 2000).***

(E) Hematological effects:

The stress response causes decrease in the levels of natural anticoagulants, inhibition of fibrinolysis and increase in platelet reactivity which initiate a postoperative hypercoagulable state. This hypercoagulability causes a series of other events such as deep venous thrombosis and myocardial ischemia ***(Dahl et al., 2003).***

(F) Immunological effects:

The stress response potentiates postoperative immunosuppression. Stress response has been reported to depress the reticulo-endothelial system which predisposes to infection ***(Carr and Goudas, 1999).***

(G) Psychogenic effects:

In many patients, uncontrolled postoperative pain can produce a series of long-term emotional disturbances, which could impair the patient's health and cause undue fear and

anxiety if subsequent surgery is required. Postoperative cognitive dysfunction occurs in up to 20% of patients after major non-cardiac surgery and may persist in about 10% of patients 3 months after surgery ***(Kehlet and Holte, 2001).***

(F) Development of chronic pain:

Recently, it is accepted that neuropathic pain can develop after surgery, can be persistent and can be the basis for ongoing suffering for the patient. The diagnosis of neuropathic pain can be obtained from the presenting features of burning, stinging or shooting pain, despite apparent tissue healing with a relative lack of response to doses of opioids used in the postoperative period ***(Macrae, 2001).***

4) Pain scales and ladder:

Pain measurement is done by two methods:

(1) Type I methods:

Those are objective methods, done by the physician as he assigns numbers about the patient's condition. It includes the following:

- ***Physiological indices:***
  - Endocrinal (increase in serum cortisol and catecholamines).

- Cardiovascular (increase in blood pressure and heart rate).
- Respiratory (increase in respiratory rate and decrease in tidal volume).

o ***Neuro-pharmacological:***

- Correlation with beta endorphin (decreased in acute painful conditions).
- Thermography (hypo-emission in chronic pain).

o ***Neurological:***

- Nerve conduction velocity.
- Evoked potentials.

o ***Behavioral:*** crying, shouting, trembling

(2) Type II methods:

They include either:

o ***Single dimension methods:***

- Verbal rating scale (VRS)
- Visual analogue scale (VAS)
- Verbal Descriptor Scale(VDS)
- Graphic rating scale **(Wong-Baker Faces scale)**

o ***Multi-dimensional methods*:**

- McGill pain Questionnaire, MPQ