INTRODUCTION

Regional anesthetic techniques provide an excellent means for managing postoperative pain following elective anesthesia of the lower half of the body. Spinal anesthesia with bupivacaine provides effective analgesia in the early postoperative period ***(Kim and Lee, 2001).***

Various adjuvants have been added to spinal local anesthetic to prolong postoperative analgesia. Intrathecal opioids provide effective postoperative analgesia but are associated with adverse effects such as itching, nausea, urinary retention, sedation, ileus and life-threatening respiratory depression. Other adjuvants such as clonidine and ketamine have also been administered but none have become established in regular clinical use because of their adverse effects ***(Whiting, 2003).***

Intrathecal midazolam has been reported to have antinociceptive action. Evidence indicates that intrathecal midazolam may be useful in the treatment of somatic pain. Recent studies have also shown that midazolam produces an analgesic action through the benzodiazepine *gamma amino butyric acid* (GABA) receptor complex in the spinal cord ***(Tucker et al., 2004).***

AIM OF THE WORK

The purpose of this study is to assess the postoperative analgesic requirements and the spinally mediated analgesic effects of intrathecal midazolam as an adjunct to intrathecal bupivacaine after elective surgery of the lower half of the body in comparison to intrathecal bupivacaine alone and intrathecal bupivacaine plus fentanyl.

PATHOPHYSIOLOGIC CONSEQUENCES OF UNTREATED ACUTE POSTOPERATIVE PAIN

Untreated pain can lead to the following consequences:

1) Respiratory system:

The incidence of post operative pulmonary complications varies from 5-28%. Most of these complications are related to inappropriate control of post-operative pain. Pulmonary function can be affected significantly depending on the site and extent of surgery or trauma.Affection of ventilation / perfusion relationships occurs, followed by abnormal gas exchange and hypoxemia. Surgery and post-operative pain causes involuntary splitting and reflex muscle spasms of the abdominal and thoracic muscles. Excursions of the diaphragm are markedly limited, particularly when ileus develops. Furthermore, in an attempt to minimize pain, the patient refrains from deep breathing and coughing. Pulmonary status deteriorates, and some patients progress to atelectasis and pneumonia. When narcotics are given in sufficient quantity, respiratory depression results. Apnea can occur in severe cases. Prolonged bed rest and immobility can produce similar changes in pulmonary function.These sequelae increased in patients with pre –existing pulmonary disease, upper abdominal; or thoracic incisions, advanced age, and obesity. Effective analgesia tends to diminish

pulmonary complications in postoperative period ***(Bongard et al., 2008).***

2) Cardiovascular system:

Cardiovascular effects of pain are initiated by the release of catecholamines from sympathetic nerve endings and the adrenal medulla, aldesterone and cortisol from the adrenal cortex, and antidiuretic hormone from the hypothalamus, as well as by activation of the renin angiotensin system. These hormones have direct effect on the myocardium and vasculature, and they augment salt and water retention, which places a greater burden on the cardiovascular system. Angiotensin II causes generalized vasoconstriction, whereas catecholamines increase heart rate, myocardial contractility, and systemic vascular resistance ***(Brown, 2005).***

The sympathoadrenal release of catecholamines and the effects of angiotensin II may result in hypertension, tachycardia, and dysrhythmias and may lead to myocardial ischemia in susceptible patients as a consequence of increased oxygen demand. In addition, a significant proportion of perioperative myocardial ischemia is related to reduction in myocardial oxygen supply without hemodynamic aberrations. Activation of the sympathetic nervous system may trigger coronary vasoconstriction, which may result in myocardial ischemia in the presence of atherosclerotic coronary artery disease. This may occur through direct activation of cardiac

sympathetic nerves, as well as through circulating catecholamines that may contribute to hypercoagulability ***(Bongard et al., 2008).***

Salt and water retention secondary to aldesterone, cortisol, and antidiuretic hormone, in combination with the previously described effects of catecholamines and angiotensin II can also precipitate congestive heart failure in patients with limited cardiac reserve ***(Barash et al., 2006).***

3) Gastro-intestinal:

Sympathetic activation may delay return of postoperative gastrointestinal motility that may develop into paralytic ileus. Although postoperative ileus is the result of a combination of inhibitory inputs from central and local factors, an increase in sympathetic efferent activity, such as from uncontrolled pain, decreases gastrointestinal activity and delays return of gastrointestinal function ***(Brown, 2005).***

Hypersecretion of gastric acid can promote stress ulceration, and together with reduced motility, potentially predisposes patients to severe aspiration pneumonitis. Nausea, vomiting and constipation are common. Abdominal distension further aggravates loss of lung volume and pulmonary dysfunction ***(Kleinman and Mikhail, 2006).***

4) Neuroendocrine Effects:

Acute pain is typically associated with a neuroendocrine stress response that is proportional to pain intensity. Minor or superficial operations are associated with little or no stress, whereas major abdominal and thoracic procedures produce major stress ***(Brown, 2005).***

Pain itself as well as the associated anxiety and apprehension also aggrevates the hypothalamic neuro-endocrine response. These are increased secretions of catabolic hormones such as catecholamines, adrenocortico-trophic hormone (ACTH), cortisol, antidiuretic hormone (ADH), glucagon and aldosterone. Secretion of anabolic hormones such as insulin and testosterone is decreased. Patients develop a negative nitrogen balance, carbohydrate intolerance and increased lipolysis. The increase in aldosterone, cortisol, and antidiuretic hormone cause salt and water retention and secondary expansion of the extra cellular space ***(Bongard et al., 2008).***

Local release of cytokines such as interleukin-2, interleukin-6, and tumor necrosis factor may contribute to abnormal physiological response such as alteration in heart rate, temperature, blood pressure and ventilation. Finally, catecholamines sensitize peripheral nociceptive endings, which serve to propagate more intense pain and may

contribute to a vicious pain-catecholamine release pain cycle ***(Stoelting et al., 2006).***

5) Hematological Effects:

Stress-related alterations in blood viscosity, platelet function, fibrinolysis, and coagulation pathways have been described. These stress-mediated effects include increased platelet adhesiveness, diminshed fibrinolysis, and hypercoagulability state. When these effects are coupled with the microcirculatory effects of catecholamines and immobilization of the patient in the postoperative period, thromboembolic events are more likely to occur ***(Barash et al., 2006).***

6) Immune Effects:

The pain-related stress response suppresses both cellular and humoral immune function and results in lymphopenia, leukocytosis, and depression of the reticulo-endothelial system. In addition, some anesthetic agents reduce chemotaxis of neutrophils and may be one factor involved in the reduction of monocyte activity. Many known mediators of stress response are potent immunosuppressants. These effects can lower resistance to pathogens and may be key factors in the development of perioperative infectious complications ***(Stoelting et al., 2006).***

7) General sense of well being:

The most common reaction to acute pain is anxiety. Sleep disturbances are also typical. When the duration of pain becomes prolonged, depression is not unusual. Some patients react with anger that is frequently directed to the medical staff ***(Brown, 2005).***

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

SPINAL ANESTHESIA

Professor Bier performed the first surgical operation using spinal anesthesia at the Royal Surgical hospital at the University of Kiel, Germany on August 16, 1898, heralding the advent of major regional anesthesia using neuro-axial blockade. Spinal anesthesia was performed by Labat at the Mount Sinai Hospital in 1927 and since then spinal anesthesia has been well incorporated into the practice of anesthesia ***(Larson, 1996).***

I-Anatomical Considerations:

The Vertebral Column:

The spine is composed of the vertebral bones and fibrocartilaginous intervertebral disks (**Figure 1**). There are 7 cervical, 12 thoracic, and 5 lumbar vertebra. The sacrum is a fusion of 5 sacral vertebra, and there are small rudimentary coccygeal vertebra. The spine as a whole provides structural support for the body and protection for the spinal cord and nerves, and allows a degree of mobility in several spatial planes. At each vertebral level, paired spinal nerves exit the central nervous system ***(Kleinman and Mikhail, 2006).***

The spinal canal contains the spinal cord with its coverings (the meninges), fatty tissue, and a venous plexus. The meninges are composed of three layers: the pia mater,

the arachnoid mater, and the dura mater; all are contiguous with their cranial counterparts. The pia mater is closely adherent to the spinal cord, whereas the arachnoid mater is usually closely adherent to the thicker and denser dura mater ***(Brown, 2005).***

Cerebrospinal fluid (CSF):

CSF is an isotonic, aqueous medium with a constitution similar to interstitial fluid. CSF is contained between the pia and arachnoid matters in the subarachnoid space ***(Kleinman and Mikhail, 2006).***

The Spinal cord:

The spinal cord normally extends from the foramen magnum to the level of L_1 in adults. The anterior and posterior nerve roots at each spinal level join one another and exit the intervertebral foramina forming spinal nerves from C_1 to S_5. At the cervical level, the nerves arise above their respective vertebrae, but starting at T_1 they exit below their vertebrae. Because the spinal cord normally ends at L_1, lower nerve roots course some distance before exiting the intervertebral foramina. These lower spinal nerves form the cauda equina ("horse tail"). Therefore, performing a lumbar (subarachnoid) puncture below L_1 in an adult avoids potential needle trauma to the cord; damage to the cauda equina is unlikely as these nerve roots float in the

dural sac below L_1 and tend to be pushed away (rather than pierced) by an advancing needle ***(Brown, 2005).***

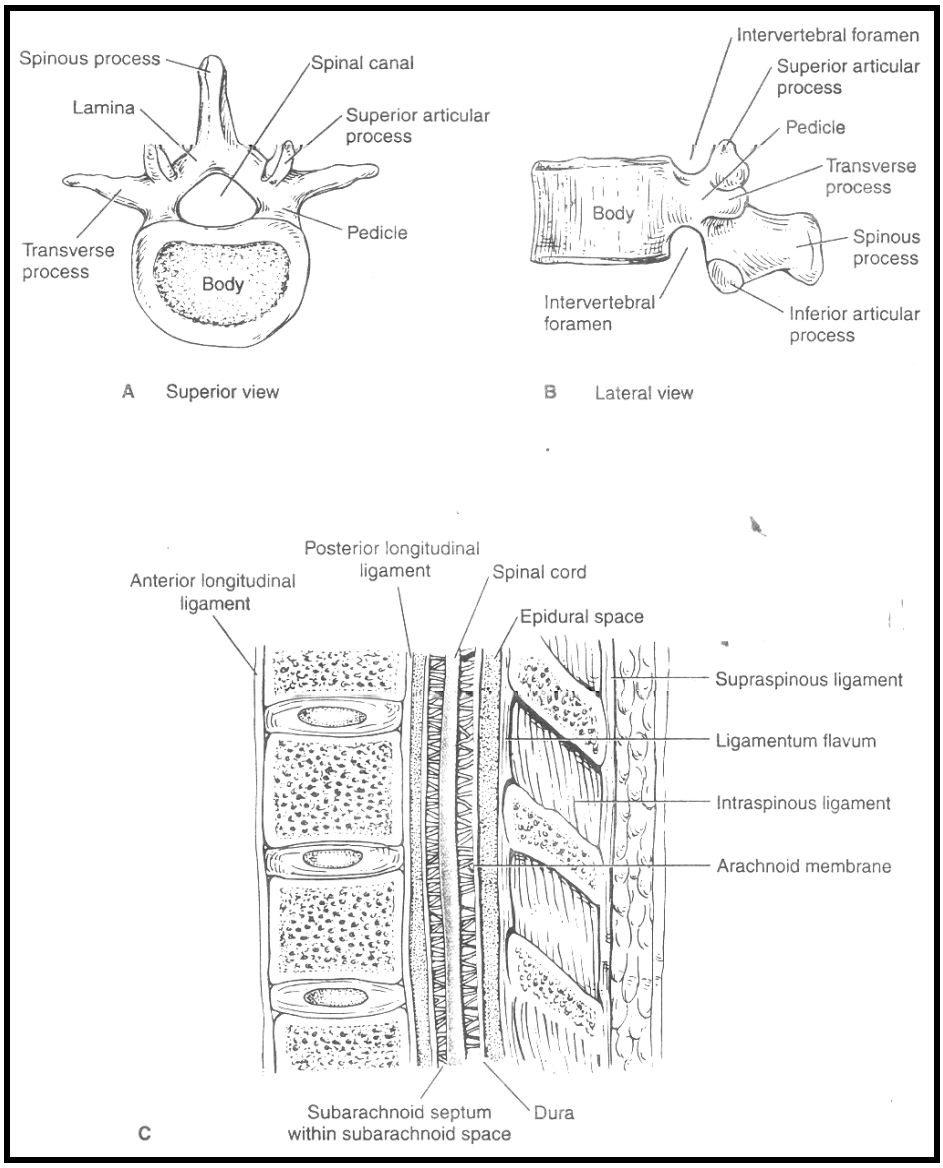

Figure (1): Sagital section through lumbar vertebrae (c), common features of vertebrae (A, B) ***(Kleinman and Mikhail, 2006).***

When performing spinal anesthesia using the midline approach, the layers of anatomy that are traversed (from posterior to anterior) are skin, subcutaneous fat, supraspinous ligament, interspinous ligament, ligamentum flavum, dura mater, subdural space, arachnoid mater, and finally the subarachnoid space. When the paramedian technique is applied, the spinal needle should traverse the skin, subcutaneous fat, ligamentum flavum, dura mater, subdural space, arachnoid mater, and then pass into the subarachnoid space ***(Bromage, 1997).***

The blood supply to the spinal cord and nerve roots is derived from a single anterior spinal artery and paired posterior spinal arteries. The anterior spinal artery is formed from the vertebral artery at the base of the skull and courses down along the anterior surface of the cord. The anterior spinal artery supplies the anterior two-thirds of the cord, whereas the two posterior spinal arteries supply the posterior one-third. The posterior spinal arteries arise from the posterior inferior cerebellar arteries and course down along the dorsal surface of the cord medial to the dorsal nerve roots ***(Kleinman and Mikhail, 2006).***

II-Physiological considerations:

The physiologic response to central block is determined by the effects of interrupting the afferent and efferent innervations of somatic and visceral structures.

Somatic structures are traditionally related with sensory and motor innervations, while the visceral structures are more related to the autonomic nervous system.

A-Somatic blockade:

Prevention of pain and skeletal muscle relaxation are classic objectives of central blockade. Nerve fibers are not homogenous. There are three main types of nerve fibers designated A, B and C. The A group has four sub-groups alpha, beta, gamma and delta. The functions of the main groups and sub-groups are summarized in table (1). The minimum concentration of local anesthetic required to stop transmission (Cm) varies depending upon fiber size ***(Casey, 2000).***

Table (1): Nerve fibers classification

Class	Action	Myelin	Size
Aα	Motor	Yes	++++
Aβ	Light touch, pressure pain	Yes	+++
Aγ	Proprioception	Yes	+++
Aδ	Pain, temperature	Yes	++
B	Preganglionic sympathetic fibers	Yes	++
C	Pain, pressure	No	+

(Kleinman and Mikhail, 2006)

B-Visceral blockade:

Most of the visceral effects of central blockade are mediated by interruption of autonomic impulses to various organ systems.

1- Cardiovascular effect:

Sympathetic blockade results in cardiovascular changes of hemodynamic consequence in proportion to the degree of sympathectomy. The sympathetic chain originates from the lumbar and thoracic spinal cord. The fibres involved in smooth muscle tone of the arterial and venous circulation arise from T_5 and L_1. Arteries retain most of their tone despite sympathectomy because of local mediators and there is no arteriolar vasoplegia, but the venous circulation does not. The consequence of total sympathectomy is an increase in the volume of the capacitance vessels, specially in the splanchnic circulation, decreasing the venous return to the heart and hypotension occurs ***(Butterworth, 1998).***

The cardiac accelerator fibers are sympathetic efferents, which increase heart rate when stimulated. When blocked by high central blockade, unopposed vagal action leads to bradycardia ***(Brown, 2005).***

Prophylactic administration of pharmacologic agents may be more effective than prehydration to prevent hypotension ***(Chan et al., 1997).*** α-adrenergic agents (e.g.,

phenylephrine) reliably increase arterial blood pressure by increasing systemic vascular resistance, however, heart rate and cardiac output may decrease because of increased after load ***(Buggy et al., 1998).*** α- and β- adrenergic agonists (e.g., ephedrine) are effective for increasing arterial blood pressure preventing hypotension but act by primarily increasing heart rate and cardiac output with a smaller increase in systemic vascular resistance ***(Butterworth, 1998).*** Initial treatment can be tailored to α- agonists on patients with hypotension and mixed α and β agonist on patients with both hypotension and bradycardia ***(Liu and McDonald, 2001).***

2- Pulmonary effects:

Clinically significant alterations in pulmonary physiology are usually minimal with neuroaxial blockade because the diaphragm is innervated by the phrenic nerve with fibers originating from C_3-C_5. Even with high levels, tidal volume is unchanged; there is only a decrease in vital capacity, which results from a loss of abdominal muscles' contribution to forced expiration ***(Kleinman and Mikhail, 2006).***

Patients with severe chronic lung disease may rely upon accessory muscles of respiration (intercostal and abdominal muscles) to actively inspire or exhale. High levels of neural blockade will impair these muscles.