EVALUATION OF THE MINIMAL EFFECTIVE DOSE OF LEVOBUBIVACAINE AND BUBIVACAINE IN CESAREAN SECTION UNDER SPINAL ANAESTHESIA.

Thesis

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CSE	combined spinal epidural
CSF	Cerepro-spinal fluid
MRI	magnetic resonance imaging
CT	computed tomography
CNS	central nervous system
C_{max}	The maximum plasma concentration
AUC	area under the plasma concentration-time curve
CYP	cytochrome P450
VAS	visual analogue scale
IQR	inter quarterial ratio

Introduction

For the local anesthetics selection, it is known that the agent's onset and duration of action, sensorial block level to motor block level and cardiac toxicity should be considered. 0.5 % heavy bupivacaine is more commonly used for spinal anesthesia for Caesarean section (***Dilek,etal;2012***).

Regional anesthesia techniques are increasingly preferred for caesarean section. With small amounts and various combinations of drugs, systemic and pharmacologic effects are avoided, a deep surgical anesthesia is obtained, and a safer, beneficial, and comfortable anesthesia is provided for the mother and child compared to other techniques. (***Erdil F,eta;2009)*** Recently, levobupivacaine, the pure L (-) enantiomer of bupivacaine, is preferred during spinal anesthesia due to its lower cardiovascular side effects and central nervous system toxicity.(***GENG Zhi-yu,etal;2011)***

The addition of low doses of opioids to local anesthetics during spinal anesthesia for caesarean section decreases the incidence of local anesthetic (LA**)**-related side effects, reduces the time to onset of the anesthetic effect, and increases the

quality of intra- and post-operative analgesia by reducing the administered dose of the LA (***Bremerich DH,etal;2007)***.

The addition of intrathecal fentanyl to spinal anesthesia is associated with an early time of onset of the *anesthetic effect* and a low incidence of side effects.

Fentanyl can be combined with local anesthetics for spinal anesthesia, and when used in this way it prolongs the duration of action and spread of sensory block as well. Fentanyl has been combined with bupivacaine for lower limb surgery and also for inguinal herniorrhaphy and caesarean section (***Gulen Guler, etal; 2012***). There are various factors affecting the spread and duration of block during spinal anesthesia. Factors affecting the spread of the block include volume and dose of the injected local anesthetic agent, rate of injection of the anesthetic solution, position of the patient during and immediately after the injection, age, weight and height of the patient, anatomical structure of the vertebral column, cerebrospinal fluid volume (CSF), level and velocity of the injection, barbotage, location and diameter of the tip of the injection needle, intra-abdominal pressure, pressure of the CSF, and concentration of the local anesthetic. On the other hand,

type of the local anesthesia, level of anesthesia and addition of a vasopressor are known to affect the duration of anesthesia.(***Nuray,etal;2011)***

AIM OF THE WORK

The aim of the present study is to investigate the effects of various doses of either levobupivacaine or bupivacaine, with intrathecal fentanyl on maternal anesthesia, analgesia, hemodynamics, and the effect on the newborn, during elective caesarean section under spinal anesthesia.

REGIONAL ANESTHESIA AND CESAREAN SECTION

The three main regional anesthetic techniques are spinal, epidural, and combined spinal epidural (CSE). Spinal and CSE anesthesia are the most common regional anesthetic choices for planned cesarean delivery. Many practitioners prefer these techniques over epidural because they have a rapid onset and lower incidence of failed block. Their use for cesarean birth was facilitated by the popularization of pencil-point needles, which dramatically reduced the incidence of post dural puncture headache (***Rudra et al., 2004).***

Regional anesthesia for cesarean delivery differs from analgesia for labor and vaginal delivery in two major ways: Operative anesthesia requires a more intense block because the nociceptive stimulus of surgery is more intense than the pain of labor. Relatively dilute concentrations of local anesthetics are administered for labor analgesia in order to avoid motor block and minimize interference with second stage pushing efforts. However, motor block is desirable during cesarean birth to obtain abdominal muscle relaxation. A more intense block is achieved by administering a high concentration of local anesthetic. The dermatomal level of anesthesia required for cesarean delivery is higher than that required for labor analgesia. A sensory block to the 10th thoracic dermatome is sufficient to achieve analgesia for labor, but for cesarean, the anesthetic level must be extended cephalad to at least the fourth thoracic dermatome to prevent nociceptive input from the peritoneal manipulation) ***(Biswus etal, 2002).***

General anesthesia is generally less desirable for cesarean delivery because the mother is unconscious, thus unable to interact with her newborn. Two potential serious complications associated with general anesthesia are failed endotracheal intubation and pulmonary aspiration of gastric contents.

Inhibition of upper airway reflexes and alterations of gastrointestinal function increase the risk of pulmonary aspiration. Airway reflexes are compromised by the loss of consciousness that occurs with induction of general anesthesia. An advantage of regional anesthesia is that the woman is awake and airway reflexes are maintained. However, aspiration may also occur during regional anesthesia if airway reflexes are compromised by injudicious sedation. Furthermore, if the regional anesthetic is inadequate, it may be necessary to induce general anesthesia ***(Bano et al., 2006).***

The choice of regional or general anesthesia is influenced by a variety of other factors, such as the urgency of the procedure, maternal hemodynamic status and patient preference**.** For scheduled cesareans, the rapidity of anesthetic induction is less of a concern, so all anesthetic options (regional and general) are available. If the cesarean must be performed urgently because of a non reassuring fetal heart rate pattern, an anesthetic technique that can be performed relatively quickly is preferred since anesthesia must be achieved expeditiously. If the cesarean is a true emergency, the time required to achieve anesthesia and facilitate a rapid delivery may be of critical importance to the well-being of the fetus and/or mother ***(Bano etal, 2006).***

Maternal medical factors also influence the choice of optimum anesthetic. A discussion of anesthetic management of specific maternal disorders is beyond the scope of this review. In general, acute hemorrhage and hemodynamic instability compromise against the use of regional anesthesia since the accompanying sympathetic block will produce vasodilatation, which will exacerbate maternal hypotension. The presence of qa significant bleeding diathesis (eg, severe thrombocytopenia) is another contraindication to regional anesthesia because of the increased risk of causing a spinal/epidural hematoma ***(Harlocker et al., 2003).***

On the other hand, if evaluation of the patient's airway anatomy suggests that intubation may be difficult, then regional anesthesia may be a more desirable choice than general anesthesia. Other reasons a regional anesthetic may be preferable include history of malignant hyperthermia, some types of cardiac or respiratory disease, and for the prevention/treatment of autonomic hyper-reflexia ***(Spiegel and Hess, 2007).***

Post–operative pain relief is an unresolved issue. One of the methods of providing postoperative analgesia is by prolonging the duration of intrathecal bupivacaine by additives such as opioids, clonidine, ketamine etc. However each drug has its limitations and a need for alternative methods or drugs always exist ***(Tan et al., 2001).***

Intrathecal opioids are synergistic with local anesthetics and intensify the sensory block without increasing the sympathetic block. The combination makes it possible to achieve spinal anesthesia with otherwise inadequate doses of local anesthetic as intrathecal opioids offer hemodynamic stability. As intrathecal morphine is associated with higher incidence of side effects, the usage of newer opioids like fentanyl is combined with milder side effects ***(Tan et al., 2001).***

Nausea and vomiting remain as "the big little problem in caesarean delivery under spinal anesthesia. Several pharmacological agents are proven to diminish this problem, but none have been proved to be effective without exhibiting significant adverse effects or high cost.Recently, intrathecal (IT) administration of lipophilic opioids such as Fentanyl and benzodiazepines like midazolam has been reported to minimize the incidence of intra-operative and early postoperative nausea and vomiting in caesarean delivery under spinal anesthesia (***Rudra et al., 2004).***

Now it has been successfully well established that regional anaesthesia is much safer than GA for caesarean section and the majority of the operative procedures for delivery are being carried out under regional anaesthesia throughout the world. Maternal preference, comorbid diseases and urgency of surgery also determine to a large extent the type of anaesthesia to be employed. Whatever the type of anaesthesia is to be administered, the most significant aspect is the decreased number of maternal-deaths***(Chang-and-Streitman,2012)*** .

GA is indicated in a number of conditions such as(***Bajwa etal 2,012***

- Patient's refusal for regional anaesthesia
- Coagulation abnormalities
- Various contra-indications of regional anaesthesia such as severe active infection at the back, neurological diseases, deformities of the spine, etc
- Fetal compromise necessitating urgent operative intervention.

The most challenging aspect of an obstetric patient receiving GA involves management of a difficult airway. The anatomic and physiologic changes during pregnancy make the scenario of airway management very challenging such as soft tissue oedema of the upper airway, weight gain, breast enlargement, increased mucosal vascularity with an increased propensity to bleed, as well as a high risk of aspiration pneumonitis**(*Bajwa and Kaur,2012).***

The hormonal imbalance decreases the tone of the upper oesophageal sphincter and therefore there is always a risk of aspiration in these patients in spite of adequate fasting. The increased gastric emptying time and increased intra-abdominal pressure due to a gravid uterus further enhance the risk of pulmonary aspiration **(Sia etal,2009).**

The availability of newer supraglottic devices such as, proseal laryngeal mask airway and intubating laryngeal mask airway have further eased the administration of GA and management of a difficult airway***(Wong CA,2009).***

Regional anaesthesia is not only associated with avoidance of airway manipulation, but also has the advantage of avoiding the poly-pharmacy practiced in GA. Regional anaesthesia also enables the parturient to remain awake during the surgical intervention and feel the first cry of the baby, which is a good psychological boost for overly anxious patients***(Macarthur and Gerad, 2008)***.

Although spinal and epidural techniques have been equally useful, spinal is more common and significant when quick delivery is required and also the cost effectiveness of spinal anaesthesia is more comforting to the patient's relatives as compared with epidural especially in developing countries. Epidural is more versatile technique as it can be used for labour analgesia and if the need arises operative intervention can be performed with the same catheter. The provision of a prolonged post-operative pain-free period makes this technique a first choice of many parturients. This method also has the advantage of extending the block height if the sensory level shows early regression during the surgical procedure. The increased costs as well as a longer time taken for achieving an adequate block are a few of its main disadvantages. However, with the addition of adjuvants such as opioids and α-2 agonists, sensory anaesthesia is achieved in a much quicker time and that too with a lower dose of Las.The combined spinal epidural anaesthesia has the dual advantage of spinal as well as of epidural anaesthesia. It not only produces a rapid and dense block, but equally produces a post-operative pain-free period through top-up doses***(Lim etal,2009) .***

Pregnancy increases the basal metabolic rate and lowers pulmonary functional residual capacity. Thus, hypoxemia is likely to develop rapidly during the period of apnea that accompanies the induction of general anesthesia. Acidic aspirate is especially injurious to the lungs. Prophylactic administration of a non particulate antacid (eg, sodium citrate), histamine 2-receptor antagonist (eg, ranitidine), proton pump inhibitor (eg, omeprazole), or prokinetic drug (eg, metoclopramide), alone or in combination, prior to induction of general anesthesia is a standard procedure to mitigate the effects of aspiration. The goal is to raise intragastric pH and, for some agents, lower intragastric volume. Although these drugs have been shown to increase pH and some decrease gastric volume, they have not been proven to reduce the frequency of aspiration pneumonitis due to the low incidence of this event. Patients at increased risk for aspiration (obese, anticipated difficult intubation) are candidates for these drugs ***(Battacharya and Dutta, 2007).***

In the supine position, the gravid uterus compresses the aorta and inferior vena cava, thereby decreasing venous return, cardiac output, and blood pressure. Regional anesthesia mediated-vasodilatation exacerbates this effect by promoting pooling of blood in capacitance vessels. Therefore, the uterus should be displaced off the great vessels by placing a wedge under the right hip (left uterine displacement) whenever the parturient is positioned supine ***(Bano etal, 2006).***

Fetal oxygenation depends upon placental perfusion; thus, a decrease in maternal blood pressure compromises fetal oxygenation and is manifested by deterioration of the fetal heart rate. Induction of anesthesia tends to reduce maternal blood pressure. This is particularly true for regional anesthesia, which results in pooling of blood in capacitance vessels due to sympathetic block mediated vasodilatation. The onset of block is more rapid with spinal than epidural anesthesia; for this reason, hypotension occurs in up to 80

percent of patients who receive spinal block. Prophylactic strategies to prevent regional anesthesia-induced hypotension include volume expansion using intravenous fluids, administration of vasopressors. Intravenous fluid loading has been a standard prerequisite to regional anesthesia. However, crystalloid preload prior to spinal anesthesia does not reliably prevent maternal hypotension, probably due to rapid redistribution of crystalloid from the intravascular space. Colloid prehydration (hydroxyethylstarch) appears to be superior to crystalloid (lactated Ringer's) in reducing, but not eliminating, the incidence of spinal-induced hypotension in patients (30 to 40 versus 60 to 80 percent respectively) (***Klienman and Mickhail, 2006).***

Most anesthesiologists use crystalloid solutions because they are usually adequate, and colloid solutions are more expensive and less readily available than crystalloid. If crystalloid is chosen for pre hydration, glucose-free solutions should be used to prevent hyperinsulinemia in the fetus. Excessive placental glucose transfer can result in compensatory release of fetal insulin (fetal hyperinsulinemia) and neonatal hypoglycemia. Prophylactic administration of vasopressors prior to, or coincident with induction of regional anesthesia will minimize the incidence and severity of hypotension ***(Chavada et al., 2009).***

If anesthetics result in neonatal depression, appropriate resuscitative measures, including ventilatory assistance, should be instituted until the effects abate. Alternatively, specific reversal agents for opioids (naloxone) and/or benzodiazepines (flumazenil) -Reversal of benzodiazepine when used in conscious sedation or general anesthesia: Initial dose: 0.01 mg/kg (maximum dose: 0.2 mg) given over 15 seconds; may repeat 0.01 mg/kg (maximum dose: 0.2 mg) after 45 seconds, and then every minute to a maximum total cumulative dose of 0.05 mg/kg or 1 mg, whichever is lower; usual total dose: 0.08-1 mg (mean: 0.65 mg) -may be administered to the

neonate. Although anesthetics may result in temporary neonatal depression, there is no evidence of any long-term effects ***(Pan et al., 2004).***

Multimodal analgesia refers to the concurrent administration of different classes of analgesics. The rationale of the multimodal approach is that each class of analgesic acts to inhibit pain at different sites of the pain pathway. Furthermore, the different analgesics potentiate one another, allowing use of relatively small doses of each agent. The net effect is to lower the incidence and severity of side effects while obtaining excellent analgesia (***Klienman and Mickhail, 2006).***

Neuraxial analgesia and the anticoagulated patient, Pregnant women may be treated with anticoagulants for a variety of indications. The most common indication for anticoagulation is the presence of a thrombophilia such as factor V Leiden mutation, prothrombin gene mutation, antithrombin deficiency, protein C deficiency, or protein S deficiency. The risk of hemorrhage into the neuraxis is increased in anticoagulated patients, thus one must consider the type of anticoagulant used, the dose, and the timing of its administration. For all patients in whom a bleeding tendency is suspected, an evaluation of coagulation status is indicated prior to neuraxial analgesia ***(Pan et al., 2004)***

The risk of spinal haematomas is extremely low, but it can have dramatic neurological consequences for patients. The risk in patients receiving enoxaparin for thrombosis prophylaxis (40 mg once daily) was reported to be 1:18 000 after epidural anaesthesia and 1:156 000 after spinal anaesthesia***(Kozek etal 2008).***

In order to minimize bleeding complications of regional anaesthetic techniques, care should be taken to avoid a traumatic puncture. The final decision to perform regional anaesthesia in patients receiving drugs that affect haemostasis has to be taken after assessment of the individual risk and benefit. If it is judged that the administration of the anticoagulant

must not be interrupted, an alternative anaesthetic technique should be used. Spinal hematoma can occur late after surgery***(Cameron etal2007).*** After performance of the block, the patient should be monitored at least until the effect of the regional anesthesia is clearly declining, that is when there is a reduction in the extent of sensory block by two segments or a return of motor function. Particular attention should be given to persistent sensory or motor deficits, radicular back pain, pressure sensitivity in the puncture area and bladder dysfunction. When there is a clinical suspicion of neuraxial haematoma, appropriate diagnostic (MRI) or treatment measures (decompressive laminectomy) must be started immediately ***(Christie etal 2007).***

Time intervals for drug withdrawal ,it is generally perceived that adhering strictly to the appropriate time intervals between the administration of anti-haemostatic drugs and regional blockade or removal of catheters improves patient safety and reduces the risk of hematoma formation. The ESA(European Society of Anesthesiology) recommendations on time intervals are mainly based on pharmacology of the anti-haemostatic agents.

For Unfractionated heparin, removal of epidural catheters should not be carried out until at least 4 h after heparin administration with normalization of coagulation parameters (aPTT, ACT) to avoid bleeding complications***(Cook etal2009).***

For Low-molecular-weight heparins (LMWH), there should be a time interval of at least 12 h between subcutaneous administration of LMWH and epidural catheter placement or removal. At a therapeutic dosage epidural catheter placement or removal should be delayed for at least 24 h after the last administration***(Moussallem etal 2009).***

Following spinal or epidural puncture, or after removal of a spinal or epidural catheter, repeat administration of LMWH should be delayed for at least 2–4 h***(Christie etal 2007)***.

On the basis of the available data, it can be assumed that non-steroidal anti-inflammatory drugs including acetylsalicylic acid, by themselves do not lead to an increased risk of spinal epidural haematomas and thus do not represent a contra-indication***(Cook etal2009)***.

Neuraxial regional anaesthesia should only be carried out if a time interval of 7 days between the last intake of clopidogrel and the neuraxial regional anaesthesia and 10 days after the last administration of ticlopidine ***(Moussallem etal 2009).***

Thrombocytopenia (platelet count <100,000/microL) occurs in approximately 7 percent of pregnancies. Nearly all women with low platelet counts in the third trimester may be classified as having gestational thrombocytopenia, immune thrombocytopenic purpura (ITP), or thrombocytopenia related to severe preeclampsia or HELLP syndrome. Gestational thrombocytopenia is the most common etiology, idiopathic thrombocytopenic purpura occurs much less frequently. An important difference between idiopathic thrombocytopenic purpura and gestational thrombocytopenia is that idiopathic thrombocytopenic purpura may be associated with severe neonatal thrombocytopenia. However, with regard to the mother, neither gestational thrombocytopenia nor idiopathic thrombocytopenic purpura is associated with a rapid decline in platelet count. This contrasts with hypertensive thrombocytopenia, which may accompany severe preeclampsia or the HELLP syndrome ***(Beilin et al., 1997).***

The precise platelet count needed to safely perform neuraxial analgesia is unknown. Currently, practitioners routinely not perform neuraxial analgesia with platelet counts below 100,000/microL. It is not necessary to

routinely obtain a platelet count before administration of regional anesthesia in uncomplicated patient, however the assessment of platelet function is much more important. **(*Howard et al., 2000).***

PATH PHYSIOLOGICAL CONSEQUENCES OF 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. 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 andpneumonia. When narcotics are given in sufficient quantity, respiratory depression may results. Apnea can occur in severe cases. Prolonged bed rest and immobility can produce similar changes in pulmonary function ***(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).***

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 gastro-intestinal function ***(Brown, 2005).***

4) Neuroendocrine Effects:

Pain itself as well as the associated anxiety and apprehension also aggrevate 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 ***(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 ***(Stoelting et al., 2006).***

7) General sense of well being:

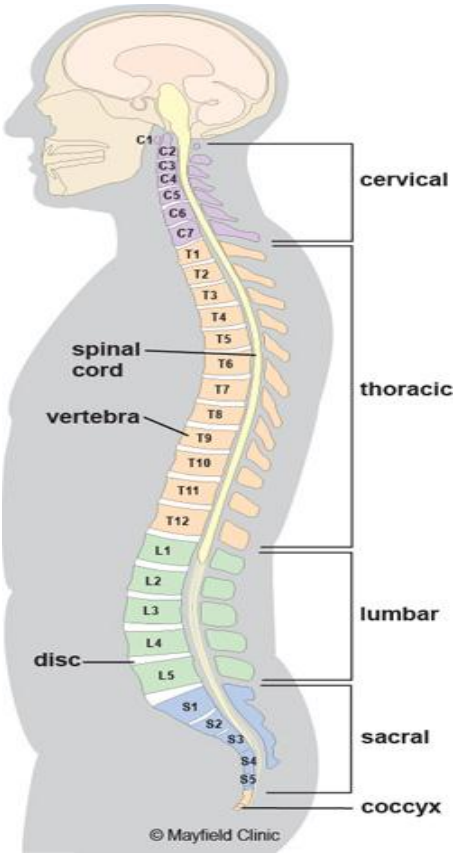
The most common reaction to acute pain is anxiety. Sleep disturbances are also typical. When the duration of pain becomes prolonged, depression is not unusual. Some patients react with anger that is frequently directed to the medical staff ***(Brown, 2005).***

REGIONAL ANESTHESIA

I-Anatomical Considerations:

The Vertebral Column:

The spine is composed of the vertebral bones and fibrocartilaginous intervertebral disks. There are 7 cervical, 12 thoracic, and 5 lumbar vertebrae. The sacrum is a fusion of 5 sacral vertebrae, and there are small rudimentary coccygeal vertebrae. 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).***



Fig(1)The five regions of the spinal column.

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).***

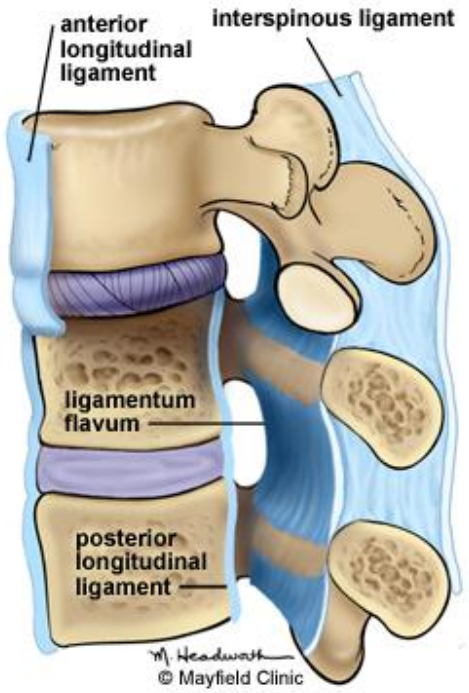
Cerebrospinal fluid (CSF):

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 equine is unlikely as these nerves float in the dural sac below L1 and tend to be pushed away rather than pierced by an advancing needle ***(Brown, 2005).***



Fig(2)ligamentum flavum anterior Longitudinal ligament, and posterior longitudinal ligament .

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 ***(Kleinmann 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 minimum concentration of local anesthetic required to stop transmission varies depending upon fiber size ***(Casey, 2000).***

Table (1): Nerve fibers classification(***Kleinman and Mikhail, 2006)***

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	+

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(**Hallworth etal 2005)**

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 ***(*Brizzi A *et al., 2010).*** 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 ***(*Bajwa *et al., 2012).***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 ***(*Hallworth etal 2005*).***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. Similarly, effective coughing and clearing of secretions require these muscles for expiration. For these reasons, neuroaxial blocks should be used with caution in patients with limited respiratory reserve ***(Brown, 2005).***

3. Urinary tract effect

Neuroaxial anesthesia at lumbar and sacral levels blocks both sympathetic and parasympathetic control of bladder function resulting in urinary retention until the block wears off ***(Brown, 2005).***

Mechanism of action of Neuro-axial Blockade:

The principal site of action for neuro-axial blockade is the nerve root. Local anesthetic is injected into CSF and bathes the nerve root in the subarachnoid space. Direct injection of local anesthetic into CSF for spinal anesthesia allows a relatively small dose and volume of local anesthetic to achieve dense sensory and motor blockade. Blockade of neural transmission (conduction) in the posterior nerve root fibers interrupts somatic and visceral sensation, whereas blockade of anterior nerve root fibers prevents efferent motor and autonomic outflow ***(Kleinman and Mikhail, 2006).***

Surface anatomy:

When preparing for spinal anesthetic blockade, it is important to find landmarks on the patient. The iliac crests usually mark the interspace between the fourth and fifth lumbar vertebrae, and a line can be drawn between them

to help locate this interspace. Care must be taken to feel for the soft area between the spinous processes to locate the interspace. Depending on the level of anesthesia necessary for the surgery and the ability to feel for the interspace, the L_{3-4} interspace or the L_{4-5} interspace can be used to introduce the spinal needle. Because the spinal cord ends at the L_1 to L_2 level, it would not be wise to attempt spinal anesthesia at or above this level***(Kaneko et al., 2005).***

A dermatome is an area of skin innervated by sensory fibers from a single spinal nerve. The tenth thoracic (T_{10}) dermatome corresponds to the umbilicus, the sixth thoracic (T_6) dermatome the xiphoid, and the fourth thoracic (T_4) dermatome the nipples. To achieve surgical anesthesia for a given procedure, the extent of spinal anesthesia must reach a certain dermatomal level ***(Reese, 2007).***

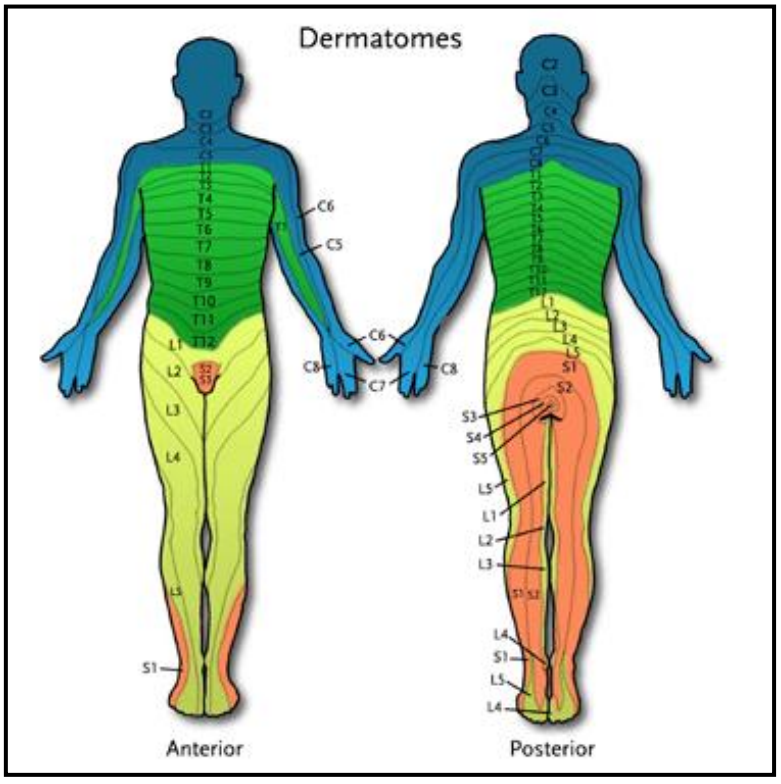


Fig. (1): Dermatomes of the body***(Reese, 2007).***

Table (2**):** Contraindications to spinal anesthesia(***Kleinman and Mikhail, 2006)***

Absolute:

- Infection at site of injection.
- Patient refusal.
- Coagulopathy or other bleeding diathesis.
- Severe hypovolemia.
- Increased intracranial pressure.
- Low cardiac output states:
    - Severe aortic stenosis.
    - Severe mitral stenosis.

Relative:

- Sepsis.
- Uncooperative patient.
- Preexixting neurological deficits.
- Demyelinating lesions.
- Stenotic valvular heart lesions.
- Severe spinal deformity.

Controversial:

- Prior back surgery at the site of injection.
- Complicated surgery.
- Prolonged operation.
- Major blood loss.
- Maneuvers that compromise respiration.

Table (3**):** Complications of spinal anesthesia***(Kleinman and Mikhail, 2006)***

Adverse or exaggerated physiological responses:

- Hypotension.
- Bradycardia.
- High block.
- Total spinal anesthesia.
- Cardiac arrest.
- Urinary retention.
- Anterior spinal artery syndrome.
- Horner's syndrome.

Complications related to needle placement

- Trauma.
- Backache.
- Postdural puncture headache.
- Diplopia.
- Tinnitus.
- Neural injury.
- Nerve root damage.
- Spinal cord damage.
- Cauda equina syndrome.
- Bleeding.
- Intraspinal hematoma.
- No effect/inadequate anesthesia.
- Inadvertent intravascular injection.
- Inflammation.
- Infection.
- Meningitis.

Drug toxicity:

- Systemic local anesthetic toxicity.
- Transient neurological symptoms.
- Cauda equina syndrome.

Some of the most bothersome and serious complications are:

1)Backache:

Although postoperative backache occurs after general anesthesia, it is more common after epidural and spinal anesthesia**.** The etiology of backache is not clear, although needle trauma, local anethestic irritation, and ligamentous strain secondary to muscle relaxation have been offered as explanations ***(Tunbull and Shepherd, 2003).***

2)Post-dural puncture headache (PDPH):

Post-dural puncture headache (PDPH) is the most common complication of spinal anesthesia. It occurs most frequently in young adults including obstetric patients, with an incidence rate of 14%, compared to 7% in individuals older than 70 years ***(Tunbull and Shepherd, 2003).***

Traditional concepts suggest that dural puncture causes leak of CSF with resultant loss of CSF causing gravitational traction of brain structures, and neurovascular response from the meninges. Prompt treatment is essential and consists of providing adequate hydration (orally or intravenously), and the analgesics. A single oral dose of caffeine was demonstrated to be safe, effective and should be considered in the early treatment of mild PDPH***(Reina et al., 2000).***

Cosyntropin, a synthetic form of adrenocorticotropic hormone, has been used in the treatment of refractory PDPH. Adrenocorticotropic hormone is believed to work by stimulating the adrenal gland to increase CSF production and β-endorphin output ***(Carter and Pasupuleti, 2000).***

If conservative therapy fails, neostgmin 2.5mg+atropin1mg intra muscular can be given,if it fails an epidural patch with 10-15ml of autologous

blood injected at the site of meningeal tear may be necessary to minimize the leakage of CSF ***(Liu and McDonald 2001).***

3)Neurologic complications:

The most benign neurologic complication is aseptic meningitis. This syndrome usually presents within 24 hours of spinal anesthesia and is characterized by fever, nuchal rigidity and photophobia. Microscopic examination of CSF is characterized by polymorph nuclear leukocytosis; bacterial CSF cultures are negative. Aseptic meningitis requires only symptomatic treatment and usually resolves within few days. Etiology of chemical meningitis was previously considered to be related to the cleansing agents and antiseptics adhering to syringes and needles used for spinal anesthesia***(Bajwa and Kaur,2012).***

Cauda equina syndrome presents after regression of the neuroaxial blockade. An acute subdural hematoma causes the syndrome and is believed to have resulted from direct vascular trauma during administration of spinal anesthesia or from vascular trauma combined with thrombocytopenia in the postoperative period. This syndrome may be permanent, or it may regress slowly over weeks or months. It is characterized by a sensory deficit in the perineal area, urinary and fecal incontinence, and varying degrees of motor deficit in the lower extremities ***(Munnur and Suresh, 2001).***

The most serious neurological complication is adhesive arachnoiditis. This reaction usually occurs several weeks or even months after spinal anesthesia. The syndrome is characterized by a gradual progression of sensory deficits and motor weakness in the lower limbs. There is a proliferative reaction of the meninges and vasoconstriction of the spinal cord vasculature***(Dobson, 2000).***

Spinal cord ischemia and infarction may occur after prolonged periods of arterial hypotension. The use of epinephrine in anesthetic solutions may reduce blood flow to the spinal cord ***(Dabson, 2000).***

4)Urinary retention:

As the sacral autonomic fibers are among the last to recover following a spinal anesthetic, urinary retention may occur ***(Brown, 2005).***

5)Spinal hematoma:

A clinically significant spinal hematoma can occur following spinal or epidural anesthesia, particularly in the presence of abnormal coagulation or bleeding disorder ***(Casey, 2000).***

When hematoma is suspected, neurological imaging (magnetic resonance imaging [MRI], computed tomography [CT], or myelography must be obtained immediately and neurosurgical consultation should be requested ***(Reese, 2007).***

6)Total spinal:

Total spinal anesthesia occurs when local anesthetic spread is high enough to block the entire spinal cord and occasionally the brain stem. Profound hypotension and bradycardia are common secondary to complete sympathetic blockade. Respiratory arrests may occur as a result of respiratory muscle paralysis or dysfunction of brain stem respiratory control centers. Management includes vasopressors, atropine, and fluids as necessary to support the cardiovascular system plus oxygen and controlled ventilation. If the cardiovascular and respiratory consequences are managed appropriately, total spinal block will resolve without sequelae ***(Reese, 2007)***

7)Failed neuraxial block

A failed neuraxial block may be defined as inadequate analgesia/anesthesia following an epidural, spinal, or combined spinal epidural anesthesia. The precise incidence of failed block is unknown; it was 12 percent in one retrospective review. Failed block may be caused by inadequate drug dosing, technical issues, or patient factors. If the volume and/or concentration of administered analgesics/anesthetics are insufficient to adequately block the required spinal segments, pain relief will be incomplete. The dose of intrathecal anesthesia needed to obtain a satisfactory block for cesarean is independent of age, weight, height or body mass index. Failed block may also be caused by impatience (eg, underestimating the latency of the administered drug and not allowing sufficient time to pass before declaring the block as failed). Operator or equipment related technical issues may also result in a failed block. As an example, if the epidural or spinal needle tip is not properly positioned, the injected drug will not be delivered to the desired location. If the aperture of the epidural or spinal needle is not wholly within the epidural or intrathecal space, respectively, a portion of the injected dose may not reach the intended site. With continuous epidural techniques, despite proper needle placement, the epidural catheter tip may not find its way into the epidural space, or may come to rest too far unilaterally, or protrude through an intervertebral foramen. These situations are more likely to occur if too great a length of catheter is threaded through the needle. More commonly, the catheter is initially inserted correctly within the epidural space, but later moves out of the space, toward the skin. Ideally, the length of epidural catheter inserted is sufficient to prevent inadvertent dislodgement, but not too great so as to minimize the likelihood of unilateral placement. In laboring patients, the optimal catheter length to insert into the epidural space appears to be 5 cm ***(Spiegel and Hess, 2007).***

Other technical causes of failed block relate to patient anatomy (eg, post-surgical scarring that inhibits the spread of medication administered into the epidural space). Some unusual causes of failed spinal anesthesia have been described, and include rare anatomic malformations such as dural ectasia, an abnormal ballooning of the thecal sac, and dural cyst. Injection of local anesthetic into an isolated area of the thecal sac may limit drug exposure to the target neural tissue. Enlarged thecal volumes per se, even in the absence of dural ectasia or cysts, may cause dilution or poor distribution of the hyperbaric local anesthetic dose. Failure of a block due to an inactive drug is possible, although very unlikely, particularly for amide-linked local anesthetics, which are very stable molecules ***(Palanisamy et al., 2007)***

8)Pruritis

Pruritus is a common side effect of neuraxial opioid administration. As an example, in one series, fentanyl (25 mcg) and bupivacaine (2 ml) were injected intrathecally, pruritus occurred in 100 percent of parturients, and 45 percent required treatment. Pruritus does not occur after the administration of local anesthetics alone. The etiology appears to be modulation of nociceptive reception, not histamine release. Thus, treatment with an antihistamine such as diphen-hydramine is not indicated, but is often used for its soporific effects***(Reich etal,2010).***

The ideal treatment for neuraxial opioid-induced pruritus is a small intravenous dose of an opioid antagonist such as naloxone (40 to 160 mcg) or the opioid agonist-antagonist nalbuphine (2.5 to 5 mg). Small doses of opioid antagonists are known to selectively reverse opioid side effects without affecting analgesia. A common approach is to administer 40 to 80 mcg naloxone intravenously, and titrate additional small doses to effect. A single dose of naloxone sometimes prevents recurrent itching. Alternatively, the

patient may be given intravenous patient-controlled analgesia (PCA) naloxone, to allow her to self titrate 40 mcg every five minutes ***(Palanisamy et al., 2007).***

9)Nausea and vomiting

Nausea occurs commonly in laboring patients due to visceral pain. Epidural and spinal local anesthetic block effectively diminish or eliminate pain, but can also precipitate nausea and vomiting. The mechanism is a decrease in blood pressure causing hypoperfusion of the medulla or cephalad spread of opioids to the chemoreceptor trigger zone. The incidence of nausea and vomiting after neuraxial opioid is much greater with the relatively poorly lipid soluble morphine compared to more lipid soluble agents, such as sufentanil, because morphine tends to travel cephalad within the aqueous CSF. The optimal treatment for opioid-induced nausea is administration of an opioid antagonist such as naloxone or the opioid agonist-antagonist nalbuphine. Nausea and vomiting resulting from hypotension are treated by administration of vasopressors ***(Biswas et al., 2002)***

10)Sepsis

Aseptic technique is important to minimize risk of infection. Epidural abscess or meningitis are uncommon complications of neuraxial block. Epidural abscess is more likely to occur after epidural techniques, whereas meningitis typically occurs after the dura has been punctured, either intentionally as part of a spinal anesthetic, or unintentionally as a complication of an epidural procedure ***(Hebl, 2006).***

The most commonly isolated bacteria were mouth commensals. Presumably, droplet contamination from medical personnel was the source of the CSF infection, which argues for a mandatory policy of wearing masks

during instrumentation of the neuraxis. Skin bacteria may also be introduced into the neuraxis during instrumentation, emphasizing the importance of meticulous skin cleansing prior to the procedure (***Hebl, 2006).***

11)Pneumochephalus

Introduction of air into the CSF during placement of neuraxial block may result in acute onset of severe headache and other neurologic signs and symptoms. This relatively rare complication may occur when air, rather than saline, is used to identify the epidural space with the loss-of-resistance technique. If the dura is inadvertently punctured, air may be injected into the CSF. If the parturient is sitting, the onset of headache and other neurologic symptoms may occur within a few seconds, as the air rapidly ascends to the brain, where it exerts its irritating effects. Use of saline rather than air for the loss-of-resistance technique can minimize the likelihood of this complication ***(Smarkusky and Decarvalho, 2006).***

PHARMACOLOGY OF LOCAL ANESTHETICS

- **Bupivicaine**

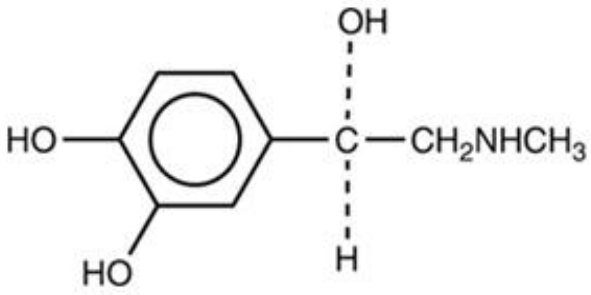


Fig. (2): Pharmacologic structure of bupivacaine ***(Pardo etal, 2002).***

Most local anesthetic agents consist of a lipophilic group (aromatic benzene ring) connected by an intermediate chain via an ester or amide linkage to an ionizable group (e.g., a tertiary amine). Local anesthetics may therefore be classified as aminoester or aminoamide compounds. The amino-ester local anesthetics are: procaine, chlorprocaine and tetracaine. The amino-amides consist of lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. The ester and amide local anesthetics differ in their chemical stability, biotransformation, and allergic potential. Amides are extremely stable agents, while esters are relatively unstable in solution. ***(Kleinman and Mikhail, 2006).***

Local anesthetics are weak bases and are made available clinically as salts to increase their solubility and stability. Inside the body they exist as the uncharged base (unionized form) or as a cation (ionized form). The relative proportions of these two forms is governed by the pKa specific for each local anesthetic and the pH of the body fluids.*(**Macarthur et al.,2008)***.

Mechanism of Action of Bupivicaine:

The primary mechanism of action of bupivacaine is blockage of voltage-gated sodium channels. The excitable membrane of nerve axons like the membrane of cardiac muscle fibres and neuronal cell bodies maintains a resting membrane potential of -90 to -60 mV. During excitation the sodium channels open, and a fast inward sodium current quickly depolarizes the membrane towards the sodium equilibrium potential (+40 mV). As a result of depolarization, the sodium channels close (inactivate) and potassium channels open. The outward flow of potassium repolarizes the membrane towards the potassium equilibrium potential (about -90 mV) repolarization returns the membrane to the resting state. The trans-membrane ionic gradients are maintained by the sodium pump ***(Pardo et al., 2002).***

Thus, there appears to be a single binding site for local anesthetics on the sodium channel. Sodium currents are reduced by local anesthetics because the drug-bound channels fail to open. Inactivation and anesthetic binding prevent the conformational changes that constitute the activation process by fully or partially immobilizing the channel. Pain impulses fail to traverse the drugged axon. Impulse activity entering the anesthetized region thus maintains its own failure ***(Marret et al., 2005).***

Pharmacokinetics:

The onset of sensory blockade following spinal block with bupivacaine is very rapid (within one minute); maximum motor blockade and maximum dermatome level are achieved within 15 minutes in most cases. Duration of sensory blockade (time to return of complete sensation in the operative site or regression of two dermatomes) averages 2 hours with or without 0.2 mg epinephrine. The time to return of complete motor

ability averages 3.5 hours without the addition of epinephrine and 4.5 hours if 0.2 mg epinephrine is added ***(Erdil et al., 2009).***

(A) Absorption:

The systemic absorption of local anesthetics is determined by the site of injection, dosage, addition of vasoconstrictor agent, and pharmacologic profile of the agent itself. The maximum blood level of local anesthetic is related to the total dose of drug administered for any particular site of administration ***(Meunier et al., 2001).***

Local anesthetic solutions may frequently contain a vasoconstrictor agent, usually epinephrine, in concentrations varying from 5 to 20 μg/ml. Epinephrine decreases the rate of absorption of certain agents from various sites of administration and thus lowers their potential toxicity. The peak blood level of bupivacaine is minimally influenced by the addition of a vasoconstrictor***(Marret et al., 2005).***

(B) Distribution:

Local anesthetics are distributed throughout all body tissues, but the relative concentration in different tissues varies. In general the more highly perfused organs show higher concentrations of local anesthetic drug than the less well perfused organs. In particular these agents are rapidly extracted by lung tissue, so that the whole blood level of local anesthetics decreases markedly as they pass through the pulmonary vasculature. The highest percentage of an injected dose of local anesthetic is found in skeletal muscle. ***(Hocking and Wildsmith, 2004).***

(C) Biotransformation and Excretion:

The pattern of metabolism of local anesthetic agents varies according to their chemical classification. The aminoamide group including bupivacaine undergoes enzymatic degradation primarily in the liver. Bupivacaine has a long elimination half life for a local anesthetic (2-7 h) accompanied by a low plasma clearance (0.58 litres/ minute); these tend to increase the risk of systemic toxicity. It was found that bupivacaine binds with plasma proteins to the extent of 70-90% ***(Coppejans et al.,2006).***

Bupivacaine is metabolized in the liver via conjugation with glucuronic acid. The excretion of bupivacaine occurs via the kidney. Less than 5% of the unchanged drug is excreted via the kidney into the urine. The major proportion of the injected agent appears in the urine in the form of various metabolites***(Coppejans et al.,2006).***

Factors affecting intrathecal spread:

Mechanisms of intrathecal drug spread:

The CSF of the vertebral canal occupies a narrow space (2-3 mm deep) surrounding the spinal cord and caudaequina enclosed by the arachnoid mater. As the local anesthetic solution is injected, it will spread initially by displacement of CSF.

The next stage which may be the most crucial, is spread due to the interplay between the densities of both CSF and local anesthetic solution under influence of gravity. Gravity will be 'applied' through patients' position (supine, sitting, etc…) ***(Hocking and Wildsmith, 2004).***

A-Characteristics of the injected solution:

1-Baricity:

Most plain solutions exhibit greater variability to effect and are less predictable, that the block may either be too low, and the block inadequate for surgery, or excessively high causing side effects **(*Hallworth etal,2005).***Hyperbaric solutions are more predictable, with greater spread in the direction of gravity**.**The greater mean spread of hyperbaric solutions may be associated with an increased incidence of cardiorespiratory side effects**,** although this is not always the case and may depend on the concentration of the glucose***(Carlos et al, 2005).***

Commercially available solutions contain up to glucose 8%, but most of the evidence shows that any concentration in excess of 0.8% will produce a solution that behaves in a hyberbaic manner, but with somewhat less extensive spread if the glucose concentration is at the lower end of the range ***(Connolly et al., 2001).***

2-Volume/ dose/ concentration injected:

Clearly, it is impossible to change one of these factors without changing the other, but this is not always appreciated. Volume is an important determinant of the spread of isobaric solution and low volume injections (1-1.5 ml) may reduce mean spread**.** A change in dose will be accompanied by a change in either volume or concentration ***(Khaw et al., 2001).***

3-Viscosity:

Addition of glucose to aqueous solution increases viscosity as well as density ***(Coppejans et al.,2006).***

B- Local anesthetic drugs and additives:

Studies of a wide range of local anesthetic drugs indicate that intrathecal spread is the same, no matter which one is used, as long as the other factors are controlled. Solutions containing vasoconstrictors spread in exactly the same way as those without, although block duration may be prolonged**.** Alkalinization of the solution does not increase spread, but does prolong duration*(**Hallworth et al.,2005).***

The addition of other drugs, such as opioids or midazolam, has a dual effect. First, such additions are achieved by mixing the adjuvant and local anesthetic solutions, usually reducing the density of the latter. In theory this might make the mixture behave in a more hypobaric manner*(**Hallworth et al.,2005).*** but no effect has been shown in clinical practice**,**suggesting that the changes in density are small. The second effect is seen with opioids, which increase mean spread and delay regression**,**but opioids do so no matter what the route of administration either intrathecal or I.V. Presumably, this is pharmacological enhancement of subclinical block at the limits of the local anesthetic's spread through the CSF ***(Boucher et al., 2001).***

Advantages of local anesthetic neural blockade include:

Adequate anesthesia plus postoperative relief of pain with reduced requirements for systemic opioids resulting in avoidance of sedation and respiratory depression. More importantly, the inhibition of the neuroendocrinal response to surgery, trauma induced nociceptive impulses, and blunting of the autonomic and somatic responses to pain facilitate breathing, coughing, sighing and early ambulation ***(Rodgers et al., 2000)***. This results in restoration of pulmonary function and reduction of post operative chest infection and pulmonary collapse. Finally, efferent sympathetic blockade results in increased blood flow to the region of

neural blockade resulting in better wound healing and reduced risk of deep venous thromobis and thromboembolism ***(Kehlet and Dahl, 2008).***

Toxicity:

Systemic reactions to local anesthetics involve primarily the central nervous system (CNS) and the cardiovascular system. In general the CNS is more susceptible to the systemic actions of local anesthetic agents than the cardiovascular system. The dose and blood level of local anesthetic required to produce CNS toxicity is usually lower than that which results in circulatory collapse ***(Carlos et al, 2005).***

(1) Central Nervous System Toxicity

The initial symptoms of local anesthetic-induced CNS toxicity involve feelings of lightheadedness and dizziness followed frequently by visual and auditory disturbances such as difficulty in focusing and tinnitus. Other subjective CNS symptoms include disorientation and occasional feelings of drowsiness. Objective signs of CNS toxicity are usually excitatory motor in nature and include shivering, muscular twitching, and tremors initially involving muscles of the face and distal parts of the extremities. Ultimately generalized convulsions of a tonic-clonic nature occur. If a sufficiently large dose or a rapid intravenous injection is administered the initial signs of CNS excitation are rapidly followed by a state of generalized CNS depression. ***(Carlos et al, 2005).***

(2) Cardiovascular System Toxicity

Local anesthetic agents can exert a direct action both on the heart and peripheral blood vessels. The primary cardiac electrophysiological

effect of local anesthetics is a decrease in the maximum rate of depolarization in Purkinje fibres and ventricular muscle. This reduction in the maximum rate of depolarization is believed to be due to a decrease in the availability of fast sodium channels in cardiac membranes ***(Mather et al., 2004).***

High blood levels of local anesthetics will prolong conduction time through various parts of the heart, as indicated in the electrocardiogram by an increase in the PR, QRS and QT intervals thus potentiating reentrant tachycardias with aberrant conduction. Extremely high concentrations of local anesthetic will depress spontaneous pacemaker activity in the sinus node resulting in sinus bradycardia, heart block and sinus arrest ***(Mather et al., 2004).***

Local anesthetic drugs also exert a dose dependent negative inotropic action on the heart. The more potent agents as bupivacaine depress cardiac contractility at the lowest concentrations ***(Carlos et al, 2005).***

Local anesthetics may depress myocardial contractility by blocking the intracellular release of calcium from the sarcoplasmic reticulum***(Carlos et al., 2005).***

Local anesthetics exert a biphasic effect on peripheral vascular smooth muscle. Low concentrations of bupivacaine produce vasoconstriction, while high concentrations increase arteriolar diameter. At doses of local anesthetics that approach lethal levels, decrease in pulmonary artery pressure and pulmonary vascular resistance were seen with both types of local anesthetic drugs ***(Mather etal, 2004).***

The cardiotoxicity of bupivacaine appears to differ from that of other local anesthetics in the following manner:

a) The dosage required for irreversible cardiovascular collapse is lower for bupivacaine than for other local anesthetic agents.

b) Ventricular arrhythmias and fatal ventricular fibrillation may occur following accidental rapid intravenous administration of a large dose of bupivacaine. The arrhythmogenic action of bupivacaine may be related to an inhibition of the fast sodium channels in the cardiac membrane ***(Mayer et al, 2004).***

c) Pregnant patients may be more sensitive to the cardiotoxic effects of bupivacaine than non-pregnant patients ***(Brown, 2005).***

d) Acidosis, hypoxia and hypercarbia markedly potentiate the cardiotoxicity of bupivacaine ***(Mather et al., 2004).***

e) Cardiac resuscitation is more difficult and prolonged(30 - 45 minutes) following bupivacaine-induced cardiovascular collapse due to its high lipid solubility, requiring a long time for redistribution ***(Mather et al, 2004)***.

f) The time that the local anesthetic agent occupies the cardiac sodium channel is known as the dwell time. The dwell timefor bupivacaine is 1.5 seconds, giving it insufficient time to dissociate from the sodium channels during diastole (0.4 seconds) resulting in accumulation of the drug and further cardiotoxicity ***(Mather et al, 2004).***

Toxicity of anesthetics may be potentiated in patients with renal or hepatic compromise, respiratory acidosis, preexisting heart block, or heart conditions. Toxicity may also be potentiated during pregnancy, at the

extremes of age, or in those with hypoxia and acidosis. The maximum safe dose of bupivacaine is 3 mg/kg. However, inadvertent intravascular injection is the most common cause of local anesthetic toxicity even if anesthetic was administered within the recommended dose range ***(Singh, 2004).***

(3) ***Allergic Reactions***

The aminoester agents may produce allergic-type reactions since these agents are derivatives of para-aminobenzoic acid which is known to be allergic. The amide local anesthetics are not derivatives of para-aminobenzoic acid and allergic reactions to them are extremely rare. Although aminoamide agents appear to be relatively free form allergic-type reactions, solutions of these agents may contain a preservative, methyl paraben whose chemical structure is similar to that of para-aminobenzoic acid ***(Shojaei and Haas, 2002).***

Management of Local Anesthetic Toxicity:

In the patient with suspected local anesthetic toxicity, the initial step is supportive and symptomatic treatment in the form of stabilization of potential life threats, impending airway compromise, significant hypotension, and treatment of dysrhythmias and seizures.

(1)CNS manifestations, such as seizures, can be treated successfully with benzodiazepines (small increments of diazepam 2.5 mg) and barbiturates (e.g. phenobarbital) and 2 mg/kg of intravenous thiopental. Avoid use of phenytoin because it shares pharmacologic properties (i.e. sodium channel blockade) with lidocaine and may potentiate toxicity**.** A recent report has suggested that the intravenous injection of 100 ml of 20% lipid emulsion may have a beneficial role in aborting central nervous system manifestations of bupivacaine toxicity ***(Bajwa and Kaur,2012). Foxall and colleagues, 2007***

demonstrated the successful application of lipid emulsion infusionin the resuscitation of bupivacaine-induced cardiac arrest also known as "lipid rescue". The proposed mechanism is that lipid infusion accelerates the decline in bupivacaine myocardial content (reduced tissue binding) by creating a lipid phase that extracts the lipid-soluble bupivacaine molecules from the aqueous plasma phase. (***Howell and Chauhan, 2009)***.

Weinberg's 2008 recommended dosing regimen for the use of lipid emulsion in humans:

In cardiac arrest secondary to local anesthetic toxicity that is unresponsive to standard therapy, intravenous administration of a lipid such as Intralipid 20% is recommended in the following regimen:

1. Administer 1 ml/kg over 1 minute.
2. Repeat twice more at 3 to 5-minute intervals.
3. Then once stability is restored convert to an infusion at a rate of 0.25 ml/kg/min, continuing until hemodynamic stability is restored ***(Weinberg, 2008).***

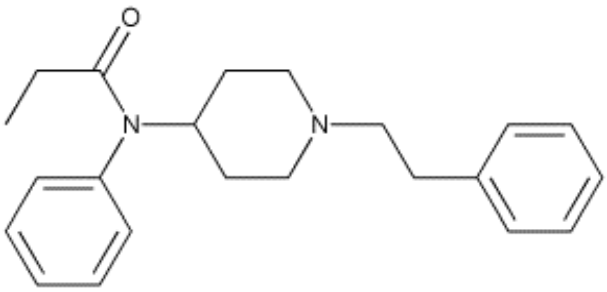
(2) Maintain airway and respiration using O_2 supply by face mask up to endotracheal intubation and mechanical ventilation if needed.

(3) In the setting of local anesthetic induced cardiac toxicity, lidocaine has been used successfully in bupivacaine-induced dysrhythmias, but its additive CNS toxicity is still a major concern. Avoiding the use of class Ib anti-arrhythmic agents, such as phenytoin, mexiletine is crucial because they may worsen toxicity. In cardiovascular collapse, the use of adrenergic drugs with α and β agonist effect (e.g. Ephedrine, epinephrine) is useful.***).***In a study, combined boluses of glucose, insulin, and potassium were successful in reversing bupivacaine-induced

cardiovascular collapse. However, the 2 units/kg dose of insulin used in this protocol may be challenging to use in clinical practice because of physicians' reluctance to administer such unusually high doses of insulin ***(Kim et al., 2004).Morris and Stacey (2003)*** stated that tachyarrhythmias due to toxicity of bupivacaine are probably best treated by electrical cardioversion or with bretylium rather than lidocaine.

Pharmacology of additives

- **Fentanyl**



C22 H28 N2 O

Fig. (3): Chemical structure of fentanyl ***(Kleinman and Mikhail, 2006).***

Fentanyl is a synthetic phenylperidine belonging to 4-anilopipridine series. It is a synthetic pure agonist at μ receptors. It is available as the citrate salt in an aqueous preservative free solution containing 50μg of fentanyl base per ml. It is a basic amine with pKa of 8.4, so that at physiological pH, only 8.4% of the drug is in its non-ionized form ***(Romberg et al., 2005).***

Mechanism of Action:

The analgesic effect of fentanyl and most opiates results via binding to G-protein coupled opiate receptors with subsequent inhibition of adenyl cyclase, activation of K^+ channels and inhibition of voltage-

gated Ca^{++} channels, all of which decrease neuronal excitability ***(Range et al., 2001).***

Spinal Local Anesthetics and Opioid mixtures:

The addition of opioids to local anesthetic solutions for spinal anesthesia, enhances surgical anesthesia and provides postoperative analgesia. Intrathecal fentanyl has the advantage of decreasing visceral sensation and may prolong the duration of anesthesia ***(Choi et al., 2000).***

Mechanism of action of spinally administered opioids and local anesthetics: Opioids and local anaesthetics exert their antinociceptive effect in the spinal cord by different mechanisms. The μ- agonist, fentanyl, exerts its action by opening K^+ channels and reducing Ca^{++} influx, resulting in inhibition of transmitter release. The μ-agonists also have a direct post-synaptic effect, causing hyperpolarization and a reduction in neuronal activity. Local anesthetic, bupivacaine, acts mainly by blockade of voltage-gated Na^+ channels in the axonal membrane. ***(Coppejans et al.,2006).***

The lipid solubility of an opioid predicts its behaviour. Opioids with low lipid solubility (hydrophilic opioids such as morphine) have a slow onset and long duration of action ***(Boylan et al., 1998)***, whereas opioids with high lipid solubility (lipophilic opioids such as fentanyl) have a rapid onset but a short duration of action. Thus the lipid solubility of an opioid determines its access to the dorsal horn via: (1) diffusion through the arachnoid granulations and (2) diffusion into the spinal radicular artery blood flow ***(George, 2006).***

The chief side effects of intrathecally administered opioids are:

1) **Respiratory depression**: The most serious side effect of intrathecal opioids is dose-dependent early or delayed respiratory depression. Opioids with relatively low lipid solubility can cause delayed respiratory

depression with a peak incidence 3 to 10 hours after injection ***(Bajwa and Kaur,2012).*** Thus close observation is recommended for 24 hours after injection (***Lirk et al.,2010).*** On the other hand the high lipid solubility of lipophilic opioids such as fentanyl allows them to be absorbed into lipids close to the site of administration. Consequently lipophilic opioids do not migrate rostrally in the CSF and cannot cause delayed respiratory depression. However their high lipid solubility allows them to be absorbed systemically into blood vessels which may cause early respiratory depression as is commonly seen with systemic administration of opioids ***(Bajwa and Kaurr,2012).***

Naloxone reverses the respiratory effects of spinal opioids. In an apneic patient 0.4 mg I.V. of naloxone will usually restore ventilation. Small incremental doses of naloxone (0.04 mg) may reverse the respiratory depression but not the analgesia. ***(Yaddanapudi et al., 2000).***

2) **Nausea and vomiting** are caused by transport of opioids to the vomiting centre and the chemoreceptor trigger zone in the medulla via CSF flow or the systemic ciculation. Nausea can usually be treated with anti-emetics such as metoclopramide (5-10 mg) or ondansetron (4-6 mg). If severe, it can be treated with naloxone (0.2 mg increments, repeated if necessary) ***(Andersen et al., 2000).***

3) **Pruritus** has an incidence of 30% and is the most common side effect occurring with spinal or epidural opioids. It is usually limited to the face and torso. Its mechanism is poorly understood but it appears to be centrally mediated due to the cephalad migration of the drug in the CSF, thus it is not common following intrathecal administration with fentanyl. ***(Battacharya and Dutta, 2007).***

4) **Urinary retention:** The mechanism of spinal opioid-induced urinary retention involves inhibition of volume-induced bladder contractions and blockade of vesical reflex. Naloxone administration is also the treatment of choice although bladder catheterization may be required ***(*Cuvas *et al.,2010).***

5) **Paralytic ileus:** intrathecal opioids may delay the recovery of gut motility. However combining intrathecal local anesthetics with opioids may hasten recovery of gut function due to segmental block of dermatomes T_5-T_{12}, antagonizing sympathetically mediated peristaltic inhibition while preserving vagal parasympathetic outflow ***(Erdil etal ,2009).***

LEVOBUPIVACAINE

On the basis of the wealth of information concerning the toxicity of bupivacaine, researchers have concluded that safer long-acting local anesthetic alternative exist **(Buckenmaier, 2002)** &**(Mather &Chang, 2001)**. If patient safety was the only issue (other than cost, convenience or availability) involved in long-acting local anesthetic selection, the use of less toxic options other than bupivacaine for large volume blocks would seem intuitive **(Panni & Segal, 2003)**.

Levobupivacaine is a synthetic new long acting local anesthetic, containing a single enantiomer of bupivacaine hydrochloride **(Foster & Markham, 2000)**.

Chemistry:

Levobupivacaine is a sterile, non pyrogenic, colorless solution with a PH of 4- 6.5. It is a pure S(-)-enantiomer of racemic bupivacaine. It is related chemically and pharmacologically to the amino amide class of local anesthetics (figure XVII). Levobupivacaine is chemically described as: (S)-1-butyl-2-piperidylformo-2¢,6¢-xylidide hydrochloride, with a molecular formula of $C_{18}H_{28}N_2O\cdot HCL$ **(Foster& Markham, 2000)**.

Like the other amides, it is a weak base that has recently been introduced in clinical routine with a molecular weight of 324.9. The solubility of levobupivacaine hydrochloride in water is about 100mg/ ml at 20°C, partition coefficient (oleyl alcohol/ water) is 1624 and a pk_a 8.09, like that of racemic bupivacaine. (PKa is the PH at which 50% of the molecules are free base and 50% of the molecules have a positive charge – ionized). Because of its significantly decreased cardiovascular and central nervous system toxicity than racemic bupivacaine and

theR(+)-enantiomer dexbupivacaine, levobupivacaine seems to be an attractive alternative to bupivacaine **(Gristwood,2002)**.

Depending on the PH, the amino group can adopt the tertiary or the quaternary form. The drug is in dynamic balance between the tertiary form, a free base, and the quaternary form, which has a positive charge, making it very water-soluble. If bicarbonate is added to levobupivacaine, the PH is increased leading to a rise in the percentage of free base molecules. Those molecules cross more easily through the axon membrane and the pharmacological action begins more quickly. In contrast, if the PH is low (acid), as happens when there is a local infection, there will be low free base molecules to cross the axon membrane resulting in smaller action over the axon ***(Bajwa and Kaur,2012).***

Structure:

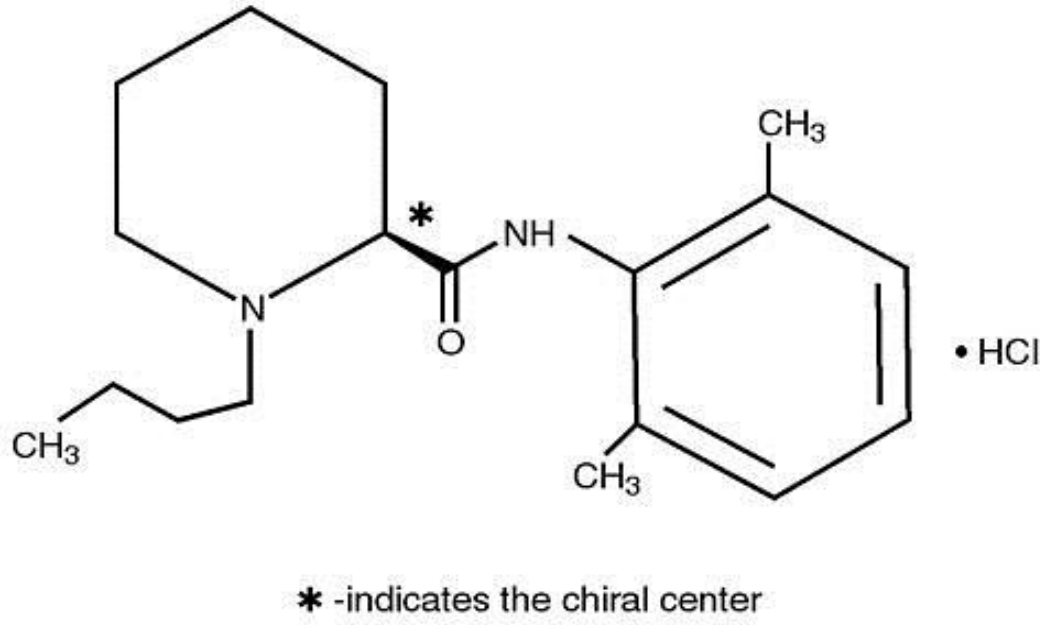


Figure (5) **Structure of levobupivacaine(Foster & Markham, 2000)**.

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PHARMACOKINETICS:

Because of their close chemical relationship, levobupivacaine and racemic bupivacaine share many pharmacokinetic propertie; therefore, it is not surprising that the preliminary clinical experience shows that both local anesthetics are largely equally effective **(*Wong ,2009)***

Table (4) **Pharmacokinetic properties of levobupivacaine(Foster& Markham, 2000):**

Absorption: C_{max}0.79µg/ ml*
Plasma protein binding> 97%**
Volume of distribution after IV administration= 67L
Metabolized by CYP3A4, CYP1A2
Elimination~71% of metabolites excreted in urine, ~24% eliminated in faeces. Total of 95% was recovered.
No in vitro or in vivo racemisation observed.

***Based on IV doses of levobupivacaine up to 150mg.**

****At concentrations between 0.1 and 1µg/ml.**

Local anesthetics act at the site of administration and thus uptake and distribution by systemic mechanisms are not factors in reaching site of action. However uptake of the drug by the general circulation is important in terminating an anesthetic action***(Guasch etal 2010).***

The maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of levobupivacaine are dose proportional **(Kopacz, et al., 2000)** Absorption of levobupivacaine from the site of administration is determined by the vascularity of the tissue.Thus, plasma concentrations are also influenced by the route of administration **(Foster & Markham, 2000)**

C_{max} was 0.58 to 1.02 mg/ L after epidural administration of 75 to 150 mg **(Kopacz, et al., 2000)** and 0.47 and 0.96 mg/ L after brachial plexus block with 1 and 2 mg/ kg, respectively, in patients; the corresponding AUC values were 3.56 to 5.32 mg/ L.h with epidural administration and 3 and 5.31 mg/ L.h after brachial plexus block. Time to C_{max} was approximately 20 to 40 minutes after epidural administration or brachial plexus block ***(Wong ,2009) .***

The elimination half-life of levobupivacaine after intravenous administration of 40mg in volunteers was approximately 1.3 hours and the volume of distribution was 67L. Levobupivacaine was highly protein bound (>97%) in human plasma in vitro at concentrations of 0.1-1mg/ L (table VI) ***(Bajwa and Kaur,2012).***

Levobupivacaine as bupivacaine crosses the placenta. However, placental transfer has not been associated with significant complications to the fetus. The excretion of the drug in breast milk has not been investigated, but it is known that some local anesthetics are excreted in breast milk ***(Cuvas et al.,2010)***.

Metabolism of levobupivacaine like racemic bupivacaine occurs in the liver by the cytochrome P450 (CYP) system, primarily CYP1A2, CYP3A4 isoforms*(Guasch etal 2010).*

A lower than expected clearance rate is anticipated in hepatic dysfunction as well as in case of administration of CYP1A2 and CYP3A4 inhibitors and inducers(table VII) ***(Foster & Markham, 2000)***.

Table (5) **Inducers and inhibitors of CYP3A4 and CYP1A2*(Foster & Markham, 2000)***.

Isoform	Inducers	Inhibitors
CYP3A4	Phenytoin Phenobarbital Rifampicin	Azole antifungals (ketoconazole) Protease inhibitors (ritanovir) Macrolides (erythromycin) Calcium channel blockers (verapamil)
CYP1A2	Omeprazole	Furafylline Aminophylline

The major metabolite of levobupivacaine (3-hydroxy-levobupivacaine) is converted to glucuronic acid and sulphate ester conjugates that are excreted in urine. Unchanged levobupivacaine is not excreted in urine. Thus, in patients with renal disease, the unchanged levobupivacaine will not accumulate. However, the metabolites that are excreted in urine may accumulate **(*Foster & Markham, 2000)***.

The pharmacokinetic properties of levobupivacaine are largely similar to those of bupivacaine, although some enantioselective features have been reported***(Guasch etal 2010).***

Two studies reported higher plasma concentrations after administration of epidural levobupivacaine than bupivacaine at the same dose **(Kopacz,etal., 2000)** ,but others reported plasma concentrations to be similar for the 2 drugs **(Bardsley, et al., 1998)** & **(Bader, et al., 1999)**.

Total plasma concentrations of levobupivacaoine are higher than those of dexbupivacaine after administration of bupivacaine **(Kopacz,etal., 2000)** .It has been suggested that systemic disposition of bupivacaine is enantioselective, particularly with regards to plasma protein binding, unbound plasma drug concentrations are lower with levobupivacaine than dexbupivacaine after administration of bupivacaine ***(Bajwa and Kaur,2012).***

It has been suggested that the pharmacokinetic differences between the enantiomers of bupivacaine may, to some extent, explain the differences in their toxicity profiles; levobupivacaine has a higher unbound clearance rate, shorter elimination half life, smaller volume of distribution and decreased affinity to brain and myocardial tissues than dexbupivacaine*(**Guasch etal 2010).***

PHARMACODYNAMICS:

A)Mode of action

Levobupivacaine is an amide-type of local anesthetic. As with all local anesthetics, acts via blockade of the voltage sensitive ion channels in neuronal membranes, preventing conduction of nerve impulses. Localized and reversible anesthesia is produced by interference with the opening of sodium channels, thus blocking the transmission of the action potential in nerves involved in sensory, motor and sympathetic activity **(Cuvas et al.,2010)**.

B)Anesthetic potency

Invitro, potency of levobupivacaine is similar to that of bupivacaine**(Cuvas et al.,2010)** and the R (+)-enantiomer of bupivacaine (dexbupivacaine). The concentration of the drug and the route of administration affected the comparative actions of

levobupivacaine, bupivacaine and dexbupivacaine invivo ***(Bajwa and Kaurr,2012).***

In general, the onset and duration of sensory and motor blocks were similar for levobupivacaine, bupivacaine and dexbupivacaine and the agents were equipotent in animal studies**(*Cuvas et al.,2010)***..

Some animal studies detected a longer duration of anesthesia and/ or greater potency with levobupivacaine than dexbupivacaine or bupivacaine***(Bajwa and Kaur,2012).*** It has been suggested that this is related to a greater vasoconstrictor action with levobupivacaine at lower doses and is in line with the trend toward a longer duration of sensory block observed with epidural levobupivacaine compared with bupivacaine in clinical studies.

Depending on the concentration and animal models, levoupivacaine has either equal or significantly more prolonged duration of sensory and / or motor block than ropivacaine at the same dose **(*Guasch, et al.,2010)*** .

Studies in humans confirm that levobupivacaine has similar potency to bupivacaine **(Fattorini, et al., 2006)**&**(Baogham, et al., 2005)**&**(Pedro, et al., 2004)**&**(Glaser, et al., 2002)**.

Levobupivacaine has been consistently less toxic than bupivacaine in animals. The lethal dose was higher with levobupivacaine than bupivacaine (in the range of 1.3- 1.6 fold higher in most animal studies), providing supportive evidence for a safety advantage for levobupivacaine over bupivacaine***(Guasch etal 2010).***

The vasoactivity of the levo and dextro enantiomers is different.

Levobupivacaine had greater vasoconstrictive properties than bupivacaine **(Newton, et al., 2005)**.

The greater vasoconstrictive effects of levobupivacaine may explain its prolonged duration of action as well as lower risk of CNS toxicity. Local anesthetics that produce vasoconstroiction in some vascular beds may also reduce uterplacental blood flow that could potentially harm the fetus ***(Bajwa and Kaur,2012).*** Administration of levobupivacaine in ewes near term of pregnancy did not affect uterine blood flow or intra-amniotic pressure; its effects were similar to bupivacaine and ropivacaine **(*Brizzi etal,2010).***

C)Cardiovascular effects

Cardiotoxicity is probably the result of both direct and indirect cardiac effects; the indirect effects may involve blockade of sympathetic cardiac innervations or other CNS- mediated mechanisms. Blockade of myocardial sodium channels causes conduction delay and QRS interval prolongation and blochade of potassium and calcium channels may also contribute to cardiotoxicity***(Cuvas et al.,2010)***.

In vitro and animal studies:

In vitro studies have indicated that levobupivacaine has the lesser cardiotoxic potential of the two enantiomers of bupivacaine. Levobupivacaine was less potent than dexbupivacaine in blocking cardiac sodium channels in the inactivated state in isolated guinea-pig ventricular myocytes and in blocking cloned human cardiac potassium cannels**(*Brizzi etal,2010).*** In line with this, levobupivacaine had less of a detrimental effect at the same concentration and/ or was less potent in terms of reducing the maximal rate of depolarization (V_{max}) **,**prolonging atrioventricular conduction and prolonging QRS interval duration*(* ***Guasch etal 2010).*** when compared with dexbupivacaine and/ or bupivacaine in other animal or human tissue studies. Higher concentrations of levobupivacaine than bupivacaine were reported to be

required for a negative inotropic effect in myocytes and for complete loss of contractile force and atrial arrest in isolated atria**.**Recovery from drug-induced disturbances in cardiac electrophysiology and contractility was more rapid with levobupivacaine than bupivacaine **(*Brizzi etal,2010).***

Studies in animals have further demonstrated that levobupivacaine has less potential for cardiotoxicity than dexbupivacaine or bupivacaine (***Guasch etal 2010).***

Studies in human volunteers:

Volunteers have been given bupivacaine or levobupivacaine intravenously at a rate of 10mg/ min, until the appearance of early symptoms of central nervous system toxicity. These appeared at a lower dose (Mean 47.1 mg) with bupivacaine than with levobupivacaine (56.1mg). Similarly there was a greater reduction in the myocardial ejection fraction and systolic and acceleration index with racemic bupivacaine when compared to levobupivacaine. When 40 mg of either levobupivacaine or racemic bupivacaine were administered over a 10min period, the EEG was significantly slower after racemic bupivacaine. Thus at similar doses, electrical activity is more affected by racemic bupivacaine**(*Brizzi etal ,2010).*** Levobupivacaine appears to cause less myocardial depression than racemic bupivacaine.

Multiple different animal models consistently indicate that the order of toxicity is bupivacaine > levobupivacaine > ropivacaine **(Groban, 2003)**& **(Santos, et al., 2001)**.

The difference in toxicity between levobupivacaine and ropivacaine may be clinically insignificant if levobupivacaine is determined to be more potent and longer acting at lower dosages, as some animal and human studies suggest **(Benhamu, et al., 2003)** &**(Sinnott & Strichartz, 2003)**. In human volunteers, levobupivacaine and ropivacaine

produced similar CNS and cardiovascular effects at equipotent doses and infusion rates **(Stewart, et al., 2003)**.

D)CNS effects

Application of local anesthetic to the nucleus tractus solitarus causes hypotension, bradycardia and arrhysthmias. The time to maximum decrease in cell firing rate was significantly longer after intravenous administration of levobupivacaine 2mg/ kg than after dexbupivacaine 2mg/ kg in anesthetised rats***(Cuvas et al.,2010)***. This suggests that uptake of bupivacaine by the CNS is enantioselective, and is slower for levobupivacaine than dexbupivacaine. All animals receiving dexbupivacaine became apnoeic, whereas those treated with levobupivacaine continued to breath, suggesting that enantiomers have differing effects on respiratory neurons.

The risk of CNS toxicity with intravenous levobupivacaine was less than that with bupivacaine at the same dose in a representative study in conscious sheep(***Guasch etal 2010).*** The mean convulsive dose of levobupivacaine was 103mg, compared with 85 mg with bupivacaine. CNS excitatory signs began sooner and lasted longer with bupivacaine.

The risk of CNS toxicity was also less with levobupivacaine than bupivacaine in human volunteers***(Cuvas et al.,2010*****)**.

The evidence from the large animal and human volunteer studies demonstrates that levobupivacaine is consistently less toxic than bupivacaine. With regard to the CNS, a higher convulsive threshold exists in animal models; there are fewer CNS symptoms in human volunteers after intravenous administration and less excitatory change in the EEG. Levobupivacaine has less arrhythmogenic potential and a trend towards more effective resuscitation in animals, requires higher lethal doses in

animal models and has less disturbance on mechanical cardiac function in humans **(*McLeod & Burke, 2001)***.

INDICATIONS:

Levobupivacaine is used for the production of local anesthesia by percutaneous infilteration, peripheral nerve block(s) and intrathecal, epidural or caudal block. Due to the fact that, sensory block is more marked than motor block with levobupivacaine; it is especially useful in painless labour **(*Galindo Arias, 2002)& (Foster &Markham, 2000)***.

Levobupivacaine has been used succefully for intravenous regional anesthesia **(*Atanassoff, et al., 2002)***.

Levobupivacaine can be administered in combination with other analgesic agents, including opioids. Levobupivacaine is available as an injectable solution and a concentrate for infusion. The following excipients are added sodium chloride for isotonicity, water for injection (it is highly soluble in water at concentration greater 100mg/ ml at 20°C), sodium hydroxide and/ or hydrochloric acid to adjust the PH ***(Foster & Markham, 2000)***.

PRESENTATION:

Aqueous solutions of 0.25%, 0.5% and 0.75% concentrations are available.Having the same strength as bupivacaine. It is available as 10ml ampoules.

The ampoules are intended for a single use only and any left over solutions should be discarded. It has a shelf half-life of two years when stored at room temperature (under 30°C) and kept away from light ***(Foster & Markham, 2000)***.

MAXIMUM DOSAGE:

The maximum dose depends on the physical status and size of patient. The initial licensing authority recommended a maximum single dose of 2mg/ kg or 150mg. whereas, the maximum recommended daily dose is 400mg (5.7mg/ kg) for levobupivacaine and in case of postoperative pain relief the dose should not exceed 18.75mg/ hr. In obstetric use concentrations higher than 0.5% should not be used. There commended dose is 150mg **(*Galindo Arias,2002)&(Foster & Markham, 2000))***.

As for pain management: if epidural administration of levobupivacaine is associated with clonidine, fentanyl or morphine; reduction of the dose of levobupivacaine should be undertaken. Use of the lowest concentration 0.125% is preferred ***(Foster & Markham, 2000)***.

In pediatrics local infilteration of 0.5% levobupivacaine has been administered in doses of 0.25-0.5ml/ kg (1.25mg/ ml) (table VIII).

Doses should be reduced according to age, weight and general condition **(*Foster & Markham, 2000)***.

***Table (6)* Dosage guidelines for levobupivacaine(Foster & Markham, 2000)**

Anesthetic technique	Indication	Concentration	Volume (dose) recommendations	Motor block	Comment
Surgical anesthesia in adults:					
• Epidural slow injection	Surgery	0.5% - 0.75%	10 – 20 ml (50 – 150 mg)	Mod /max	Give over ≥ 5 min
• Epidural slow injection	Caesarean section	0.5%	10 – 30 ml (75 – 150 mg)	Mod /max	Give over 15 – 20 min
• Intrathecal	Surgery	0.5%	3 ml (15 mg)	Mod /max	
• Peripheral nerve block	Surgery	0.25% -0.5%	1 - 40 ml (max 150 mg)	Mod /max	
• Peribulbar	Ophthalmic	0.75%	5 -15 ml (37.5 – 112.5 mg)	Mod /max	
• Local infiltration	Surgery	0.25%	1 – 60 ml (max 150 mg)	NA	
Surgical anesthesia in children:					
• Ilioinguinal/ ilio-hypogastric nerve block	Surgery in children < 12y	0.25 – 0.5%	0.25 – 0.5 ml /kg (1.25 mg /kg per side)	NA	
Pain management in adults:					
• Epidural injection	Labor	0.25%	6 – 10 ml (15 – 25 mg)	Min /mod	Wait ≥ 15 min between doses.
• Epidural infusion	Labor	0.125%	4 – 10 ml /h (5 – 12.5 mg /h)	Min /mod	Dilute to 0.125% with saline 0.9%.
• Epidural infusion	Postoperative pain	0.125% - 0.25%	5 – 15 ml /h (12.5 – 18.75 mg /h)	Min /mod	Dilute to 0.125% with saline 0.9%.

Max = maximum; min = minimum; mod = moderate; NA = not applicable

The concentration of levobupivacaine used was 0.25% to 0.75% for non obstetric surgical procedures, 0.5% for caesarean section, 0.125 to0.25% for women in labor and 0.0625 to 0.5% for postoperative pain management. The total dose (concentration times volume)depends on the nature of the procedure and the anesthetic technique. Special caution is recommended for hypoproteinemic patients as patients with nephritic syndrome, sever hepatic disease and newborn. Also, debilitated, acutely ill or elderly patients should receive reduced doses of levobupivacaine according to their physical condition **(*Galindo Arias, 2002)*** & ***(Foster & Markham, 2000)***.

PRECAUTIONS

To avoid accidental intravascular injection, careful aspiration prior to and following injection is recommended. Aspiration should be repeated before and during each administration of the main dose. Thus by using these precautions accidental intravascular injection could be easily detected while monitoring the vital signs of the patient ***(Foster & Markham, 2000)***..

Due to the fact that, local anesthetics cause bradycardia and hypotention, all patients must have an accessible intravenous line (colloids and crystalloids), vasopressors, resuscitations equipment and the presence of highly experienced personnel***(Cuvas et al.,2010).***

Metabolism may be affected by CYP3A4 and CYP1A2 inhibitors and inducers **(*Foster & Markham, 2000)***. Therefore, dosage adjustment may be required if levobupivacaine is given in association with CYP3A4, CYP1A2 inhibitors.

Limited information concerning the use of local anesthetic in early pregnancy is available and the relevance of such data for human safety is

unknown. However, levobupivacaine should be avoided in early pregnancy unless absolutely necessary if the benefits outweigh the risks. It is likely transmitted through the mother's milk, but the risk of affecting the baby at therapeutic doses is minimal(***Guasch etal 2010).***

SIDE EFFECTS:

(A)Allergic reactions

Allergic reactions are rare with the amide-linked group of local anesthetics and complications as a result of overdose and unintentional intravascular injection may be serious**(*Foster & Markham, 2000)***.

(B)CNS Effect

Accidental intrathecal injection

Symptomatology of central nervous system toxicity includes: numbness of the tongue, light headedness, dizziness, blurred vision, twitches followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest **(*Foster & Markham, 2000)***.

Neurological damage is rare. It may be due to: direct injury to the spine or spinal nerves, anterior spinal artery syndrome, injection of an irritant or non-sterile substance. Effect of such an injury ranges from localized parasthesia or anesthesia, motor weakness, loss of sphincter control and paraplegia. Fortunately, permanent damage is very rare **(*Foster & Markham, 2000)***

A number of terms are used to describe transient neurological symptoms including transient radicular irritation, transient lumbar pain, and transient neurological toxicity. There are no reports of transient neurological symptoms in association with spinal anesthesia using ropivacaine or levobupivacaine **(*Milligan, 2004)***.

(C)Cardiovascular Effects

Cardiotoxicity is related to depression of the conduction system and a reduction in cardiac contractility and excitability. It may present as: low cardiac output, hypotension and electrocardiographic changes ranging from: heart block, bradycardia and ventricular tachyarrythmias which may lead to cardiac arrest. This is usually preceded by major central nervous system toxicity i.e. convulsions***(Cuvas et al.,2010).***

Inadvertent intravascular injection is one of the major dangerous complications because it results in immediate toxic reactions.

Management of cardiovascular side effects includes:

- Pretreatment with a fluid load and/ or vasopressors to guard against hypotension. There are also required once hypotension occurs.

- Atropine is used for management of bradycardia.

- Ventricular arrhythmias are treated by cardioversion.

Convulsions must be treated by thiopentone or diazepam.

- Neuromuscular blockers should be used only if:

1- The airway can be maintained.

2- A fully paralyzed patient can be effectively managed

Frequently reported complications, regardless of casualty includes: hypotension 22%, nausea 13%, anemia 11%, postoperative pain 8%, vomiting 8%, back pain 7%, fever 6%, dizziness 6%, fetal distress 6%, and headache 5% **(*Foster & Markham, 2000)***.

There have been reports of cases where the drug has been given in a higher doses than that recommended, with no apparent toxicity. In one case, a single dose of levobupivacaine of 250mg for a brachial plexus

block, far exceeding the maximum recommended dose (150mg), without toxicity symptoms, although further data will be needed before the safety of this level of dosage is confirmed. There is report where approximately 1.7mg/ kg racemic bupivacaine was injected probably by an accidental intravenous injection during an attempted supraclavicular brachial plexus block. The patient lost consciousness, developed a tachycardia, hypertension and generalized twitching, was managed with oxygen and propofol, with a successful recovery after a few minutes with no sequelae. The authors stressed the risks associated with administration of high doses of bupivacaine, even in experienced hands underline the need for possibly safer agents such as levobupivacaine***(Cuvas et al.,2010).***

(CONTRAINDICATIONS):

Bupivacaine and levobupivacaine are avoided in:

* Coagulation disorders or patient under anticoagulant therapy (***Cuvas et al.,2010).***

* Patients with a known hypersensitivity to local anesthetics of the amide group.

* Patients suffering from severe hypotension e.g. cardiogenic or hypovolemic shock.

* Bier's block (intravenous regional anesthesia).

* Paracervical block in obstetrics because it may have higher risk on the fetus due to systemic toxicity of bupivacaine.

* The use of 0.75% in obstetrics is avoided due to enhanced risk of complications based on experience with bupivacaine***(Cuvas et al.,2010).***

Epidural and spinal anesthesia have its own contraindications regardless of the type of local anesthetic administered:

*Tuberculosis of the spine.

*Pyrogenic infection of the skin at or adjacent to the lumbar site of injection.

*Cardiogenic or hypovolemic shock.

Appropriate treatment, equipment and personnel should be readily available in the event that a serious adverse event occurs **(*Foster & Markham, 2000)***.

PATIENTS & METHODS

- **ETHICS COMMITTEE:**

The study was approved by the ethics committee of benha faculty of medicine and a written informed consent obtained from each patient.

- **TYPE OF STUDY:**

Prospective, comparative, double blind and randomized study.

- **INCLUSION CRITERIA:**

- One hundred tewenty female patients was randomly allocated into two equal groups.each group was subdivided in two equal subgroup**s.**
- Hight from 155-170 cm
- Wight from 70-100 kg
- ASA physical status classes I ,II.
- Age range between 20 -40 years.
- Type of operation: Elective cesarean section.
- Methods of randomization: Closed envelope.
- These patients will randomly allocated into two equal groups

- **Group A**

  Patients of this group formed of 60 Patients

  divided into two subgroups:-

  A1: formed of 30 patients undergo spinal anaesthesia using 10mg levobupivacaine 0.5% with 25 microgram fentanyl total volum injected2.5ml.

  A2: formed of 30 patients undergo spinal anaesthesia using 7.5mg levobupivacaine 0.5% with 25 microgram fentanyl total volum injected 2ml.

I.V line was administered under complete aseptic conditions,all cases were injected in the sitting position they were administered 3 ml (60 mg) 2 % lidocaine infiltration anesthesia through L3-4 after disinfected with antiseptic solution Patients received intrathecal injection of the previous drugs according to each group using a 23-25G spinal needle at the level intervertbral disk L3-L4, after injection Patients were lying flat.

Group B :

Patients of this group formed of 60 Patients divided into two subgroups

B1: formed of 30 patients undergo spinal anaesthesia using 10mg bupivacaine 0.5% with 25 microgram fentanyl total volum injected 2.5ml.

B2: formed of 30 patients undergo spinal anaesthesia using 7.5mg bupivacaine 0.5% with 25 microgram fentanyl total volum injected 2ml

I.V line was administered under complete aseptic conditions,all cases were injected in the sitting position they were administered 3 ml (60 mg) 2 % lidocaine infiltration anesthesia through L3-4 after disinfected with antiseptic solution Patients received intrathecal injection of the previous drugs according to each group using a 23-25G spinal needle at the level intervertbral disk L3-L4, after injection Patients were lying flat.

EXCLUSION CRITERIA:

- patient refusal.
- Age<20 or >40years
- infection at site of the injection.
- any preexisting neurological disease
- the patients with known history of allergy to local anesthetics drugs.
- failed spinal anesthesia
- Obese Patients.
- Known to be cardiac patient.
- Known to be Diabetic patient.
- Known to be Hypertensive patient..
- Patients receiving any anti-coagulant
- **Anesthetic management:**

All patients were evaluated initially by medical history and a complete physical examination ,routine preoperative investigations were done (e.g CBC, PT, PTT, INR, liver function tests ,kidney function tests and ECG) for evaluation of the patient medical status. No premedication was administered .Patients was admitted to the operating room fasting for 6 h. A peripheral i.v.18G catheter was inserted and preoperatively preloading with 20 ml per kg of 0.9%normal saline standard monitoring was conducted and recorded every 2 min ,4min,6min, 8min,10min,15min,20min,30min,60min and 90

min after the block and throughout the surgery, including heart rate (HR), noninvasive arterial blood pressure, electrocardiogram (3 leads), and peripheral oxygen saturation ($SpaO_2$). A nasal cannula was applied and supplemental oxygen given throughout the procedure at 3 L/min. Mean arterial pressure (MAP) decrease of 30 % of MAP before block, accepted as hypotension, It was treated with 5 ml/kg fluid replacement and iv 5 mg ephedrine.

THE RECORDED DATA OF PATIENT

The hemodynamic parameters were monitored after2,4,6,8,10,15,20,30,60 min and 90 min and if the mean arterial blood pressure decreased by more than 30% below pre aesthetic level the patient was given intermittent doses of ephedrine 5-10 mg IV. Heart rate also recorded if there is bradycardia iv atropine was given.

Sensorial-motor block was recorded at 1st, 3rd and 5th min and it was recorded every 15 min until reversal of motor block.

Pin-prick test is used for sensorial block evaluation. Highest dermatome level as maximum sensorial block level, the duration time to T4 dermatomal block after drug administration as the onset for T4 sensorial block, sensorial block reversal time in two dermatome and time to first analgesic need were recorded as first analgesia time.

The most frequently used measure of motor block is the Bromage scale. In this scale, the intensity of motor block is assessed by the patient's ability to move their lower extremities (0=Free movement of legs and feet; 1=Just

able to flex knees with free movement of feet; 2=Unable to flex knees, but with free movement of feet; 3=Unable to move legs or feet).

"Onset of motor block" is recorded as when Bromage scale is "1" after administration of local anesthetics, "onset of highest motor block" is recorded as time to reach highest scale of motor block, "motor block time" is recorded as time to complete termination of motor block, "maximum motor block level" is recorded as highest motor block scale that is reached.

"Duration of baby birth" is recorded as time to clamping of umbilical cord after administration of local anesthetics. "Operation duration" is recorded as time until skin closure from the administration of local anesthetics.

Pain intensity was recorded during skin incision, uterus incision, and closure of peritoneam, postoperative 30 min, and postoperative 60 min and when there is pain. In assessment of pain intensity, 10 cm visual analogue scale (VAS) is used. Before operation, VAS was explained to patients as; "0" no pain,"10"intolerable-pain

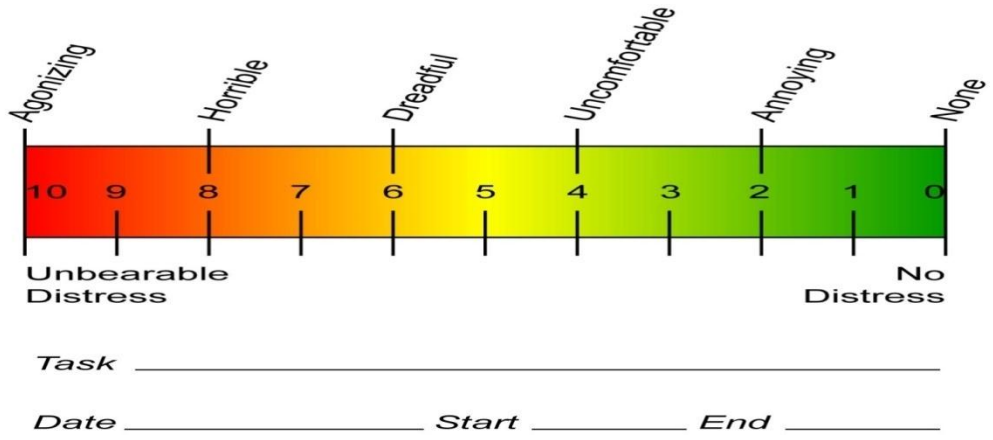


Fig (7) *(VAS)from(Melzack R. McGill Pain Questionnaire (MPQ) major properties and scoring methods.)* [Pain 1975; 1:277-99]

Newborn 1 min and 5 min apgar scores was recorded. Side effects such as pruritus, nausea, vomiting, anxiety, respiratory depression, and headache were followed.

- **Data management and statistical analysis:**

- Analysis of data was done by using SPSS version 16.
- Quantitative data was presented as mean ± Standard deviation.
- Qualitative data was presented as numbers and percentages.
- Quantitative data analyzed by using ANOVA test.
- P – Value < 0.05 considered statistically significant.

Result

In the current study; One hundred eighty female patients will randomly allocated into two equal groups. each group will be subdivided in three equal subgroup**s. Group A** Patients of this group formed of 90 patients divided into three subgroups

A1: formed of 30 patients undergo spinal anaesthesia using 10mg levobupivacaine 0.5% with 25 microgram fentanyl

A2: formed of 30 patients undergo spinal anaesthesia using 7.5mg levobupivacaine 0.5% with 25 microgram fentanyl

Group B Patients of this group formed of 90 Patients divided into three subgroups

B1: formed of 30 patients undergo spinal anaesthesia using 10mg bupivacaine 0.5% with 25 microgram fentanyl

B2: formed of 30 patients undergo spinal anaesthesia using 7.5mg bupivacaine 0.5% with 25 microgram fentanyl

Table(7) Age, weight,hight ,gestational age and duration of surgery in different groups(Mean±S.D)

	A1(NO30)	A2(NO30)	B1(NO30)	B2(NO30)	P value
Age(years)	27.13±6.263	27.77±5.894	5.894±6.105	5.894±5.998	>0.05
Weight(kg)	81.53±10.536	82.93±10.326	82.17±10.249	84.17±9.724	>0.05
Hight(cm)	161.40±4.643	161.10±4.930	160.97±4.731	162.13±4.805	>0.05
Gestational age(weeks)	38.17±1.392	38.13±1.358	37.80±1.495	37.87±1.525	>0.05
Duration of surgery(min)	55.83±17.225	55.00±17.370	54.50±16.679	55.33±17.515	>0.05

NO:number of patients

Group A1:patients received10mg levobupivacaine 0.5% with 25 microgram fentanyl

Group A2:patients received7.5mg levobupivacaine 0.5% with 25 microgram fentanyl

GroupB1:patients received10mg bupivacaine 0.5% with 25 microgram fentanyl

GroupB2:patients received7.5mg bupivacaine 0.5% with 25 microgram fentanyl

- There was no significant differences *identified between* the two groups and subgroups regard to age **as** mean and stander deviation in group A1:was27.13±6.263,A2:27.77±5.894,B1:27.10±6.105,B2: 27.13±5.998 as p value > 0.05 as show in table(7)and figure (8).

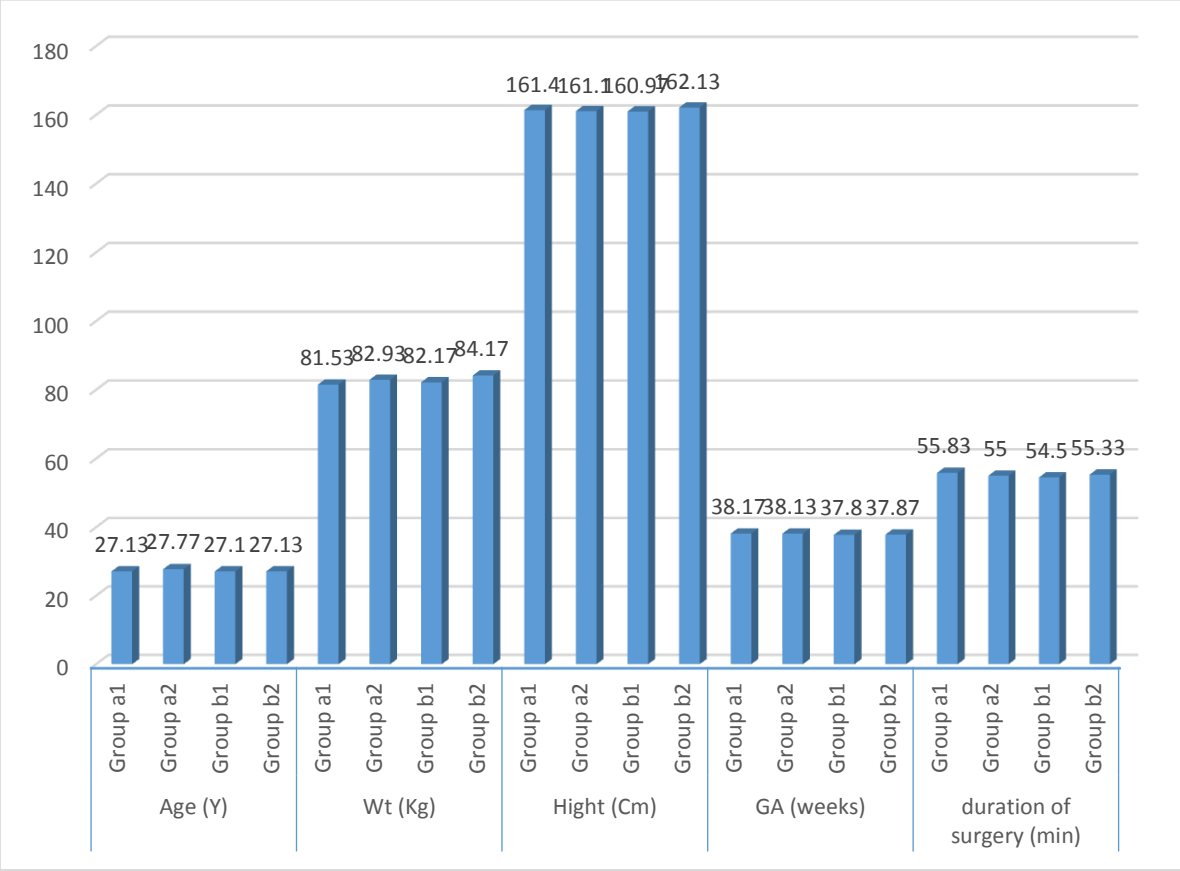
- There was no significant differences identified *between* the two groups and subgroups regard to weight **as** mean and stander deviation in group A1:was81.53±10.536A2:82.93±10.326,B1:82.17±10.249,B2: 84.17±9.72 as p value > 0.05 as show in table(7)and figure (8).

- There was no significant differences identified *between* the two groups and subgroups regard to height as mean and stander deviation in group A1:was161.40±4.643A2:161.10±4.930,B1:160.97±4.731,B2: 162.13±4.80 as p value > 0.05 as show in table(7)and figure (8).

- There was no significant differences identified *between* the two groups and subgroups regard to gestational age **as** mean and stander deviation in

group A1: was38.17±1.392A2: 38.13± 1.358,B1: 37.80±1.495,B2: 37.87±1.52 as p value > 0.05 as show in table(7)and figure (8).

- There was no Significant differences identified *between* two groups and subgroups regard to duration of surgery **as** mean and stander deviation ingroupA1:was55.83±17.225A2:55.00±17.370,B1:54.50±16.679,B2: 55.33±17.515 as p value > 0.05 as show in table(7)and figure (8).



Fig(8) Age, weight,hight ,gestational age and duration of surgery in different groups

Group A1:patients received10mg levobupivacaine 0.5% with 25 microgram fentanyl

Group A2:patients received7.5mg levobupivacaine 0.5% with 25 microgram fentanyl

GroupB1:patients received10mg bupivacaine 0.5% with 25 microgram fentanyl

GroupB2:patients received7.5mg bupivacaine 0.5% with 25 microgram fentanyl

Table(8) Heart rate(beat/min) in different groups at basal level,at2,4,6,8,10,15,20,30,60and90 min (Mean±S.D)

Heart Rate(beat/min)	A1(NO30)	A2(NO30)	B1(NO30)	B2(NO30)	Pvalue
Basal-Heart Rate	87.67±2.767	92.00± 2.233	87.67±2.767	92.00±2.233	> 0.05
Heart-Rate at2min	93.33±5.074	89.33± 13.929	94.33±6.074	90.33±13.529	<0.05
Heart-Rate at4min	88.67±5.403	98.67± 6.764	101.67 ±5.503	89.67±6.764	<0.05
Heart-Rate at6min	94.00±6.798	99.67± 9.589	104.67±6.798	95.67±9.589	<0.05
Heart-Rate at8min	84.67±7.893	99.67± 9.732	101.67±7.893	83.67±9.732	<0.05
Heart-Rate at10min	113±9.444	84.33± 12.233	111±9.444	85.33±12.233	<0.05
Heart-Rate at15min	111±9.838	97.67±11.626	110±9.838	98.67±11.626	<0.05
Heart-Rate at20min	102±7.256	99.33± 8.009	104.00±7.256	98.33±8.009	<0.05
Heart-Rate at30min	103.33±9.432	99.00±3.457	105.33±9.334	96±3.756	<0.05
Heart-Rate at60min	88.33±8.151	89.67± 2.090	90.33±8.151	92.67±2.090	> 0.05
Heart-Rate at90min	93.00±10.173	95.33± 1.729	94.00±11.173	95.55±2.729	> 0.05

NO=number of patients

Group A1:patients received10mg levobupivacaine 0.5% with 25 microgram fentanyl

Group A2:patients received7.5mg levobupivacaine 0.5% with 25 microgram fentanyl

GroupB1:patients received10mg bupivacaine 0.5% with 25 microgram fentanyl

GroupB2:patients received7.5mg bupivacaine 0.5% with 25 microgram fentanyl

- Basal heart rate and heart rate at 2,4,6,8,10,15,20,30,60,90 was recorded and we found that there was no significant differences identified *between the* two groups and subgroups regard to basal heart rate **as** mean and stander deviation in group A1:was87.67±2.767A2:92.00± 2.233,B1: 87.67±2.767,B2: 92.00±2.233 as p value > 0.05 as show in table(8)and figure (9).

- There was significant differences identified *between the* two groups and subgroups regard to heart rate at 2 min **as** mean and stander deviation in group A1: was 93.33±5.074A2: 89.33± 13.929,B1: 94.33±6.074,B2: 90.33±13.529as p value <0.05as show in table(8)and figure (9)as group A2 showed more heart rate stability.

- There was significant differences identified *between the* two groups and subgroups regard to heart rate at 4 min **as** mean and stander deviation in group A1: was 88.67±5.403A2: 98.67± 6.764,B1: 101.67 ±5.503,B2: 89.67±6.76 as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(8)and figure(9) as group A2 showed more heart rate stability.

- There was significant differences identified *between the* two groups and subgroups regard to heart rate at 6 min **as** mean and stander deviation in group A1: was 94.00±6.798A2:99.67±9.589,B1:104.67±6.798,B2: 95.67±9.589 as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroups B1comparing to subgroupB2.as show in table(8)and figure(9) as group A2 showed more heart rate stability .

- There was significant differences identified *between the* two groups and subgroups regard to heart rate at 8 min **as** mean and stander deviation in group A1: was 84.67±7.893A2: 99.67± 9.732,B1: 101.67±7.893,B2: 83.67±9.732as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroups B1comparing to subgroupB2.as show in table(8)and figure(9) as group A2 showed more heart rate stability.

- There was significant differences identified *between the* two groups and subgroups regard to heart rate at 10 min **as** mean and stander deviation in group A1: was 113±9.444A2: 84.33± 12.233,B1:111±9.444,B2: 85.33±12.233 as p value <0.05**;**also there was significant differences in

between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(8)and figure (9) as group A2 showed more heart rate stability.

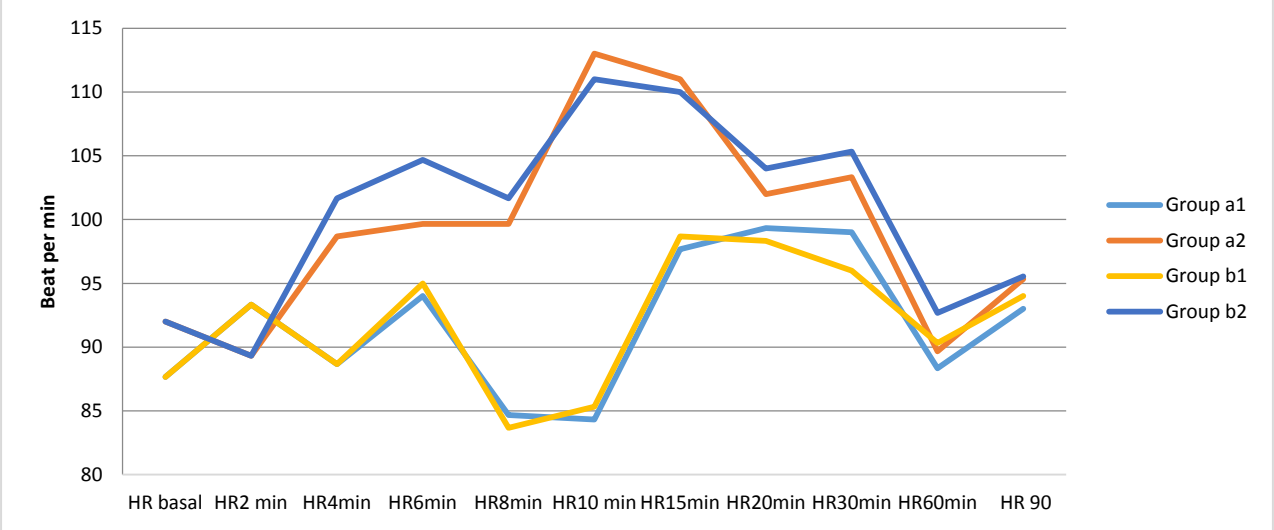
- There was significant differences identified *between the* two groups and subgroups regard to heart rate at 15 min **as** mean and stander deviation in groupA1:was111±9.838A2:97.67±11.626,B1:110±9.838,B2:98.67±11.626 as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(8)and figure (9) as group A2 showed more heart rate stability.

- There was significant differences identified *between the* two group and subgroup regard to heart rate at 20 min **as** mean and stander deviation in group A1: was 102±7.256A2: 99.33± 8.009,B1: 104.00±7.256,B2: 98.33±8.009 as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(8) and figure (9) as group A2 showed more heart rate stability.

- At 30 min there was significant differences identified *between the* two groups and subgroups regard to heart rate **as** mean and stander deviation in group A1: was 103.33±9.432 A2: 99.00± 3.457,B1: 105.33±9.334,B2: 96±3.756as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(8)and figure (9) as group A2 showed more heart rate stability.

- There was no significant differences identified *between the* two groups and subgroups regard to heart rate at 60 min **as** mean and stander deviation in group A1: was 88.33±8.151A2: 89.67± 2.090 ,B1: 90.33±8.151,B2: 92.67±2.090 as p value > 0.05 as show in table(8)and figure (9).

- There was no significant differences were identified *between the* two groups and subgroups regard to heart rate at 90 min **as** mean and stander deviation in group A1: was 93.00±10.173A2: 95.33± 1.729,B1: 94.00±11.173,B2: 95.55±2.729 as p value > 0.05 as show in table(8)and figure (9).



Fig(9) The heart rate(beat/min) in different groups at basal level and at2,4,6,8,10,15,20,30,60and90 min

Group a1:patients received10mg levobupivacaine 0.5% with 25 microgram fentanyl

Group a2:patients received7.5mg levobupivacaine 0.5% with 25 microgram fentanyl

Groupb1:patients received10mg bupivacaine 0.5% with 25 microgram fentanyl

Groupb2:patients received7.5mg bupivacaine 0.5% with 25 microgram fentanyl

Table(9) The mean arterial blood pressure in different groups at basal level,at2,4,6,8,10,15,20,30,60and90 min (Mean±S.D)

The mean arterial blood pressure(mmHg)	A1(NO30)	A2(NO30)	B1(NO30)	B2(NO30)	Pvalue
The basal mean arterial blood pressure	96.50±3.560A2	96.00± 1.526	96.50±3.556	95.50±1.842	> 0.05
The mean arterial blood pressure at2 min	83.67±0.925	89.00± 0.830	82.33±0.356	88.33±0.479	<0.05
The mean arterial blood pressure at4 min	84.00±2.034	A286.50± 0.409	81.87±0.607	88.50±0.209	<0.05
The mean arterial blood pressure at6 min	84.50±0.543	285.50± 0.609	83.50±2.543	87.50±0.409	<0.05
The mean arterial blood pressure at8 min	83.67±1.369	85.67± 1.569	81.67±1.269	87.67±1.769	<0.05
The mean arterial blood pressure at10 min	65.33±4.180	78.00± .830	65.33±4.180	B278.00±.830	<0.05
The mean arterial blood pressure at15 min	70.33±3.497	75.00± . 2.197	71.33±3.457	77.00±2.197	<0.05
The mean arterial blood pressure at20 min	77.00±0.661	82.00± 0.860	78.00±1.761	81.00±0.830	<0.05
The mean arterial blood pressure at30 min	81.67±2.269	85.67± 0.269	83.67±1.359	86.67±1.129	<0.05
The mean arterial blood pressure at60 min	83.67±**1.925**	84.00± **.830**	82.67±2.925	85.00±0.690	> 0.05
The mean arterial blood pressure at90 min	83.67±3.560	96.50± 1.526	94.50±3.560	96.10±1.526	> 0.05

NO=number of patients

Group A1:patients received10mg levobupivacaine 0.5% with 25 microgram fentanyl

Group A2:patients received7.5mg levobupivacaine 0.5% with 25 microgram fentanyl

GroupB1:patients received10mg bupivacaine 0.5% with 25 microgram fentanyl

GroupB2:patients received7.5mg bupivacaine 0.5% with 25 microgram fentanyl

- Basal mean arterial blood pressure and mean arterial blood pressure at,2,4,6,8,10,15,20,30,60,90 was recorded and we found that there was no significant differences identified *between* two groups and subgroups regard to basal mean arterial blood pressure **as** mean and stander deviation in group A1: was 96.50±3.560A2: 96.00± 1.526,B1: 96.50±3.556,B2: 95.50±1.842 as p value > 0.05 as show in table(9)and figure (10)**.**

- There was significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at 2 min **as** mean and stander deviation in group A1: was 83.67±0.925 A2: 89.00± 0.830 ,B1: 82.33±0.356,B2: 88.33±0.479 as p value <0.05; also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(9)and figure (10) as groupA2showed more stability in the mean arterial blood pressure**.**

- There was significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at 4 min **as** mean and stander deviation in group A1: was 84.00±2.034 ,A286.50± 0.409,B1: 81.87±0.607,B2: 88.50±0.209 as p value <0.05; also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(9)and figure (10) asgroupA2showed more stability in the mean arterial blood pressure**.**

- There was significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at6 min **as** mean and stander deviation in group A1: was 84.50±0.543,A285.50± 0.609,B1: 83.50±2.543,B2: 87.50±0.409 as p value <0.05; also there was significant

differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(9)and figure (10) asgroupA2showed more stability in the mean arterial blood pressure**.**

- There was significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at8 min **as** mean and stander deviation in group A1: was 83.67±1.369,A2: 85.67± 1.569,B1: 81.67±1.269,B2: 87.67±1.769and as p value <0.05; also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(9)and figure (10) as groupA2showed more stability in the mean arterial blood pressure**.**

- There was significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at 10 min **as** mean and stander deviation in group A1: was 65.33±4.180,A2: 78.00± .83,B1: 65.33±4.180,B278.00±.830 as p value <0.05; also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(9)and figure (10) asgroupA2showed more stability in the mean arterial blood pressure**.**

- There was significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at 15 min **as** mean and stander deviation in group A1: was 70.33±3.497,A2: 75.00± . 2.197,B1 71.33±3.457,B2: 77.00±2.197 as p value <0.05; also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as

show in table(9)and figure (10) asgroupA2showed more stability in the mean arterial blood pressur

- There was significant differences identified *between the* two group and subgroup regard to mean arterial blood pressure at 20 min **as** mean and stander deviation in group A1: was77.00±0.661A2: 82.00± 0.860,B1: 78.00±1.761,B2: 81.00±0.830as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(9)and figure (10) asgroupA2showed more stability in the mean arterial blood pressure**.**

- There was significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at 30 min **as** mean and stander deviation in group A1: was 81.67±2.269A2: 85.67± 0.269,B1: 83.67±1.359,B2: 86.67±1.129as p value <0.05**;**also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(9)and figure (10) asgroupA2showed more stability in the mean arterial blood pressure**.**

- There was no significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at 60 min **as** mean and stander deviation in group A1: was 83.67±**1.925** A2: 84.00± **.830**,,B1: 82.67±2.925,B2: 85.00±0.690as p value > 0.05 as show in table(9)and figure (10).

- There was no significant differences identified *between the* two groups and subgroups regard to mean arterial blood pressure at 90 min **as** mean and stander deviation in group A1: was 83.67±3.560A2: 96.50± 1.526, ,B1:

94.50±3.560,B2: 96.10±1.526as p value > 0.05 as show in table(9)and figure (10).

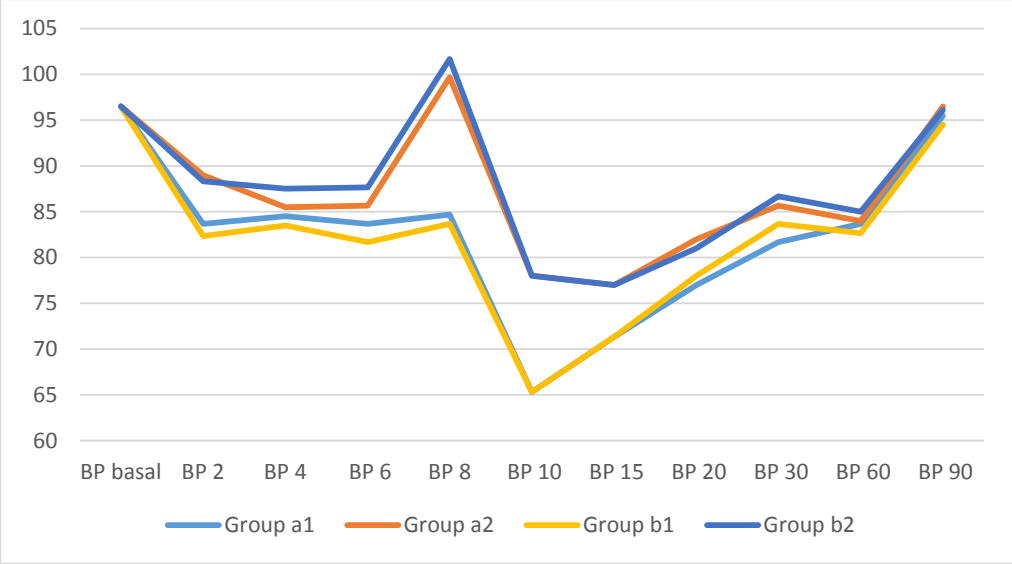


Fig (10) Mean arterial blood pressure(mmHg)in different groups at 2,4,6,8,10,15,20,30,60,90 min

Group A1:patients received10mg levobupivacaine 0.5% with 25 microgram fentanyl

Group A2:patients received7.5mg levobupivacaine 0.5% with 25 microgram fentanyl

GroupB1:patients received10mg bupivacaine 0.5% with 25 microgram fentanyl

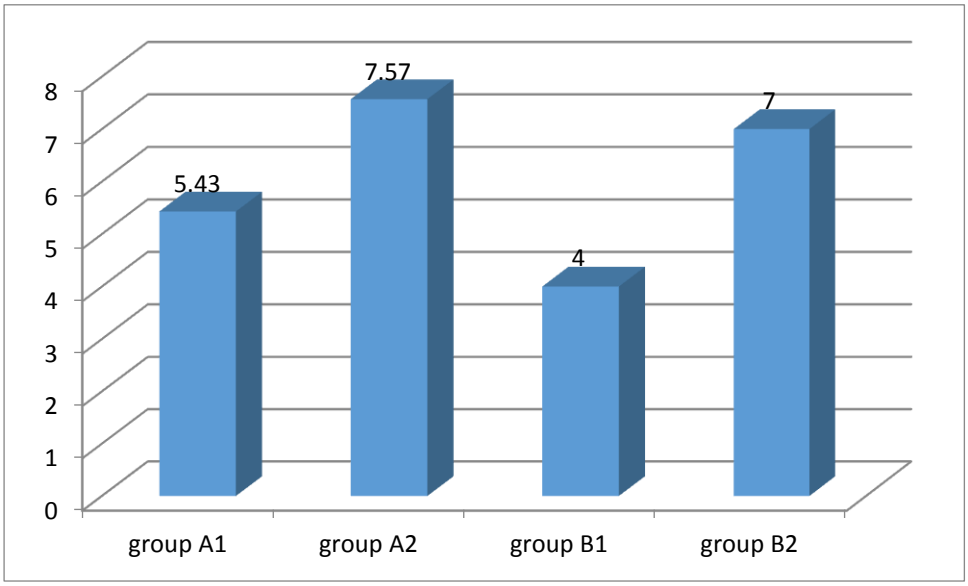
GroupB2:patients received7.5mg bupivacaine 0.5% with 25 microgram fentanyl

Table (10) The onset of sensory block(min) at the level ofT4 in different groups.

		N	Mean	S.D	p-value
The onset of sensory block at the level ofT4(min)	Group A1	30	5.43	1.135	<0.001
	Group A2	30	7.57	1.135	
	Group B1	30	4.00	.830	
	Group B2	30	7.00	.830	

- There was significant differences identified *between the* two groups and subgroups regard the onset of sensory(min) block **as** mean and stander deviation in group A1:was5.43±1.135A2: 7.57± 1.135,B1: 4.00±.830,B2: 7.00±.830 as p value <0.05.also there was significant differences in

between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2-as-show-in-table(10)and-figure-(11)as-groupB1-had-the-most-rapid-onst**.**



- **Fig (11)** The onset of sensory block at level ofT4(min) in different groups.

Table (11) The duration of sensory block(min) in different groups

		N	Mean	S.D	p-value
The duration of sensory block(min)	Group A1	30	200.00	4.152	<0. 01
	Group A2	30	193.23	2.670	
	Group B1	30	202.00	4.152	
	Group B2	30	195.33	2.670	

- There was significant differences identified *between the* two groups and subgroups regard to the duration of sensory block(min) **as** mean and stander deviation in group A1: was 200.00±4.152A2: 193.23± 2.670 ,B1:

202.00±.4.152,B2: 195.33±2.670as p value <0.05. Also there was significant differences in between subgroup A1comparing to subgroup A2 and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(11)and figure (12)as groupB1 had the longest duration of sensory block **.**

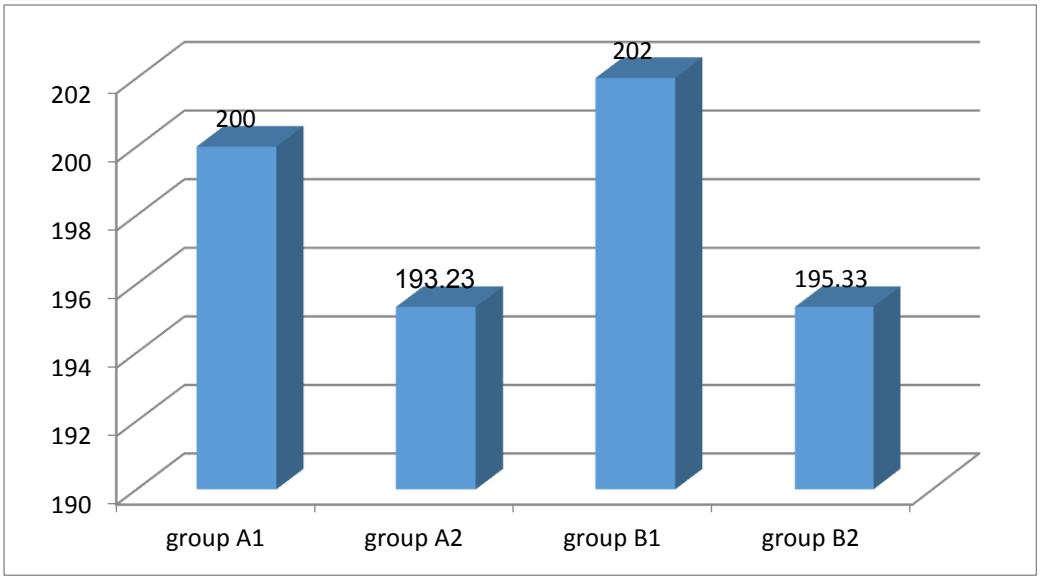
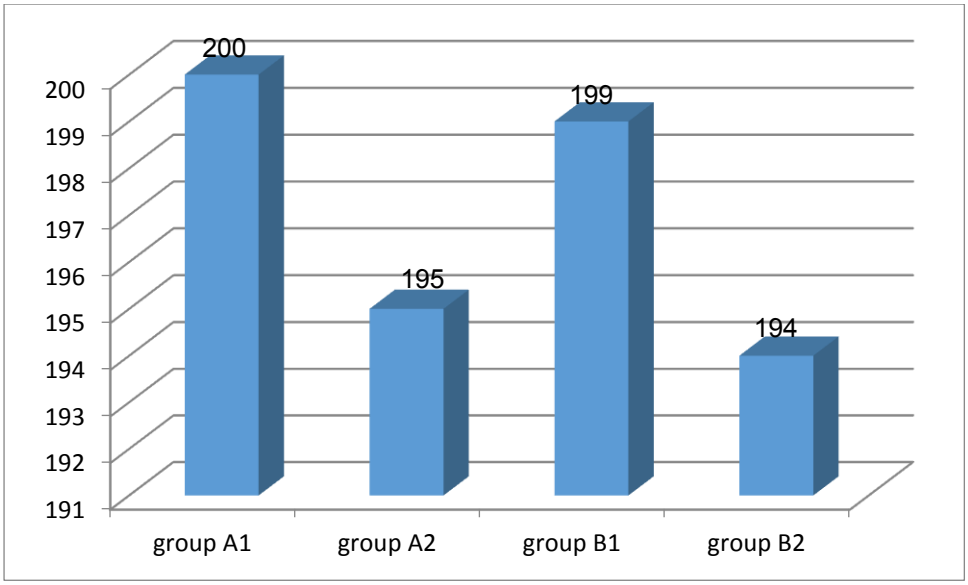


Fig (12) The duration of sensory block(min) in different groups.

Table (12) The 1st analgesic request (min) in different groups.

		N	Mean	S.D	p-value
The 1st analgesic request (min)	Group A1	30	200.00	2.694	<0. 01
	Group A2	30	195.00	4.152	
	Group B1	30	199.00	2.994	
	Group B2	30	194.00	4.654	

- There was significant differences identified *between the* two groups and subgroups regard to the 1st analgesic request (min) **as** mean and stander deviation in group A1: was200.00 ±2.694A2: 195.00 ± 4.152,B1: 199.00 ±2.994,B2: 194.00 ±4.654 as p value <0.05,as show in table(12)and figure (13) as groupA1 had the latest first analgesic request.



- **Fig (13)** The 1st analgesic request (min) in different groups.

Table(13) Pain during skin incision ,closure of peritoneum ,after 30 min and after 60 min in different groups

	Group A1		Group A2		Group B1		Group B2		p-value
	median	IQR	median	IQR	median	IQR	median	IQR	
Skin	0	0	0	1	0	0	0	0	>0.05
Peritoneal closure	0	0	0	1	0	0	0	0	>0.05

30 min	0	0	0	1	0	0	0	0	>0.05
60 min	0	0	0	1	0	0	0	1	>0.05

IQR:inter quarterial ratio 0:no pain 1:there is pain

- There was no significant differences identified *between the* two groups and subgroups regard to pain during skin incision ,closure of peritoneum ,after 30 minand after 60 min as p value >0.05,as showed in table(13).

Table (14) The onset of motor block (min) in different groups

		N	Mean	S.D	p-value
The onset of motor block (min)	Group A1	30	6.50	2.106	<0.001
	Group A2	30	7.50	0.106	
	Group B1	30	5.70	1.606	
	Group B2	30	6.80	1.306	

- There was significant differences identified *between the* two groups and subgroups regard to mean the onset of motor block(min) **as** mean and stander deviation in group A1: was6.50±2.106A2:7.50±0.106,B1: 5.70±.1.606,B2:6.80±1.306as p value <0.05. also there was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(14)and figure (14)as groupB1had the most rapid onset of motor block and groupA2had the most delayed onset of motor block.

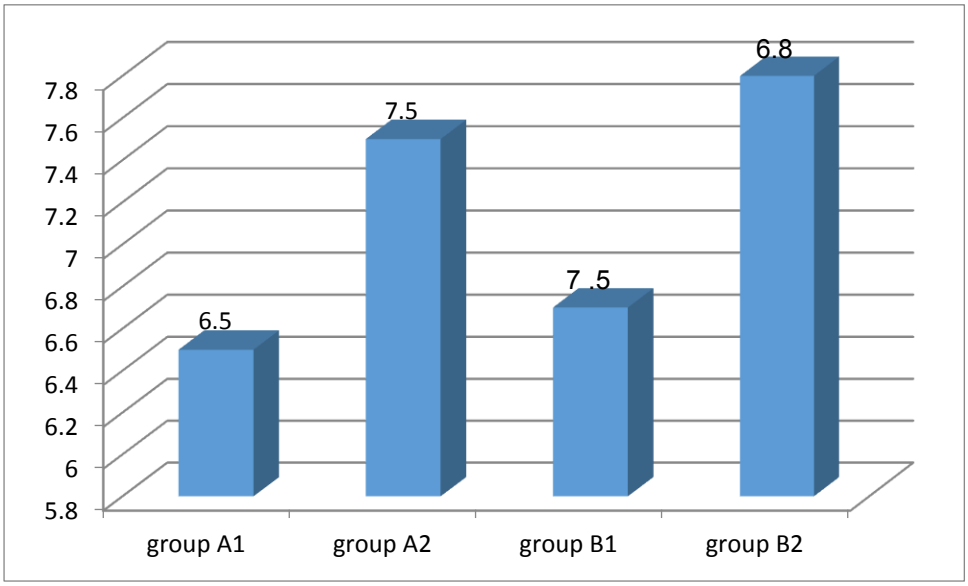


Fig (14) The onset of motor block (min) in different groups

Table (15) The duration of motor block(min) in different groups

		N	Mean	S.D	p-value
The duration of motor block(min)	Group A1	30	175.67	10.929	<0. 01
	Group A2	30	125.00	4.152	
	Group B1	30	183.67	11.929	
	Group B2	30	133.00	5.152	

- There was significant differences identified *between the* two groups and subgroups regard to the duration of motor block(min) **as** mean and stander deviation-in-groupA1:was175.67±10.929A2:125.00±4.152,B1: 183.67±.11.929,B2:133.00±5.152as-p-value<0.05.alsothere was significant differences in between subgroup A1comparing to subgroup A2and there was significant differences in between subgroup B1comparing to subgroupB2.as show in table(15)and figure (15)as groupB1had the longest duration of motor block.

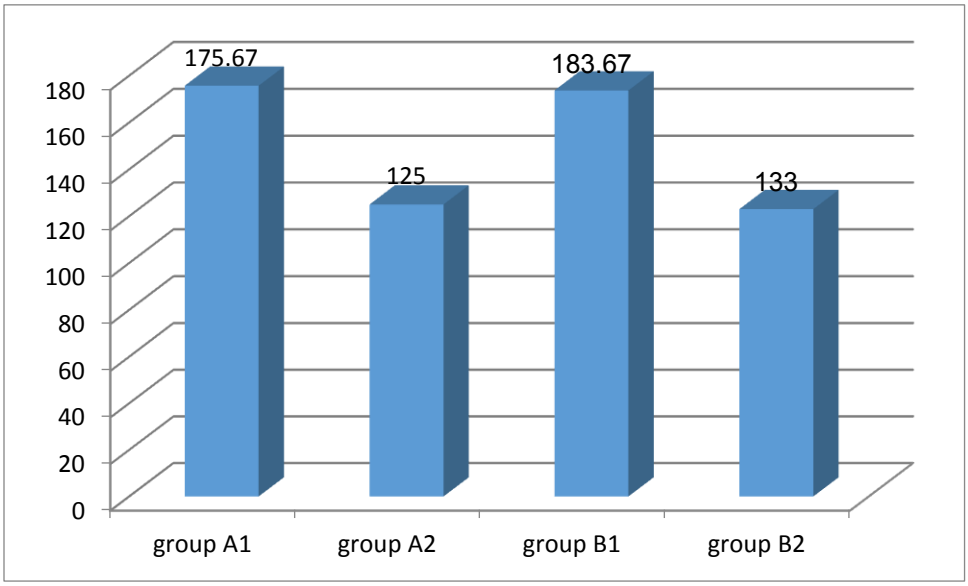


Fig (15) The duration of motor block(min) in different groups

Table (16) Neonatal APGAR score at 1 min and 5 min in different groups

		N	Mean	S.D	p-value
Neonatal APGAR score at 1 min	Group A1	30	8.6	0.579	>0.05
	Group A2	30	9.00	0.830	
	Group B1	30	8.7	.479	
	Group B2	30	9.00	0.930	
Neonatal APGAR score at 5 min	Group A1	30	9.88	.460	>0.05
	Group A2	30	9.77	.420	
	Group B1	30	9.65	.410	
	Group B2	30	9.73	.430	

- There was no significant differences identified *between the* two groups and subgroups regard to neonatal APGAR score at 1 min and 5 min as p value >0.05at one min A1:8.6±0.579,A2: 9.00±0.830,B1: 8.7±.479

  B2:9.00±0.930; at 5 min A1: 9.88±.460,A2: 9.77±0 .420,B1: 9.65±.410 B2: 9.73±0.430 as showed in table(16)and figure (16) .

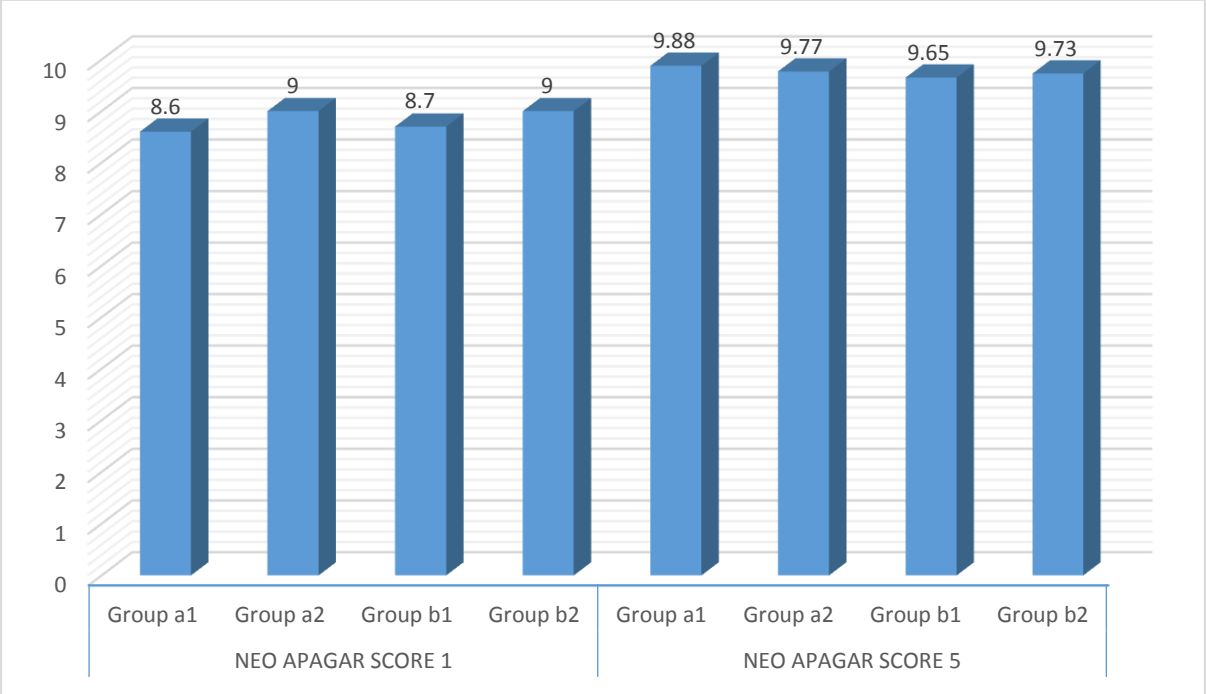


Fig (16) Neonatal APGAR score at 1 min and 5 min in different groups

Table (17) Shivering in different groups.

		Group A1		Group A2		Group B1		Group B2		p-value
		No.	%	No.	%	No.	%	No.	%	
Shivering	0	24	80.0%	29	96.7%	22	73.3%	29	96.7%	<0.05
	1	6	20.0%	1	3.3%	8	26.7%	1	3.3%	

NO:number of patients 0:no shivering 1:there is shivering

- There was significant differences identified *between the* two groups and subgroups regard to the incidence of shivering as p value <0.05A1: 6patient ,A2:1 patient,B1: 8 patient B2:1patien as both groupsA2,B2 were nearly equal while groupA1was less than groupB1 regarded to the incidence of shivering.

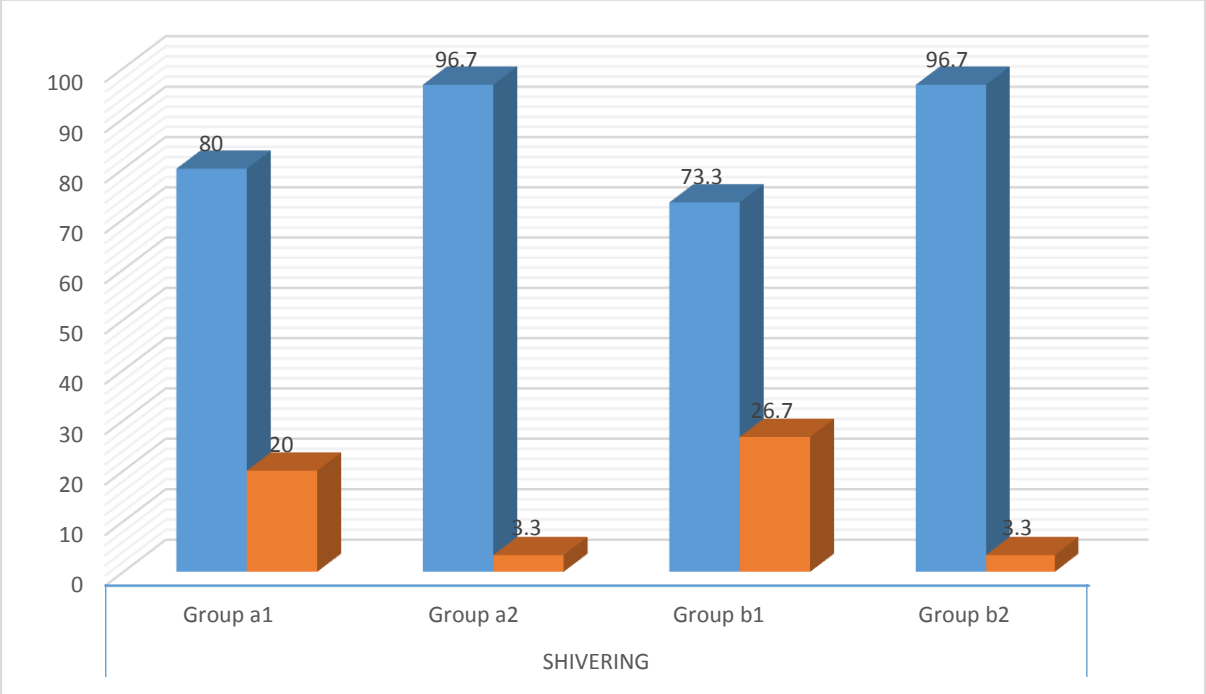


Fig (17) Shivering in different groups

Table (18) Nausea and vomiting in different groups

		Group A1		Group A2		Group B1		Group B2		p-value
		No.	%	No.	%	No.	%	No.	%	
Nausea and vomiting	0	23	76.7%	29	96.7%	22	73.3%	28	93.3%	<0.05
	1	7	23.3%	1	3.3%	8	26.7%	2	6.7%	

NO:number of patients 0:no nausea or vomiting 1:there is nausea or vomiting

- There was significant differences identified *between the* two groups and subgroups regard to the incidence of nausea and vomiting as p value <0.05A1: 7patient ,A2:1 patient,B1: 8 patient B2: 2 patient as group A2had the least incidence of nausea and vomiting while group B1had the largest incidence of nausea and vomiting.

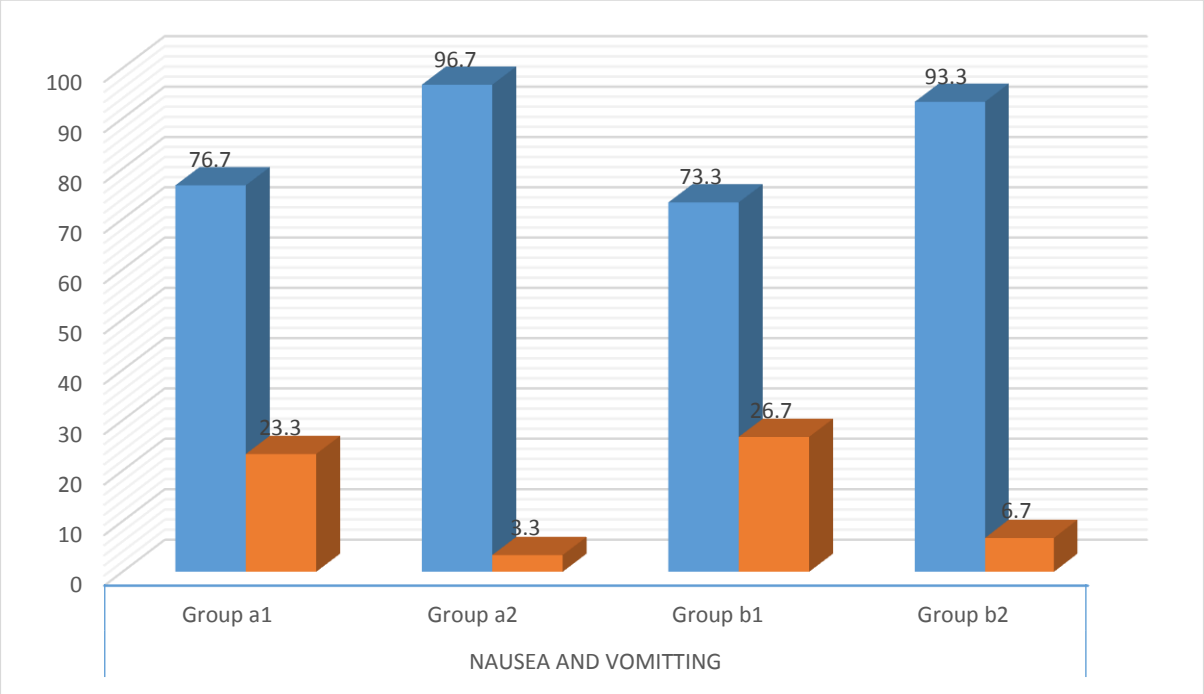


Fig (18) Nausea and vomiting in different groups

table (19) Prurities in different groups

		Group A1		Group A2		Group B1		Group B2		p-value
		No.	%	No.	%	No.	%	No.	%	
Prurities	0	27	90.0%	28	93.3%	27	90.0%	28	93.3%	>0.05
	1	3	10.0%	2	6.7%	3	10.0%	2	6.7%	

NO:number of patients 0:no prurities 1:there is prurities

- There was no significant differences identified *between the* two groups and subgroups regard to the incidence of prurities as p value >0.05 A1: 3 patient ,A2:2 patient,B1: 3 patient B2: 2 patient.

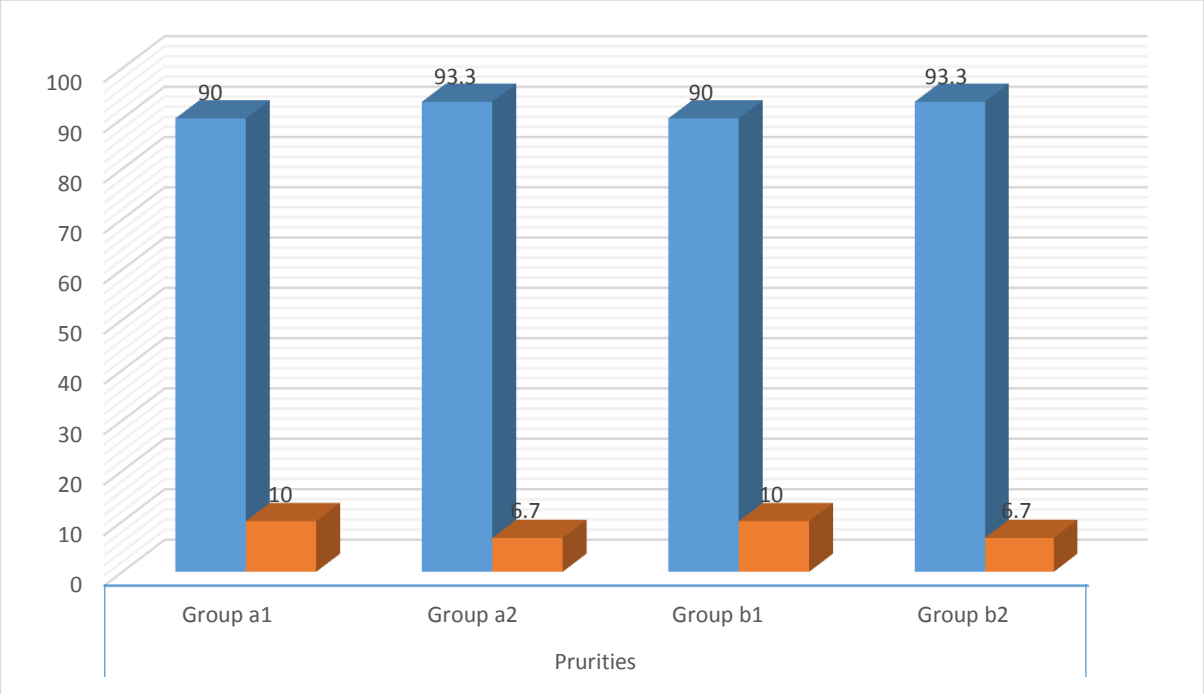


Fig (19) Prurities in different groups.

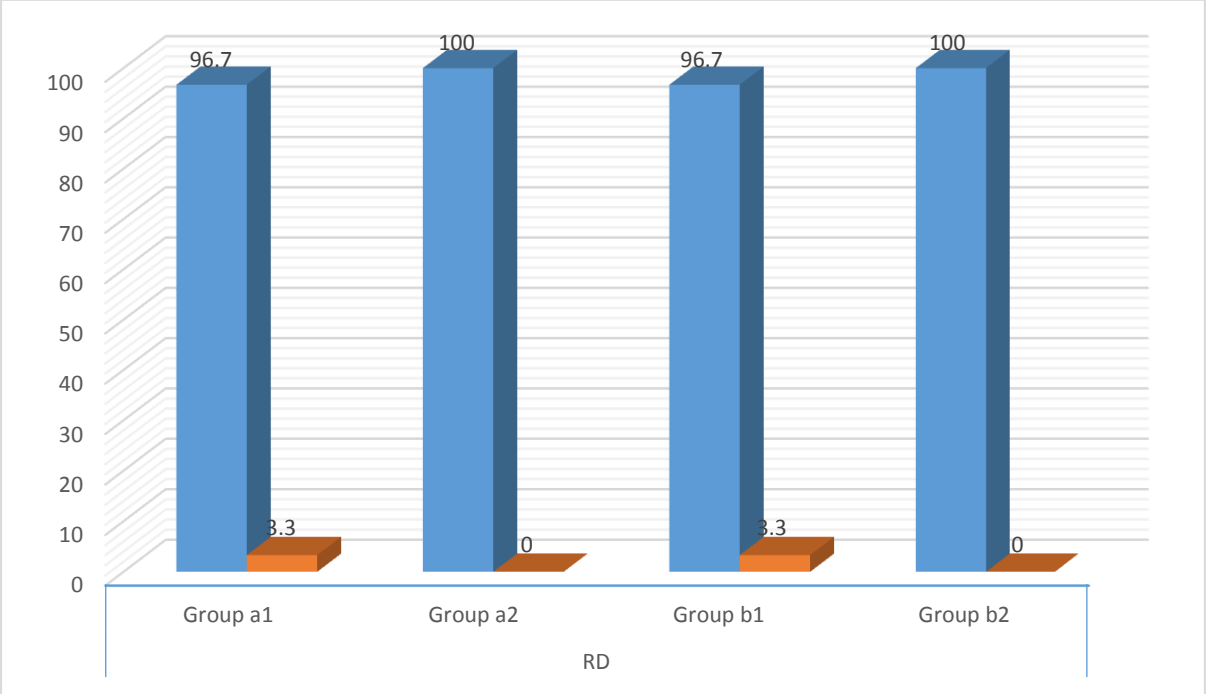
Table (20) Post puncture respiratory depression in different groups.

		Group A1		Group A2		Group B1		Group B2		p-value
		No.	%	No.	%	No.	%	No.	%	
Post puncture respiratory depression	0	29	96.7%	30	100.0%	29	96.7%	30	100.0%	>0.05
	1	1	3.3%	0	0.0%	1	3.3%	0	0.0%	

NO:number of patients 0:no post puncture respiratory depression

1:there is post puncture respiratory depression

- There was no significant differences identified *between the* two groups and subgroups regard to the incidence of post puncture respiratory depression as p value >0.05 A1, b1: one patient ,and no patient in A2,B2.



RD: Post puncture respiratory depression

Fig (20) Post puncture respiratory depression in different groups.

Table (21) Post puncture headache in different groups.

		Group A1		Group A2		Group B1		Group B2		p-value
		No.	%	No.	%	No.	%	No.	%	
Post puncture headache	0	27	90.0%	28	93.3%	27	90.0%	28	93.3%	>0.05
	1	3	10.0%	2	6.7%	3	10.0%	2	6.7%	

NO:number of patients 0:no post puncture headache. 1:there is post puncture headache.

- There was no significant differences identified *between the* two groups and subgroups regard to the incidence of post puncture headache as p value >0.05 A1: 3 patient ,A2:2 patient,B1: 3 patient B2: 2 patient.

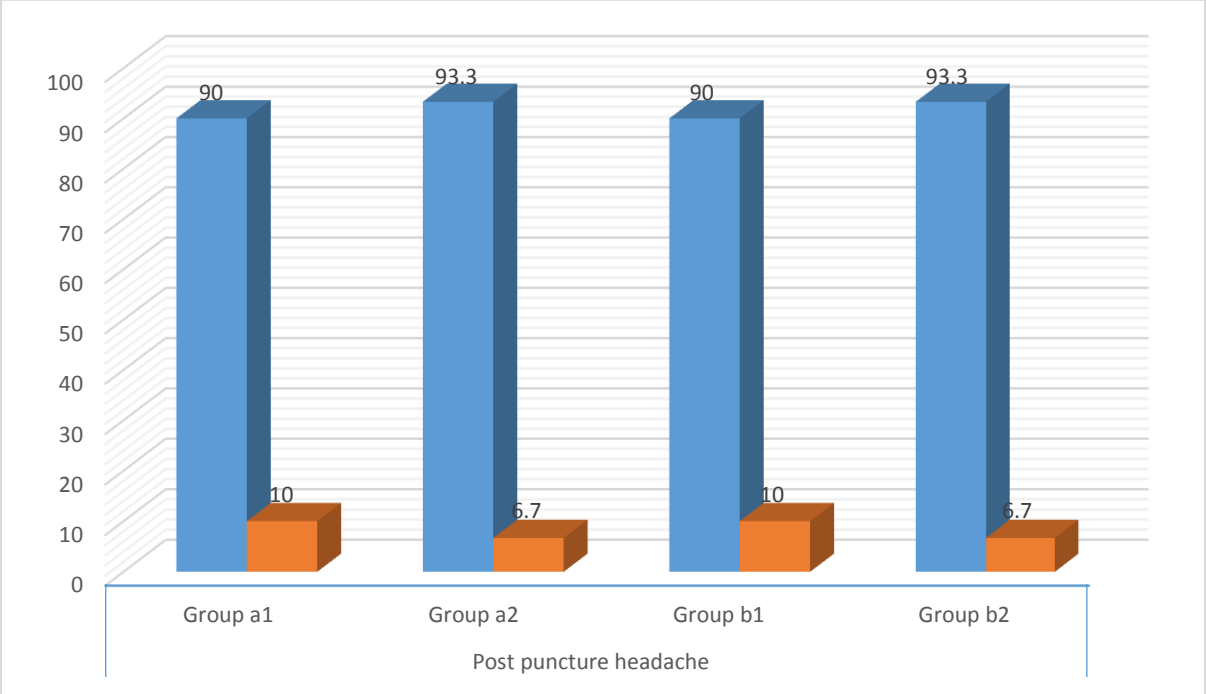


Fig (21) Post puncture headache in different groups.

DISCUSSION

Recent trends of obstetric anesthesia show increased popularity of regional anesthesia among obstetric anaesthetists. General anesthesia is associated with higher mortality rate in comparison to regional anesthesia ***(Bogra J, etal 2005).*** Regional anesthesia has some risks; deaths are primarily related to excessive high regional blocks and toxicity of local anesthetics. Reduction in doses and improvement in technique to avoid higher block levels and heightened awareness to the toxicity of local anesthetics have contributed to the reduction of complications related with regional anesthesia ***(Albright GA, etal 1986).***

Over the last decade, spinal anesthesia has been refined with the addition of opioids to local anesthetic solutions. It was reported that use of only local anesthetics in cesarean operation under spinal anesthesia, is not sufficient in prevention of nausea and visceral pain during uterine manipulation and peritoneum closure,its short duration of action and has disadvantages such as early need for analgesia ***(Bogra J, etal 2005 , Albright GA, etal 1986and Hamber EA, etal 1999).*** The addition of morphine significantly prolongs post operative analgesia to 18-24 h, whereas the more lipophilic opioid such as sufentanil and fentanyl improve and prolong intraoperative analgesia and reduce the amount of local anesthetics required to perform a sufficient dermatome spread and block intensity necessary for Caesarean section. By adding opioids to spinal anesthesia, a reduction in local anesthetic dose is possible. This reduction in local anesthetic requirements reduces the intensity and duration of motor blockade and allows patients to ambulate faster. Initial reports on low-dose spinal anesthesia suggest that this may also reduce maternal hypotension ***(Ben-David B, et al; 2000).*** Today, 0.5% heavy bupivacaine is most commonly used for spinal anesthesia for caesarean section . Recent studies have claimed successful anesthesia with very

low doses of intrathecal bupivacaine (5-9 mg) when co administered with opiods ***(Sarvela J, et al ;2002).***

Due to lower cardiovascular side effect and central nervous system toxicity,the use of levobupivacaine as pure S(-) enantiomer of bupivacaine is progressively increased ***(Santos AC, DeArmas PI, 2001).***

In the current study, One hundred twenty female patients was randomly allocated into two equal groups. each group was subdivided in two equal subgroup**s. Group A** Patients of this group formed of 60 Patients divided into two subgroups,A1: formed of 30 patients undergo spinal anaesthesia using 10mg levobupivacaine 0.5% with 25 microgram fentanyl,A2: formed of 30 patients undergo spinal anaesthesia using 7.5mg levobupivacaine 0.5% with 25 microgram fentanyl **;Group B** Patients of this group formed of 60 Patients divided into two subgroups**,**B1: formed of 30 patients undergo spinal anaesthesia using 10mg bupivacaine 0.5% with 25 microgram fentanyl,B2: formed of 30 patients undergo spinal anaesthesia using 7.5mg bupivacaine 0.5% with 25 microgram fentanyl.There was significant differences *identified between the* two groups and subgroups as regard the heart rate and the mean arterial blood pressure at 2 ,4,6,8,10,15,20,30min;There was significant differences *identified between the* two groups and subgroups as regard the onset ,duration of sensory block and 1st analgesic request. There was significant differences *identified between the* two groups and subgroups regard to the onset ,duration of motor block .There was significant differences *identified between the* two groups and subgroups as regard the incidence of nausea and vomiting and shivering; but no significant different related to neonate or other complication as group A2which received7.5mg levobupivacain+25 microgram fentanyl showed more

hemodynamic stability ,less duration of motor block and less incidence of nausea and vomiting and shivering .

Kiran and Singal 2002 conducted a double-blind comparison of three doses (7.5 mg, 8.75 mg and 10 mg) of 0.5% hyperbaric bupivacaine in women undergoing elective caesarean section under spinal anaesthesia. Sixty women were randomised into 3 groups of 20 patients. Group A recived 7.5 mg, group B 8.75 mg and C 10 mg of study drug. The time to maximum sensory blockade did not differ among the groups ($P > 0.05$). Mean time to start of regression of sensory block was greater in group C than in groups A and B ($P < 0.001$ and $P < 0.05$ respectively). Time required for complete regression of sensory block was longer in group C than in groups A and B ($P < 0.001$). Duration of motor block was greater in group C than in groups A and B ($P < 0.001$ and < 0.05 respectively). Neonatal outcome was good in all the groups. None of the patients in any group experienced pain before delivery. After delivery of the baby, however, group C women had a lower incidence of visceral pain than did groups A and B ($P < 0.05$). The incidence of hypotension was greater in groups B and C than in group A ($P < 0.05$). Group C women had a greater incidence of bradycardia than groups A and B ($P < 0.05$). The 7.5-mg dose of 0.5% hyperbaric bupivacaine was observed to provide acceptable analgesia without any significant incidence of adverse effects such as maternal hypotension or bradycardia ,advocated the use of 7.5 mg bupivacaine for Caesarean section as this dose was associated with a decreased incidence of hypotension ,but again, a large number of patients rated the analgesic quality as poor and this agree with the current study but the difference that we use fentanyl .

Ginosar et al. 2004 worked on 48 parturient undergoing elective cesarean delivery under combined spinal-epidural anesthesia were enrolled in this double-

blind, randomized, dose-ranging study. Patients received a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-mg intrathecal isobaric bupivacaine with 10 microg fentanyl and 200 microg morphine. Overall anesthetic success was recorded when no intraoperative epidural supplement was required during the cesarean delivery. ED50 and ED95 values for overall anesthetic success were determined using a logistic regression model; ED50 and ED95 values for overall anesthetic success were 7.25 and 12.0 mg, respectively. No advantages for low doses could be demonstrated with regard to hypotension, nausea, vomiting, pruritus, or maternal satisfaction, although this study was underpowered to detect significant differences in secondary outcome variables..reported ED50 and ED95 of hyperbaric bupivacaine in cesarean section with combined spinal epidural technique is 7.6 mg and 11.2 mg, respectively and this agreed with the current study as we found 7.5mg bupivacain was effective for cesarean section .

Dilek Subaşı etal 2012, *They were worked in two group Group BF receiving 7.5 mg (1.5 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl, or Group LF receiving 7.5 mg (1.5 ml) hyperbaric levobupivacaine and 25 mcg (0.5 ml) fentany;* anesthesia was 95 % successful with 25 mcg fentanyl added to 7.5 mg hyperbaric bupivacaine. Only in two patients, it was not sufficient and local anesthetics were administered. levobupivacaine had lesser motor potency. Bromage score at 3rd and 5th min were 1-2 in levobupivacaine and 2-3 in bupivacaine. On the other hand, max sensory block level was found to be higher in levobupivacaine group. In levobupivacaine group, T2 was predominant at sensory block, and in bupivacaine group, T3 was more. Preoperative VAS scores were similar in both groups, whereas postoperative 30th and 60th min VAS scores were lower in bupivacaine group and this agreed with the current study as we found motor block in levobupivacaine group was less than bupivacaine.

In the study of ***Bremerich et al.2011*** fixed doses of intrathecal hypertonic levobupivacaine 0.5 % (10 mg) and bupivacaine 0.5 % (10 mg) combined with either intrathecal fentanyl (10 and 20 microg), or sufentanil (5 microg) were compared in terms of sensory and motor block characteristics and they reported levobupivacaine 0.5 % (10 mg) produce short and less pronounced motor block than bupivacain regardless the type of opioide used and this agreed with the current study as we found motor block in levobupivacaine group was less than bupivacaine. ,but we compared lesser 7.5 mg hyperbaric levobupivacaine and 7.5 mg bupivacaine combined with higher fentanyl dose (25 mcg) .

Also in the study of ***Gautier P et al 2003,*** Ninety parturients were enrolled. A combined spinal-epidural technique was used. Patients were randomly assigned to receive one of the following isobaric i.t. solutions: bupivacaine 8 mg (n=30), levobupivacaine 8 mg (n=30), or ropivacaine 12 mg (n=30), all combined with sufentanil 2.5 microg. An i.t. solution was considered effective if an upper sensory level to pinprick of T4 or above was achieved and if intraoperative epidural supplementation was not required. Sensory changes and motor changes were recorded. they foud that Anaesthesia was effective in 97, 80, and 87% of patients in the bupivacaine 8 mg, levobupivacaine 8 mg, and ropivacaine 12 mg groups, respectively. Bupivacaine 8 mg was associated with a significantly superior success rate to that observed in the levobupivacaine group ($P<0.05$). It also provided a longer duration of analgesia and motor block ($P<0.05$ vs levobupivacaine and ropivacaine) and this disagreed with the current study as we found that the sensory block of both levobupivacaine and bupivacaine was nearly equal while the motor block of levobupivacaine was less than bupivacaine this is may be because they did not add narcotics like our study

Ayesha goyal ;etal2015 worked on BF group receiving 10 mg (2 ml) hyperbaric bupivacaine and 25 mcg (0.5 ml) fentanyl and LF group receiving 10 mg (2 ml) isobaric levobupivacaine and 25 mcg (0.5 ml) fentanyl. Sensory and motor block characteristics of the groups were assessed with pinprick, cold swab, and Bromage scale; observed hemodynamic changes and side-effects were recorded. Effects on the neonate were observed by APGAR score at 1 and 5 min and umbilical cord blood gas analysis. , they found that levobupivacaine and hyperbaric bupivacaine combined with fentanyl produced a similar quality of sensorial blockade as well as maternal hemodynamic and neonatal effects in CS under spinal anesthesia. Combination of fentanyl with levobupivacaine induced less motor blockade than hyperbaric bupivacaine when administered via the intrathecal route and this agreed with the current study as we found motor block in levobupivacaine group was less than bupivacaine while sensory block of both levobupivacaine and bupivacaine was nearly equal. Ayesha goyal ;etal, also stated that the relatively higher prevalence of hypotension in both groups can be attributed to the high dose of the local anesthetics. Itching was recorded in both groups which is commonly reported with intrathecal use of fentanyl and this agree with the current study.

Guler et al2012;They compared fixed doses of intrathecal 0.5% levobupivacaine (10 mg) and 0.5% hyperbaric bupivacaine (10 mg) combined with intrathecal fentanyl (25 μg) in terms of the characteristics of sensory and motor blockade in parturients undergoing elective CS with spinal anesthesia. In their study, levobupivacaine exhibited advantage of significantly shorter and less pronounced motor blockade with better hemodynamic stability than racemic bupivacain and both of them produce similar effect on the neonatal and this agreed with the current study.

. In a study by ***Lirk* et al.*2010*** intrathecal bupivacaine, ropivacaine, and levobupivacaine used for CS produced similar effects on neonates (as evaluated by APGAR scores and the pH of arteries in the umbilical cord) and this agreed with the current study.

In the study of ***Coppejans HC, Vercauteren MP 2006*** after combination of sufentanil with bupivacaine, ropivacaine, and levobupivacaine, APGAR scores and the pH of arteries in the umbilical cord in neonates did not differ and this agreed with current study. Hypotension was the most common side-effect seen in about 50% of parturients in their study (26.67% in levobupivacine and 66.67% in bupivacine) during spinal anesthesia. This is due to engorgement of epidural veins from aortocaval compression in a pregnant woman with displacement of CSF, which may contribute to unwanted cephalad extensions of the blockade, which can be associated with an increased risk of hypotension and this agreed with the current study as hypotension was less in levobupivacine group than bupivacine group.

Akcaboy EY etal 2011 they used a combination of for 5 mg levobupivacaine with 25 μg fentanyl for transurethral prostate surgery and they found that combination can provide stable hemodynamic profile, patient and surgeon satisfaction and effective sensorial blockade with less motor blockade in spinal anaesthesia; so it could be used at low doses as a good alternative to bupivacaine and this agreed with the current study,but we used higher dose(7.5mg levobupivacaine+25 μg fentanyl).

Turkmen A etal 2012 were randomized patients into one of the following two groups: bupivacaine + fentanyl group (group B; n = 25), 7.5 mg of 0.5% bupivacaine + 15 microg fentanyl intrathecally; levobupivacaine + fentanyl group (group L; n = 25), 7.5 mg of 0.5% levobupivacaine + 15 microg fentanyl

intrathecally. The patients were immediately placed in supine position with 20-30 degrees head up-tilt. The level of sensory and motor blocks were evaluated by pin-prick test and Bromage scale, respectively. and they found that The time to sensory block at the T4 dermatome was shorter in group B (group B, 4.8 min; group L, 6.0 min; $p < 0.05$). The time to maximum motor block was also shorter in group B (group B, 3.4 min; group L, 4.7 min; $p < 0.05$). The duration of analgesia was longer in group L compared to group B (group B, 102 min; group L, 118 min; $p < 0.05$). Turkmen *et al,* stated that both bupivacaine, and levobupivacaine share a similar sensory block pattern. But, the development of motor block was faster and lasted longer with hyperbaric bupivacaine which was similar to the observations of Guler *et al*., Subaşı *et al*., and also this agreed with the current study.

Subaşı D,etal etal 2012 had worked on prospective study, 50 parturients, who were scheduled for cesarean section were enrolled after Ethics Committee approval had been obtained. The patients were randomized into one of the following two groups: bupivacaine + fentanyl group (group B; n = 25), 7.5 mg of 0.5% bupivacaine + 15 microg fentanyl intrathecally; levobupivacaine + fentanyl group (group L; n = 25), 7.5 mg of 0.5% levobupivacaine + 15 microg fentanyl intrathecally. The patients were immediately placed in supine position with 20-30 degrees head up-tilt. The level of sensory and motor blocks were evaluated by pin-prick test and Bromage scale, respectively; and they found that The time to sensory block at the T4 dermatome was shorter in group B (group B, 4.8 min; group L, 6.0 min; $p < 0.05$). The time to maximum motor block was also shorter in group B (group B, 3.4 min; group L, 4.7 min; $p < 0.05$). The duration of analgesia was longer in group L compared to group B (group B, 102 min; group L, 118 min; $p < 0.05$) and this agreed with the current study.

Joginder Pal Attri ;etal 2015 had a prospective randomized double blind study, 100 patients ASA I and II of either sex, 20-65 years of age, scheduled for infraumbilical surgeries under spinal anesthasia, after approval from the Ethics Committee. Informed consent was taken and patients were randomly divided into two groups of 50 each, received either 2 ml of 0.5% isobaric levobupivacaine (group L) or 2 ml of 0.5% isobaric levobupivacaine + 25 μg fentanyl (group LF) intrathecally. Patients were monitored for sensory and motor block characteristics, postoperative analgesia, haemodynamics,side effects and complications for 24h they found that Onset of sensory block and time to maximum sensory block was rapid in group LF (4.8 ± 1.50 and 8.46 ± 1.87 min) as compared to group L (7.6 ± 1.46 and 15.80 ± 2.43 min) ($P < 0.000$). Maximum sensory block was T6 in group LF and T8 in group L. Maximum Bromage score was 2 in both groups but was achieved earlier in group LF ($P < 0.000$). Duration of sensory and motor block was significantly prolonged in group LF (270.98 ± 28.60 and 188.52 ± 9.81 min) as compared to group L (197.58 ± 11.20 and 152.76 ± 9.79 min). Total duration of analgesia was also prolonged in group LF (265.16 ± 26.18 min) as compared to group L (168.16 ± 11.08 min). Patients remained haemodynamically stable and side effects and complications were comparable in both groups. Addition of fentanyl to levobupivacaine leads to early onset and prolonged duration of sensory and motor block as well as postoperative analgesia with stable haemodynamics and minimal side effects.

Gunusen I etal 2011 ,*worked on* One hundred twenty women undergoing elective cesarean section with a combined spinal-epidural technique were enrolled. The parturients were randomly assigned to receive one of the following: levobupivacaine 5 mg (group 5), 7.5 mg (group 7.5) or 10 mg (group 10), all combined with fentanyl 25, 15 or 10 μg, respectively they found that Anesthesia

was effective in 60, 82.5 and 100% of the patients in the levobupivacaine 5, 7.5 and 10 mg groups, respectively. Levobupivacaine 10 mg provided longer durations of analgesia and motor block and greater patient and surgeon satisfaction, although the incidence of hypotension was lower in groups 5 and 7.5 than in group 10 (12.5, 17.5 and 42.5%, respectively). Intraoperative epidural supplementation was higher in group 5 than in group 7.5 (40 and 17.5%, respectively), whereas no patients in group 10 were given an epidural bolus dose ,they concluded; The incidence of hypotension was higher in the levobupivacaine 10 mg group, even though this group presented more effective anesthesia and greater patient and surgeon satisfaction compared with the levobupivacaine 5 and 7.5 mg groups. As a result, we believe that levobupivacaine 7.5 mg combined with fentanyl 15 μg is suitable for combined spinal-epidural anesthesia in elective cesarean section and this agreed with the current study.

Hakan Erbay R etal 2010 had double-blind, randomized, controlled study, a total of 60 patients undergoing transurethral surgery who were ASA I-III were randomized into two groups. Group B received 7.5 mg hyperbaric bupivacaine plus 25 μg fentanyl, and Group L received 7.5 mg hyperbaric levobupivacaine plus 25 μg fentanyl intrathecally. The onset time to T10 dermatome, times to maximum sensory and motor block levels, time to two-segment regression of sensory block, time to Bromage score zero, time to full recovery of sensory block, and hemodynamic values, as well as adverse effects, they found that The onset time of block to T10, time to maximum sensory block, and time to two-segment regression were similar in both groups. The time to maximum motor block was shorter in Group B (7 ± 3 min) than in Group L (12±5 min), ($P<0.001$). The time to a Bromage score of zero (recovery of motor block) was shorter in Group L (105±19 min) than in Group B (113±7 min), ($P=0.04$). The time to full recovery of sensory

block was shorter in Group B (127±14 min) than in Group L (157±34 min), (P<0.001). The requirement for analgesia was earlier in Group B (305±50 min) than in Group L (389±146 min), (P=0.004).and they concluded ;Although both techniques provide adequate spinal block and have few similar side effects for transurethral surgery, the use of low-dose hyperbaric levobupivacaine plus fentanyl may be preferable to low-dose hyperbaric bupivacaine plus fentanyl because of the reduced motor block, shorter duration of motor block, longer duration of sensory block and longer time to the first requirement for analgesia and this agreed with the current study .

Summary

Spinal anesthesia is a preferred method in elective and emergency caesarean section surgeries ***(Gogarten W;2003).*** Levobupivacaine is a frequently used local anesthetic (LA) due to its longer sensory block, lower cardiac toxicity, and shorter motor block properties***(Morrison S.G,etal;2000).*** The addition of opioids to LA spinal anesthesia increases anesthesia quality and ensures effective analgesia during intra operative and early postoperative periods***(Lee Y.Y.,etal;2005).*** For this reason, the strongly lipophilic drugs sufentanil and fentanyl are preferred during caesarean section surgeries***(Karaman S.,etal;2006).*** . However, these agents may cause dose-dependent side effects on fetal heart rate in newborns such as bradycardia, as well as various side effects in the mother such as maternal hypotension, pruritus, nausea, vomiting, and respiratory depression***(Demiraran Y etal;2006).***

No significant differences *identified between* the two groups and subgroups regard to age, weight, height, gestational age and duration of surgery.

There was significant differences *identified between* the two groups and subgroups regard to heart rate at 2 ,4,6,8,10,15,20,30min as group A2 which received 7.5mg levobupivacain showed more heart rate stability.

There was significant differences *identified between* the two groups and subgroups regard to mean arterial blood pressure at 2 ,4,6,8,10,15,20,30min as group A2 which received 7.5mg levobupivacain showed more stability in the mean arterial blood pressure.

There was significant differences *identified between* the two groups and subgroups regard to the onset ,duration of sensory block and 1st analgesic request

as group B1 which received 10mg bupivacain showed the most rapid onset and the longest duration of sensory block and the latest 1st analgesic request.

There was significant differences *identified between* two groups and subgroups regard to the onset ,duration of motor block as group B1 which received 10mg bupivacain showed the most rapid onset and the longest duration of motor block .

There was significant differences *identified between* the two groups and subgroups regard to the incidence of nausea and vomiting and shivering as group B1 which received 10mg bupivacain had the largest incidence of nausea and vomiting and shivering,;whiel group A2 which received 7.5mg levobupivacain had the least incidence of nausea and vomiting and shivering, but no significant different related to neonate or other complication

CONCLUSION

we would like to state that both levobupivacaine and hyperbaric bupivacaine provide fast and effective induction of surgical anesthesia for elective CS with no adverse effects on neonates. Intrathecal 7.5 mg hyperbaric levobupivacaine and 25 mcg fentanyl combination is good alternative to 7.5 mg bupivacaine - 25 mcg fentanyl combination in cesarean surgery as it is less effective in motor block, but it maintains hemodynamic stability at higher sensorial block levels. We conclude that single-shot spinal anesthesia performed with both Intrathecal 7.5 mg hyperbaric levobupivacaine and 25 mcg fentanyl combination is good alternative to 7.5 mg bupivacaine - 25 mcg fentanyl combination in cesarean surgery .

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الملخص العربي

عند اختيار التخدير الموضعي ينبغي ان ناخذ في الاعتبار سرعه ومدة العمل ومدىاغلاق الاستقبال الحسى والحركي ومدىالتاثير علي القلب ويعتبر الهيفي ماركين من اكثر الادويه شيوعا في الاستخدام.

،ويفضل التخدير الموضعي في الولاده القيصريه حيث يمكن استخدام انواع مختلفه من العقارات الطبية بجرعة اقل تعطي فعاليه اعلى واقل خطوره علي الام والطفل مقارنة بانواع اخرى من التخدير

مؤخرا , يفضل استخدام عقار الليفوبيوبفكين فى التخدير الشوكى نظرالقله آثاره الجانبيةعلي القلب والأوعية الدموية والجهاز العصبي المركزي

ان اضافةجرعات منخفضة من المواد الأفيونية المخدرة إلى عقارات التخدير الموضعي أثناء التخدير الشوكي لاجراء الولادة القيصرية يقلل من حدوث الاثار الجانبية نتيجة استخدام عقارات التخدير الموضعي وايضا يزيد من سرعة وكفاءة هذه الادوية اثناء اجراء الولادة القيصرية ويقلل الاحساس بلالم بعدها

اناضافه جرعه قليله من الفينتانيل فى التخدير الشوكى يزيد من سرعة و جوده المخدر الموضعى ويقلل نسبة حدوث الاثار الجانبية

كما انه يزيد من فترة وانتشار الاغلاق للاستقبال الحسى و يمكن استخدامه لاجراء جراحات الاطراف السفليه وتصحيح الفتق الارابو الولادة القيصرية هناك العديد من العوامل التي تؤثر على انتشار ومدة التخدير الشوكي منها جرعه وحجم المخدر و معدل الحقن ووضعيه المريض اثنا وبعد الحقن مباشرةوعمر ووزن وطول المريضوقطر الابره وكثافه الادويه ونوعيه العقار المخدرواضافه الادويه القابضه للاورده الدموية

الهدف من هذا الموضوع هو مقارنة هذا العقار الجديد (الليفوبيوبيفاكين) مع عقار شائع ومعروف (البيوبيفاكين) بتركيز ٠,٥٪ من أجل التخدير النصفي في القيصريه

وفى هذا البحث استخدمنا تركيز٠,٥٪لكلا الدوائيين (الليفوبيوبيفاكين والبيوبيفاكين)،

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نقاط البحث تضمنت تقييم عدم الإحساس بالألم بواسطة الوخز في أوقات ثابتة وتم تسجيل الوقت اللازم لبدء تأثير المخدر وأعلى مستوى وصل إليه تأثير المخدر وكذلك بدء تراجع تأثير المخدر عن أقصى مستوى وصل إليه ومتابعة العلامات الحيوية (نبضات القلب وضغط الدم) قبل بدء العملية وبعد الحقن مباشرة ثم كل نصف ساعة لمدة ساعتين والأعراض الجانبية وكذلك المضاعفات التي تحدث أثناء أو بعد العملية، أيضاً تم تقييم توقف الجهاز الحركي في الأطراف السفلية بواسطة طريقة (برومـاج).

وقد أوضحت هذه الدراسة على تأثير عقاري الليفوبيوبيفاكين والبيوبيفاكين خارج وداخل الأم الجافية وجود فوارق كبيرة بين الدوائين من حيث عدم الإحساس بالآلام بمواصفاته المختلفةومن حيث التأثير على توقف الجهاز الحركي في الأطراف السفلى وأيضاً وجود فوارق ذات دلالة إحصائية في التغيرات في ضغط الدم والنبض بين كلا الدوائين.و|الك عند استخدام الجرعات الاقل

خلاصة القول أن عقار الليفوبيوبيفاكين مخدر موضعي ذو تأثير قوى وممتد المفعول وأن تأثير الفقدان الحسي والحركي لهذا الدواء مماثل لدواء البيوبيفاكين أثناء التخدير مع أثار جانبية أقل من البيوبيفاكين، لذلك يمكن استخدامه كبديل للبيوبيفاكين في حالة إعطاء مخدر موضعي في حالات الجراحة القيصريه.

دراسة مقارنة فاعليه اقل جرعه من عقار الليفوبيوبفكين والبيوبيفكين في تخدير الولاده القيصريه تحت التخدير النصفي

رسالة لتوطئة للحصول على درجة الدكتوراه فى التخدير والعناية المركزة

مقدمة من

الطبيب/ شيماء عزت امين

تحت إشراف

الأستاذ الدكتور/ حسين محمد عبدالمنعم

استاذ التخدير والعناية المركزة

كلية طب بنها

الأستاذ الدكتور محمد احمد ابراهيم الربيعي

استاذ مساعد التخدير والعناية المركزة

كلية طب بنها

الدكتور/ السيد محمد عبد العظيم

مدرس التخدير والعناية المركزة

كلية طب بنها

كلية طب بنها

2015