INTRODUCTION

Intrathecal administration of local anesthetics for caesarean section provides adequate intra-operative anesthesia and postoperative analgesia. Intrathecal administration of midazolam has been reported to exert a spinally mediated anti-nociceptive action. Intrathecal midazolam binds with GABA receptors in the spinal cord, leading to activation of a spinal cord opioid pathway *(Ho and Ismail, 2008).*

Intrathecal lipophilic opioid (fentanyl) and benzodiazepine (midazolam) have been studied as adjuvants with local anesthetic (bupivacaine) in spinal anesthesia for caesarean delivery, and may provide improved intra-operative and postoperative analgesia and thereby decrease discomfort from intra-operative peritoneal manipulations which may initiate emetic episodes *(Obara et al., 2003).*

Several investigations have shown that intrathecal administration of midazolam produces a dose dependent modulation of spinal nociceptive processing in humans and is not associated with neurotoxicity, respiratory depression or sedation *(Rudra et al., 2004).*

AIM OF THE WORK

The purpose of this study is to assess the postoperative analgesic effect of intrathecal midazolam as an adjuvant to bupivicaine after caeserean delivery in comparison to intrathecal bupivicaine alone and intrathecal bupivicaine plus fentanyl.

REGIONAL ANESTHESIA AND CAESAREAN 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 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 a 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).*

However, beneficial analgesia has to be balanced against their known adverse effects. Bupivicaine and midazolam both agents have been investigated in an attempt to quantify their most effective doses when co-administered with 0.5% bupivacaine for spinal anesthesia in elective caesarean delivery. However, there appears to

be little information on whether one is more suitable than the other (*Dobrydnjov et al., 2002).*

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 opoids 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.

Neither of the two pharmacological agents has been known to possess antiemetic properties, Probably they reduce the incidence of emesis by improving the quality and duration of pain relief with 0.5% bupivacaine (*Rudra et al., 2004).*

The anesthetic plan for cesarean delivery should take into account the well-being of two patients: the mother and the fetus. Regional anesthesia is the most common method of anesthesia for delivery because it allows the mother to be awake and immediately interact with her baby. It is also safer for the mother than general anesthesia: a population based study of anesthesia related maternal deaths in the United States reported that maternal mortality associated with regional and general anesthesia was 2 and 32 per million cases, respectively (*Rudra et al., 2004).*

Pregnancy induces a variety of physiological changes that have important clinical implications for anesthesia as increased intra-abdominal pressure, relaxation of the lower esophageal sphincter, and assumption of a recumbent position during labor/delivery increase the risk for pulmonary aspiration of gastric contents if upper airway reflexes are compromised. Pain, anxiety, sedatives, and opioids contribute by prolonging

intestinal transit time, therefore, all patients are considered to have "full stomach," regardless of the time of their last meal, and insertion of a cuffed endotracheal tube is mandatory to protect the trachea if the woman is obtunded, as occurs with general anesthesia. Edema of upper airway tissues, especially in preeclamptic/eclamptic parturients, may render endotracheal intubation *(Battacharya and Dutta, 2007).*

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, and mechanical interventions. 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. Ephedrine (25 to 50 mg intramuscularly) prior to induction of regional anesthesia is one option, although prophylactic

use may produce "overshoot" hypertension *(Chavada et al., 2009).*

Mechanical interventions, such as use of leg wrapping or compression boots, have also been used to decrease the incidence and severity of regional anesthesia-induced hypotension. Moreover, sequential compression boots may help prevent thrombus formation in patients undergoing surgery *(Pan et al., 2004).*

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 recommendations below are based on the Second Consensus Conference on Neuraxial Anesthesia

and Anticoagulation. The use of aspirin should not influence the decision to place a neuraxial block. Clopidrogel has been associated with several case reports of epidural hematomas. The American Society of Regional Anesthesia and Pain Medicine (ASRA) currently recommend a waiting period of 14 days between the last dose of ticlopidine and 7 days after the last dose of clopidrogel and the placement of a neuraxial block. Anticoagulation regimens, such as mini-dose aspirin and low-dose subcutaneous heparin (5000 units every 12 hours) are NOT associated with increased risk of spinal/epidural hematoma and do not need to be halted prior to spinal or epidural analgesia. Standard unfractionated intravenous heparin therapy is usually discontinued with the onset of labor. Subcutaneous heparin therapy is stopped 24 hours prior to a planned induction or cesarean section or with the onset of spontaneous labor. Neuraxial anesthesia may be administered when the partial thromboplastin time returns to normal. If anticoagulation with standard intravenous heparin is required in patients who have recently had epidural catheterization, heparin should not be given for at least one hour after the epidural catheter has been inserted or removed. In patients receiving intravenous heparin, the epidural catheter may be removed two to four hours after the last heparin dose,

after the patient's coagulation status has been evaluated. Since heparin-induced thrombocytopenia may occur, patients receiving heparin for more than four days should have a platelet count assessed prior to neuraxial block and catheter removal *(Harlocker et al., 2003).*

Neuraxial blocks should not be performed until at least 12 hours after the last dose of low dose (prophylactic) LMWH (eg, Enoxaparin 40 mg), and not until at least 24 hours after the last dose in patients receiving high-dose (therapeutic) LMWH (eg, Enoxaparin 1 to 1.5 mg/kg every 12 hours). In addition: If postoperative LMWH is to be used, the first dose should not be administered prior to 24 hours postoperatively if a twice-daily dosing regimen is planned, and not prior to six to eight hours postoperatively if a single-daily dosing regimen is planned. For the twice-daily dosing regimen, epidural catheters should be left in place. For the single-daily dosing regimen, epidural catheters may be maintained, but the catheter should not be removed for at least 10 to 12 hours after the last LMWH dose *(Harlocker et al., 2003).*

Neuraxial blocks should not be performed until laboratory tests of coagulation (prothrombin time, International normalized ratio [INR]) are normal in