# THE EFFECT OF PHENYLEPHRINE AND EPHEDRINE IN FETAL OUTCOME IN THE TREATMENT OF HYPOTENSION DURING SPINAL ANAESTHESIA FOR CAESAREAN DELIVERY

by

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# ABBREVIATIONS

| | |
|---|---|
| ASA | American Society of Anaesthesiologist |
| BP | Blood Pressure |
| BW | Body Weight |
| CNS | Central Nervous System |
| CSF | Cerebrospinal Fluid |
| DBP | Diastolic Blood Pressure |
| FRC | Functional Residual Capacity |
| GI | Gastrointestinal |
| HCL | Hydrochloride |
| HR | Heart Rate |
| IM | Intramuscular |
| IV | Intravenous |
| ICP | Intracranial Pressure |
| LES | Lower Oesophageal Sphincter |
| MAC | Minimum Alveolar Concentration |
| MAO | Monoamine Oxidase |
| MAP | Mean Arterial Pressure |
| $PaCO_2$ | Partial Pressure of Carbon Dioxide in Arterial Blood |
| $PaO_2$ | Partial Pressure of Oxygen in Arterial Blood |
| RPP | Rate Pressure Product |
| SBP | Systolic Blood Pressure |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SVT | Supraventricular Tachycardia |
| UD | Skin Incision to Delivery Interval |

# ABSTRAK

**Latar belakang:**

Halangan simpatetik yang dicirikan oleh hipotensi ialah komplikasi utama bius spinal pada pesakit obstetric. Rawatan dan pencegahan kesan hipotensi adalah penting kerana hipotensi boleh menyebabkan berkurangnya perfusi darah dalam aliran uteroplacenta, ini membahayakan fetus dan ibu tersebut. Pelbagai ubat dan kaedah telah digunakan untuk menghadapi tindakbalas ini tetapi semuanya ada masalah tersendiri. Banyak kajian dijalankan menggunakan ubat phenylephrine atau ephedrine untuk mencegah refleks hipotensi menunjukkan keputusan yang memberangsangkan disamping dapat mengurangkan keasidan darah fetus. Kedua-dua ubat phenylephrine dan ephedrine bertindak pantas dalam jangkamasa yang pendek, kami merangka satu kajian untuk membandingkan kebolehan ubat ini mengurangkan keasidan darah fetus dalam rawatan kesan hipotensif disebabkan tindak balas daripada bius spinal.

**Objektif:**

Objektif penyelidikan secara `rawak dan dua tutupan' ini adalah untuk membandingkan kesan ke atas fetus yang dilahirkan di antara ibu yang mendapat hipotensi kesan daripada bius spinal dan dirawat dengan phenylephrine atau ephedrine semasa pembedahan caesarean.

**Kaedah:**

Lima puluh empat pesakit yang mempunyai status fisikal I atau II (mengikut klasifikasi American Society of Anaesthesiology, ASA) dan dijadual menjalani pembedahan elektif caesarean dibahagi secara `rawak dan dua tutupan' kepada dua kumpulan. Kedua-dua kumpulan akan menerima sama ada suntikan intravenous ephedrine 6 mg/ml (kumpulan kawalan) atau suntikan intravenous phenylephrine 200 mcg/ml sebagai rawatan hipotensi kesan bius spinal. Denyut nadi (HR), tekanan darah sistolik (SBP), tekanan darah diastolic (DBP) dan tekanan purata arteri (MAP) direkodkan sebelum rawatan tambahan diberikan dan dicatat sebagai data asal $T_0$. Data juga diambil setiap minit selepas bius spinal sehingga kelahiran fetus. Semasa kelahiran, sampel darah arteri umbilical diambil dan dianalisa untuk asid bes. Skor Apgar bayi pada 1 dan 5 minit selepas keahiran dicatat. Komplikasi-komplikasi lain yang dihadapi pesakit seperti loya, muntah dan gangguan denyut jantung juga diperhatikan dan direkodkan.

**Keputusan:**

Kedua-dua kumpulan ephedrine dan phenylephrine menunjukkan peningkatan tekanan darah sistolik, tekanan darah diastolic dan tekanan purata arteri apabila digunakan ketika pesakit mengalami hipotensi. Kumpulan phenylephrine menunjukkan purata pH umbilical arteri fetus pada nilai 7.314 berbanding dengan kumpulan yang menerima ephedrine (kawalan) iaitu 7.2793. Purata peningkatan pH umbilical arteri ini adalah signifikan dari segi statistik. Jumlah keseluruhan komplikasi juga dapat dikurangkan pada kumpulan yang menerima phenylephrine jika dibandingkan dengan kumpulan yang mendapat suntikan ephedrine (kawalan).

**Kesimpulan:**

Perawatan hipotensi akibat bius spinal pada pembedahan caesarean dengan menggunakan phenylephrine mampu meningkatkan purata pH arteri umbilical fetus berbanding penggunaan ephedrine. Jumlah keseluruhan komplikasi juga berjaya dikurangkan dalam kumpulan yang menerima rawatan dengan phenylephrine.

# ABSTRACT

**Background:**

Sympathetic blockade manifested by hypotension is one of the most common complications of the regional anaesthesia in obstetric patients. Its prophylaxis and treatment are primarily directed towards the concern that hypotension may result in decreased uteroplacental perfusion, thus compromised fetus and maternal. Various drugs and methods have been used in attempts to attenuate this response but all have limitations. Many studies using phenylephrine or ephedrine as a prophylaxis drug to suppress these reflexes had shown promising results and reduce the occurrence of fetal acidosis. As both phenylephrine and ephedrine had rapid onset and short duration of action, we formulated a comparative study to evaluate the capability of this drug to reduce the fetal acidosis in the treatment of hypotensive response to spinal anaesthesia.

**Objectives:**

The objectives of this double-blinded, randomized study were to compare the fetal outcome after given phenylephrine or ephedrine as a treatment of hypotension in spinal anaesthesia during caesarean delivery.

**Methods:**

Fifty four patients, ASA physical status I or II, undergoing elective lower segment caesarean section surgery were assigned randomly in a double blind, to receive bolus dose of either ephedrine (6mg/ml) or phenylephrine (200mcg/ml), given intravenously as

a treatment of hypotension post spinal anaesthesia. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded prior to spinal anaesthesia as baseline $T_0$ and every minute after spinal anaesthesia untill delivery of the fetus. At delivery, the umbilical artery blood was obtained and acid base analysis performed. Apgar scores at 1 and 5 min after delivery was recorded. Patients were also monitored for complications such as nausea, vomiting and arrhythmia.

**Results:**

Both ephedrine and phenylephrine groups showed the increase of SBP, DBP and MAP in the treatment of hypotension. Phenylephrine group showed mean umbilical artery pH 7.314 when compared to ephedrine (control) group 7.279. The entire increased in umbilical artery pH was significant statistically. Total overall complications were also significantly lower in phenylephrine group when compared to ephedrine (control) group.

**Conclusion:**

Phenylephrine was able to increase the mean fetal umbilical artery pH in the treatment of hypotension in post spinal anaesthesia patients when compared to ephedrine (control) group. The total complications also were lower in patients treated with phenylephrine.

# CHAPTER 1: INTRODUCTION

Hypotension is one of the most common complications of the regional anaesthesia in obstetric patients. The incidence of hypotension is high (Weeks, 2000), occurring as many as 40–85% despite rapid and appropriate treatment. This hypotension is defined as a decrease in systolic blood pressure of 10 - 20% or to less than 100 mmHg, is a result of preganglionic sympathetic nerve blockade, so paralysis of the sympathetic vasoconstrictor nerves to the arterioles and venous capacitance vessels decreased intravascular resistance and venous capacitance secondary to the pooling of blood in the lower extremities and abdomen. Its prophylaxis and treatment is primarily directed towards concern that hypotension may result in decreased uteroplacental perfusion, thus compromised fetus and maternal nausea and vomiting.

Traditional teaching (Tsen, 2000) is that hypotension can be minimized or prevented by the administration of intravenous fluids, positioning of the patient using left uterine displacement, and by the prophylactic and therapeutic use of vasopressors, in particular ephedrine. The recommendation for the preferential use of ephedrine in the population is based on animal studies (Ralston *et al.*, 1974, Hollmen *et al.*, 1984) which suggested a more selective constriction of systemic vessels with ephedrine than with phenylephrine. Other research suggested that alpha adrenergic agents reduce uteroplacental perfusion by increasing uterine vascular resistance (Tong *et al.*, 1992). Ephedrine, however, readily crosses the placenta and may cause fetal tachycardia, which may misinterpret as fetal distress.

Many articles debating the type and amount of fluid preload, whether or not prophylactic vasopressor use is more efficacious than therapeutic use, and which vasopressor is the preferred agent in this setting. Of the three `traditionally taught` measures; only the use of left uterine displacement appears to be supported and accepted practice utilized by all obstetric anaesthesiologists. Intravenous ephedrine, (Ueland *et al.*, 1968) given either in small bolus doses or by infusion, has been recommended to prevent hypotension after spinal anaesthesia during scheduled caesarean delivery. (Tong, 1992, Morgan, 1994). However, recent studies have challenged the efficacy of this approach. In addition, in many studies ephedrine was associated with lower umbilical cord pH. (Chan *et al.*, 1997, Shearer *et al.*, 1997, Morgan *et al.*, 2000, Rolbin *et al.*, 1982, Hughes *et al.*, 1985, Rout *et al.*, 1992).

## 1.1 OBJECTIVES OF THE STUDY

The objectives of this study were:

1. To compare the fetal umbilical artery pH after injection of intravenous phenylephrine or ephedrine as a treatment of hypotension after given local anesthetic into subarachnoid space in caesarean delivery.

2. To compare the fetal apgar score after injection of intravenous phenylephrine or ephedrine as a treatment of hypotension after given local anaesthetic into subarachnoid space in caesarean delivery.

# CHAPTER 2: LITERATURE REVIEW

## 2.1 SPINAL ANAESTHESIA

Spinal anaesthesia is produced by injection of local anaesthetic solutions into the lumbar subarachnoid space. Local anaesthetic solutions placed into lumbar cerebrospinal fluid act on superficial layers of the spinal cord, but the principal site of action is the preganglionic fibers as they leave the spinal cord in the anterior rami.

### 2.1.1 Historical Development

The first phase in the history of spinal anaesthesia, from 1899 to 1905, was characterized by the use of only cocaine for spinal anaesthesia. High frequency of conspicious central nervous system side effects, including tremors, hyperreflexia, severe headaches, and muscle spasms and pains. By the turn of the century, new and totally synthetic drugs were being developed. In 1905, Heinrich Braun, a German surgeon, reported the use of procaine for operative spinal anaesthesia. It was the first neurologically safe local anesthetic. Equally important, understanding of the causes of hypotension during spinal anaesthesia and how to manage it. (Babcock, 1913, Labat, 1922). So, too, came refinements in the techniques of spinal anaesthesia, by making procaine solutions hyperbaric by adding glucose or hypobaric, initially by adding alcohol. The popularity of spinal anaesthesia was further advanced by the synthesis of tetracaine, dibucaine and these new local anaesthetics provided longer duration of spinal anaesthesia than procaine. Duration of spinal anaesthesia was further extended by the use of continuous spinal anaesthesia. By the mid-1940s spinal anaesthesia had reached a peak of its popularity, a popularity soon followed by almost equally

widespread avoidance and neglect. The era of neglect of spinal anaesthesia was brought about by a combination of circumstances, including the fear of neurological complications and scientifically unsound but widely publicized articles on extraordinarily high incidences of neurological sequelae. Around 1965, spinal anaesthesia began a recovery that has persisted and even accelerated over the last 30 years. One studies of Dripps and Vandam demonstrating that, when properly performed, spinal anaesthesia is neurologically safe (Dripps *et al.*, 1954). Another factor was the introduction of new amide-type local anaesthetics. Finally, there was gradual acceptance of the fact that general anaesthesia, too, has risks and hazards, a concept to which the halothane hepatitis controversy of the 1960s and 1970s also contributed.

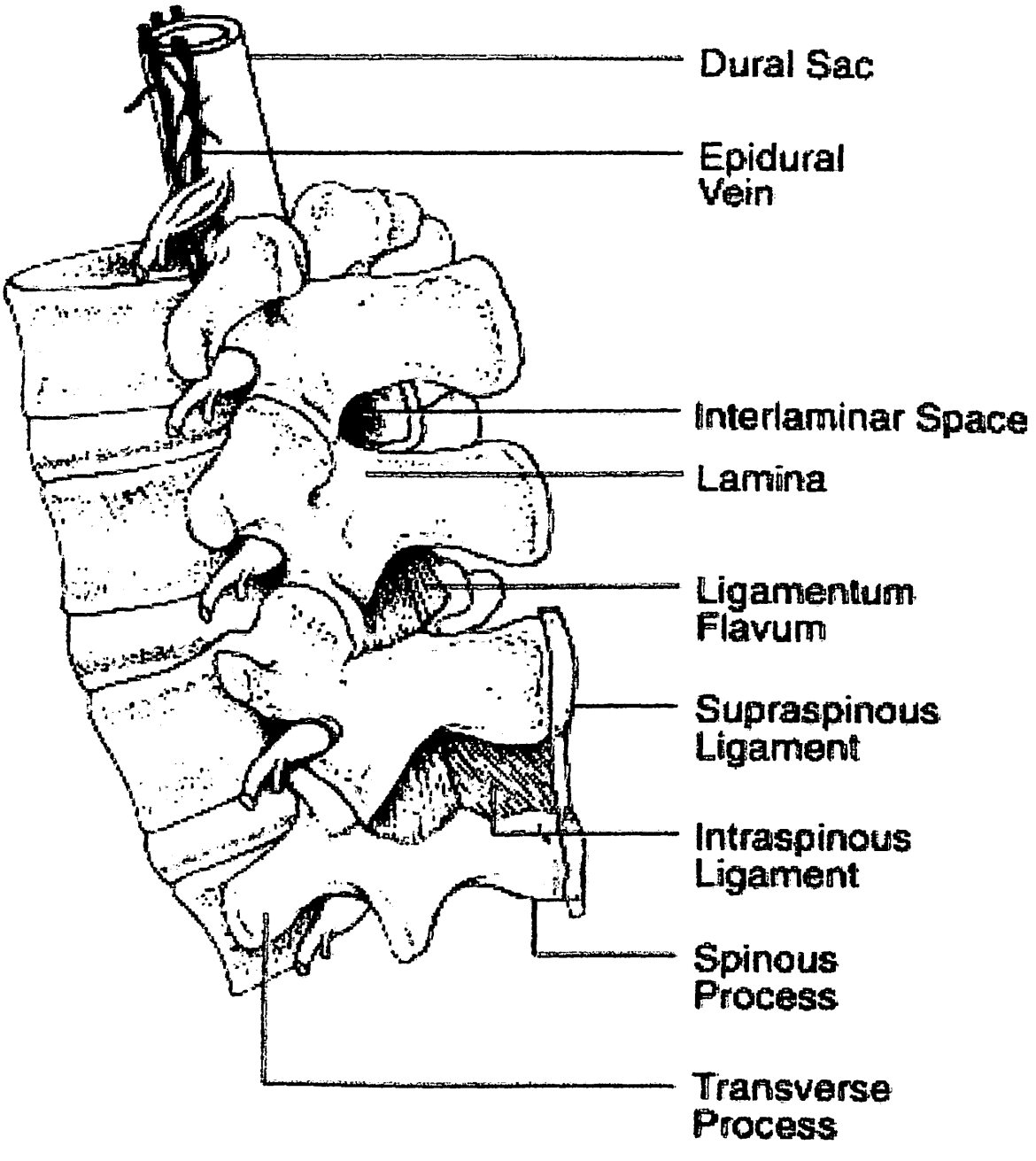
### 2.1.2 Spinal Anaesthesia In Obstetric

In 1950, Greenhill stated that spinal anaesthesia was the most dangerous anaesthetic to perform in pregnant women, leading to a case fatality rate in excess of that observed after general anaesthesia (Greenhill *et al.*, 1950). At that time, several reports referred to incidence of death after spinal anaesthesia for caesarean delivery as high as 1:139. (Franken *et al.*, 1934).

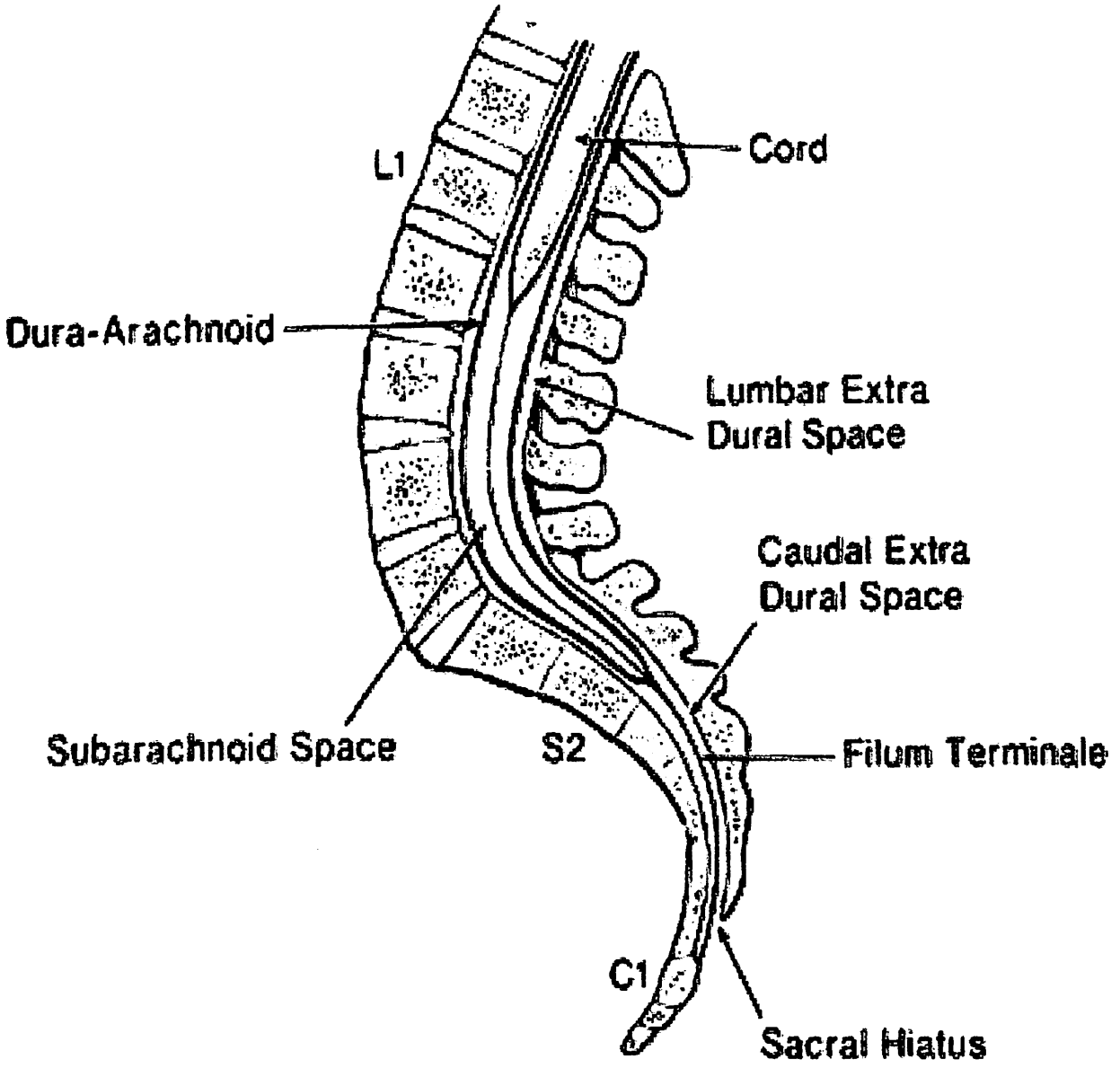
However, spinal anaesthesia was performed by personnel not trained in the technique and equipment for monitoring and resuscitation were scarce. In addition, many physicians left their patients unattended once the spinal anaesthetic had been performed.

Over the last decades, spinal anaesthesia has been the preferred anaesthetic method in caesarean section in many countries including Malaysia. Simplicity of the technique, faster onset, produces dense blocks, cost effective and devoid of significant side effects including local anaesthetic toxicity makes it a popular technique in comparison to other form of anaesthesia. Other advantage includes avoidance of intubation difficulty, which is higher in obstetric population due to oedema of the larynx and reduce oxygen reserve (Hawthorne *et al.*, 1996). Reports from the Confidential Enquiries into Maternal Death from the United Kingdom (Thomas *et al.*, 2002) as well as reports from the United States have demonstrated that maternal mortality is significantly reduced in patients receiving neuraxial as opposed to general anaesthesia. In the latter report, spinal anaesthesia was associated with a reduced incidence of systemic local anaesthetic toxicity (Hawkins *et al.*, 1997).

### 2.1.3 Brief Review on Anatomy of Vertebral Column




**Anatomy of vertebral column**
*(Adopted from Handbook of Clinical Anesthesia; fourth edition)*




**Lumbosacral portion of vertebral column showing terminal spinal cord & its coverings.**
*(adopted from Neural Blockade; fourth edition)*

Spinal agents must be delivered within arachnoid's membrane (figure 2.2) in between the spinal vertebral column (figure 2.1). The arachnoid membrane is composed of overlapping layers of epithelial cells connected by tight junctions. This anatomic arrangement allows the arachnoid membrane to function as the principal meningeal barrier (90% of resistance) to materials crossing in and out of the cerebrospinal fluid (CSF). The arachnoid membrane serves not only as a passive container of CSF but also actively processes and transports agents attempting to cross the meninges. Recent studies demonstrated that metabolic enzymes are expressed in the arachnoid that can affect agents (e.g., epinephrine) and neurotransmitters important for spinal anaesthesia (e.g., acetylcholine). Active transport of compounds across the arachnoid membrane occurs in the area of the neural root cuffs. Here, unidirectional transport of materials from the CSF into the epidural space occurs and may contribute to clearance of spinal anaesthesia agents. Another potential clinical consideration of the lamellar structure of the arachnoid is easy separation of the arachnoid membrane from the dura during spinal puncture. This mechanical arrangement allows easy subdural deposition of spinal agents despite the free return of CSF during spinal injection, which may help to explain individual effects of spinal anaesthesia. (Michael and Philips , 2001).

## 2.2 MECHANISM OF SPINAL ANAESTHESIA

Transmission of pain from peripheral tissues to the brain is modulated in the dorsal horn of the spinal cord. Incoming impulse can be enhanced or attenuated by transmitters derived from primary afferent A-delta and C-fibers, interneuron or descending bulbospinal fibers (Dickenson, 1995).

After noxious stimulation, excitatory neurotransmitter such as excitatory amino acids (glutamate, aspartate) and peptides (substance P, calcitonin gene related peptide, somatostatin) are released from afferent fibers. Compensatory inhibitory neurotransmitter includes norepinephrine, acetylcholine and serotonin. It is the interplay between excitatory and inhibitory spinal neuronal systems determines the message delivered to higher levels of the central nervous system.

### 2.2.1 Local Anaesthetics

The site of action of local anaesthetics is the sodium channel of the neuronal cell. It reversibly bind to the intracellular surface of the sodium channel in its resting state and prevent the conformational change of the central pore which finally prevent the passages of sodium ions and blocking the transmission of pain.

Unfortunately, we cannot apply local anaesthetic directly to the intracellular surface of the sodium channel. Whether we placed it in the epidural space or directly into the cerebrospinal fluid, the local anaesthetic must diffuse across at least two barriers to reach its site of action which are the lipid bilayers of the neuronal membrane and the overlying epineurium which is a non polar environment.

By raising the pH, the equilibrium of the injected local anaesthetic can be shifted to favour the uncharged state which will speed the clinical onset of the block (by adding bicarbonate to the local anaesthetic). Neuronal morphology also has an important clinical implication for local anaesthetic blockade.

The smaller and more poorly myelinated the neuron, the more susceptible it is to local anaesthetic block. For example, the type C-fibers transmitting first stage sensation are readily blocked with a very low concentration of local anaesthetic whereas the A delta fibers innervating the perineum require a higher local anaesthetic concentration for effective blockade.

**2.2.2 Bupivacaine**.

An amide local anaesthetic. Presented as a clear colorless solution bupivacaine hydrochloride. The 0.25% or 0.5% solutions are available combined with 1:200,000 adrenaline. A 0.5% (heavy) solution containing 80mg/ml of glucose is also available. Bupivacaine produce reversible neural blockade and diffuse in their uncharged base form through neural sheaths and the axonal to form a cationic species which enters the internal opening of the sodium ion channel, thereby decreasing sodium ion conductance and preventing depolarization of the cell membrane. In general, similar to Lignocaine but it is markedly cardiotoxic. Bind specifically to myocardial proteins. In toxic doses, it decreases myocardial contractility and the peripheral vascular resistance producing hypotension and possibly cardiovascular collapse.

The absorption of bupivacaine is related to the site of injection (intercostals > epidural > brachial plexus > subcutaneous). Addition of adrenaline does not prolong the duration of action. In the plasma, 95% of bupivacaine bind to the protein, with the volume of distribution Vd of 4-103 l. It is metabolise in the liver by N-dealkylation, primarily to pipcolyl-oxylidine. 5% of the dose is excreted in the urine as pipcolyl-oxylidine, 16% is excreted unchanged.

The clearance is 0.47 l/min and the elimination half life is 2.7 hours. Bupivacaine may be administered by infiltration, intrathecally, epidurally and for major nerve blockade.

### 2.2.3 Opioids

Opioids were the first clinically used selective spinal analgesics after the discovery of opioid receptors in the spinal cord. Intrathecal opioids selectively decrease nociceptive afferent input from Ad and C fibers without affecting dorsal root axons or somatosensory evoked potentials. Hydrophilic opioids such as morphine provide excellent selective spinal analgesia because of small volume of distribution and slow clearance from the spinal cord. However, slow spinal cord penetration and prolonged duration in CSF caused by hydrophilicity also results in slow onset (30 min), prolonged duration of action (61 hours), and risk of delayed respiratory depression from rostral spread in CSF. Intrathecal opioids block transmission of pain-related information by binding at pre and postsynaptic receptors in the dorsal horn of the spinal cord and also at brainstem sites, which they can reach via cephalad cerebrospinal (CSF) spread. Opioid binding to specific mu, delta, and kappa receptors increases potassium conductance and hence hyperpolarizes the nerve membrane. Presynaptic effects include a reduced released of primary afferents neurotransmitter, such as substance P and glutamate (Dickenson, 1995). Post synaptically, opioids hyperpolarize second order projecting neurons. Furthermore, activation of presynaptic mu receptors on primary nerve terminals has been shown to induce release of spinal adenosine, which seems to be an important mediator in spinal opioid analgesia (Cahill et al., 1995). The intrathecal administration of opioid can deliver analgesia with fewer systemic side effects than equivalent dose of systemic opioids.

Three out of four side effects of intrathecal opioids (pruritus, nausea and vomiting, urinary retention and respiratory depression) (Chaney, 1995) seem to be related to cephalad migration of the drug in the CSF and subsequent interaction with opioid receptors in the brainstem (trigeminal nucleus, area postrema, ventral medulla respectively). The most feared side effect: - respiratory depression is thought to be less frequent with the lipophilic opioid, leaving little drug to ascend cephalad in CSF. Most side effects however are dose dependent and less common in patients chronically exposed to intrathecal opioid.

## 2.3 PHYSIOLOGIC RESPONSE TO SPINAL ANAESTHESIA

### 2.3.1 Cardiovascular Responses

The most common serious side effects from spinal anaesthesia are hypotension and bradycardia (Carpenter *et al.*, 1992, Arndt *et al.*, 1998) and closed claims surveys of 40,000–550,000 spinal anaesthetics indicate an incidence of cardiac arrest from 0.04–1/10,000 (Auroy *et al.*, 1997, Aromaa *et al.*, 1997). Large surveillance studies typically observed incidences of hypotension around 33% and bradycardia around 13% in populations.

Risk factors for hypotension in populations include block height T5 or greater , age 40 yr or greater, baseline systolic blood pressure less than 120 mmHg and spinal puncture above L3–L4. Risk factors for development of bradycardia include baseline heart rate less than 60 beats/min , American Society of Anaesthesiologists physical status I, use of β blockers, prolonged PR interval on electrocardiogram , and block

height T5 or greater. Cardiovascular effects of spinal anaesthesia typically include a decrease in arterial blood pressure and central venous pressure with only minor decreases in heart rate, stroke volume, or cardiac output even in patients with poor left ventricular function (ejection fraction, 50%). Typical preservation of cardiac output during spinal anesthesia allows maintenance of oxygen delivery to vital organs such as the brain, as demonstrated by lack of change in jugular bulb oxygen saturation. The decrease in sympathetic activity and motor block also leads to a decrease in total body oxygen consumption that correlates with extent of spinal anaesthesia. Hypotension occurs from decreases in systemic vascular resistance and central venous pressure from sympathetic block with vasodilatation and redistribution of central blood volume to lower extremities and splanchnic beds. Various prophylactic and rescue regimens have been advocated for hemodynamic disturbances with emphasis on prevention of hypotension. Prophylactic measures include prehydration with crystalloid or colloid or administration of vasoactive agents. On the whole, prehydration of crystalloid (250– 2,000 ml) appears to temporarily increase preload and cardiac output without consistently increasing arterial blood pressure or preventing hypotension. Pharmacokinetics of crystalloid explains its poor efficacy, as crystalloid is quickly redistributed from the intravascular to the extravascular space. Administration of large volumes of crystalloid does not appear to confer additional benefit over small volumes (250 ml) and may be detrimental to patients with limited cardiopulmonary reserve. Prehydration with colloid (500 ml) appears to be more effective than crystalloid at maintaining arterial blood pressure and perhaps decreasing incidence of hypotension depending on definition and population. The greater effectiveness of colloid is a result of greater effect for increasing central venous pressure and cardiac output caused by slower redistribution out of the intravascular space. In contrast to

prophylaxis, treatment of hypotension during spinal anaesthesia will be effective with crystalloid or colloid because of changes in kinetics induced by spinal anaesthesia and intravascular hypovolemia. Both clinical scenarios alter kinetics of crystalloid and colloid to allow retention within the intravascular space. Prophylactic administration of pharmacologic agents may be more effective than prehydration for prevention of hypotension. α-Adrenergic agonists (e.g., metaraminol, phenylephrine) reliably increase arterial blood pressure by increasing systemic vascular resistance; however, heart rate and cardiac output may decrease because of increased afterload. Mixed α- and β-adrenergic agents (e.g., ephedrine, epinephrine) are also effective for increasing arterial blood pressure and preventing hypotension but act by primarily increasing heart rate and cardiac output with a smaller increase in systemic vascular resistance. These different physiologic mechanisms for α- versus mixed α- and β-adrenergic agents also occur in treatment of hypotension during spinal anaesthesia. Thus, initial treatment can be tailored to α only for patients with hypotension and mixed α and β for patients with both hypotension and bradycardia. In patients with cardiac disease abrupt increase of the blood pressure and heart rate (leading to increased oxygen demand) can result in myocardial ischemia and lead to myocardial dysfunction or overt tissue infarction (Barash *et al.*, 2001).

### 2.3.2 Thermoregulation

Hypothermia is associated with an increased incidence of myocardial ischemia, cardiac morbidity, wound infection, blood loss, and transfusion requirements (Sessler, 2000). Both general and regional anaesthesia impairs temperature homeostasis to a similar degree (Szmuk *et al.*, 1997, Cattaneo *et al.*, 2000).

There are three main mechanisms causing core hypothermia (Sessler, 2000, Szmuk *et al.*, 1997, Leslie and Sessler, 1996, Frank *et al.*, 1999). The first is redistribution of central heat to the periphery caused by vasodilatation from sympathetic block. This effect is maximal during the first 30–60 min, causes a decrease in core temperature of approximately 1–2°C, and depends on extent of sensory block and patient age. The second mechanism is loss of thermoregulation characterized by reduced shivering and vasoconstriction thresholds during spinal anaesthesia. This abnormal tolerance for hypothermia occurs because of subjective warmth exceeding the actual surface temperature increase from sympathectomy. This exaggerated sense of warmth is proportional to extent of sensory and sympathetic block (Szmuk *et al.*, 1997) and decreases thresholds for shivering and vasoconstriction. Thus, hypothermia may occur during spinal anaesthesia without a conscious perception of cold (Ben-David *et al.*, 1997). Finally, with loss of thermoregulatory vasoconstriction below the level of the sympathetic block, there is increased heat loss from vasodilatation. Spinal anaesthesia will predictably cause core hypothermia within 30–60 min, and patients should be monitored and actively warmed (Sessler, 2000). Spinal anaesthesia accelerates rewarming compared with general anaesthesia because of the residual sympathetic block and vasodilatation (Szmuk *et al.*, 1997).

### 2.3.3 Supraspinal Effects on Consciousness

Central neuraxial anaesthesia may have direct effects on suppression of consciousness, and multiple studies have observed that patients appear drowsy after spinal anaesthesia despite lack of sedative medications (Pollock *et al.*, 2000, Hodgson and Liu, 2000). Correspondingly, both spinal and epidural anaesthesia reduce the hypnotic

requirements of midazolam, isoflurane, sevoflurane, and thiopental in surgical patients and laboratory studies (Hodgson *et al.*, 1999). Possible mechanisms for decreased consciousness during spinal anaesthesia include rostral spread of local anaesthetics or decrease in reticular activating system activity caused by interruption of afferent input (Pollock *et al.*, 2000). Degree of sedation caused by spinal anaesthesia is related to peak block height, with greater sedation observed with greater block heights (Gentili *et al.*, 1998). This finding indirectly supports the hypothesis that greater loss of afferent input from extension of spinal anaesthesia increasingly suppresses consciousness. Time of maximal sedation with spinal anaesthesia shows a biphasic distribution, with one peak occurring during peak spinal block (~30 min after injection) and a second peak occurring later, approximately 1 h after injection (Pollock *et al.*, 2000). Mechanisms for the second peak in sedation are unclear and may include late rostral spread of local anaesthetic into the brain or psychological relief over regression of spinal anaesthesia. Clinical relevance for these observations is the decreased need for pharmacologic sedatives with the use of spinal anaesthesia.

## 2.4 PHYSIOLOGIC CHANGES DURING PREGNANCY

### 2.4.1 Hematologic Alterations

Increased mineralocorticoid activity produces sodium retention and increased body water content (Lund and Donovan, 1967). Plasma volume and total blood volume begin to increase in early gestation, resulting in a final increase of 40–50% and 25–40% respectively, at term. The relatively smaller increase in red blood cell volume (20%) accounts for a reduction in hemoglobin (to 11–12 $g \cdot dl^{-1}$) and hematocrit (to 35%) (Lund and Donovan, 1967).

The leukocyte count ranges from 8000–10,000 per $mm^3$ throughout pregnancy, platelet count remains unchanged. Plasma fibrinogen concentrations increase during normal pregnancy by 50%, whereas clotting factor activity is variable (Pritchard and Macdonald, 1980). Serum cholinesterase activity declines to a level of 20% below normal by term, and reaches a nadir in the puerperium. Total plasma protein concentration declines to less than 6 $g \cdot dl^{-1}$ at term, whereas the total amount in the circulation increases (Coryell *et al.*, 1950). The albumin–globulin ratio declines because of the relatively greater reduction in albumin concentration. A decrease in serum protein concentration may be clinically significant, in that the free fractions of protein-bound drugs can be expected to increase.

### 2.4.2 Cardiovascular Changes

Oxygen consumption increases during pregnancy, the maternal cardiovascular system adapts to meet the metabolic demands of a growing fetus. Decreased vascular resistance due to estrogens, progesterone, and prostacyclin may be the initiating factor (Goodman *et al.*, 1982). Lowered resistance is found in the uterine, renal, and other vascular beds; at term, there is an increase in heart rate (15–25%), and cardiac output (up to 50%) above that of the nonpregnant state. Arterial blood pressure decreases slightly because the decrease in peripheral resistance exceeds the increase in cardiac output. Additional increases in cardiac output occur during labor (when cardiac output may reach 12– 14 $\cdot min^{-1}$) and also in the immediate postpartum period owing to added blood volume from the contracted uterus. From the second trimester, aortocaval compression by the enlarged uterus becomes progressively more important, reaching its maximum at 36–38 weeks, after which it may decrease as the fetal head descends into the pelvis (Kerr *et al.*, 1964).

Studies of cardiac output, measured with the patient in the supine position during the last weeks of pregnancy, have indicated a decrease to nonpregnant levels; however, this decrease was not observed when patients were in the lateral decubitus position (Kerr *et al.*, 1964). Supine hypotensive syndrome, which occurs in 10% of pregnant women because of venous occlusion, results in maternal tachycardia, arterial hypotension, faintness, and pallor (Howard BK *et al.*, 1953). Compression of the lower aorta in this position may further decrease uteroplacental perfusion and result in fetal asphyxia. Therefore, uterine displacement or lateral pelvic tilt should be applied routinely during the second and third trimesters of pregnancy. Changes in the electrocardiogram may also occur. Left axis deviation results from the upward displacement of the heart by the gravid uterus, and there is also a tendency toward premature atrial contractions, sinus tachycardia, and paroxysmal supraventricular tachycardia.

### 2.4.3 Ventilatory Changes

Increased extracellular fluid and vascular engorgement may not only lead to edema of the extremities but may compromise the upper airway. Many pregnant women complain of difficulty with nasal breathing, and the friable nature of the mucous membranes during pregnancy can cause severe bleeding, especially on insertion of nasopharyngeal airways or nasogastric and endotracheal tubes. Airway oedema may be particularly severe in women with pre-eclampsia, in patients placed in the trendelenburg position for prolonged periods, or with concurrent use of tocolytic agents. It may also be difficult to perform laryngoscopy in obese, short-necked parturient with enlarged breasts. Use of a short-handled laryngoscope has proved helpful.

The level of the diaphragm rises as the uterus increases in size and accompanied by an increase in the anteroposterior and transverse diameters of the thoracic cage. From the fifth month, the expiratory reserve volume, residual volume, and functional residual capacity (FRC) decrease the latter to 20% less than in the nonpregnant state (Prowse and Gaensler, 1965).

Concomitantly, there is an increase in inspiratory reserve volume, so that total lung capacity remains unchanged. In most pregnant women, a decreased FRC does not cause problems, but those with pre-existing alterations in closing volume as a result of smoking, obesity, or scoliosis may experience early airway closure with advancing pregnancy, leading to hypoxemia.

The trendelenburg and supine positions also exacerbate the abnormal relationship between closing volume and FRC. The residual volume and functional residual capacity return to normal shortly after delivery. Progesterone-induced relaxation of bronchiolar smooth muscle decreases airway resistance, whereas lung compliance remains unchanged.

Minute ventilation increases from the beginning of pregnancy to a maximum of 50% above normal at term (Prowse and Gaensler, 1965). This is accomplished by a 40% increase in tidal volume and a 15% increase in respiratory rate.

Dead space does not change significantly, and thus alveolar ventilation is increased by 70% at term.

After delivery, as blood progesterone levels decline, ventilation returns to normal within 1–3 weeks (Moya and Smith, 1965).

### 2.4.4 Metabolism

Basal oxygen consumption increases during early pregnancy, with an overall increase of 20% by term (Prowse and Gaensler, 1965). However, increased alveolar ventilation leads to a reduction in the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) to 32 mm Hg and an increase in the partial pressure of oxygen in arterial blood ($PaO_2$) to 106 mm Hg. The plasma buffer base decreases from 47 to 42 $mEq \cdot l^{-1}$, and therefore the *p*H remains practically unchanged. The maternal uptake and elimination of inhalational anesthetics is enhanced because of the increased alveolar ventilation and decreased FRC (Moya and Smith, 1965). However, the decreased FRC and increased metabolic rate predispose the mother to development of hypoxemia during periods of apnea/hypoventilation, such as may occur during airway obstruction or prolonged attempts at tracheal intubation (Archer and Marx, 1974). Human placental lactogen and cortisol increase the tendency toward hyperglycemia and ketosis, which may exacerbate pre-existing diabetes mellitus. The patient's ability to handle a glucose load is decreased, and the transplacental passage of glucose may stimulate fetal secretion of insulin, leading in turn to neonatal hypoglycemia in the immediate postpartum period (Datta *et al.*, 1982).

### 2.4.5 Gastrointestinal Changes

Enhanced progesterone production causes decreased gastrointestinal motility and slower absorption of food. Gastric secretions are more acidic and lower esophageal sphincter (LES) tone is decreased. A delay in gastric emptying can already be demonstrated by the end of the first trimester (Simpson *et al.*, 1988).

Uterine growth leads to upward displacement and rotation of the stomach, with increased pressure and a further delay in gastric emptying. By the 34th week, evacuation of a watery meal may be prolonged by 60% (Davison *et al.*, 1970). Pain, anxiety, and administration of opioids (systemic or neuraxial) and belladonna alkaloids may further exacerbate this delay.

The risk of regurgitation on induction of general anaesthesia depends, in part, on the gradient between the LES and intragastric pressures. In most patients, the gradient increases after succinylcholine administration because the increase in LES pressure exceeds the increase in intragastric pressure. However, in parturients with "heartburn," the LES tone is greatly reduced (Brock-Utne *et al.*, 1981).

The efficacy of prophylactic nonparticulate antacids is diminished by inadequate mixing with gastric contents, improper timing of administration, and the tendency for antacids to increase gastric volume. Administration of histamine ($H_2$) receptor antagonists, such as cimetidine and ranitidine, requires careful timing. A good case can be made for the administration of intravenous (IV) metoclopramide before elective cesarean section. This dopamine antagonist hastens gastric emptying and increases resting LES tone in both nonpregnant and pregnant women (Wyner and Cohen, 1982). However, conflicting reports have appeared on its efficacy and on the frequency of side effects such as extrapyramidal reactions and transient neurological dysfunction (Cohen *et al.*,, 1984, Scheller and Sears, 1987). Although no routine prophylactic regimen can be recommended with certainty, it is the authors' preference to administer at least a nonparticulate antacid before caesarean section and to use regional anaesthesia whenever possible.

A rapid-sequence induction of anaesthesia, application of cricoids pressure, and intubation with a cuffed endotracheal tube are required for all pregnant women receiving general anaesthesia from the 12th week of gestation (Simpson *et al.*, 1988).

These recommendations also pertain to women in the immediate postpartum period because there is uncertainty as to when gastric volume returns to normal.

### 2.4.6 Altered Drug Responses

The minimum alveolar concentration (MAC) for inhalational agents is decreased by 8–12 weeks of gestation and may be related to an increase in progesterone levels (Gin and Chan, 1994). In addition, lower doses of local anaesthetic are needed per dermatomal segment of epidural or spinal block.

This has been attributed to an increased spread of local anaesthetic in the epidural and subarachnoid spaces, which occurs as a result of epidural venous engorgement.

An increased neural sensitivity to local anaesthetics also has been suggested, which may be mediated by progesterone (Datta *et al.*, 1983).

### 2.4.7 Placental Transfer

Placental transfer of drugs depend on the physicochemical characteristics of the drug itself, maternal drug concentrations in the plasma, properties of the placenta, and hemodynamic events within the fetomaternal unit.

Drugs cross biologic membranes by simple diffusion, the rate of which is determined by the Fick principle,

which states that:

$Q/t = KA(C_m - C_f)/D$

where Q/t = rate of diffusion,

K = diffusion constant,

A = surface area available for exchange,

$C_m$ = concentration of free drug in maternal blood,

$C_f$ = concentration of free drug in fetal blood, and

D = thickness of diffusion barrier.

The diffusion constant (K) of the drug depends on physicochemical characteristics such as molecular size, lipid solubility, and degree of ionization. Compounds with a molecular weight of less than 500 Daltons are unimpeded in crossing the placenta, whereas those with molecular weights of 500–1000 Daltons are more restricted.

Most drugs commonly used by the anaesthesiologist have molecular weights that permit easy transfer. If blood flow to the fetal side of the placenta can be measured, as in some animal models, calculating the placental clearance may be a more appropriate way of expressing drug transfer to the fetus (Reynold F and Knott C, 1989). Drugs that are highly lipid soluble cross biologic membranes more readily, and the degree of ionization is important because the nonionized moiety of a drug is more lipophilic than the ionized one.

Local anaesthetics and opioids are weak bases, with a relatively low degree of ionization and considerable lipid solubility. In contrast, muscle relaxants are less lipophilic and more ionized, and their rate of placental transfer is therefore more limited.

The relative concentrations of drug existing in the nonionized and ionized forms can be predicted from the Henderson-Hasselbalch equation:

$$pH = pKa + \log(\text{base})/(\text{cation})$$

The ratio of base to cation becomes particularly important with local anaesthetics because the nonionized form penetrates tissue barriers, whereas the ionized form is pharmacologically active in blocking nerve conduction. The *p*Ka is the *p*H at which the concentrations of free base and cation are equal. For the amide local anaesthetics, the pKa values (7.7–8.1) are sufficiently close to physiologic *p*H that changes in maternal or fetal biochemical status may significantly alter the proportion of ionized and nonionized drug present. At equilibrium, the concentrations of nonionized drug in the fetal and maternal plasma are equal. In the case of the acidotic fetus, a greater tendency for drug to exist in the ionized form, which cannot diffuse back across the placenta into the maternal plasma, causes a larger total amount of drug to accumulate in the fetal plasma and tissues. This is the mechanism for the phenomenon termed ion trapping (Brown *et al.*,1976).

The effects of maternal plasma protein binding on the rate and amount of drug transferred to the fetus are not so well understood. Animal studies have shown that the transfer rate is slower for drugs that are extensively bound to maternal plasma proteins (Hamshaw *et al.*,1984). In sheep, the low fetomaternal ratio of bupivacaine plasma concentrations has been attributed to the difference between fetal and maternal plasma protein binding, rather than to extensive fetal tissue uptake (Kennedy *et al.*,1986).