GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF ANAESTHESIA

MANAGEMENT OF SPINAL ANAESTHESIA-INDUCED HYPOTENSION DURING CAESAREAN SECTION; A COMPARISON OF EPHEDRINE AND NOREPINEPHRINE

BY

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Management of Spinal Anaesthesia-Induced Hypotension During Caesarean Section; A Comparison of Ephedrine and Norepinephrine

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DECLARATION

I, Dr. Patience Adjepong, declare that the content of this dissertation is my work and has not been submitted to any other institution for the award of a degree nor has it been published in any journal.

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DEDICATION

To God, for His goodness.

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LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologists
AV	Atrioventricular
BMI	Body Mass Index
BP	Blood Pressure
CO	Cardiac Output
CS	Caesarean Section
CSE	Combined Spinal Epidural
CSF	Cerebrospinal Fluid
DSMB	Data Safety Management Board
ECG	Electrocardiogram
GA	General Anaesthesia
GDHS	Ghana Demographic and Health Survey
HR	Heart Rate
IV	Intravenous
KATH	Komfo Anokye Teaching Hospital
MAP	Mean Arterial Pressure
OAA	Obstetric Anaesthetists' Association
PDPH	Postdural Puncture Headache
SAP	Systolic Arterial Pressure

SV	Stroke Volume
SVR	Systemic Vascular Resistance
TSA	Trial Sequential Analysis

STRUCTURED ABSTRACT

Introduction

For the majority of caesarean sections, spinal anaesthesia is the preferred anaesthetic technique due to its better safety profile. Hypotension has been the most common adverse effect of spinal anaesthesia for decades. Spinal anaesthesia-induced hypotension if not managed promptly and appropriately could lead to poor maternal and neonatal outcomes. Common vasopressors used in the management of hypotension during spinal anaesthesia include phenylephrine and ephedrine. Currently, norepinephrine is being studied as an alternative to phenylephrine and ephedrine for the management of spinal anaesthesia-induced hypotension. This study sought to compare the effectiveness of intravenous ephedrine and norepinephrine in the aversion of spinal anaesthesia-induced hypotension.

Methods

This was a prospective, randomised, double-blind controlled study. After ethical clearance and informed consent, parturients were randomised into A (Ephedrine group) and B (Norepinephrine group). The Ephedrine group received prophylactic ephedrine 5mg, augmented with rescue boluses of ephedrine 5mg intravenously. The Norepinephrine group received prophylactic norepinephrine 5µg, augmented with rescue boluses of norepinephrine 5µg intravenously. The primary outcome was the incidence of spinal anaesthesia-induced-hypotension in the two groups. Secondary outcomes included, the incidence of maternal reactive hypertension, bradycardia, nausea and vomiting, and first and fifth-minute Apgar scores of the neonate. A systematic sampling method was used to select all participants. The chi-squared test was used to analyse categorical data, which were presented as numbers and percentages. Shapiro's rank test was used to determine whether continuous data were normally distributed. STATA version 17 (College Station, Texas) statistical software was used for all computations. A *p*-value of less than 0.050 with a 95% confidence interval was used as the threshold for statistical significance in all tests.

Results

The study involved 138 participants, 69 in each group. The mean demographics of the participants were age (31.99±5.04) years, parity (2.82±1.49), gestational age (38.56±0.75) weeks, and body mass index (BMI) (26.58±3.52) kg/m². The incidence of spinal anaesthesia-induced hypotension was 62.32% in the ephedrine group and 42.03% in the norepinephrine group (p= 0.017). The incidence of reactive hypertension was 13.04% in the ephedrine and 8.82% in the norepinephrine group (p= 0.429). The incidence of bradycardia was 4.35% in the ephedrine group and 4.35% in the norepinephrine group (p= 0.612). The incidence of nausea and vomiting was 8.70% in the ephedrine and 10.14% in the norepinephrine group (p= 0.710). The Apgar scores of neonates in the first and the fifth minutes were not statistically different between the two groups (p= 0.878 and p= 0.827 for the first and the fifth minutes respectively).

Conclusion

Norepinephrine maintained maternal systolic arterial pressure better than ephedrine during spinal anaesthesia for caesarean section. However, the outcomes for nausea and vomiting, reactive hypertension, and bradycardia, as well as neonatal outcomes obtained for parturients who received either norepinephrine or ephedrine were similar.

Keywords:

CAESAREAN SECTION; SPINAL ANAESTHESIA; SPINAL ANAESTHESIA-INDUCED HYPOTENSION; EPHEDRINE; NOREPINEPHRINE; REACTIVE HYPERTENSION; BRADYCARDIA

CHAPTER ONE

INTRODUCTION

1.1 Background

Worldwide, more than 213 million pregnancies are recorded every year. An estimated 190 million, representing 89%, occur in low and middle-income countries, especially in Africa.[1] In 2012, the number of pregnancies recorded for every 1000 women aged 15 – 44 years averaged about 133 worldwide compared to 224 in Africa.[1] In Ghana, the 2017 Maternal health survey reported a total fertility rate (defined as the number of children per woman of reproductive age) of 3.9.[2]

Caesarean section (CS) is a commonly performed surgical intervention in obstetric practice as a result of several indications including obstetric complications and maternal preference.[3,4] Weiser *et al*[3] reported that worldwide, nearly one (1) out of every fourteen (14) surgical operations performed, and almost a third of surgical operations in most low and middle-income countries are caesarean sections. Kushner *et al*[5] also reported the caesarean section percentage out of the total number of surgical cases for Sierra Leone, Uganda, Niger, and Malawi as 41.5%, 34.2%, 26.0%, and 23.3% respectively. In Ghana, the average caesarean section rate was 16% in 2017.[2] Caesarean section rate differs among the different regions of the country and also among health facilities. The availability of emergency obstetric care at various healthcare facilities and the socioeconomic and educational status of the people in the region may account for this difference.[6]

Caesarean section can be performed using general anaesthesia (GA) or regional anaesthesia.[7] Regional anaesthesia is normally chosen over general anaesthesia because of its association with less maternal and neonatal morbidity and mortality.[7] The most frequent negative effects associated with general anaesthesia are avoided by regional anaesthesia. These complications include pulmonary aspiration, difficult airway management, difficult intubation, and adverse effects of general anaesthetics on the foetus. Regional anaesthesia also possesses the benefit of an awake mother at delivery facilitating early mother and child bonding which is desirous to most women and caregivers.[7,8] Single-shot spinal anaesthesia, epidural anaesthesia, and combined spinal epidural (CSE) anaesthesia are the main types of regional anaesthetic techniques used for caesarean section.[7,8] Some of the advantages spinal anaesthesia has over

epidural anaesthesia (such as its technical ease of placement, rapid onset of action, more reliable surgical anaesthesia, low risk of local anaesthetic systemic toxicity, and minimal failure rate) make it the regional anaesthetic technique of choice for many elective, urgent and some emergency caesarean sections.[8]

Like any other procedure in medicine, spinal anaesthesia also has adverse effects despite these advantages.[9] These include minor complications such as mild hypotension, nausea and vomiting, and backache and major complications such as nerve injury, epidural haematoma, and cardiovascular collapse. The most common side effect of spinal anaesthesia is hypotension.[9] The rapid onset of sympathetic block after induction of spinal anaesthesia leaving less time for compensation causes a greater risk of increased incidence and severity of hypotension than in epidural or general anaesthesia.[8]

The incidence of spinal anaesthesia-induced hypotension varies with the chosen definition and study population. Many definitions have been employed in different studies. A systematic review by Klohr *et al*[10] found fifteen (15) different definitions of spinal anaesthesia-induced hypotension in sixty-three (63) articles. When these definitions were applied to a cohort of patients, the incidence of spinal anaesthesia-induced hypotension was found to range from 7.4% to 74.1%.[10] Zwane et al[11] also reported the prevalence of spinal anaesthesia-induced hypotension during caesarean deliveries to range from 15.8% to 91.4% when fifteen different definitions were used in a study done in South Africa. The commonest definitions used in most studies are a decrease in blood pressure or systolic arterial pressure to 80% or lower of baseline or a combination of a drop in systolic arterial pressure to 100 mmHg and a drop in blood pressure or systolic arterial pressure to 80% or lower of baseline value.[10] The prevalence and degree of severity of spinal anaesthesia-induced hypotension are higher in the obstetric population compared to the non-obstetric population. The increased sensitivity to local anaesthetics, aortocaval compression by the gravid uterus, and the anatomical and physiological changes of pregnancy could account for this.[12]

Several theories have been used to describe the cause of hypotension during spinal anaesthesia. Sympathetic blockade leads to a significant reduction in systemic vascular resistance (SVR) and venodilation has gained much popularity as the possible cause of the decrease in blood pressure after induction of spinal anaesthesia. Other factors such as aortocaval compression and patient positioning may play a role by affecting venous return[13,14] This sudden decrease in blood pressure leads to maternal discomfort with signs and symptoms such as nausea and

vomiting, sensation of dizziness, loss of consciousness, and cardiac arrest as well as foetal complications such as neonatal acidosis and neurobehavioural changes.[15]

Spinal anaesthesia-induced hypotension, if not treated promptly, can lead to adverse maternal and neonatal outcomes.[15] Numerous ways of preventing and treating spinal anaesthesia-induced hypotension have been employed in clinical practice.[15] These include administration of crystalloid or colloid infusions before the conduct of anaesthesia (preloading) or at induction of anaesthesia (co-loading), use of compression stockings, use of lower doses of local anaesthetic, aiming for an appropriate spinal block level, use of left uterine displacement manoeuvres to avoid aortocaval compression and administration of vasopressors.[15] Most of these measures especially when used alone have not yielded many positive results.[16] The use of vasopressors, especially in combination with fluid loading has led to some gains in the control of spinal anaesthesia-induced hypotension.[16] Kuhn *et al*[17] and Hasanin *et al*[18] demonstrated positive outcomes when vasopressors were used to keep maternal blood pressure at or close to the pre-anaesthetic baseline levels. An international consensus statement published in 2018 recommended a combination of preventive strategies to maintain maternal blood pressure at more than or equal to 90% of the baseline pre-anaesthetic value during caesarean section. These strategies include the use of vasopressors both prophylactically and therapeutically in addition to left uterine displacement and intravenous fluid co-loading.[19]

Ephedrine and phenylephrine are the commonest vasopressors used in clinical practice for the management of hypotension during spinal anaesthesia in the obstetric setting. Previous studies of vasopressors used during spinal anaesthesia were in favour of ephedrine as it was thought to preserve uteroplacental blood flow, unlike potent alpha-adrenergic agonists that cause intense vasoconstriction.[20] Cooper *et al*[21] later found that the use of ephedrine especially in larger doses was linked to a higher occurrence of foetal acidosis than a pure alpha agonist, phenylephrine. This was reported as a possible result of ephedrine's highly lipid-soluble nature which leads to a greater placental transfer and stimulation of metabolic processes in the foetus increasing foetal oxygen demand more than its supply.[22] A meta-analysis by Veeser *et al*[23] also concluded in favour of phenylephrine over ephedrine for the management of hypotension as a result of spinal anaesthesia. Other studies have also shown much preference for phenylephrine in terms of positive maternal and foetal outcomes.[23] Despite these advantages, Fitzgerald *et al*[16] and other authors have found phenylephrine to be associated with maternal bradycardia (proposed to be baroreceptor mediated and dose-dependent), and an increase in afterload which could

result in reduced cardiac output. This raises concerns and limits the use of phenylephrine in mothers with hypotension as well as bradycardia and those with cardiac comorbidities.

Norepinephrine is a vasopressor with potent alpha (α) and moderate beta (β) adrenergic agonist activities. It is mostly used in critical care settings for the management of septic shock. Currently, it is being considered as a possible option to phenylephrine and ephedrine for the management of spinal anaesthesia-induced hypotension for good outcomes.[18]

1.2 Problem Statement

It was once thought that reducing aortocaval compression (by utilising left uterine displacement) and raising blood volume (by intravenous fluid loading) to promote venous return, and ultimately cardiac output (CO) would minimize the incidence and severity of maternal hypotension during spinal anaesthesia resulting in improved outcomes.[24] These methods alone have been found to be less effective. However, the addition of vasopressors to the above strategies has led to some success in the management of spinal anaesthesia-induced hypotension.[25] Suboptimal fluid therapy in terms of timing and volume and also the unavailability of phenylephrine and to a lesser extent ephedrine in most less-resourced hospitals in Ghana have made the management of spinal anaesthesia-induced hypertension challenging. Choosing the optimal course of action to guarantee haemodynamic equilibrium under spinal anaesthesia for caesarean section remains one of the major concerns in obstetric anaesthesia. Due to the promising results shown by norepinephrine (which is readily available and familiar to most anaesthetists) in the prevention of spinal anaesthesia-induced hypotension[18], there is a need for further research to be carried out in this area. Despite the significant achievements made in obstetric anaesthesia, prevention of spinal anaesthesia-induced hypotension is a major research area that needs to be addressed especially in sub-Saharan Africa due to the paucity of research in this field.

This study, therefore, seeks to compare ephedrine and norepinephrine in the prevention of spinal anaesthesia-induced hypotension during elective caesarean section in parturients presenting at the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana.

1.3 Rationale of the Study

The average caesarean section rate has been increasing in many countries over time.[4] In Ghana, the caesarean section rate increased from 13% in 2014 to 16% in 2017.[2] Most of these caesarean sections are conducted under spinal anaesthesia.[7] The most common side effect of spinal anaesthesia is hypotension.[15,26] In Ghana, a review of Komfo Anokye Teaching Hospital's 2018 to 2020 records showed that an average of 3015 caesarean sections (2125 emergencies, 890 electives) were done annually, of which an average of 2815, representing 93%, were done under spinal anaesthesia. Also, a review of Komfo Anokye Teaching Hospital's 2020 anaesthetic records showed that more than 70% of the parturients that had these caesarean sections under spinal anaesthesia experienced a decrease in blood pressure from baseline after induction of spinal anaesthesia. Given that spinal anaesthesia-induced hypotension is the most frequent side effect of spinal anaesthesia[15], more extensive research must be directed at its prevention and treatment.

The commonest vasopressors used in the management of spinal anaesthesia-induced hypotension, ephedrine, and phenylephrine, have been linked with some maternal and neonatal adverse effects. Ephedrine although readily available and affordable, is associated with tachycardia, tachyphylaxis, and foetal acidosis.[21] Phenylephrine is also associated with maternal bradycardia.[16] In addition, most anaesthetists are not familiar with the use of phenylephrine probably due to its relative unavailability in most parts of sub-Saharan Africa. Given this, there is the need to search for a readily available and affordable vasopressor within the sub-Saharan African region which has a better obstetric side effect profile. The search for the vasopressor of choice continues unabated.

Norepinephrine which is readily available in sub-Saharan Africa is being studied in other parts of the world as a possible alternative to phenylephrine and ephedrine for the prevention and management of spinal anaesthesia-induced hypotension that would not compromise cardiac function.[27] Most of these studies on norepinephrine were done among Caucasians with limited data from sub-Saharan Africa.

This study assessed the effectiveness of ephedrine and norepinephrine in the management of spinal anaesthesia-induced hypotension.

1.4 Aims of the Study

1.4.1 Main Objective

The main aim of the study was to compare the effectiveness of intravenous ephedrine and norepinephrine in the management of spinal anaesthesia-induced hypotension during elective caesarean section.

1.4.2 Specific Objectives

1. To compare the incidence of maternal spinal anaesthesia-induced hypotension among parturients in the ephedrine group receiving ephedrine and the norepinephrine group receiving norepinephrine.

2. To compare the incidence of nausea and vomiting among parturients in the ephedrine group receiving ephedrine and the norepinephrine group receiving norepinephrine.

3. To compare the incidence of reactive hypertension and bradycardia in parturients in the ephedrine group receiving ephedrine and the norepinephrine group receiving norepinephrine.

4. To compare the outcomes of neonates born to parturients in the ephedrine group receiving ephedrine and the norepinephrine group receiving norepinephrine, using their Apgar scores in the first and fifth minutes after delivery.

1.5 Null Hypothesis

1.5.1 Null Hypothesis

There is no difference in the incidence and severity of spinal anaesthesia-induced hypotension among parturients receiving intravenous ephedrine and norepinephrine during caesarean section.

1.5.2 Alternate Hypothesis

There is a difference in the incidence and severity of spinal anaesthesia-induced hypotension among parturients receiving intravenous ephedrine and norepinephrine during caesarean section.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Prevalence of Caesarean Section

Caesarean section (CS) also known as caesarean delivery, is one of the most common surgical procedures performed worldwide.[4] CS is the delivery of one or more babies through an incision on the mother's abdomen and uterus. Caesarean sections are done as a result of several indications such as previous caesarean sections, malpresentation of foetus, multiple gestation, maternal preference, advanced maternal age, abnormal placentation, prolonged labour, foetal distress, and many more.[4] In certain life-threatening situations, caesarean section is offered to save either the mother's and/ or the baby's lives.[4]

Worldwide, the rate of caesarean section is on the rise. Caesarean section rate is defined as a percentage calculated by dividing the number of caesarean births by the total number of live births in a given year.[4] Betran *et al*[4] after analysing the global and regional caesarean section rate trend of 154 countries (94.5% of world live births) from 2010–2018 confirmed this increasing trend. Worldwide, 21.1% of women give birth by undergoing caesarean section.[4] Although, a greater percentage of caesarean sections are done in emergency settings, the increasing number of elective cases especially as a result of maternal and obstetrician preferences without any medical indication is worrisome.[4] Though caesarean section is a valuable asset in preserving maternal and neonatal health, it also has its short and long-term complications. Hence non-medical use of caesarean section could lead to an increased risk of maternal morbidity and mortality.[4,6]

Despite the increasing trend in caesarean section in both developed and developing countries, there are significant inequalities when it comes to individual access to this important life-saving procedure depending on one's location. While Latin America and the Caribbean have a high average caesarean section rate of 42.8%, sub-Saharan Africa has an average caesarean section rate of 5%.[4] Within sub-Saharan Africa, there are substantial differences in the caesarean section rates of the various countries and also within the countries. Differences in developmental status, healthcare system, socio-economic status, and cultural beliefs of the people of and within these countries could account for these discrepancies.[28]

In Ghana, Okyere *et al*[6] found significant inequalities in the prevalence of births by caesarean section after analysing data from the Ghana Demographic and Health Surveys (GDHS) in 1998, 2003, 2008, and 2014. There was a steep rise in the caesarean section rate from 4.0% in 1998 to 12.8% in 2014. This increase was concentrated in urban areas and this could be a result of the high socioeconomic status and educational levels of the women in such areas.[6]

However, accessibility of emergency obstetric care services, including caesarean sections, when necessary, despite one's location or status is crucial for improved maternal and neonatal outcomes of pregnancy.[6]

2.2 Anaesthesia for Caesarean Section

Caesarean section accounts for a high proportion of surgical operations in settings with limited resources.[3] Caesarean section can be done under both general and regional anaesthesia. A systemic review by Iddrisu and Khan[7]
found that, for caesarean section, regional anaesthesia is preferred to general anaesthesia because of its superior maternal and foetal outcomes. Important determinant factors of the outcome of a caesarean section include the type of anaesthetic and its conduct.[7] The use of regional anaesthesia has several advantages over general anaesthesia, including lesser prevalence of nausea and vomiting, decreased blood loss, an awake mother ensuring early mother and child bonding, reduced postoperative pain, and a shorter hospital stay.[7,8] These in addition to the avoidance of possible airway complications and other negative complications of general anaesthesia make regional anaesthesia preferred over general anaesthesia.

The main types of regional anaesthetic techniques used for caesarean section are spinal anaesthesia, epidural anaesthesia and combined spinal epidural anaesthesia.[7,8] When selecting the anaesthetic technique, the woman's preference is weighed against the benefits and risks involved before the most appropriate technique is chosen with her consent.

Spinal anaesthesia has several advantages which make it the anaesthetic technique of choice for most caesarean sections. These include its ease of placement, rapid onset of action, more reliable surgical anaesthesia, minimal risk of local anaesthetic systemic toxicity, and low failure rate.[8] The definitive endpoint which is the presence of cerebrospinal fluid at the needle hub leads to more successful and reliable blocks compared to epidural anaesthesia.[8]

The extremely small dose of local anaesthetic employed eliminates the danger of toxicity. It has been proposed that extradural venous engorgement from aortocaval compression when the woman assumes the supine position after the intrathecal injection may cause the local anaesthetic to spread to higher levels compared to the non-obstetric population.[12] This increased spread together with the increased sensitivity of the nerves to local anaesthetics in pregnancy results in lesser dose requirements for spinal anaesthesia in the obstetric patient.[12] Hormonal changes during pregnancy have been proposed as the cause for this altered increase in nerve sensitivity to local anaesthetics.[12] The rapid onset spinal anaesthesia becomes advantageous over epidural when urgent delivery is warranted. Also, if not contraindicated, spinal anaesthesia can be employed when citing an epidural becomes difficult.[9]

The combined spinal-epidural anaesthetic technique offers the advantage of a spinal anaesthetic with rapid onset of a dense block, as well as the ability to administer additional anaesthetics through the epidural catheter for prolongation of the block and also for postoperative analgesia. Epidural and combined spinal epidural anaesthesia techniques can be used in patients who cannot withstand the sudden profound hypotension of spinal anaesthesia and also in cases where the total operative time is expected to take longer than allowed for with a typical spinal anaesthetic dose. The risk of profound hypotension is higher with spinal anaesthesia than with epidural anaesthesia because of the rapid onset of sympathectomy of spinal anaesthesia which leaves not enough time for cardiac compensation.[8]

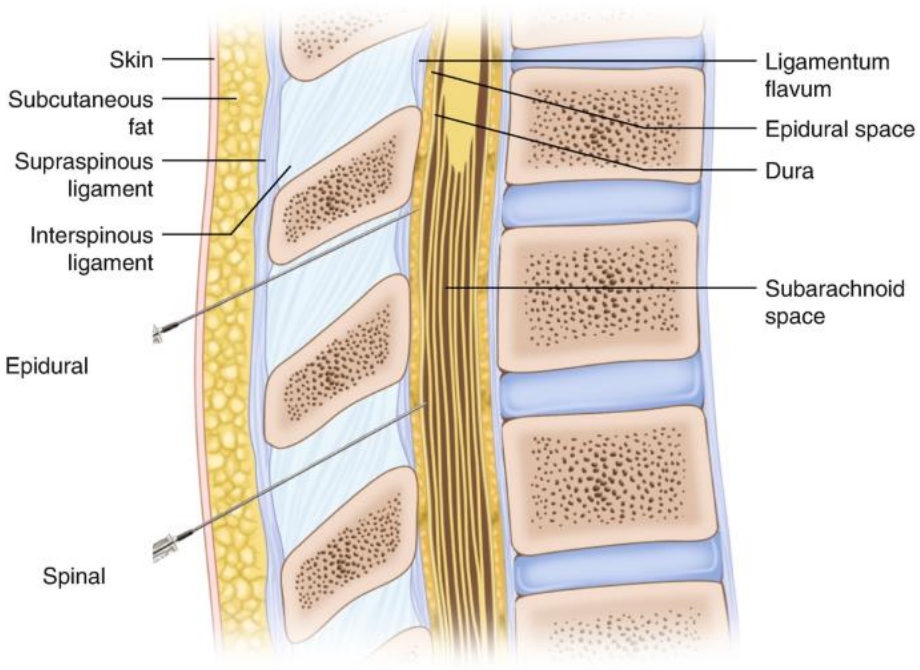

Figure 2.1: Injection points for Spinal and Epidural Anaesthesia

Source: Neuraxial Block: Overview[30]

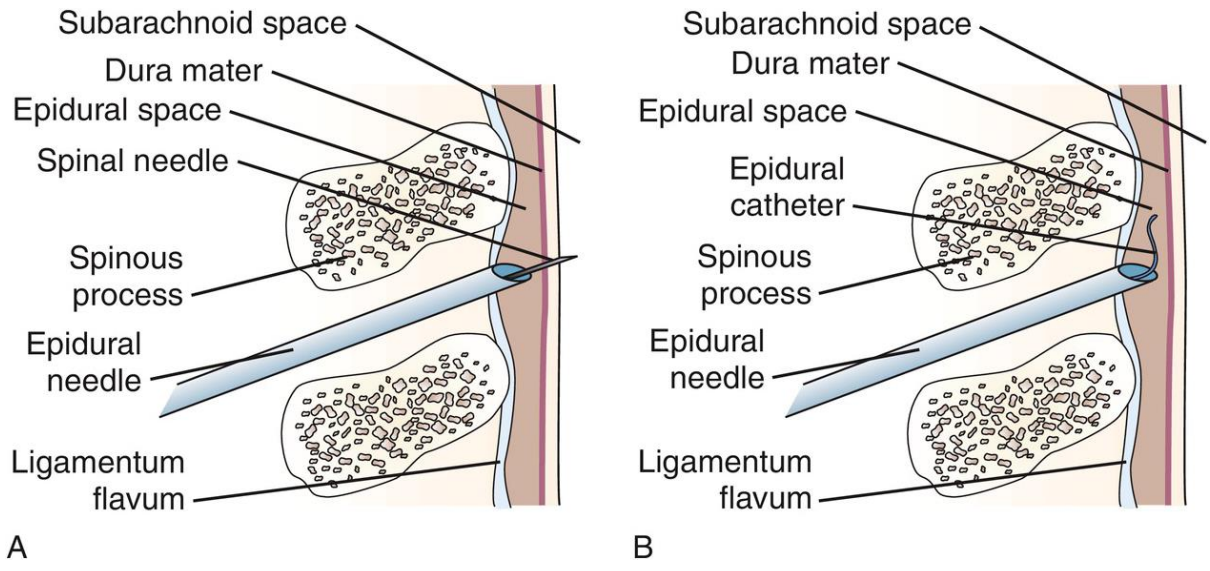

Figure 2.2: Injection points for Spinal and Epidural Anaesthesia (Needle through needle technique)

Source: High-Risk Pregnancy: Management Options[31]

2.3 Spinal Anaesthesia

Spinal anaesthesia is a form of neuraxial regional anaesthesia which involves the injection of a local anaesthetic into the cerebrospinal fluid in the subarachnoid space through a fine specialised spinal needle.[32] Spinal anaesthetic comprises a local anaesthetic, commonly bupivacaine, with or without an opioid. Either isobaric or hyperbaric local anaesthetic preparations can be employed for spinal anaesthesia. Hyperbaric treatments are mostly used since they allow for anatomic and gravitational regulation of the block distribution.[8] To effect the block, the local anaesthetic primarily affects the nerve roots, the dorsal root ganglia, and the superficial parts of the cord resulting in the motor, sensory, and autonomic (sympathetic) blockade. Though the level of sensory blockade can be assessed clinically, the sympathetic block level is unpredictable and could even be several levels above the sensory block.[32]

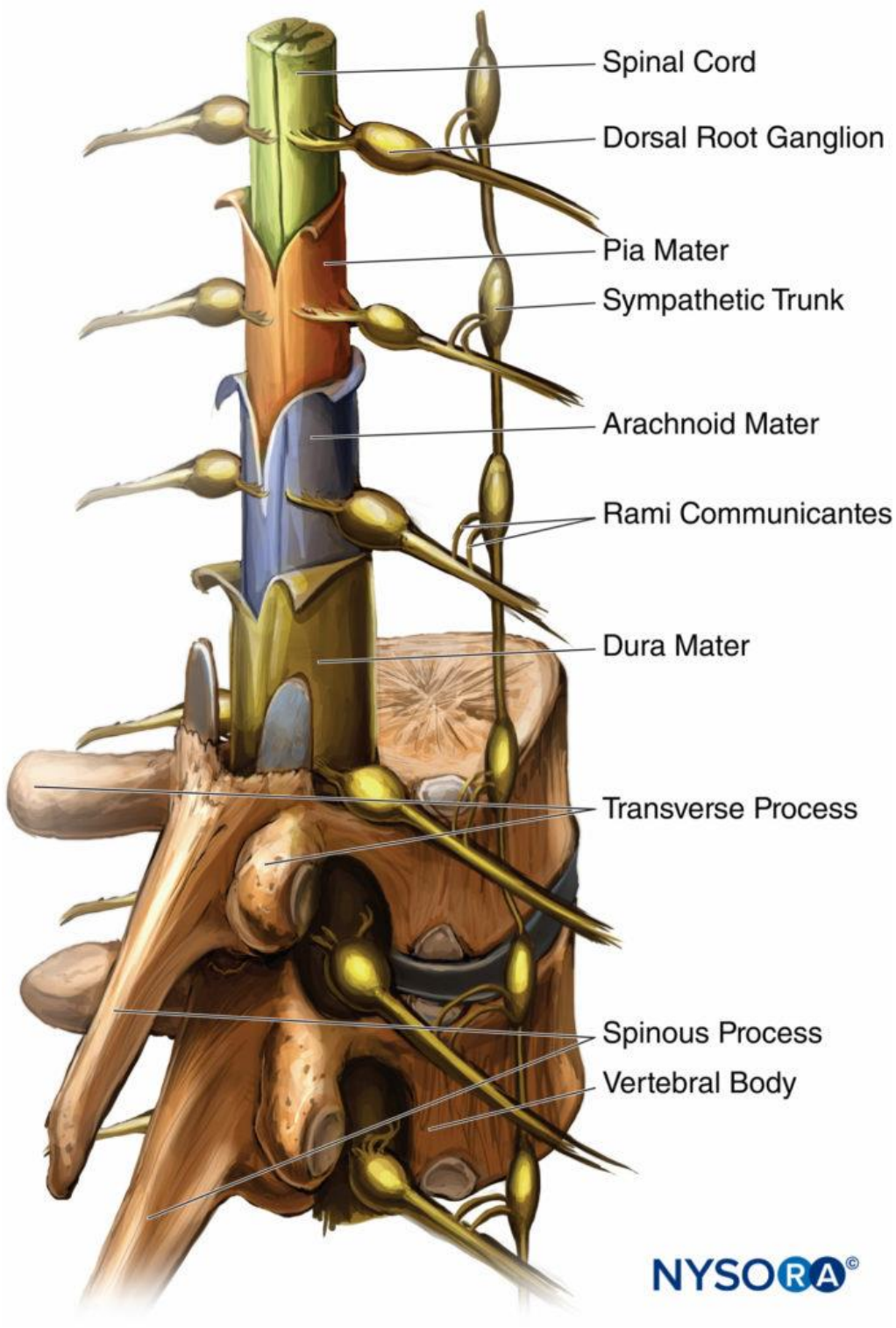

Figure 2. 3: Spinal cord with meningeal layers, dorsal root ganglia, and the sympathetic nerve trunk

Source: www.NYSORA.com[14]

Spinal anaesthesia has been used for centuries. In the 1940s it gained popularity but this was short-lived as there were reported cases of paraplegia after its use. However, in the 1950s there was a resurgence of its use when its safety issues were addressed with safer standardised techniques.[9] The 1950s also saw an increase in the use of spinal anaesthesia in obstetrics and for both labour analgesia during vaginal birth and caesarean sections.[9] This popularity was also short-lived as a result of the preference for epidural anaesthesia in the 1960s. Despite the numerous advantages of spinal anaesthesia such as the resultant quality block despite its simplicity and minimal drugs and side effects involved, its inability to provide continuous anaesthesia or analgesia and increased risk of hypotension gave epidural anaesthesia the advantage.[9] With the development of smaller gauge needles with modern bevels (causing a lesser incidence of post-dural puncture headache) and safer means of administration of spinal anaesthesia, there was a resurgence in the popularity and use of spinal anaesthesia.[9]

Although spinal anaesthesia is the favoured anaesthetic technique for most obstetric surgical procedures in the absence of any contraindication, administering spinal anaesthesia in pregnant patients involves some special considerations. As a result of the anatomical and physiological changes brought about by pregnancy, special considerations are necessary during anaesthesia for the pregnant woman to improve outcomes. Previously, spinal anaesthesia was associated with a higher morbidity and mortality rate than general anaesthesia when administered to pregnant patients.[33] This probably was due to factors such as the administration of spinal anaesthesia by inexperienced people who lacked the necessary training in the care of patients under spinal anaesthesia.[33] Lack of adequate monitoring and resuscitation equipment and inappropriate dosing of local anaesthetic in the obstetric population could have also contributed to this high morbidity and mortality rate. Recent data on maternal mortality in pregnant patients do not support this claim. Studies from the Confidential Inquiries into Maternal Mortality in the United Kingdom and reports from the United States have shown that maternal mortality has dramatically decreased in patients undergoing neuraxial anaesthesia as opposed to general anaesthesia.[34,35]

Spinal anaesthesia has also been associated with a high incidence of foetal acidosis than general and epidural anaesthesia probably as a result of the high occurrence of hypotension reducing uteroplacental blood flow to the foetus and high doses of ephedrine administered in this group as attributed by the authors.[36]

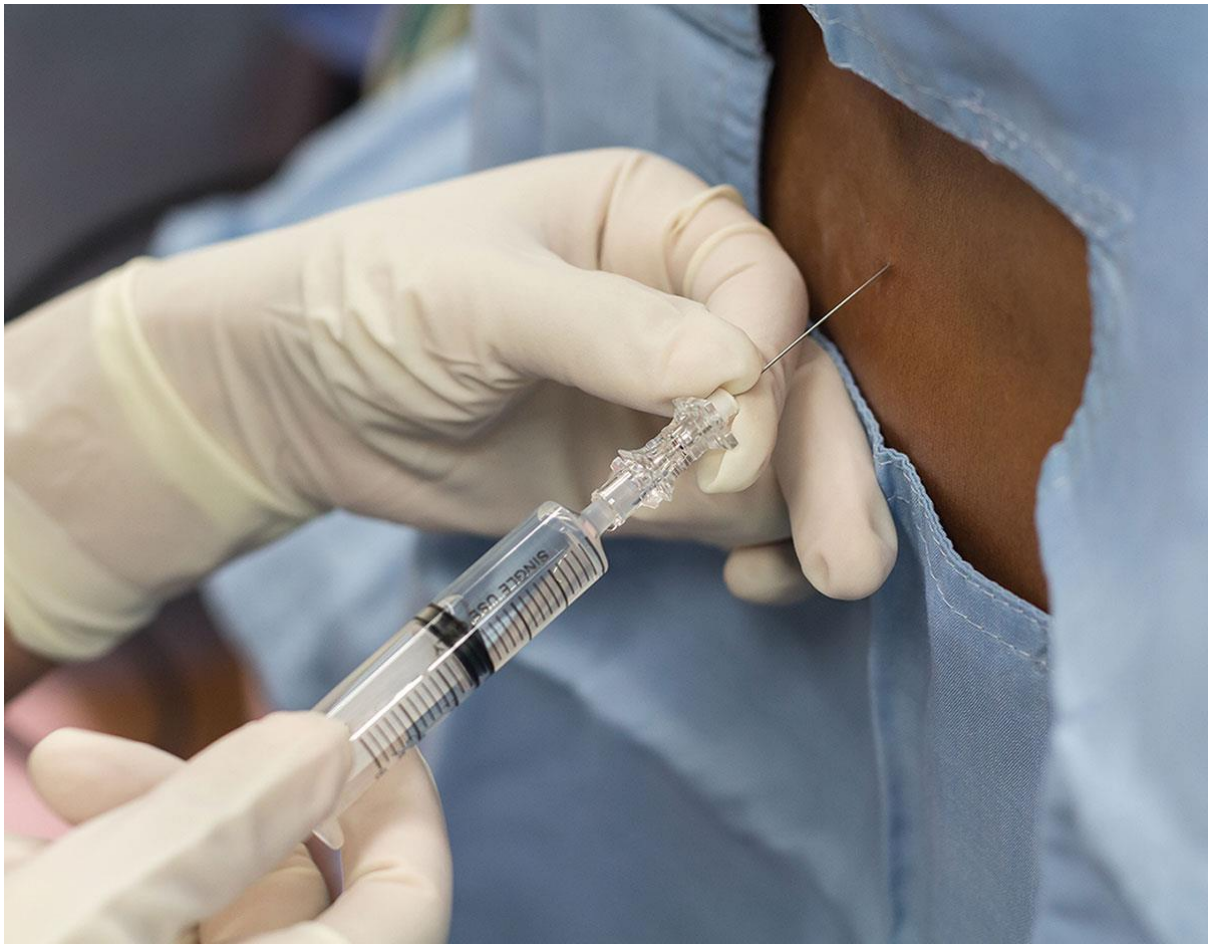

Figure 2. 4: Performing Spinal Anaesthesia for Caesarean Section

Source: Anesthesia Patient Safety Foundation[37]

2.3.1 Complications of Spinal Anaesthesia

Despite the advantages of spinal anaesthesia, it is not without complications. Spinal anaesthesia is associated with a range of complications, some of which can be serious and potentially life-threatening. Complications of spinal anaesthesia can be broadly divided into minor and major complications. Minor complications of spinal anaesthesia include mild hypotension, nausea and vomiting, shivering, pruritus, and urinary retention.

Major complications include direct needle trauma to the spinal cord or nerve roots, infections, cauda equina syndrome, and total spinal. Major complications though severe are rare.[14,38] Complications of spinal anaesthesia can also be grouped under the various body systems such as neurological, cardiovascular, and respiratory.

Neurological complications can be classified as transient or permanent complication. Transient neurological complications include paresthesias, backache, post-dural puncture headache (PDPH), direct trauma to the spinal cord or spinal nerve roots, aseptic and septic meningitis, and transient neurological deficit.[9,39] Paresthesias are abnormal sensations such as tingling, numbness, or pins and needles, and are usually self-limiting and resolve spontaneously within a few days. Backache and post-dural puncture headaches are common complications of spinal anaesthesia. Postdural puncture headache is thought to be due to leakage of cerebrospinal fluid (CSF) from the dural puncture site leading to traction on intracranial pain-sensitive structures. It is a dull throbbing pain with a front-occipital distribution that may radiate to the neck and shoulders. PDPH is aggravated in the sitting or upright position but improved in the supine position. There may be the presence of other symptoms such as neck stiffness, tinnitus, photophobia, and nausea.[9]

Permanent neurological complications, although rare, include nerve injury, spinal cord injury, and cauda equina syndrome. Nerve injury can result from direct trauma to the nerve or ischaemia due to vascular injury. Spinal cord injury can occur due to spinal cord ischaemia due to vascular injury or from direct mechanical trauma. Cauda equina syndrome is a rare but serious complication that can result from damage to nerve roots below the level of the spinal cord. Risk factors for permanent neurological complications include extremes of age, female sex, obesity, and the use of hyperbaric local anesthetics.[9,39]

Cardiovascular complications associated with spinal anaesthesia include hypotension, bradycardia, arrhythmias, cardiovascular collapse, and cardiac arrest.[9] Hypotension is the most common cardiovascular complication of spinal anaesthesia. It is caused by sympathetic blockade decreasing systemic vascular resistance and affecting preload, cardiac contractility, and afterload. Arterial vasodilation leads to a decrease in systemic vascular resistance. Sympathetic block-mediated venodilation and aortocaval compression, when put in the supine position, reduce venous return leading to a reduction in preload.[9,40] Considering the above aetiology, optimising intravascular volume status, avoidance of aortocaval compression, and counteracting vasodilation with the use of vasopressors can help manage hypotension during

spinal anaesthesia for CS.[19] Severe bradycardia and arrhythmias are less common but can occur especially in patients with pre-existing cardiovascular disease. Bradycardia could be a result of high block affecting the cardiac accelerator fibres originating from T1-T4 spinal segments, the reverse Bainbridge reflex due to decreased venous return, or less commonly Bezold-Jarisch reflex (BJR) which occurs mostly in cases of severe haemorrhage. Bradycardia could also be drug-induced such as from beta-blockers or phenylephrine.[9,14] Bradycardia can be managed pharmacologically or by treating the cause.[9] Although severe bradycardia is rare, it can be life-threatening, preceding cardiac arrest hence the need for prompt treatment whenever it occurs.[9]

Respiratory complications associated with spinal anaesthesia include respiratory depression. Respiratory depression can result from the use of opioids as part of the spinal anaesthetic or from a high sensory block that affects the intercostal muscles.[9,26] Respiratory depression can be managed by administering an opioid antagonist (naloxone) if caused by an opioid or by providing respiratory support if necessary.

Other complications of spinal anaesthesia include nausea and vomiting, shivering, failed spinal blockade, urinary retention, high or total spinal anaesthesia, infection, epidural haematoma, epidural abscess, and death.[26]

To reduce the risk of complications, it is important to identify and manage risk factors, as well as to be aware of the signs and symptoms of these complications. Risk factors for complications of spinal anaesthesia include patient-related factors such as age, sex, body mass index, multiple medical conditions, and medication use, as well as procedural elements like the quantity and kind of the local anaesthetic used, the site and technique of injection, and the use of adjuncts such as opioids or sedatives.[41] To reduce the risk of complications, it is important to carefully select patients for spinal anaesthesia based on their risk profile and to carefully monitor patients during the procedure.

Despite these potential risks and complications, spinal anaesthesia remains a valuable tool for many surgical procedures. With the advancement in anaesthetic care and equipment, the overall incidence of major complications is relatively low.[9]

2.4 Spinal Anaesthesia-Induced Hypotension

Although it has many benefits, such as rapid onset, excellent analgesia, and minimal respiratory depression, spinal anaesthesia is associated with some adverse effects, the most common of which is hypotension which can lead to significant morbidity and mortality. Risk factors for spinal anaesthesia-induced hypotension include age, height, weight, body mass index, baseline blood pressure, preoperative hydration status, the level of sympathetic blockade, and baricity and dosage of the local anaesthetic solution.[33]

2.4.1 Pathophysiology of Spinal Anaesthesia-Induced Hypotension

Spinal anaesthesia causes a pre-ganglionic sympathetic nervous system blockade before the synapse on the sympathetic chain ganglion.[42] The extent and strength of the sympathetic blockade are linked to the degree of cephalad distribution of the local anaesthetic inside the cerebrospinal fluid in the subarachnoid space. The sympathetic block level is challenging to forecast and can often reach numerous dermatomes beyond the sensory block level.[12] The sympathetic block affects nerve fibres regulating vascular tone which arise from T5–L1 spinal segments. This blockade causes arterial vasodilation which results in decreased systemic vascular resistance. Decreased venous tone leads to the pooling of blood in the peripheries causing reduced venous return to the heart which can also be worsened by aortocaval compression.[14,42] To buttress this, Reiz[40] reported that systemic vasodilatation, decreased cardiac performance, and vagal overactivity due to sympathetic blockade are the main causes of spinal anaesthesia-induced hypotension.

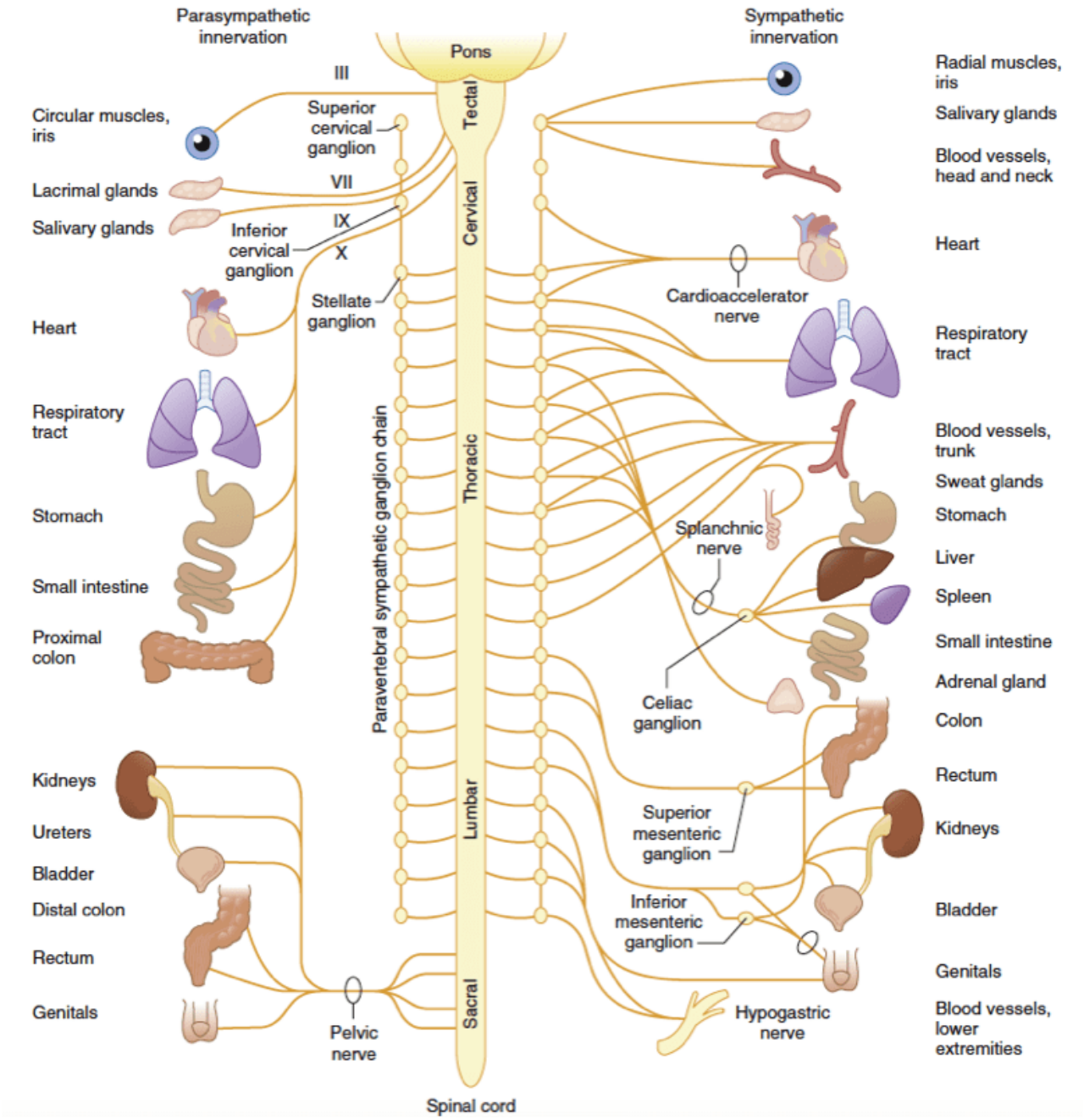

Figure 2. 5: Schematic Representation of the Autonomic Nervous System

Source: www.NYSORA.com[43]

Earlier studies reported that a reduction in cardiac output as a result of the pooling of large volumes of blood to the lower extremities after spinal blockade causing a decrease in venous return was the main cause of spinal anaesthesia-induced hypotension.[44] Therefore, the treatment of spinal anaesthesia-induced hypotension was targeted at mechanisms that improve venous return such as fluid loading, raising or mechanical compression of the lower limbs, leg wrapping, and avoidance of aortocaval compression with left uterine displacement. These strategies were found not to be so effective alone hence the notion that a decrease in cardiac output was the major cause of spinal anaesthesia-induced hypotension was challenged.[45,46]

Some studies that used minimally invasive haemodynamic monitoring in healthy patients undergoing caesarean section under spinal anaesthesia found that the reduction in systemic vascular resistance coupled with a decrease in preload may cause a compensatory baroreceptor-mediated increase in heart rate (HR) to sustain cardiac output.[13,42,47] In the instance of a higher thoracic sympathectomy blocking the cardiac accelerator fibres which originate from the T1-T4 spinal segment, this compensatory mechanism is abolished, leading to bradycardia and severe hypotension. It has been proposed that high blocks can also increase the risk of cardioinhibitory reflexes such as the Bezold-Jarisch reflex. The Bezold-Jarisch reflex is characterized by the triad of bradycardia, hypotension, and peripheral vasodilation. Its activation increases parasympathetic activity via vagal afferents and decreases sympathetic outflow.[15] Bezold-Jarisch reflex can cause severe bradycardia, profound hypotension, and cardiovascular collapse.[15] Additionally, it has been postulated that when venous return is decreased under spinal anaesthesia, especially in situations of severe blood loss leading to inadequate preload, a reverse Bainbridge reflex could come into play resulting in a drop in heart rate.[42] Reverse Bainbridge reflex as opposed to Bainbridge reflex causes a reflex-induced reduction in heart rate when venous return decreases. The reduction in heart rate is to give more time for diastolic filling of the heart.[42]

A study by Hofhuizen *et al*[48], involving 64 elderly patients, found that there was a pronounced decrease in cardiac output and blood pressure after the onset of spinal anaesthesia. The researchers avoided fluid preloading in these elderly patients. On average, there was no significant change in systemic vascular resistance but there was a decrease in stroke volume of more than 15% from baseline value in more than 50% of the participants. This reduction in stroke volume (SV) was also not made up for by a boost in heart rate to sustain cardiac output. They therefore concluded that the hypotension that occurred was a result of a decrease in stroke

volume and not systemic vascular resistance as documented by many studies recently.[48] Their findings could have been influenced by their choice of study population (elderly patients) as the elderly may sometimes have blunted sympathetic compensatory mechanisms and are at increased risk of cardiovascular comorbidities. Also, the absence of fluid loading could have worsened their intravascular volume status leading to a significant decrease in preload and subsequently stroke volume.[48] The small sample size used could also have affected the outcome of the study.

In pregnancy, aortocaval compression aggravates spinal anaesthesia-induced hypotension. Aortocaval compression causes a reduction in venous return and subsequently cardiac output.[44] The gravid uterus presses the inferior vena cava against the lumbar vertebral bodies obstructing venous return, reducing cardiac output, and leading to hypotension. In the normal healthy pregnant woman, this reduction in blood pressure is compensated for to some extent by a reflex increase in neurogenic vasoconstrictor tone leading to increased vascular resistance and increased venous return. This compensatory mechanism helps minimise the degree of hypotension.[9] With spinal anaesthesia, this compensatory mechanism is impaired.

Although the frequency and intensity of spinal anaesthesia-induced hypotension are higher in obstetric patients compared to non-obstetric patients, certain groups within the obstetric population such as those in labour and those with severe pre-eclampsia have been found to have reduced incidence and severity of hypotension during spinal anaesthesia. The high vascular resistance in and enhanced sensitivity of blood vessels to vasopressors in pregnant women with pre-eclampsia probably makes them less susceptible to the decrease in systemic vascular resistance as a result of spinal anaesthesia and also a possible decrease in vasopressor requirement.[49] Also, the increased sympathetic tone during labour could account for the reduced incidence and severity of hypotension during spinal anaesthesia.

2.4.2 Prevention of Spinal Anaesthesia-Induced Hypotension

Hypotension is a well-recognised spinal anaesthesia complication, and many studies have investigated various strategies to prevent and manage it.[19] The control of spinal anaesthesia-induced hypotension is a crucial consideration for the anaesthesiologist as it helps improve patient outcomes and reduce the risk of complications.[19,24] It is therefore important for

anaesthesiologists to consider strategies for preventing hypotension when managing patients undergoing spinal anaesthesia to ensure their safety and well-being. The prevention and treatment of spinal anaesthesia-induced hypotension depend on several factors, including the patient's risk factors and the degree of hypotension. Several interventions have been proposed to prevent spinal anaesthesia-induced hypotension. These interventions include preloading or co-loading with intravenous fluids, administration of vasopressors, and use of prophylactic lower limb compression devices.[19] The prophylactic use of lower limb compression devices has been proposed to help lower the rate of occurrence and severity of spinal anaesthesia-induced hypotension by increasing venous return and cardiac output.[24]

One significant preventative measure is the avoidance of aortocaval compression by lateral displacement of the gravid uterus.[45] This important measure was introduced after aortocaval compression was recognised as a potent cause of reduced venous return and hypotension. Recent invasive studies have confirmed the decrease in cardiac output associated with the supine position of the pregnant woman causing aortocaval compression, hence the recommended mandatory use of lateral tilt in obstetric patients from twenty (20) weeks gestation.[45] Intraoperatively, aortocaval compression can be prevented by placing a wedge under the right hip, tilting the table, or manually displacing the uterus to the left side. The recommended angle of tilt is 15 degrees [45]

Intravenous fluid loading in combination with other measures such as left lateral tilt and vasopressors has been shown to help decrease the occurrence of spinal anaesthesia-induced hypotension by increasing the intravascular volume, venous return, and ultimately cardiac output and SVR.[19]

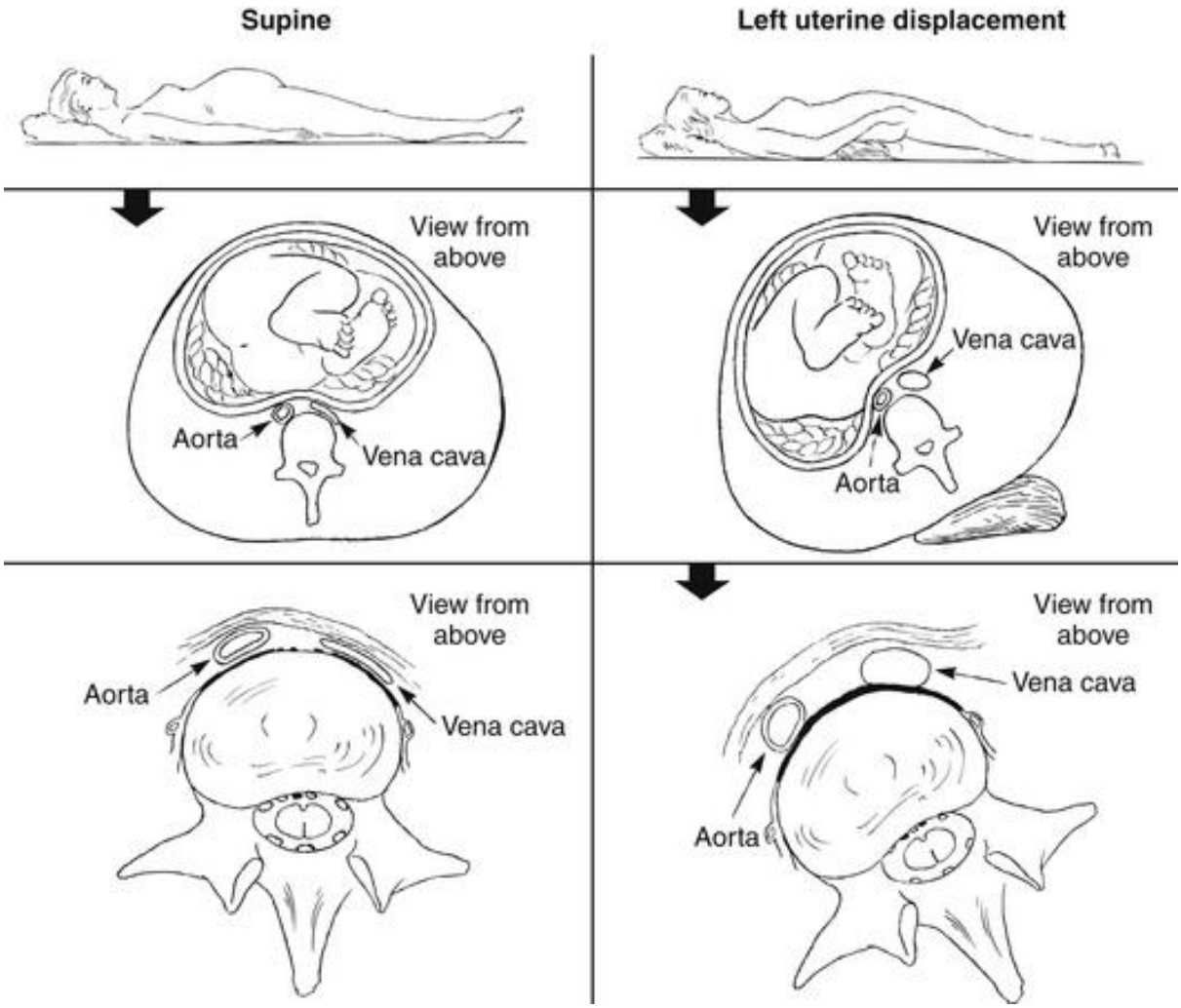

Figure 2. 6: Effects of left uterine displacement on the diameter of the abdominal aorta and the inferior vena cava

Source: Anesthesia Key- Obstetric Anesthesia[50]

One important consideration in managing spinal anaesthesia-induced hypotension is the use of vasopressors.[16] Several studies have evaluated the use of different vasopressors to prevent and treat hypotension during spinal anaesthesia. The use of vasopressors with alpha agonist activity, such as phenylephrine, ephedrine, and norepinephrine, has already been shown to decrease the occurrence of spinal anaesthesia-induced hypotension by increasing systemic vascular resistance, hence maintaining blood pressure. The addition of some beta-agonist activity could be a plus in maintaining cardiac output and avoiding bradycardia.[19]

The timing of vasopressor administration is also crucial. Some studies have shown that prophylactic administration of vasopressors before the onset of hypotension is more effective than their therapeutic administration after the onset of hypotension.[19] Prophylactic administration of phenylephrine infusion has been shown in a meta-analysis to be effective in reducing the frequency of hypotension, and vasopressor requirement during spinal anaesthesia for caesarean section.[51] Others also argue that prophylactic administration of vasopressors should be individualised based on the patient's risk factors for hypotension as some individuals such as those with preeclampsia and those in labour may have a decreased incidence and severity of spinal anaesthesia-induced hypotension.[49]

2.4.3 Management of Spinal Anaesthesia-Induced Hypotension

A multimodal approach is required for the effective management of spinal anaesthesia-induced hypotension. The use of a single strategy is not as effective as a combination of strategies. An international consensus statement on the management of hypotension during caesarean section under spinal anaesthesia, recommends the use of left lateral uterine displacement, intravenous fluid-loading in addition to vasopressors, preferably prophylactic vasopressor administration, to sustain systolic arterial pressure at more than or equal to (≥) 90% of baseline pre-anaesthetic value, avoiding drops more than 20% of the baseline value.[19] Although the consensus statement recommends alpha-adrenergic agonist drugs as the most appropriate agents to prevent or treat hypotension following spinal anaesthesia, vasopressors with some beta-agonist activity like norepinephrine may be better options.[19] The additional beta-agonist activity will enhance the ionotropy and chronotropy of the heart to sustain cardiac output.[52,53]

The recommended 15° angle of table tilt used for the left lateral uterine displacement results in increased cardiac output and maternal systolic arterial pressure with a concomitant decrease in vasopressor requirement. Another recommendation is the use of maternal heart rate as a good surrogate for cardiac output and a guide for patient management.[19] Although prophylactic vasopressor use is deemed beneficial, it should be used with caution in pregnant women with severe pre-eclampsia as they develop less hypotension after spinal anaesthesia than healthy women. For women with cardiac disease, the choice of vasopressor and its administration should be done on an individual basis with caution after careful assessment of the patient.[19]

During spinal anaesthesia for a caesarean section, it is crucial to maintain a normal maternal heart rate to ensure haemodynamic stability. Dyer *et al*[47] in their study which compared time-based impacts of bolus administration of phenylephrine and ephedrine on maternal cardiac activity under spinal anaesthesia for elective caesarean delivery, found a good correlation between changes in cardiac output and changes in heart rate. They, thus, emphasised the significance of using heart rate as a substitute measure of cardiac output during spinal anaesthesia for caesarean section, where cardiac output is not measured.[47] Hence maintaining a normal maternal heart rate possibly signifies maintenance of cardiac output.

One of the primary management strategies for spinal anaesthesia-induced hypotension is fluid therapy. The administration of intravenous fluids before and during spinal anaesthesia has been shown to reduce the incidence and severity of hypotension in patients undergoing spinal anaesthesia.[19] Fluid loading is used to compensate for the reduction in preload caused by the venodilation as a result of the sympathetic block of spinal anaesthesia. This helps increase cardiac output and maintain maternal haemodynamic stability.[54] To prove this Ngan Kee *et al*[55], found an increased incidence of hypotension in patients who received vasopressor (phenylephrine) and maintenance intravenous fluid only compared to those who received vasopressor (phenylephrine) in addition to fluid loading during induction of spinal anaesthesia for caesarean section. Parturients who received fluids in addition to the phenylephrine infusion had better haemodynamic control with less vasopressor requirement. The incidence of maternal nausea and vomiting was also low in those who received fluid loading compared to those who did not [55]

A multi-centre trial demonstrated that mixed colloid-ringers lactate-based fluid preload reduces maternal hypotension compared with a pure-based Ringer's lactate. In this study, a total of 167 patients from twelve (12) different study sites were randomised into two groups. One group made up of 82 participants were given 500 ml of six per cent HES (130/0.4) (a third-generation hydroxyethyl starch) followed by 500 ml of Ringer's lactate while the other group (RL group), made up of 85 participants received a two 500 mL of Ringer's lactate solution. These solutions were administered intravenously before the induction of spinal anaesthesia. Prophylactic boluses of phenylephrine (50 to 150mcg) were given intravenously as soon as systolic arterial pressure recording dropped 5% or more guided by a protocol. 30 patients (36.6%) in the HES group experienced hypotension (defined as systolic arterial pressure recording below 80% of baseline) in contrast to 47 patients representing 55.3% in the RL group.[56] Colloid pre-load was

thus found to be superior to crystalloid pre-load for preventing reductions in blood pressure. Although the better safety profile of crystalloids makes it preferable to colloids, the third-generation hydroxyethyl starch used in this study has a better safety profile than the older generations hence the comparable outcomes in terms of adverse effects such as renal and coagulation impairments observed in the two groups.[56]

A study by Dyer *et al*[57] concluded that crystalloid co-loading is better at preventing hypotension than crystalloid preloading. They demonstrated that administration of 20ml/kg of crystalloid solution as rapidly as possible during induction of spinal anaesthesia led to a significant decrease in the occurrence of hypotension and vasopressor requirement compared to a similar volume administered before the induction of spinal anaesthesia. The twenty-minute period before induction of spinal anaesthesia over which the fluid preloading was done could have been too long allowing for more extravascular crystalloid fluid redistribution than with the co-loading, possibly affecting the outcome.

However, unlike crystalloids, colloid preloading and co-loading have been demonstrated to have a similar effect in the regulation of hypotension under spinal anaesthesia.[58] To maintain systolic blood pressure at or above 90% of baseline while using intravenous vasopressor boluses (ephedrine 5 mg/mL + phenylephrine 25 mcg/mL), 500 mL of 6% hetastarch (the colloid frequently used in the obstetric population due to its better safety profile) was administered intravenously, either gradually ahead of spinal anaesthesia (pre-loading) or as promptly as feasible with the spinal anaesthesia (co-loading). There was no significant difference in the incidence of hypotension and vasopressor requirement among the study groups [58]

Rijs *et al*[59] conducted an extensive meta-analysis, trial sequential analysis (TSA), and meta-regression of fluid loading therapy to prevent spinal hypotension in women undergoing elective caesarean section using a total of 49 studies (involving 4317 patients). They revealed that though the occurrence of hypotension when crystalloid is administered before the induction of anaesthesia was higher than when colloid was used, the trial sequential analysis showed that the data was not adequate for a definite conclusion that colloid preload is more effective than crystalloid preload in preventing hypotension. Additionally, they discovered that although classical meta-analysis suggested that crystalloid coload was superior to crystalloid preload at preventing hypotension, the trial sequential analysis again did not support this finding. Their argument for using network meta-analysis and trial sequential analysis was that

network meta-analysis allowed for conclusions from both direct and indirect comparisons between interventions and trial sequential analysis provided more definite and reliable conclusions. They also stated that findings of meta-analyses that do not incorporate trial sequential analysis are often premature due to a lack of sufficient data.[59]

Other non-pharmacological strategies, such as left uterine displacement at a recommended angle of 15° once the woman is placed supine to reduce inferior vena cava compression and lower extremity compression by compression devices and compression stockings used to prevent venous pooling in the legs help in the management of hypotension.[24]

2.4.4 Pharmacology of Vasopressors

Potent pharmacological agents that increase mean arterial pressure by causing vasoconstriction are called vasopressors. The marked vasoconstriction caused by vasopressors leads to an increase in systemic vascular resistance leading to blood pressure increase. Some vasopressors also possess positive chronotropic and ionotropic effects and hence can cause increases in heart rate and contractility as well. Vasopressors are mostly used in the management of the critically ill and the perioperative setting for the prevention and treatment of hypotension.[52,53]

Vasopressors commonly act on adrenoceptors to cause their effects. They act on three main receptors. These are alpha-adrenergic, beta-adrenergic, and dopaminergic receptors. Non-adrenergic vasopressors act on other receptors. For example, stimulation of vasopressin receptors on vascular smooth muscle cells by vasopressin causes marked peripheral vasoconstriction to increase blood pressure. Vasopressors act on specific receptors to cause their effect. Vasopressors can cause their effect by direct stimulation of the receptors or by indirect release of norepinephrine to cause their effect. Activation of alpha-1 adrenergic receptors, found on vascular walls causes vasoconstriction. Activation of beta-1 adrenergic receptors commonly found in the heart leads to increases in heart rate and contractility. The action of vasopressors mostly affects the cardiovascular system but other systems of the body could also be affected.[52,53]

Table 2. 1: Locations and Responses of Select Receptors

Receptor	Primary Location	Stimulation Response
Alpha$_1$	vascular smooth muscle	Vasoconstriction
Beta$_1$	Heart	positive inotropy and chronotropy
Beta$_2$	vascular and bronchial smooth muscle	vasodilation, bronchodilation
Dopamine$_1$	renovascular smooth muscle	renal vasodilation
Vasopressin$_1$	vascular smooth muscle	Vasoconstriction
Angiotensin II	vascular smooth muscle	Vasoconstriction

Source: Elsevier. health[60]

Table 2.1 shows the location of the various adrenoceptors and non-adrenoceptors and their resultant effect.

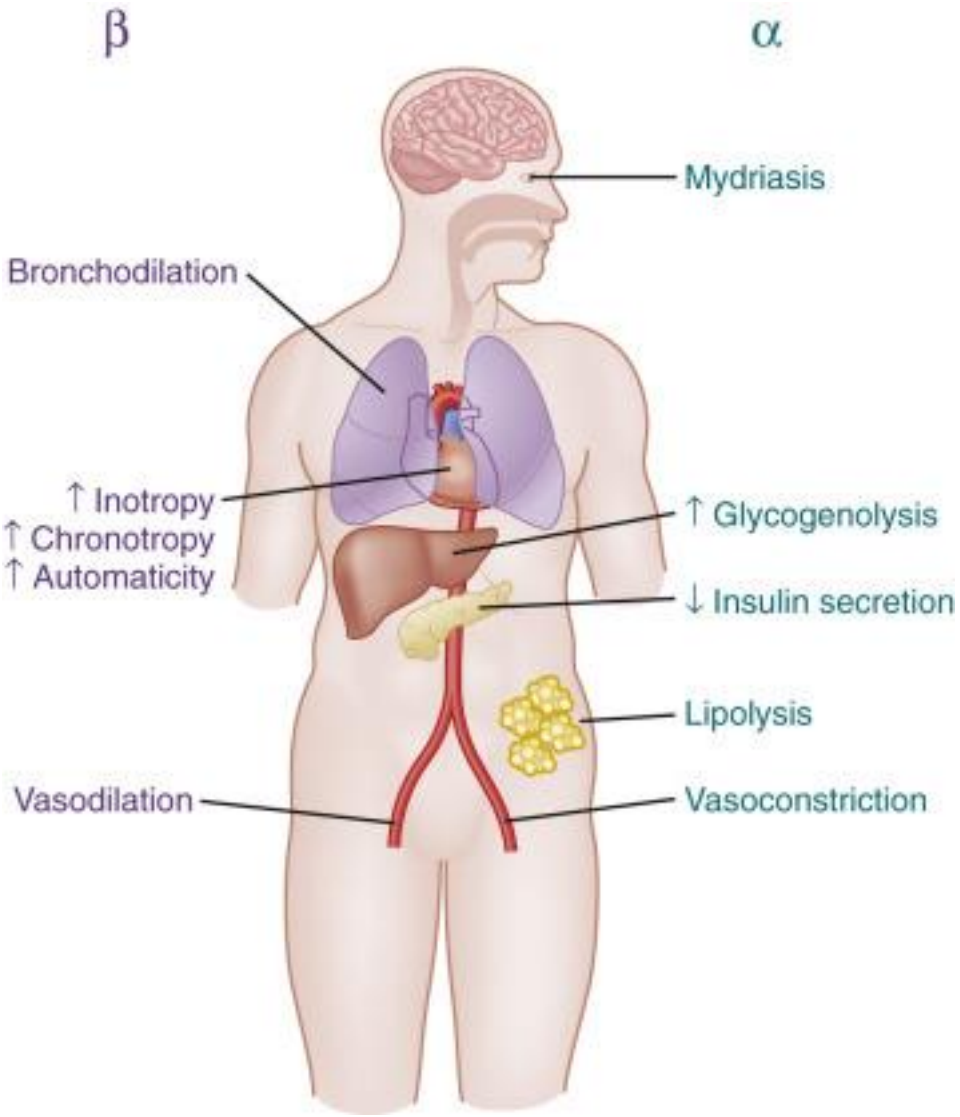

Figure 2. 7: Effects of Vasopressors and Inotropes on the Body

Source: Pharmacology and Physiology for Anesthesia (Second Edition)[61]

Vasopressors used during spinal anaesthesia for caesarean section include ephedrine, phenylephrine, norepinephrine, and epinephrine (adrenaline). Norepinephrine is an endogenous catecholamine released by postganglionic adrenergic nerves. It possesses potent alpha-1 adrenergic agonist activity with modest beta-1 adrenergic agonist activity. Norepinephrine, therefore, causes marked vasoconstriction with moderate increases in cardiac contractility and rate. Ephedrine acts as both a direct and indirect sympathomimetic. It acts on beta-1, beta-2, and alpha-1 adrenergic receptors. Epinephrine is a non-selective alpha and beta agonist. Epinephrine possesses more beta activity at low doses but has more alpha activity at high doses. Phenylephrine is a pure alpha-1 agonist. It is a synthetic alpha-adrenergic agonist. Phenylephrine causes marked vasoconstriction with almost no increase in heart rate or contractility.[52,53]

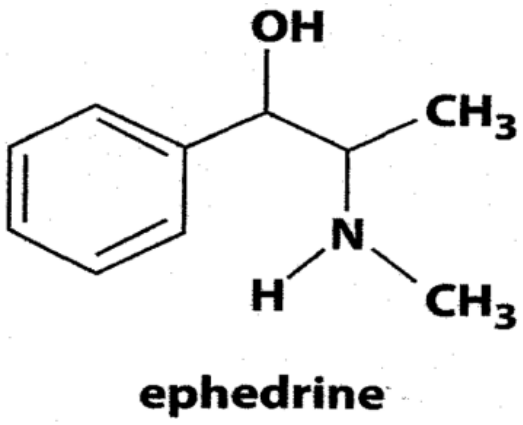

Figure 2. 8: Chemical Structure of Ephedrine

Source: A Review of the Human Clinical Studies Involving Citrus aurantium (Bitter Orange) Extract and its Primary Protoalkaloid p-Synephrine[62]

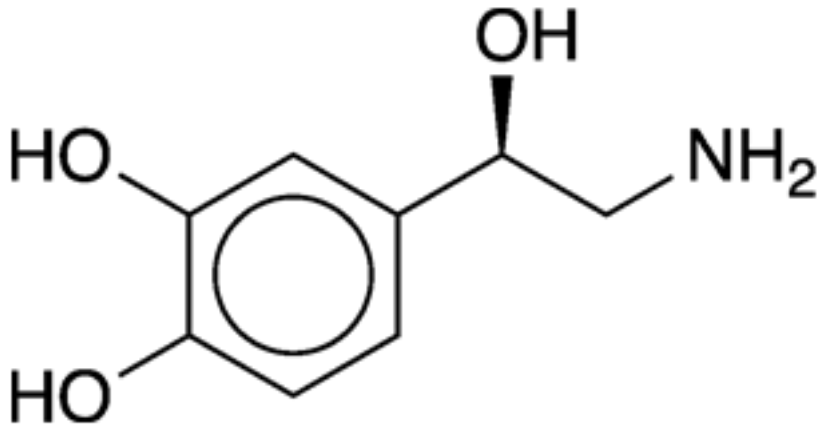

Figure 2. 9: Chemical Structure of Norepinephrine

Source: American Chemical Society[63]

Table 2. 2: Receptor Pharmacology of Vasopressors

Drug	Dose* (mcg/kg/minute)	Receptors				
		Alpha$_1$	**Beta$_1$**	**Beta$_2$**	**Dopamine**	**Vasopressin**
Angiotensin II		-	-	-	-	-
	0.5 to 5	-	+	-	++++	-
	5 to 10	+	++	-	+++	-
Dopamine	**10 to 20**	+++	++	-	+	-
	0.01 to 0.1	+	+++	++	-	-
Epinephrine	**0.1 to 0.2**	+++	++	++	-	-
Norepinephrine		++++	++	-	-	-
Ephedrine		+	++	++	-	-
Phenylephrine		+++	-	-	-	-
Vasopressin		-	-	-	-	+++

*Dose listed for dose-related receptor activity only

Source: Elsevier.Health[60]

2.4.5 Vasopressors in the Management of Spinal Anaesthesia-Induced Hypotension

Fitzgerald *et al*[16] in a comprehensive review of strategies for preventing hypotension in women undergoing spinal anaesthesia for caesarean sections concluded that vasopressors were less frequently associated with maternal hypotension, nausea, and vomiting than the other therapies. Their review included randomised controlled trials that contrasted a preventative intervention for hypotension with a different intervention or a passive control. The interventions applied in these studies included: leg compression, vasopressors, and intravenous fluid bolus administered either before or immediately after induction of anaesthesia.

2.4.6 The Use of Norepinephrine in the Management of Spinal Anaesthesia-Induced Hypotension

Norepinephrine, also called noradrenaline, is a catecholamine that acts as a neurotransmitter in both the peripheral and central nervous systems.[64] Norepinephrine is the primary neurotransmitter responsible for most of the adrenergic activity of the sympathetic nervous system.[64] Norepinephrine effects are a result of its direct stimulation of adrenoceptors.
Its potent alpha-1 adrenergic potency leads to profound vasoconstriction whereas activation of its modest beta-1 activity leads to positive chronotropic and ionotropic effects on the heart. [64]

Recently, low-dose norepinephrine is been studied as an alternative to commonly used vasopressors for the treatment of anaesthesia-induced hypotension with favourable outcomes.[65] Maternal and foetal outcomes of norepinephrine and phenylephrine in most studies are comparable.[65] Incidences of hypotension, reactive hypertension, nausea, or vomiting are similar when comparing the use of norepinephrine and phenylephrine in the management of hypotension during spinal anaesthesia for caesarean delivery.[65] However, norepinephrine is associated with a lesser incidence of bradycardia compared to phenylephrine. This however did not affect the outcomes.[65] This difference could be due to the modest beta-adrenergic agonist property of norepinephrine. Although phenylephrine has a fast onset of action, the onset of action of norepinephrine is even faster than that of phenylephrine.[65]

In a study of placental transfer and foetal metabolic effects of phenylephrine and ephedrine during spinal anaesthesia for caesarean section, Ngan Kee *et al*[22], found ephedrine easily crosses the placental barrier to the foetus, unlike phenylephrine. Also, another study, though in vitro, on placental transfer and metabolism of norepinephrine found that norepinephrine did not easily traverse the placental barrier to the foetus.[66] These studies showed that maternal to foetal transfer of phenylephrine and norepinephrine are comparable and lesser than that of ephedrine.

Although most studies have found continuous infusion of norepinephrine to be more effective at maintaining haemodynamic stability, other studies have also used intermittent intravenous boluses and had similar favourable outcomes.[65] In sub-Saharan Africa, vasopressors used for the management of intra-operative hypotension are mostly given as intravenous boluses, possibly due to lack of equipment and skill, cost-effectiveness, and familiarity with most anaesthetists. Onwochei *et al*[67] reported the effective intermittent intravenous bolus norepinephrine dose which could prevent spinal anaesthesia-induced hypotension in 90% of women undergoing elective caesarean section as 5.49μg (95% CI, 5.15-5.83μg). Elnabtity *et al*[68] also reported a favourable outcome after using a norepinephrine prophylactic bolus dose of 5μg and rescue boluses of 5μg to manage spinal anaesthesia-induced hypotension during caesarean section. Sharkey *et al*[69] also successfully used intermittent intravenous dosing of 5μg norepinephrine to manage spinal anaesthesia-induced hypotension during caesarean section.

Although norepinephrine is mostly administered via central veins as a result it increased risk of tissue injury caused by extravasation from peripheral intravenous lines[70], the administration of dilute concentrations such as 6μg/ml or less via peripheral veins for shorter durations is safe without potential harm to surrounding tissues. It is however advisable to be given via a large vein, preferably in the antecubital fossa.[65]

2.4.7 The Use of Ephedrine in the Management of Spinal Anaesthesia-Induced Hypotension

Ephedrine, a sympathomimetic amine, is both a direct and indirect alpha (α) and beta (β) adrenoceptor agonist. Ephedrine in addition to its primary indirect adrenergic receptor

activation also possesses weak direct effects. Ephedrine's indirect action causes the release of norepinephrine from sympathetic postganglionic neurons and also inhibits norepinephrine reuptake. Repeated dosing of ephedrine can lead to tachyphylaxis as a result of depletion of norepinephrine stores.[64] The cumulative effect of ephedrine's main indirect and associated direct adrenergic receptor activity could account for its relatively slow onset and long duration of action. Ephedrine possesses a progressive onset of action peaking at 90 sec, whereas the onset of action of phenylephrine is almost immediate peaking at about 40 seconds.[47]

Ephedrine increases blood pressure by stimulation of β1-adrenoceptors which lead to increased heart rate and cardiac contractility, and α-adrenoceptor stimulation which causes peripheral vasoconstriction.[64] Ephedrine is thus useful when there is bradycardia or a low-normal heart rate along with hypotension. The use of ephedrine in patients with tachycardia must be done with caution as the tachycardia could be worsened.[71]

Ephedrine which was initially the preferred vasopressor for the management of spinal anaesthesia-induced hypotension has largely been superseded by phenylephrine in most developed countries due to the amount of supporting evidence in favour of phenylephrine.[19,20] However, ephedrine is still widely used in sub-Saharan Africa possibly due to its availability and affordability.

The relative potency ratio for norepinephrine and phenylephrine in the prevention of spinal anaesthesia-induced hypotension during caesarean section was estimated by Ngan Kee *et al*[72] as 13.1(95% Cl, 10.4 to 15.8). Saravanan *et al*[73] also estimated the relative potency ratio of phenylephrine and ephedrine in the prevention of spinal anaesthesia-induced hypotension during caesarean section as 81.2 (95% CI, 73.0 to 89.7). Combining these findings, the relative potency ratio for norepinephrine and ephedrine in the prevention of spinal anaesthesia-induced hypotension during caesarean section can be estimated as approximately 1000:1. Considering the effective intermittent intravenous bolus of 5 to 6μg of norepinephrine and the relative potency ratio for norepinephrine and ephedrine for prevention of spinal-anaesthesia induced hypotension as 1000:1, the effective intermittent intravenous bolus of ephedrine for prevention and treatment of spinal anaesthesia induced hypotension can be indirectly estimated as 5mg to 6mg.

2.4.8 Role of Prophylactic Vasopressor in the Management of Spinal Anaesthesia-Induced Hypotension

A study by Kang *et al*[74] in 1982 found that prophylactic continuous infusion of ephedrine was very effective at preventing maternal hypotension during elective caesarean section as against a control group that received ephedrine only when hypotension occurred. The prophylactic ephedrine infusion was started at a dose of 5 mg/min with further adjustments aimed at preventing systolic arterial pressure from dropping below 90% of the baseline value. A rescue bolus of 10mg of ephedrine was administered if the continuous infusion of ephedrine failed to maintain the systolic arterial pressure within the set target. An intravenous bolus dose of 20 mg of ephedrine was administered to the control group whenever systolic blood pressure dropped to or below 80% of baseline. Despite the prophylactic continuous infusion in the study group, the total ephedrine consumption was similar between the two groups. Also, the frequency of nausea and vomiting was significantly reduced in the prophylactic ephedrine group. However, doses of ephedrine of more than (>)14 mg should not be used for the prevention of hypotension during spinal anaesthesia for caesarean section as it can increase the risk of reactive hypertension with no additional benefits. Hence, ephedrine 12mg was proposed as the possible highest dose of ephedrine for preventing hypotension with fewer side effects.[75]

A meta-analysis looking at the use of prophylactic phenylephrine for the management of spinal anaesthesia-induced hypotension during caesarean section found that compared to bolus doses solely administered in response to a drop in systolic arterial pressure, constant infusions initiated soon after the onset of spinal anaesthesia considerably reduced the occurrence of spinal hypotension.[76] A Cochrane review (including 125 studies made up of 9469 women) of randomised controlled trials comparing means of maternal hypotension prevention following spinal anaesthesia found that the outcomes of both prophylactic ephedrine and phenylephrine in combating hypotension during spinal anaesthesia for caesarean section were similar. The risk of maternal hypotension was 428 per 1000 with the use of prophylactic ephedrine and 465 per 1000 with phenylephrine. The review also found that no single or combined preventive intervention completely abolished the occurrence of hypotension in a proportion of women undergoing caesarean section under spinal anaesthesia.[24]

Prophylactic administration of vasopressors is currently being encouraged due to its favourable maternal and foetal outcomes such as reduction in maternal hypotensive episodes and lower

occurrence of nausea and vomiting juxtaposed with the administration of vasopressors when hypotension occurs.[19,74,76] Although prophylactic administration of vasopressors has been regarded by some as being too aggressive since it can cause reactive hypertension, prophylactic infusion of vasopressors can be titrated to achieve a targeted goal to avoid unwanted excessive effects.[77] A global consensus statement on the treatment of hypotension during caesarean section under spinal anaesthesia also recommends the use of prophylactic vasopressor to maintain maternal haemodynamic stability.[19]

2.4.9 American Society of Anesthesiologists (ASA) Guidelines on Vasopressor Use during Spinal Anaesthesia for Caesarean Section

The use of vasopressors in the management of hypotension during spinal anaesthesia for caesarean section is guided by various professional organizations and expert recommendations. These guidelines provide evidence-based recommendations to help healthcare providers ensure patient safety and optimize outcomes. This section outlines some key guidelines and recommendations for vasopressor use during spinal anaesthesia for caesarean section.

The American Society of Anesthesiologists has established guidelines for the management of spinal anaesthesia-induced hypotension during caesarean section. According to the ASA Practice Guidelines for Obstetric Anesthesia, ephedrine, and phenylephrine are both acceptable choices for the prevention and treatment of hypotension during caesarean section. The choice between these agents should be based on individual patient factors, such as maternal heart rate, blood pressure, and presence of any cardiac comorbidity.[78] More research and supporting data would be required for on norepinephrine's safety and efficacy for it to be recommended in such guidelines.

2.5 Nausea and Vomiting during Spinal Anaesthesia-Induced Hypotension

Spinal anaesthesia-related hypotension is closely associated with the discomfort of nausea and vomiting. Nausea and vomiting are common complications in the obstetric population undergoing a surgical procedure.[79]

This increase in the incidence of nausea and vomiting could be due to the increased risk and occurrence of hypotension during spinal anaesthesia and the hormonal, physiological, and anatomical changes of pregnancy.[15]

Hypotension during spinal anaesthesia may lead to decreased cerebral perfusion. This could result in the brain stem ischaemia leading to the activation of the vomiting centre.[80] The hypotension causes decreased oxygen delivery to the tissues. The chemoreceptor trigger zone in the brainstem is sensitive to reduction in cerebral oxygenation and hence gets triggered when its oxygen supply is reduced as a result of hypotension causing nausea and vomiting.[79–82]

Additionally, spinal anaesthesia as a result of the sympathetic blockade causes a decrease in blood flow to the splanchnic circulation.[83] In the presence of hypotension, this reduction in splanchnic blood flow is further worsened causing hypoperfusion of the gastrointestinal tract causing the release of emetogenic substances. This causes nausea and vomiting.[80]

It has also been proposed that the sympathetic blockade by local anaesthetics causes uninhibited vagal action. This results in gastrointestinal hyperactivity which can also cause nausea and vomiting.[80] Peri-operatively, other factors could be responsible for an increased incidence of nausea and vomiting. These include intra-operative visceral pain, prolonged surgery, high-risk parturient, and body mass index (BMI) of more than 35 kg/m^2. Other factors such as vagal hyperactivity, intravenous and neuraxial opioids, manipulation and exteriorisation of the uterus, and uterotonic agents such as ergometrine and oxytocin may also play a role.[84] Severe bradycardia during spinal anaesthesia has been associated with nausea and vomiting. The resultant decrease in cardiac output as a result of the severe bradycardia could lead to cerebral, brainstem and splanchnic hypoperfusion activating the chemoreceptor trigger zone and causing the release of emetogenic substances leading to nausea and vomiting.[85]

Magni *et al*[86] in their research found the frequency of nausea and/or vomiting during spinal anaesthesia for caesarean section to be 33% in a South African population. In this study, the incidence of nausea and vomiting was influenced by ethnicity. Factors traditionally known to contribute to peri-operative nausea and vomiting incidence did not affect the outcome.[87] Magni

et al[86], found hypotension and ethnicity as the main factors affecting the incidence of intraoperative nausea and vomiting. Factors such as smoking, heart rate, and history of motion sickness in the past did not substantially exacerbate nausea and/or vomiting during spinal anaesthesia for caesarean section. Though the incidence of nausea and vomiting was high in patients in whom the uterus was exteriorised, the timing of nausea and vomiting was before delivery and exteriorisation of the uterus. Hence the prevalence of nausea and vomiting in their study could not be attributed to the exteriorisation of the uterus.

Additionally, numerous studies have linked blood pressure regulation to intraoperative nausea and vomiting. Carpenter *et al*[88], in a study on the adverse outcomes of spinal anaesthesia, found a significant association between the incidence of hypotension and the incidence of nausea and vomiting. Ngan Kee *et al*[77], also proposed that the incidence of intraoperative nausea and vomiting is directly proportional to the degree of reduction in baseline blood pressure. The authors recorded the occurrence of intraoperative nausea and vomiting to be 4%, 14%, and 40% at 100%, 90% and 80% of baseline systolic blood pressure respectively.

Hypotension, therefore, must be one of the first considerations when a patient complains of nausea after the onset of spinal anaesthesia.[14]

2.6 Foetal/ Neonatal Complications of Spinal Anaesthesia-Induced Hypotension

Skillman *et al*[89] in their study of the effects of decreases in uteroplacental vascular flow of foetal lamb found that a sustained decrease of more than (>) half the uterine blood flow within 10 minutes resulted in bradycardia and acidaemia in a hitherto healthy foetus. The results of their study, therefore, suggested that mild to moderate decreases in uteroplacental blood flow for short periods in foetal lamb may not affect foetus outcome due to adequate maternal compensation. Considering foetal/ neonatal complications of spinal anaesthesia-induced hypotension, the duration of hypotension could be more significant than its magnitude. Maayan-Metzger *et al* [90] in a study of 919 mother-infant pairs following an elective caesarean section that engaged the use of regional anaesthesia found that a transient decrease in blood pressure of more than or equal to (≥) 30% did not have any negative effect on the neonate.

In this study, although nearly half of the mothers experienced an average reduction of arterial blood pressure of more than one-third of their baseline values, the neonatal outcome was not affected. The neonatal outcome was not significantly affected probably because this study was done in elective term healthy gestations with uncompromised foetuses who tend to tolerate brief reductions in maternal blood pressures. Already compromised, preterm foetuses or those with certain abnormalities may not be resilient to these brief reductions in maternal blood pressure.[90]

Hollmen *et al*[91] reported that following epidural anaesthesia using lidocaine, babies born to mothers who experienced severe and prolonged hypotension during delivery elicited abnormal neurologic responses. Mothers who experienced brief mild to moderate hypotension had infants with no neurologic abnormality. The duration of hypotension correlated with the severity of the abnormal neurologic response and its recovery time. Though brief periods of maternal hypotension generally do not significantly affect neonatal outcomes, prolonged periods of maternal hypotension could result in neurobehavioural changes in the affected neonate.[91]

Maternal hypotension can also cause foetal acidosis due to decreased uteroplacental blood flow with a resultant decreased oxygen supply to the affected foetus. A study by Corke *et al*[92] also reported that babies born to mothers who experienced hypotension during caesarean section were found to be more acidotic than those born to mothers without hypotension. Even with this decrease in pH, the values were within the normal range. However, sustained hypotension has been found to lead to ischaemic changes in the neonate. An increase in umbilical venous oxypurines and lipid peroxides suggestive of ischaemic-reperfusion injury has been found in babies with mothers who experienced prolonged hypotension.[93] Spinal anaesthesia hypotension results in decreased uterine blood flow as uteroplacental blood flow is not autoregulated.

Robson *et al*[94], in their study on maternal and foetal haemodynamic effects of spinal anaesthesia, suggested that changes in maternal cardiac output are better reflectors of reduced uteroplacental perfusion than changes in arterial pressure after finding that changes in maternal cardiac output correlated with changes in neonatal acid-base status at birth.

Dyer *et al*[47] after studying the haemodynamic effects of vasopressors also reported that heart rate response to vasopressors correlated with cardiac output changes. Since cardiac output monitoring is expensive, invasive, and also not routinely done, it is appropriate to use changes in maternal heart rate and blood pressure as good surrogate markers of maternal cardiac output monitoring in uncomplicated obstetric deliveries in resource-poor areas.[47,95]

After a systematic review by Habib *et al*[96], on the effects of vasopressors on maternal and foetal outcomes during spinal anaesthesia for caesarean section, the authors stated that prophylactic use of vasopressors was effective in preventing hypotension during spinal anaesthesia and led to favourable neonatal outcomes.

Also, Liu *et al*[97], in a systematic review and meta-analysis comparing the efficacy and safety of prophylactic norepinephrine and phenylephrine in spinal anaesthesia for caesarean section, found that prophylactic use of norepinephrine like phenylephrine is beneficial in maintaining maternal and foetal hemodynamic stability.

2.7 APGAR Score of the Neonate

The Apgar score is a scoring system that is used for the early assessment of the newborn. It incorporates five physical components that are assessed and scored individually. A score of 0, 1, or 2 is assigned to each of these clinical signs depending on the state of the newborn. The individual scores are summed up to give the total score out of ten (10). The assessment is done at the first minute of birth and repeated at the fifth minute. A score of 7-10 is considered normal. Neonates with lower scores may need resuscitation and further care. Despite its usefulness as a tool for rapid assessment of the newborn after delivery, the Apgar score has some limitations. The assessment of the physical signs of the score could be subjective and could also be influenced by gestational age, congenital abnormality, and maternal factors such as anaesthesia. The Apgar score may also not be able to detect early changes in neurological and metabolic abnormalities in the newborn.[98,99]

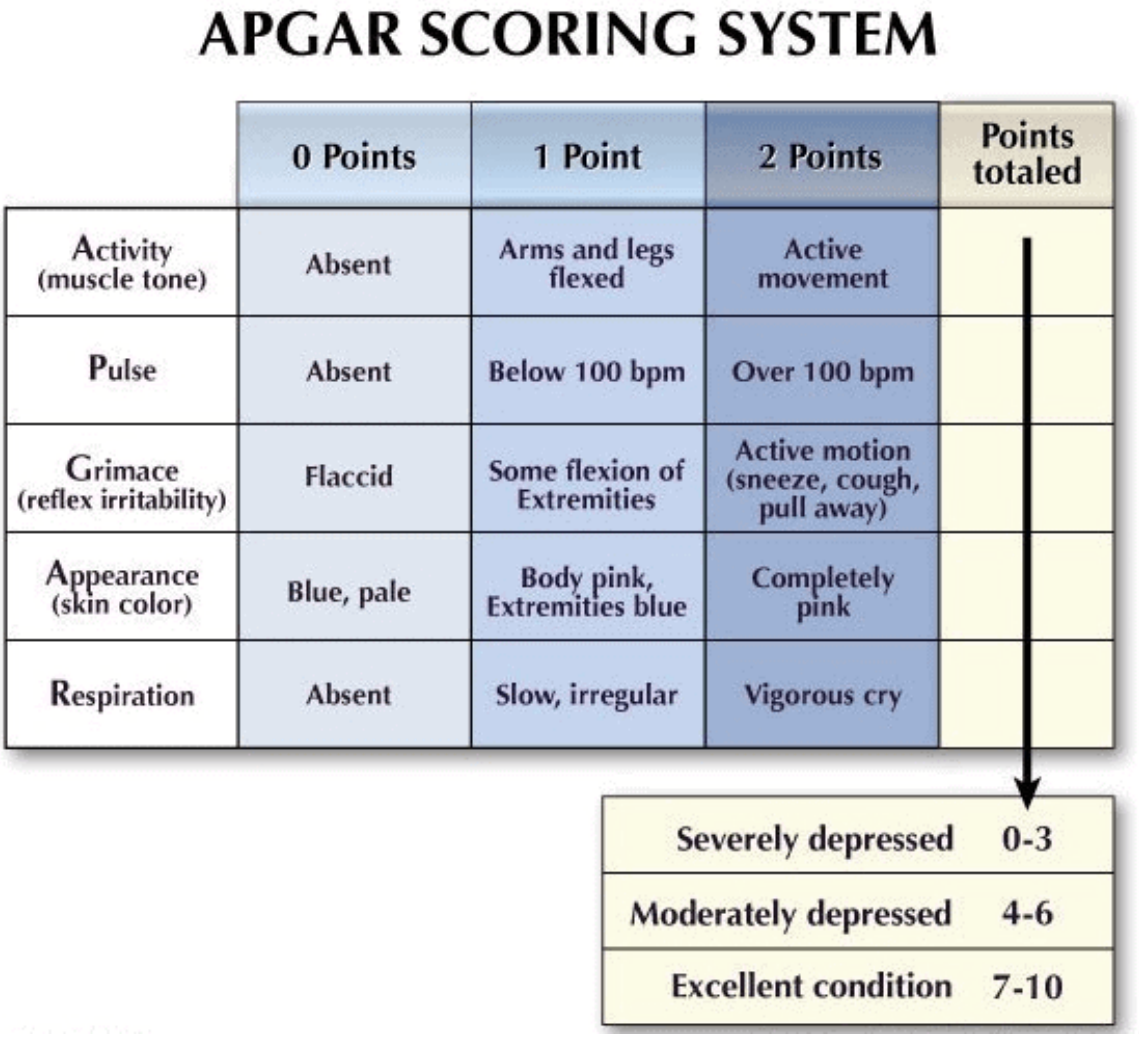

Figure 2. 10: APGAR Scoring system

Source: Birth Injury Lawyers Alliance[100]

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Design

The study was a prospective randomised double-blind controlled trial to compare the effectiveness of prophylactic ephedrine and norepinephrine in the prevention of spinal anaesthesia-induced hypotension in parturients undergoing elective caesarean section at Komfo Anokye Teaching Hospital.

3.2 Study Site

The study was conducted at the Komfo Anokye Teaching Hospital (KATH) situated in Kumasi in the Ashanti Region of Ghana. KATH is a tertiary hospital and the largest hospital within the Ashanti Region with a bed capacity of 1500. Being situated in the Ashanti Region, it serves as a link between the northern and southern parts of Ghana. The research was carried out in the Obstetrics Theatre of KATH. This theatre can be found within the Nana Afia Kobi Serwaa Ampem (NAKSA) Block of KATH. It has three theatre rooms with three operating beds.

The Obstetrics and Gynaecology Directorate of KATH has an average of 16,247 antenatal care attendants and 8932 obstetric case admissions annually. An average of 3015 caesarean sections (2125 emergencies, 890 electives) are done annually, out of which 93% are done under spinal anaesthesia.

3.3 Study Population

The study included all American Society of Anesthesiologists (ASA) class II and III antenatal clinic attendants at Komfo Anokye Teaching Hospital booked for elective CS from November 2022 to February 2023.

3.4 Inclusion Criteria

All parturients with normal singleton pregnancy at 38 weeks gestation (term pregnancy, as prematurity and post-term could affect the neonatal outcome) and above, aged between 18 and 45 years, who were scheduled for elective caesarean section under spinal anaesthesia at the Komfo Anokye Teaching Hospital.

3.5 Exclusion Criteria:

1. Patient refusal. Patients who did not consent to be part of the study.
2. Patients with documented allergy or hypersensitivity to ephedrine or norepinephrine.
3. Patients classified as above ASA physical class III: these are high-risk pregnancies
4. Patients undergoing emergency CS: there was not enough time for patient education and informed consent. Also, some emergency cases are high-risk pregnancies or may have independent risk factors for intra-operative hypotension.
5. Multiple gestations: could be an independent risk factor for intra-operative hypotension.
6. BMI ≥ 35 Kg/m^2: high BMI could be an independent risk factor for spinal hypotension.
7. Pre-existing or pregnancy-induced hypertension, diabetes mellitus, cardiovascular disease, and cerebrovascular disease: these are high-risk pregnancies.

3.6 Sampling

A systematic sampling method was used for the recruitment of parturients into the study. This was achieved by recruiting every other parturient who met the inclusion criteria and gave consent after the first parturient had been recruited.

3.7 Sample Size Determination

The incidence of hypotension has been reported as 43.8% and 30.6% after norepinephrine and ephedrine prophylactic infusion respectively.[101] Using α set at 0.05, β at 0.20, along with the power of the test (1–β) at 0.84, sixty-nine (69) subjects per group will be required to detect an intergroup difference after a 10% potential dropouts or data missing were accounted for.

Sample Size Formula

$$n = \frac{(r+1)}{r(\lambda-1)^2 p_2^2}\left[Z_\alpha\sqrt{(r+1)p_c(1-p_c)} + Z_\beta\sqrt{\lambda p_2(1-\lambda p_2) + r p_2(1-p_2)}\right]^2$$

Where n = minimum sample size required

r = the ratio of patients treated with norepinephrine and ephedrine infusion (ratio, r= 1:1)

λ = relative risk ($\lambda = \frac{43.8\%}{30.6\%}$) ($\lambda = 1.4$)

p_1 = incidence of hypotension when ephedrine was administered ($p_1 = 0.306$)

p_2 = incidence of hypotension when norepinephrine was administered ($p_2 = 0.438$)

Z_α = Standard normal values (95% confidence level, $Z_\alpha = 1.96$)

Z_β = power to detect difference (80% power, $Z_\beta = 0.84$)

P_c = the average incidences of tachycardia when norepinephrine and ephedrine were administered

but $P_c = \frac{0.306+0.438}{2}$

$P_c = 0.372$

$$n = \frac{(1+1)}{1(1.4-1)^2(0.438)^2}\left[1.96\sqrt{(1+1)(0.372)(1-0.372)} + 0.84\sqrt{1.4(0.438)(1-1.4(0.438)) + 1(0.438)(1-0.438)}\right]^2 \quad n = \frac{2}{0.03072}\left[1.96\sqrt{0.4672} + 0.84\sqrt{0.2372+0.2462}\right]^2$$

$n = 65.10[(1.96)(0.6835) + (0.84)(0.6953)]^2$

$n = 65.10[(1.340) + (0.584)]^2$

$n = 65.10 * 1.924$

$n = 125$

Thus, allowing for a 10% non-response rate, the sample size was 138 (69 participants per group).

3.8 Process of Study

The study was registered with the Research and Development Unit of KATH and ethical approval was sought from the Institutional Review Board (IRB) of KATH.

Based on the calculated sample size, one hundred and forty-two (142) parturients who met the inclusion criteria were enrolled in the study. The parturients scheduled for routine elective caesarean section and who met the inclusion criteria were identified at the Anaesthesia Preoperative Assessment Clinic and informed of possible recruitment into the study. All participants gave written informed consent to voluntarily participate in the study.

A systematic sampling method was used for the recruitment of parturients into the study. This was achieved by recruiting every other parturient who met the inclusion criteria and gave consent after the first parturient had been recruited. The study, procedures involved, and their complications were clearly explained to these participants and a signed or thumb-printed informed consent was obtained.

Interpreters were provided for non-English speaking patients since the patient information leaflets, consent forms, and questionnaires were all in English. Those who agreed to be participants signed or thumb-printed the informed consent form. The attending obstetricians of the parturients were also informed of the study.

A pilot study was carried out on 10 patients over a week to test the data collection form and to orient and educate hospital staff and research assistants who would be assisting in the study. This was to ensure the study's proper conduct and the data's accuracy.

The enrolled participants were randomised into two (2) groups, the Ephedrine group and the Norepinephrine group of seventy-one (71) parturients each. Randomisation was done by balloting without replacement, using 142 pieces of paper which were divided into two batches of 71 each.

One batch had “A” written on each piece of paper and the other batch had “B” written on each piece of paper. Each piece of paper was folded in such a way that the labelling was undetectable after which they were all placed in an opaque envelope. The ballot was administered by a medical officer at the preoperative area in the theatre.

The enrolled participants each picked a piece of paper at random from the opaque envelope. The participant was assigned to the group on the picked piece of paper.

The Ephedrine group received a prophylactic dose of ephedrine 5mg (1ml of 5mg/ml solution), augmented by rescue doses of ephedrine 5mg (1ml of 5mg/ml solution) intravenously. The Norepinephrine group received a prophylactic dose of norepinephrine 5µg (1ml of 5µg/ml solution), augmented by rescue doses of norepinephrine 5µg (1ml of 5µg/ml solution) intravenously.

The study drug was prepared daily by only one specialist anaesthesiologist together with a pharmacist who was well educated on the study and whose main function was to prepare drugs. To prepare the norepinephrine solution, the anaesthesiologist took 1ml of 1mg/ml solution of norepinephrine and added 3ml of normal saline to make 4ml of 250µg/ml solution. The anesthesiologist then took 1ml of the 250µ/ml solution and added 49ml of normal saline to make 50ml of 5µg/ml solution of norepinephrine in a 50ml syringe. To prepare the ephedrine solution, the anaesthesiologist took 5ml of the 50mg/ml preparation of ephedrine making a total of 250mg. He then added 45ml of normal saline to the 5ml of ephedrine to make 50ml of 5mg/ml solution of ephedrine in a 50ml syringe. The identity of the study drugs was known only to this anaesthesiologist. The investigator and the study participants were blinded to the constitution of each drug solution. The anesthesiologist in charge of drug preparation only drew up the drug the participant picked. He drew 1ml of the study drug and labelled it as “1” to be administered as the prophylactic drug. He then drew up 20ml of the appropriate rescue drug and labelled it as “2”.

Rescue doses were administered as 1ml bolus whenever maternal systolic arterial pressure (SAP) dropped 10% or more from the baseline pre-anaesthetic value.

The anaesthesiologist ensured that members of each group received the same study drug solutions and only revealed the constitution of each study drug solution at the end of the data analysis.

All participants were given oral Ranitidine 150mg the night before surgery (at 10:00 pm) and 150 mg on the day of surgery, 2 hours before the CS.

After routine fasting (8 hours off solid feeds and 2 hours off clear fluids and water) and antacid premedication, the participant was brought to the pre-anaesthetic area of the obstetric theatre. The baseline blood pressure of each participant was measured and recorded by taking the mean of three consecutive readings 2 minutes apart using a non-invasive oscillometric technique in the supine position with a right-sided wedge as subsequent readings were done in the same position. The difference between these readings was not more than 10%. An intravenous (IV) line was secured using a 16 or 18-gauge IV cannula in the antecubital fossa.

In the operating room, the following monitoring was established: continuous electrocardiography (ECG), pulse oximetry, and non-invasive blood pressure. Participants were preloaded with 10ml/kg of lactated ringer's solution just before anaesthesia. The subarachnoid block was performed by the principal investigator. The proceduralist scrubbed and put on a sterile gown and gloves. The parturient was helped into the sitting position and her back was prepared with chlorhexidine and alcohol solutions. Under strict asepsis, the L3-L4 intervertebral space using the midline approach was identified after the parturient was well positioned with the back straight and arched. Local skin infiltration was carried out at the intended interspace using 2mls of 2% lidocaine. A 25-gauge spinal needle was introduced into the sub-arachnoid space and 10mg (2 ml) of hyperbaric 0.5% bupivacaine with added 20µg of preservative-free fentanyl was injected slowly at a rate of 0.2ml per second through the spinal needle. Two parturients from the ephedrine group and one parturient from the norepinephrine group were excluded from the study as a result of failed spinal anaesthesia. One more parturient from the norepinephrine group was excluded from the study as a result of the conversion of spinal anaesthesia to general anaesthesia due to a prolonged and complicated surgery.

The prophylactic study drug was administered by another anaesthetist during intrathecal injection and not before or after as the onset of action of these vasopressors is fast coupled with their short duration of action to achieve the best results as the duration of performance of the subarachnoid block may vary.

The participant was then positioned supine with a left uterine displacement using a right-sided wedge. The sensory block level was assessed by testing sensitivity to cold using alcohol-soaked swaps 5 minutes after intrathecal injection to ensure an appropriate level of blockade (T_4–T_6 dermatome). If an adequate block was not achieved after 10 minutes, the parturient was excluded.

Maternal heart rate was monitored continuously and blood pressure readings were recorded at 1-minute intervals after intrathecal injection until delivery of the foetus, then every 2 minutes until 10 minutes after the delivery, and thereafter every 5 minutes until the end of surgery.

A bolus of 1ml of the appropriate rescue drug was administered whenever maternal SAP dropped 10% or more from the baseline value, to maintain the systolic arterial pressure within 90% or more of the baseline pre-anaesthetic value. Any episode of bradycardia was treated with intravenous atropine 0.6 mg and repeated as required.

Intra-operatively, it was ensured that the participant was adequately fluid-filled by replacing fluid deficit and ongoing losses appropriately in addition to administration of maintenance fluid. Maintenance fluid was administered by infusing lactated ringer's solution at a rate of 8 ml/kg/h for all groups according to the parturient's standard weight.

The participant was also continually assessed for signs of hypovolaemia such as tachycardia, weak or thready peripheral pulse, capillary refill time, dry mucosal surfaces and the necessary correction made.

After the delivery of the baby, 10 units of oxytocin was given as a slow intravenous infusion. Apgar scores of the neonate at the first (1^{st}) and fifth (5th) minutes after delivery were recorded by the attending paediatrician or midwife (who had been trained on Apgar scoring) and reported to the anesthesiologist. Blood pressure monitoring and intervention were continued until the end of surgery.

The frequency of maternal hypotension, reactive hypertension, bradycardia, tachycardia, and nausea and vomiting were recorded. The time of the first requirement of rescue vasopressor dose, the total number and total volume of each vasopressor used and the total volume of intravenous fluid administered were recorded. The time of induction of anaesthesia to the delivery of the baby was recorded. Apgar scores of the neonate at the first (1^{st}) and fifth (5th) minutes after delivery were also recorded. The study was terminated at the end of the surgery.

The following definitions for the aforementioned terms were employed:

- Spinal anaesthesia-induced hypotension was defined as SAP less than 80% of the baseline reading or SAP after intrathecal injection.
- Intraoperative hypertension was defined as a 20% or more increase in baseline SAP or mean arterial pressure (MAP) reading.
- Reactive hypertension was defined as a 20% or more increase in baseline SAP or MAP as a result of vasopressor administration.
- Bradycardia was defined as a heart rate (HR) of less than 60 beats/min (bpm).
- Tachycardia was defined as HR greater than (>) 100 bpm.

3.9 Study Period

The study was carried out from November 2022 to April 2023.

3.10 Data Management and Analysis

3.10.1 Data Collection

The data collection tool was in two parts: a structured questionnaire and monitoring charts. The questionnaire was self-designed to collect the socio-demographic and medical data of the patient. Samples of the questionnaire and monitoring charts are attached in Appendix 1.

3.10.2 Data Handling

Data collection sheets were sealed in a large envelope after completing them. These envelopes were then locked up in a cupboard to ensure the security of the information gathered. The data was then transferred onto a password-protected electronic Microsoft Excel database by the investigator. The data was scrutinized for errors and discrepancies. Only the investigator, supervisors, and the Institutional Review Board had access to this information upon request.

3.10.3 Data Analysis

Data collected from the facility each day was entered into Excel with the help of data entry clerks, which was password-protected to prevent access by unauthorised persons. Only the principal investigator had the password and could access the Excel sheet. All analysis was carried out using STATA version 17 (College Station, Texas) statistical software. The study employed both descriptive and inferential statistics in analysing the data.

The key variables used were socio-demographic characteristics (Age, Parity, BMI and Gestational age), and maternal complications (Nausea and vomiting, Breathlessness, Headache and palpitations). Other variables included surgery time, and Vitals (SAP, MAP, HR). The systolic arterial pressure was categorised into hypotension (on a drop to less than 80% of systolic arterial pressure of baseline value) and hypertension (based on an increase of more than 120% of baseline systolic arterial pressure). A heart rate of less than 60 bpm was classified as bradycardia.

Social and demographic information of the respondents was presented using percentages, frequencies, means, standard deviations, graphs and tables. Categorical data (vasopressor requirement, occurrence of nausea and vomiting, Apgar scores) were reported as numbers and percentages and were analysed using the chi-squared test. Continuous data (age, gestational age, durations of surgery and anaesthesia) were checked for normality using the Shapiro rank test. Normally distributed data were presented as means (standard deviations) and were analysed using an unpaired student t-test. Skewed data were expressed as medians (quartiles) and were analysed using the Mann-Whitney U test.

All analyses in this report were narrowed to cases that were reported during the study period. Statistical significance for all testing was set at a *p*-value of 0.050 with a 95% confidence interval.

3.11 Ethical and Legal Considerations

3.11.1 Approval for Study

A research permit was sought from the Research and Development Unit of the Komfo Anokye Teaching Hospital (KATH) (Appendix 5). Ethical approval for the study was granted by the KATH Institutional Review Board (IRB) (Appendix 6). Permission to carry out the study and support was also sought from the Directorate of Anaesthesia and Intensive Care as well as the Directorate of Obstetrics and Gynaecology, KATH. In the unlikely event of protocol deviation, the KATH IRB would have been notified and ethical clearance would have been sought for that deviation but there was no protocol deviation.

3.11.2 Ethical Considerations

Potential clinical risks associated with the study, (such as hypotension, hypertension, tachycardia, and bradycardia), were minimised by ensuring strict continuous monitoring of participants for early detection and appropriate management. Vasopressors (study drugs) were only administered when needed to avoid overdosing or underdosing hence minimising adverse effects such as reactive hypertension, tachycardia, bradycardia and hypotension. To avoid underdosing, the study drug was administered whenever there was a 10% or more drop in the participant's baseline blood pressure. Overdosing of vasopressor was also avoided by stopping the administration of the study drug when a participant's blood pressure was within 90% or more of the baseline blood pressure of the participant. Intravenous atropine was administered when needed to treat bradycardia.

All participants were also monitored closely for the occurrence of adverse events or unresponsiveness to study drugs intra-operatively. The risk of adverse events in participants of this study was not different from those not included in the study. No adverse event occurred throughout the study. A Data Safety Monitoring Board (DSMB) was also set up to monitor the conduct of the study.

3.11.3 Informed Consent

The study procedure, expected benefits, adverse effects, and risks of the study were clearly explained to all participating parturients using a participant information leaflet (Appendix 2). A translator was used for those who did not understand English. Then, a signed or thumb-printed informed consent was obtained (Appendix 3).

3.11.4 Confidentiality

Patient confidentiality was maintained throughout data collection. To ensure anonymity, all data sheets had designated codes with no identifier on them and were securely stored under lock and key in a cabinet only accessible to the investigator. Electronic records were encrypted and password-secured. Only the investigator, supervisors, and the Ethics Board had access to this information when needed. Participants could freely withdraw from the study at any time without any consequence to them or the treatment they would receive at KATH.

CHAPTER FOUR

4.0 RESULTS

4.1 Introduction

The findings on the comparison of the effectiveness of prophylactic ephedrine and norepinephrine in the prevention and management of spinal anaesthesia-induced hypotension at Komfo Anokye Teaching Hospital are presented in this chapter. The results are presented in tables and figures followed by a narration. A total of 142 patients were recruited for the study. Data from 138 patients were analysed.

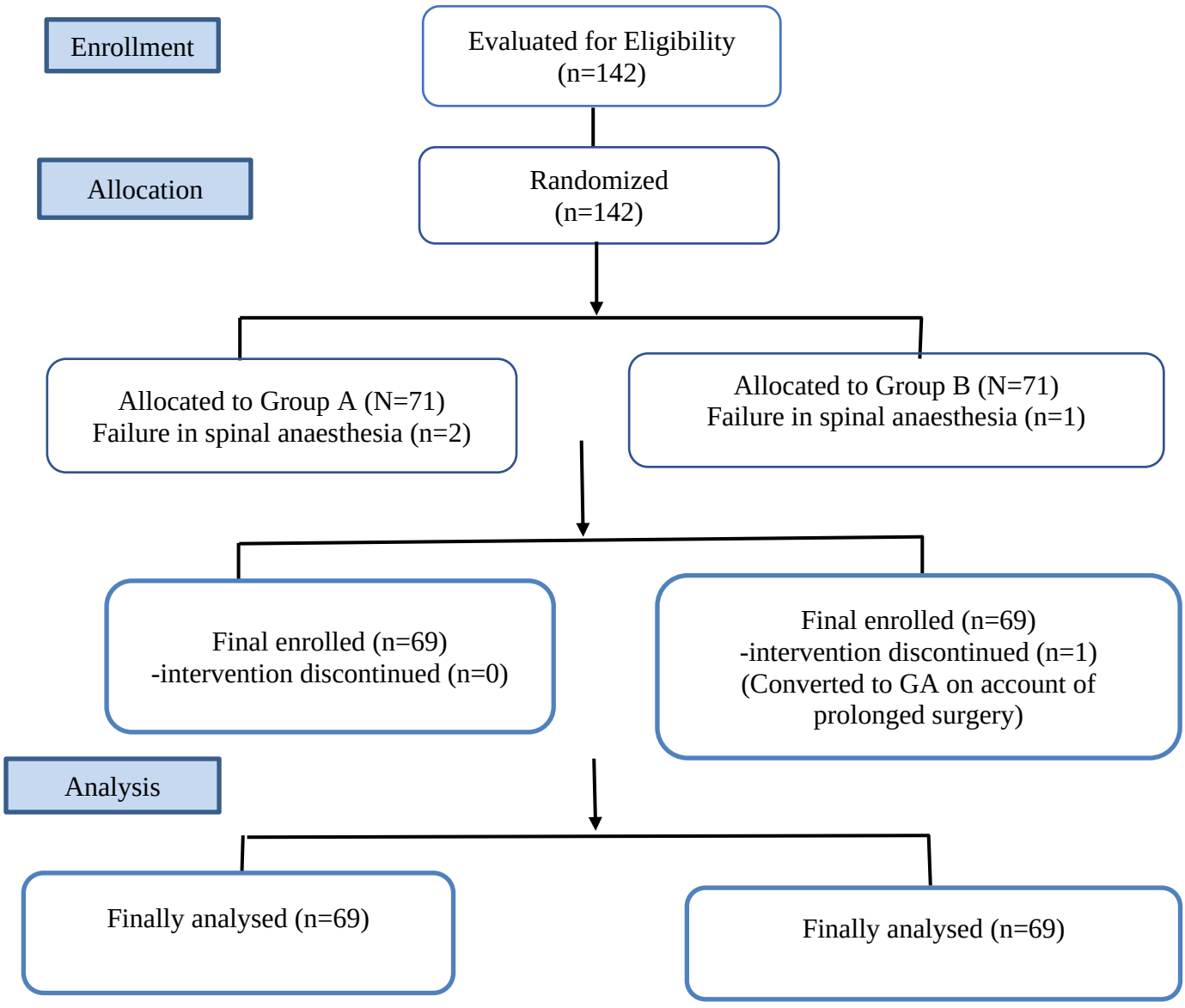

Figure 4. 1: Flow chart of participant enrollment

4.2 Patient Characteristics

Table 4. 1: Overall Patients' Characteristics and Duration of Surgery

PARAMETER	MEAN (+/-SD)
Age (years)	31.99±5.04
Parity	2.82±1.49
Gestational age (weeks)	38.56±0.75
Body mass index (BMI) (kg/m²)	26.58±3.52
Duration of surgery (minutes)	46.73±11.29

4.3 Patients' Characteristics and Duration of Surgery

Table 4. 2: Patients' Characteristics and Duration of Surgery of Groups

	Ephedrine (n = 69)	**Norepinephrine (n = 69)**	***P value***
Age (years)	31.97±4.82	32.0±5.27	0.973
Parity	2.68±1.28	2.53±1.50	0.543
BMI (kg/m²)	26.55±2.49	27.0±3.07	0.342
Gestational Age (weeks)	38.53±0.67	38.57±0.82	0.736
Duration of Surgery (minutes)	46.03±10.29	47.44±12.26	0.463

4.4 Maternal Haemodynamics

4.4.1. Incidence of Hypotension)

Table 4. 3: Incidence of Hypotension

	Ephedrine (N)	**N (%)**	**Norepinephrine (N)**	**N (%)**	**X^2**	***p- value***
Incidence of Hypotension	43	62.32	29	42.03	5.69	0.017

4.4.2 Incidence of Reactive Hypertension

Table 4. 4: Incidence of Hypertension

	Ephedrine (N)	**N (%)**	**Norepinephrine (N)**	**N (%)**	**X^2**	***p- value***
Incidence of Hypertension	9	13.04	6	8.82	0.62	0.429

4.4.3 Bradycardia

Table 4. 5: Incidence of Bradycardia

	Ephedrine	**Norepinephrine**	***p- value***
Incidence of Bradycardia	3(4.35%)	3(4.35%)	0.612

4.5 Incidence of Nausea and Vomiting and other discomforts

Table 4. 6: Maternal Side Effects (Incidence of Nausea and Vomiting and other Discomforts)

Maternal Side Effect	**Ephedrine** N (N%)	**Norepinephrine** N (N%)	***p- value***
Nausea/vomiting	6 (8.70%)	7 (10.14%)	0.710
Breathlessness	3 (4.3%)	2 (2.9%)	0.652
Headache	1 (1.4%)	0 (0.0%)	0.319
Palpitations	0 (0.0%)	1 (1.4%)	0.319
Dizziness	0 (0.0%)	1 (1.4%)	0.319

4.6 APGAR Score Variation (mean ± SD)

Table 4. 7: APGAR Score Variation (mean ± SD)

Time of scoring (min)	**Ephedrine**	**Norepinephrine**	***p- value***
At 1 min	7.58 ± 0.60	7.57 ± 0.50	0.878
At 5 min	8.83 ± 0.38	8.81 ± 0.39	0.827

4.7 Time between Spinal Anaesthesia and Start of Surgery and Delivery of foetus

Table 4. 8: Time between Spinal Anaesthesia and Start of Surgery and Delivery of Foetus

	Ephedrine	**Norepinephrine**	***p- value***	***95% CI***
Time interval between initiation of spinal anaesthesia and start of surgery (min)	10.92±2.55	11.20±2.37	0.510	Ephedrine (10.31 – 11.54) Norepinephrine (10.63 -11.77)
Time interval between initiation of spinal anaesthesia and delivery of foetus (min)	14.28±2.48	15.62±3.30	0.008	Ephedrine (13.69-14.88) Norepinephrine (14.82-16.41)

4.8 Time to first rescue vasopressor

Table 4. 9: Time to First Rescue Vasopressor

	Median (min)	**95% CI**	***p-value***
Ephedrine group	3	2.589 – 3.497	0.368
Norepinephrine group	3	2.822 – 3.902	

4.9 Number and Doses of Vasopressor

Table 4. 10: Number and Doses of Vasopressor

	Ephedrine	**Norepinephrine**	***p- value***
Total number of rescue vasopressor doses	5.15±2.81	5.06±3.66	0.874
Total volume of vasopressor administered (ml)	6.16±2.80	6.06±3.66	0.855

CHAPTER FIVE

5.0 DISCUSSION

5.1 Baseline Maternal Haemodynamics, Sensory Block Level, Peri-Operative Fluid and Adverse Effects

There was no statistically significant difference between the studied groups in baseline maternal blood pressure, systolic arterial pressures, and heart rates ($p = 0.017$). The volume of fluid for preloading, the total volume of fluid administered ($p = 0.560$), and sensory block height (T4-T6) were also similar among the study groups. The prophylactic vasopressor dose was administered at the time of intrathecal injection of local anaesthetic for both groups.

5.2 Incidence of Maternal Spinal Anaesthesia-Induced Hypotension with the Use of Prophylactic Ephedrine and Prophylactic Norepinephrine

The results of the present study showed that prophylactic norepinephrine maintained systolic arterial pressure better than ephedrine. There was a statistically significant lower incidence of spinal anaesthesia-induced hypotension (defined as a decrease in systolic arterial pressure below 80% of baseline pre-anaesthetic value) in the norepinephrine group compared to the ephedrine group (*p*-value of 0.017). More patients in the ephedrine group (62.32%) compared to (42.03%) in the norepinephrine group dropped their systolic arterial pressure below 80% of their baseline value at least once after induction of spinal anaesthesia till the end of surgery.

Norepinephrine compared to ephedrine resulted in less hypotension possibly because of its potent alpha-1-adrenergic agonist activity which causes marked vasoconstriction to counteract the vasodilation and subsequent significant decrease in systemic vascular resistance caused by the sympathetic block of spinal anaesthesia.[13,64] Also, the fast onset of norepinephrine compared to ephedrine could be advantageous in causing a rapid countereffect to the hypotensive effect of the sympathectomy of spinal anaesthesia.[65]

The result of the present study is consistent with that of a study by Elnabtity *et al*[68] which also found the incidence of hypotension in the norepinephrine group to be significantly lower than

that of the ephedrine group (*p*-value 0.020). In their study, maternal blood pressures and uterine artery blood flow were better sustained by norepinephrine than ephedrine. However, ephedrine was associated with increased mean arterial pressure which could be attributed to the dose of 10mg used which is higher than the 5mg used in the present study.

A study by Elagamy *et al*[102] also had results consistent with the present study. Their results also showed that norepinephrine maintained maternal blood pressure better with a lower number of hypotensive episodes when compared to ephedrine. However, the mean number of rescue vasopressor doses for both groups in their study was lower than that for the two groups in the present study. This could be attributed to the higher doses of ephedrine and norepinephrine (10 mg of ephedrine and 16 mcg of norepinephrine) used in their study compared to that (5 mg of ephedrine and 5 mcg of norepinephrine) used in the present study. Also, the statistically significant higher mean arterial pressure recorded in the norepinephrine group could be accounted for by the higher dose of norepinephrine used about ephedrine considering the derived relative potency ratio of norepinephrine to ephedrine of approximately 1000:1.[72,73]

Hassani *et al*[103] after a study comparing ephedrine and norepinephrine in treating anaesthesia-induced hypotension in hypertensive patients having spinal surgery under general anaesthesia found that norepinephrine is more effective than ephedrine in the maintenance of mean arterial pressure in hypertensive patients undergoing spinal surgery under general anaesthesia. Although the study population and type of anaesthesia in their study differ from that of the present study, their results were consistent with the present. This probably implies norepinephrine could be effective in the management of hypotension under other forms of anaesthesia due to its combined strong alpha-1 and modest beta-1 agonist activity.

On the contrary, a randomized double-blind study comparing prophylactic norepinephrine and ephedrine infusion for preventing maternal spinal hypotension during elective caesarean section under spinal anaesthesia by Xu *et al*[101] reported the incidence of hypotension as 43.8% and 30.6% in the norepinephrine and ephedrine infusion groups, respectively. This finding conflicts with the findings of the present study which recorded a significantly lower incidence of hypotension in the norepinephrine group. The authors stated in their limitations that the dosages of norepinephrine and ephedrine used in their study were not equipotent as the norepinephrine used (norepinephrine bitartrate) was twice less potent than it should be. This could have affected the outcome of the study.

A double-blinded, randomised controlled trial by Ngan Kee *et al* [104] which compared the administration of norepinephrine as a prophylactic infusion against bolus administration without prophylaxis in 110 healthy women having spinal anaesthesia for elective caesarean suggested that prophylactic infusion of norepinephrine was significantly superior to bolus administration in the management of spinal anaesthesia induced hypotension. A median total dose of 61.0 mcg [interquartile range {IQR}, 47.0–72.5] in the perfusion group compared to 5.0mcg [IQR, 0–18.1] µg) ($p < .001$) in the bolus group was given until uterine incision. 17% of patients in the infusion group compared to 66% in the bolus group had hypotension. The huge difference in the mean total dose of norepinephrine administered to the two groups, the different modes of administration of norepinephrine, and the lack of prophylaxis in the bolus group could have accounted for this outcome which is not consistent with the present study. Although, the same bolus dose of norepinephrine was used in this study and the present study, the lower incidence of hypotension in the present study could be a result of the prophylactic dose and administration of rescue doses when systolic arterial pressure drops below 90% instead of 80% of baseline values.

Sub-analyses within specific time intervals indicated a fairly significant proportion of the incidence of spinal anaesthesia-induced hypotension (more than or equal to 60%) occur within the first 10 minutes, with 90% or more occurring within the first 20 minutes in both groups ($p = 0.050$). Since the mean time of delivery falls within the first twenty (20) minutes after induction of spinal anaesthesia, prompt and active management of hypotension within this time should be ensured to maintain adequate uteroplacental blood flow to the foetus since uteroplacental blood flow is not autoregulated.[19]

5.3 The Incidence of Nausea and Vomiting in Parturients Receiving Prophylactic Ephedrine and Prophylactic Norepinephrine

Results of the present study showed no statistical difference in the incidence of nausea and vomiting about ephedrine and norepinephrine (8.70.4% vs. 10.14%, p=0.710) despite the apparent difference in the incidence of hypotension between the two groups favouring norepinephrine. Although hypotension has been proposed as a major factor in the incidence of intra-operative nausea and vomiting, other factors such as intra-operative visceral pain,

prolonged surgery, vagal hyperactivity, intravenous and neuraxial opioids, manipulation and exteriorisation of the uterus, and uterotonic agents such as oxytocin may have also played a role and affected the outcome of the present study.[84,86,87]

A study by Ashagrie *et al*[84] on the incidence and factors associated with intraoperative nausea and vomiting during caesarean section under spinal anaesthesia recorded a significantly lower incidence of nausea and vomiting in the presence of a moderately high incidence of hypotension without prophylactic vasopressor administration compared to other studies. The authors attributed this outcome possibly to the administration of prophylactic anti-emetics in 95.2% of the participants of the study.

In agreement with the present study, although Elnabtity *et al*[68] and Elagamy *et al*[102] reported a significant difference in the incidence of hypotension between the ephedrine and norepinephrine groups in favour of norepinephrine, the incidence of nausea, vomiting, and other maternal complications during spinal anaesthesia for caesarean section were comparable, and no significant differences were detected between the studied groups.

In addition, although Xu et al[101] reported a higher incidence of hypotension in the norepinephrine group compared to the ephedrine group which conflicted with the findings of this results, they also found no difference between the two groups in terms of nausea and vomiting.

Fitzgerald *et al*[16] also stated in their systematic review and network meta-analysis that the differences between incidences of intra-operative nausea and vomiting among trials may be a result of the way these studies are conducted and how their results are reported. Factors aside from hypotension affecting the outcome of the occurrence of nausea and vomiting such as the use of prophylactic anti-emetics, administration of medications with a high risk of nausea and vomiting, and the surgical technique may affect the outcome of intra-operative nausea and vomiting.

This finding of the present study is consistent with Habib *et al*[96] who found that the use of prophylactic vasopressors markedly reduces the incidence of intra-operative nausea and vomiting during caesarean section despite the cause.

Elnabtity *et al*[68] and Elagamy *et al*[102] had similar results in similar studies comparing norepinephrine and ephedrine in the management of hypotension during spinal anaesthesia for

caesarean section. There was no difference between the groups in terms of nausea/vomiting, headache, shivering, restlessness, etc.

5.4 The Difference between the Incidence of Reactive Hypertension and Bradycardia in Parturients Receiving Prophylactic Ephedrine and Prophylactic Norepinephrine

The findings of the present study show that although there were more patients in the ephedrine group as compared to the norepinephrine group in terms of reactive hypertension, the difference was not statistically significant. (p = 0.420). The two groups recorded the same incidence of bradycardia of 4.35% (p=0.612). The incidence of bradycardia was low in both studied groups probably due to the beta-adrenergic agonist hence the positive chronotropic activity of both drugs.[64]

The findings of the current study are in agreement with that of Fitzgerald *et al*[16] who also found no significant differences in rates of reactive hypertension and maternal bradycardia between ephedrine, phenylephrine, and norepinephrine.

Elnabtity *et al*[68] reported a lower incidence of hypertension, bradycardia, and tachycardia in the norepinephrine group compared to the ephedrine group. The increased mean arterial pressure and heart rate in the ephedrine group could be attributed to the strong beta-adrenergic agonist activity and the higher 10mg dose of ephedrine used in their study compared to the 5mg ephedrine used in the current study.

The results generated from this study are in agreement with a study by El Shafei *et al*[105] where they found no difference between an ephedrine group and a norepinephrine group considering bradycardia and hypertension. The authors compared norepinephrine with ephedrine in preventing spinal anaesthesia-induced hypotension in coronary artery disease patients undergoing knee arthroscopy. Although norepinephrine recorded lower heart rates compared to ephedrine, the values were mostly within the normal range. The less increase in heart rate caused by norepinephrine could be a result of its modest beta-agonist activity compared to that of ephedrine and also the low dose of 5 mcg used in this study.

Ahmed *et al*[106] in agreement with the present study found no difference in the incidence of bradycardia among the ephedrine and norepinephrine groups but reported a markedly higher

incidence of tachycardia in the ephedrine group (p=0.001) possibly due to its stronger beta-adrenergic agonist activity than norepinephrine.[19]

5.5 The Outcomes of Neonates Born to Parturients Receiving Prophylactic Ephedrine and Prophylactic Norepinephrine

There were no observed differences in neonatal Apgar score at one minute or five minutes among the two study groups (p-value of 0.878 and 0.827 for the 1st and 5th minute after delivery respectively). No group recorded an Apgar score of less than 7. The study done in low-risk healthy pregnancies with healthy uncompromised foetuses undergoing elective caesarean sections and the very brief periods of hypotension may have accounted for these good comparable outcomes of the neonates in the two groups. The prompt use of vasopressors in maintaining maternal blood pressures at 90% or more of baseline values could have also accounted for this outcome.

This finding of the current study is consistent with the findings of Maayan-Metzger *et al*[90] who reported that a transient decrease in maternal blood pressure did not affect neonatal Apgar scores.

Elagamy *et al*[102], Ahmed *et al*[106], and Xu *et al*[101] all reported no significant difference between groups of ephedrine and norepinephrine regarding neonatal Apgar scores. Neonatal outcomes were generally favourable for both ephedrine and norepinephrine groups in these studies.

Studies that analyse neonatal acid-base status as part of neonatal outcome, mostly report favourable neonatal acid-base status after vasopressor use, except for ephedrine, which has been associated with foetal acidosis, especially at higher doses. Even the decreased pH in neonates after ephedrine use tends to be of less clinical significance in healthy babies. In general, the rate of abnormal neonatal metabolic status in most studies involving healthy and low-risk mothers and neonates and promptly managed hypotensive episodes is extremely low.[16,107]

The findings of the current study are consistent with a recent international consensus statement on the management of hypotension during caesarean section, which recommends alpha-agonist drugs and states those with modest beta-agonist activity like norepinephrine might have a better

profile (as a result of the additional benefit of the chronotropic and ionotropic effects) for the management of spinal anaesthesia-induced hypotension.[19] Fitzgerald *et al*[16] in their systematic review and network meta-analysis found that, although phenylephrine, norepinephrine, and metaraminol were found to be effective in managing hypotension during spinal anaesthesia for caesarean section, the occurrence of hypotension was more with ephedrine. In this review, which involved 109 trials (8561 women), norepinephrine was ranked as more effective than ephedrine (95%CI) in the prevention of spinal anaesthesia-induced hypotension.

5.6 Mean Time to Surgery and Delivery of Baby

There was no statistically significant difference between ephedrine and norepinephrine groups in terms of the time interval between spinal anaesthesia initiation (p = 0.138) and the start of surgery. However, there was a statistically significant difference in the time interval between the induction of spinal anaesthesia and the delivery of the foetus for the two groups (14.28±2.48 for the ephedrine group and 15.62±3.30 for the norepinephrine group (p = 0.008)). Although the time from onset of anaesthesia to delivery was longer in the norepinephrine group compared to the ephedrine group, the incidence of hypotension was rather lower in the norepinephrine group. The effect of aortocaval compression could have been minimised by the left uterine displacement effected by the right-sided wedge. There was however no difference between the overall duration of surgery for both groups.

The findings partly agree with Elagamy *et al*[102] who recorded no significant difference in the time interval between the initiation of spinal anaesthesia and the start of surgery and the interval between the initiation of anaesthesia and the delivery of foetus among the ephedrine and norepinephrine groups. They also found a mean time of surgery (min) of 46.40 ± 4.9 for the phenylephrine group, 43.8 ± 6 for the norepinephrine group, and 43.2 ± 5.18 for the ephedrine group (p-value of 0.089) which is comparable to the mean time of surgery in the present study which was 46.03±10.29 for ephedrine group and 47.44±12.26 for the norepinephrine group (p-value of 0.463). They found no significant difference between ephedrine and norepinephrine groups in terms of the surgical time intervals.

5.7 Mean number of Rescue Vasopressor requirement and time to first rescue vasopressor

In the present study, there was no statistically significant difference between the mean number of rescue vasopressors doses received during the spinal anaesthesia between the Ephedrine group (5.15±2.81) and the norepinephrine group (5.06±3.66), *p*= 0.874, although norepinephrine recorded a lower incidence of hypotension compared to ephedrine. Studies that record significantly lower incidence of hypotension in the norepinephrine group compared to the ephedrine group, mostly record lower boluses of norepinephrine used compared to ephedrine. Hassani *et al*[103], Elnabtity *et al*[68], and Xu *et al*[101] in their studies found norepinephrine to be superior to ephedrine in terms of hypotension control and hence recorded lower rescue norepinephrine boluses in comparison to ephedrine despite the difference in dosages between studies. Ahmed *et al*[106] also found norepinephrine to be superior to ephedrine in maintaining haemodynamic stability and also recorded lower mean norepinephrine doses compared to ephedrine in the management of hypotension during spinal anaesthesia for caesarean section ($p = 0.001$)

5.8 Limitations

I acknowledge some limitations of the present study that might have affected the outcome of the results:

1. The use of different interpretators could have affected interpretations hence possibly affecting outcomes such as the incidence of nausea and vomiting.

2. The use of traditional clinical signs in assessing the volume status of participants may not be so accurate and hence could have affected fluid therapy and haemodynamics of participants affecting the outcome of the study.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

1. The incidence of maternal spinal anaesthesia-induced hypotension is lower in patients who received norepinephrine than in patients who received ephedrine.

2. There is no statistically significant difference in the incidence of nausea and vomiting in parturients who received ephedrine and norepinephrine.

3. There is no difference in the incidence of reactive hypertension and bradycardia in parturients who received either ephedrine or norepinephrine.

4. The APGAR scores of neonates in the first and fifth minutes of delivery show no statistically significant difference between parturients who received either ephedrine or norepinephrine.

6.2 Recommendations

1. Given the superiority of norepinephrine in preventing spinal-induced hypotension, there should be a greater advocacy of its use in obstetric practice in Ghana.

2. It may be helpful to conduct a study with a larger sample size to establish any other benefit of norepinephrine such as reduction in perioperative nausea and vomiting.

3. In this study, only the APGAR score was assessed to determine neonatal outcomes. Future studies to look at other neonatal outcomes such as neonatal blood gas analysis as well as perinatal morbidity and mortality would be beneficial.

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APPENDICES

Appendix 1 – Participant Information Leaflet and Consent Form

Research Topic

Management of Spinal Anaesthesia-Induced Hypotension during Caesarean Section; a Comparison of Ephedrine and Norepinephrine

Name of Investigator

This research is being carried out by Dr. Patience Adjepong, a specialist anaesthesiologist at the Directorate of Anaesthesia and Intensive Care, Komfo Anokye Teaching Hospital, Kumasi.

Background

A significant number of women across the world, especially in Africa, are likely to give birth during their lifetime. Delivery by operation known as caesarean section (CS) is a common surgical operation performed worldwide as a result of pregnancy-related issues or maternal preference. Currently, spinal anaesthesia, which is an injection given at your back to cause numbness of the body part where the operation is being done to prevent you from experiencing pain, is the most common anaesthetic technique used for most CS. Spinal anaesthesia has many advantages and some disadvantages. Spinal anaesthesia most often causes a decrease in blood pressure after it is given. This decrease in blood pressure (hypotension) if not prevented or treated well when it occurs can harm the mother or baby. Several means of prevention and treatment of this hypotension include giving of infusion and drugs called vasopressors through your veins. These vasopressors also have their advantages and disadvantages hence the need to search for the best vasopressor at all times.

The most common vasopressor used for treating this hypotension at Komfo Anokye Teaching Hospital is ephedrine. Another drug called norepinephrine is currently giving good results when used to prevent and treat hypotension as a result of spinal anaesthesia.

After you agree to be part of this study, you will ballot to be placed in one of two groups namely: the Ephedrine group and the Norepinephrine group. The group you pick will not be known to you and the investigator.

The Ephedrine group will receive the medication, ephedrine, through the veins at the time of injection at the back even before the blood pressure drops and will be given additional

ephedrine anytime the blood pressure drops 10% or more. The Norepinephrine group will receive the medication, norepinephrine, through the veins at the time of injection at the back and will be given additional norepinephrine anytime the blood pressure drops 10% or more.

This study sets out to compare the effectiveness of ephedrine and norepinephrine in preventing and treating hypotension as a result of spinal anaesthesia during elective (scheduled) CS.

Aims of Research

The main aim of the study is to compare the effectiveness of ephedrine and norepinephrine when used to prevent hypotension as a result of spinal anaesthesia during elective caesarean section.

Study Procedure and what is required of each participant

After the study has been explained to you and you have agreed to be part, you will sign a consent form. Your blood pressure would be checked and recorded just before the operation. In theatre, you will be given an infusion through your veins after which an injection would be given at your back which will numb the middle and lower parts of your body. This is called spinal anaesthesia. You will remain awake and be able to breathe on your own but feel no pain during the operation. At the time of injection at your back, the test drug will be injected into your vein and your blood pressure will be checked frequently and recorded.

This drug will help keep your blood pressure from decreasing. However, if the blood pressure decreases, additional doses of the drug will be given to you to maintain it till the operation is done. Any discomfort in the form of nausea and vomiting experienced by you will also be managed and recorded. How well your baby is after delivery will also be assessed and recorded.

Risks of the Study

The risks involved in this study may include; pain at the site of injection of the drug, headache, abnormal heartbeats, high blood pressure, nausea and vomiting. The necessary precautions, however, would be taken to avoid and minimise these risks. Any side effect or adverse outcome that may occur would be recognised and managed accordingly.

Benefits of the Study

This study seeks to find an effective means of managing spinal anaesthesia-induced hypotension during caesarean section. Being part of this study will help contribute to the scientific knowledge of the management of spinal anaesthesia-induced hypotension.

Confidentiality

All data collected will be locked up in a special cupboard and analysed on a computer secured with a password. Only the investigator, supervisors, and the Ethics Board will have access to this information when needed. Strict anonymity would be ensured. No name or identifier will be used in any publication or report from this study.

Voluntariness

Your participation in this research is entirely voluntary. You are not under any obligation to be part of this study.

Alternatives to participation:

If you choose not to participate in this study, it will not affect your treatment in this hospital. You will receive the required treatment from the hospital and staff.

Withdrawal from the research:

You may freely withdraw from the research at any point in time without having to explain yourself. You may also choose not to answer any question you find uncomfortable or private.

Consequence of Withdrawal:

There will be no consequence, loss of benefit or care to you if you choose to withdraw from the study.

Contacts:

Please do not hesitate to contact me if you have any questions or concerns regarding this study;

Dr. Patience Adjepong
Tel: 0202536192
Email: patadjepong@yahoo.com

You may also contact my supervisors:

Dr William Addison,
Directorate of Anaesthesia and Intensive Care,
Komfo Anokye Teaching Hospital,
P. O. Box 1934, Kumasi.
Email: williamaddison@yahoo.com

Prof. Akwasi Antwi-Kusi
Directorate of Anaesthesia and Intensive Care,
Komfo Anokye Teaching Hospital,
P. O. Box 1934, Kumasi.
Email: antwikusi@yahoo.com

If you have any concerns about the conduct of this study, your welfare or your rights as a research participant, you may contact:

The Office of the Chairman,
Institutional Review Board,
Komfo Anokye Teaching Hospital,
Kumasi.

Consent Form

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information about the study, including that on procedures, risks and benefits, to enable the prospective participant to make an informed decision to or not to participate.

NAME: _____

DATE: _____

SIGNATURE/ THUMBPRINT: _____

Statement of person giving consent:

I have read the information on this study/research or have had it translated into a language I understand. I have also talked it over with the interviewer to my satisfaction.

I understand that my participation is voluntary (not compulsory).

I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it.

I can freely stop being part of this study at any point in time without being disadvantaged or needing to explain myself.

I have received a copy of this information leaflet and consent form to keep for myself.

NAME: _____

DATE: _____ SIGNATURE/THUMBPRINT: _____

Statement of person witnessing consent (For Non-Literate participants)

I, _____ (Name of witness), certify that the information given to _____(Name of participant), in the language she understands, is a true reflection of what I have read from the study Participant Information Leaflet attached.

WITNESS NAME: _____

DATE: _____ SIGNATURE/THUMBPRINT: _____

Appendix 2 – Questionnaire

Management of Spinal Anaesthesia-Induced Hypotension during Caesarean Section; a Comparison of Ephedrine and Norepinephrine

Patient ID:

Date:

Group: A ☐ **B** ☐ **(**please tick)

SOCIO-DEMOGRAPHY

Participant code …… Age ……

Sex: Female [ ]

Parity:

Gestational age:

CLINICAL CHARACTERISTICS

BMI:

Indication for surgery…….

ASAClassification:……

Appendix 3 – Monitoring Charts

Baseline BP (mmHg):

Baseline SAP (mmHg):

90% of SAP:

Baseline DAP (mmHg):

Baseline MAP (mmHg):

Baseline HR (bpm):

Fluid preloading (ml):

Total fluid administered (ml):

Sensory block height:

Time interval between initiation of spinal anaesthesia and start of surgery:

Time interval between initiation of spinal anaesthesia and delivery of foetus:

Duration of surgery:

Neonatal APGAR scores: 1^{st} minute: …… 5^{th} minute: ……

Time of administration of prophylactic vasopressor:

Time of first rescue dose of vasopressor:

Time interval between administration of prophylactic vasopressor and first rescue dose:

Total number of rescue vasopressor doses:

Total volume of vasopressor administered:

Incidence of Nausea and vomiting:

Indicate presence of any additional discomfort:

Monitoring Charts

Table 4.0 Before Delivery

Time after intrathecal injection (min)	1	2	3	4	5	6	7	8	9	10	11
BP (mmHg)											
SAP (mmHg)											
MAP (mmHg)											
Vasopressor administration (Yes / No)											
Volume of Vasopressor administered											
HR (bpm)											
Atropine administration (dose)											

Monitoring Chart

Table 5.0 Before and After Delivery

Time after intrathecal injection (min)											
BP (mmHg)											
SAP (mmHg)											
MAP(mmHg)											
Vasopressor administration (Yes / No)											
Volume of Vasopressor administered											
HR (bpm)											
Atropine administration (dose)											

Monitoring Chart

Table 6.0 After Delivery

Time after intrathecal injection (min)											
BP (mmHg)											
SAP (mmHg)											
MAP (mmHg)											
Vasopressor administration (Yes / No)											
Volume of Vasopressor administered											
HR (bpm)											
Atropine administration (dose)											

Appendix 4 - Ethical approval

Dr. Adjepong

GHANA COLLEGE OF PHYSICIANS AND SURGEONS

OUR REF: BA.100.001.49
Cell: 0243-690073
Email: exams@gcps.edu.gh

GHANA COLLEGE OF PHYSICIANS & SURGEONS

TEACHING HOSPITAL
RECEIVED
15 NOV 2022
ANAESTHESIA

P. O. Box MB 429
Ministries-Accra
Ghana

25th October 2022

The Head
Department of Anaesthesia
KATH
Kumasi

Dear Sir/Madam,

REQUEST FOR ETHICAL APPROVAL

Dr. Patience Adjepong, a Senior Resident in Anaesthesia, Ghana College of Physicians and Surgeons has submitted the revised Research Proposal for her Dissertation. Comments by the College Dissertation Review Committee have been duly addressed.

Kindly arrange for this Research Proposal to be submitted to the Research and Ethics Committee of the Komfo Anokye Teaching Hospital for ethical approval to enable her start her research work which is a requirement for the award of the Fellowship of the College.

Enclosed is a copy of the Research Proposal.

Counting on your usual cooperation.

Yours sincerely,

Prof. Richard Adanu
RECTOR

cc: Dr. Patience Adjepong

KOMFO ANOKYE
TEACHING HOSPITAL

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Our Ref. No.: *KATH IRB/AP/032/22*

Your Ref... No:.....

Komfo Anokye Teaching Hospital Institutional Review Board

9th August 2022

Dr. Patience Adjepong
Anesthesia and Intensive Care Directorate
Komfo Anokye Teaching Hospital,
P. O. Box KS 1934,
Kumasi.

Dear Dr. Adjepong,

Ethics Approval

Protocol title:	Management of Spinal Anaesthesia-Induced Hypotension during Caesarean Section; a Comparison of Ephedrine and norepinephrine
Study site:	Obstetrics & Gynaecology Directorate of the Komfo Anokye Teaching Hospital, Kumasi
Sponsor:	Self-funded

We write in response to the clarifications and revised documents following review by the Komfo Anokye Teaching Hospital Institutional Review Board (KATH IRB) in respect of the research study referenced above.

We are pleased to inform you that KATH IRB, per your correspondence of 9th August 2022, has given approval for the following study documents:

- *Protocol version 1.1 last updated 15th June 2022*
- *Informed consent form, version 1.2 last updated 9th August 2022*
- *Case report form, version 1.1 last updated 15th June 2022*

This approval **is subject to clinical trial clearance from the Ghana Food and Drugs Authority (FDA).**
Please inform KATHIRB when approval is given by the FDA with documentation.

Approval for the study is in effect until 8**th August 2023** and it is the responsibility of the Principal Investigator to maintain the study in good standing at the Komfo Anokye Teaching Hospital. The Board anticipates to be notified of the actual start date of your project.

Prior to the expiration of the study approval, you must submit to the KATH IRB an "Application for Continuing Review" along with provision of "Annual Report" when the study is ongoing, or a "Termination Report" if the research has been completed.
You must hastily report to the KATH IRB should a modification to the research be proposed, and without delay if an unanticipated development occurs before the next required review. Regulations do not permit you to modify conduct of the study in its present form prior to ethics approval; except where urgent action is required to eliminate an apparent immediate hazard to a study subject or other person. It is of utmost importance data generated from this study must be used for the intended purposes only.

Thank you.

Sincerely,

Prof. Kwabena Antwi Danso, BSc, MB ChB, FWACS, FGCS, FACOG
Chairman, KATH IRB

KOMFO ANOKYE TEACHING HOSPITAL

RESEARCH AND DEVELOPMENT UNIT (R & D)

CERTIFICATE OF REGISTRATION

REG. NO: RD/CR21/175

This is to certify that

Prof/Dr/Mrs/Mr/Ms. Patience Adjepong

has registered his/her proposed study titled Management of Spinal Anaesthesia-Induced Hypothesion during Caesarean Section; A Comparison of Ephedrine and Norepinephrine.

To be conducted at the Obstertrics and Gynaecology Directorate

Date of issue: 23-September-2021 Date of expiry: 22-September-2022

Deputy Director for Research

Dr Kwadwo Sarbeng

Signature

K20/0457210 *

*Receipt number

Note

This certificate does not constitute ethical clearance for the conduct of the study but site approval. Ethical clearance from the KATH Institutional Review Board (KATH-IRB) is required to conduct the study at KATH.

Version RD/REG-11TH DECEMBER, 2019