COMPARISON OF INTRAVENOUS EPHEDRINE WITH PHENYLEPHRINE FOR THE MAINTENANCE OF ARTERIAL BLOOD PRESSURE DURING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA

DISSERTATION REQUIRED IN PART FULFILMENT FOR THE AWARD OF FELLOWSHIP IN ANAESTHESIA OF THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA

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DECLARATION

It is hereby declared that this work is original unless otherwise acknowledged.

This work has not been presented to any other examining body for fellowship or any journal for publication.

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This is to certify that the candidate carried out this reported study in the Department of Anaesthesia, University College Hospital, Ibadan, Nigeria.

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ACKNOWLEDGEMENT

I hereby express my sincere gratitude to Professor O.A Soyannwo and Professor S.D Amanor Boadu my teachers and my supervisors who painstakingly supervised this research and read this write up.

I thank the Head of Department, Dr A.A Sanusi and all the Consultants and the Staff of the Department of Anaesthesia, UCH Ibadan for their useful suggestions during the planning and execution of this study.

I also want to acknowledge other colleagues and especially resident doctors on Labour ward duty who called me when there were cases for elective Caesarean Section. They contributed in no small way to this research.

I cannot but express my appreciation to my husband and children for being supportive throughout the duration of this study and my residency training programme.

Above all I thank the Almighty God, the Alpha and the Omega for his guidance and help thus far.
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LIST OF ABBREVIATIONS

% percentage

= equal to

< less than

> greater than

Kg kilogramme

mg milligramme

ASA American Society of Anesthesiologists

CSF Cerebrospinal fluid

Min minutes
SUMMARY

The aim of this prospective study was to compare the effects of intravenous bolus of Ephedrine with Phenylephrine for the maintenance of maternal arterial blood pressure during elective Caesarean section under spinal anaesthesia. The study population included sixty two healthy parturients ASA I or ASA II at term with singleton pregnancy scheduled for elective Caesarean section who consented to spinal anaesthesia.

Parturients were preloaded with 10ml/kg of crystalloid (Normal Saline or Ringers lactate) before the induction of spinal anaesthesia and 2.5 ml of 0.5% hyperbaric Bupivacaine was used for the spinal anaesthesia. Group A received intravenous bolus Ephedrine 5mg and Group B, Phenylephrine 100ug for the maintenance of maternal blood pressure. Hypotension was defined as a decrease in systolic blood pressure of more than 30% below baseline or below 100mmHg. Bradycardia was defined as heart rate <60 beats/min.

Patients' characteristics, spinal block height and baseline haemodynamic values were similar in the two groups studied. Seven patients (22.5%) in the Ephedrine group and eight patients (25.8%) in the Phenylephrine group developed hypotension.
Both vasopressors effectively restored the systolic blood pressures but phenylephrine values were greater than ephedrine values and was statistically significant in the 15th minute of the procedure, with p value 0.04. Also, the intra operative diastolic blood pressures were higher in the phenylephrine group compared to the ephedrine group, and were significant in the 15th and the 20th minutes of the procedure with p value of 0.03 and 0.04 respectively.

There was significant difference in heart rate between the two groups, analysis showed a higher heart rate values in ephedrine group compared to phenylephrine group which showed a downward trend with p value ranging from 0.01 to 0.04.

The mean oxygen saturation trends in the two groups were similar, because all patients had oxygen therapy routinely in this study, the effect of the vasopressor or spinal anaesthesia could not be ascertained. Changes in the respiratory parameters showed no statistical difference between the two groups.

Three patients (9.6%) developed nausea in the Ephedrine group and 4 (12.8 %) patients in the Phenyephrine group and these occurred in the hypotensive patients, no patient vomited during the procedure.
There was no need to repeat ephedrine or phenylephrine because no patient developed refractory hypotension.

The mean APGAR Scores were similar for the two groups; no baby had Apgar score of < 8 in either group.

In conclusion, Phenylephrine is safe and can be used as effectively as Ephedrine. It’s administration results in higher blood pressure values than Ephedrine in parturients undergoing Caesarean section under spinal anaesthesia.
CHAPTER ONE

INTRODUCTION

The use of spinal anaesthesia for surgical procedures dates back to 1885, when August Bier performed the first successful clinical subarachnoid block. It was not until 1940’s when Adriani and associates established safe standardised technique that this method of analgesia became popular in anaesthesia for obstetrics.¹

Regional anaesthesia for Caesarean section is increasing in popularity and gradually replacing general anaesthesia because of high incidence of deaths from failed intubation, hypoxia and Mendelson syndrome that are associated with general anaesthesia.² This fuels the present enthusiasm for performing Caesarean section under spinal anaesthesia. Conducting spinal anaesthesia however poses its own problems of which hypotension is the most frequent complication.³ The incidence of maternal hypotension is usually reported in the literature to range from 50-85%.⁴,⁵,⁶

Maternal hypotension poses a risk to the mother, causing cerebral hypo perfusion leading to maternal nausea and vomiting and in the baby it causes reduced utero placental blood flow leading to hypoxia and acidosis. However, when hypotension is recognised promptly and effectively treated, very little, if any, untoward side
effects occur to either the mother or the baby.

The prevention and management of hypotension has been the subject of much investigations and controversiess. The main stay of treating spinal anaesthesia induced hypotension is the use of intravenous vasopressors. Vasopressors that have been so employed include ephedrine, methoxamine, metaraminol, phenylephrine, and epinephrine. Of these ephedrine has been the vasopressor of choice in obstetric anaesthesia.

Ephedrine has mixed alpha and beta agonist properties and its pharmacological actions are partly dependent on the displacement of norepinephrine from sympathetic nerve endings and partly due to direct stimulation of adrenoceptors. It is less likely to compromise uteroplacental perfusion and therefore does not affect the foetus adversely. However, ephedrine crosses the placental barrier and provoke an increase in foetal heart rate and increase in foetal catecholamine levels. This increase in beta adrenergic stimulation can cause an increase in oxygen consumption and increase in glucose and lactic acid concentrations.

Phenylephrine is another vasopressor that can be used to treat hypotension. It does not cross the placenta and does not cause foetal acidemia as ephedrine does. It is a pure alpha
stimulating agent, it acts by counteracting the decrease in systemic vascular resistance induced by spinal anaesthesia. It has been found to be safe and effective when given in bolus intravenous doses to patients undergoing Caesarean section.\textsuperscript{11} The alpha agonist phenylephrine has been compared with ephedrine in terms of maintenance of blood pressure during spinal anaesthesia by many authors in the advance countries.\textsuperscript{7,8,10} There is however paucity of literature on such studies in Nigeria.

This study was designed to compare the effects of ephedrine with phenylephrine for the maintenance of arterial blood pressure in parturients undergoing Caesarean section under spinal anaesthesia at University College Hospital, Ibadan.
AIM OF STUDY

To compare the effects of bolus Ephedrine with Phenylephrine for the maintenance of maternal blood pressure during elective Caesarean section under spinal anaesthesia.

OBJECTIVES

- To determine the incidence of hypotension following spinal anaesthesia in obstetric patients.
- To compare the effects of bolus doses of Phenylephrine and Ephedrine on the blood pressure, heart rate and oxygen saturation.
- To compare the side effects of the two drugs.
- To compare the neonatal outcomes of the two interventions.

JUSTIFICATION OF STUDY

1. To confirm or refute other studies which have demonstrated that phenylephrine is safe and effective in maintenance of maternal blood pressure during elective Caesarean section under spinal anaesthesia.

2. The study will also serve as a local reference material for other workers in this area of spinal anaesthesia in future.

3. To continue research in obstetric anaesthesia, solving the problem of hypotension in obstetric anaesthesia.
CHAPTER TWO

LITERATURE REVIEW

Spinal anaesthesia is commonly used for Caesarean section. The advantages for the mother include remaining awake for the birth thereby initiating early bonding with the baby, avoiding the risks with general anaesthesia and facilitating effective postoperative pain relief. The use of spinal anaesthesia in obstetrics warrants specific considerations because there are alterations in maternal anatomy and physiology that have clinical anaesthetic implications and present potential hazard for the mother and the foetus during anaesthesia.

Fundamental to obstetric anaesthesia is a thorough understanding of the following, maternal physiological changes in pregnancy and special aspect of spinal anaesthesia in obstetric. Perioperative foetal effect of spinal anaesthesia, hypotension and spinal anaesthesia, and understanding of pharmacology of the drugs used to treat spinal - induced hypotension will be discussed.

MATERNAL PHYSIOLOGICAL CHANGES IN PREGNANCY

Pregnancy affects practically every system in the mother but of primary importance are the physiological changes in the cardiovascular system.
There is increase in blood volume from 60-65 to 80-85ml kg⁻¹ which is mainly due to an expansion of plasma volume. The plasma volume increase starts shortly after conception and implantation, and is maximal at 30-32 weeks. Red cell volume increases linearly but not as much as plasma volume. Thus haemoglobin concentration falls from 14 to 12gdl⁻¹, and the haematocrit falls.¹² The increase in blood volume is accompanied by an increase in cardiac output within the first 10 -12 weeks by 1.5 litre min⁻¹. By the third trimester, cardiac output has increased by about 44% as a result of about 17% increase in heart rate and 27% increase in stroke volume.¹² This is to meet the increased oxygen consumption.

The systemic vascular resistance falls during pregnancy to about 25% below the pre pregnant values and may be as low as 800 dynes.sec.cm⁻¹.¹³ Systolic blood pressure does not change significantly during pregnancy but there may be a significant fall in diastolic blood pressure below the pre pregnant value until 28 weeks of gestation.¹² However, the mean arterial pressure remain relatively constant throughout pregnancy. There is no demonstrable increase in both central vein and pulmonary capillary wedge pressure in pregnancy, despite increase in maternal cardiac output.¹⁴

The gravid uterus affects the maternal circulation not only
because of the blood it contains but also by its sheer size and weight. By pressing on inferior vena cava, the gravid uterus obstructs venous return from an average normal level of 11.4cm H$_2$O to approximately 24cmH$_2$O at term.$^{15}$ This is most pronounced when the patient is in the supine position with the weight of uterus and foetus pressing on the inferior vena cava. This results in supine hypotension syndrome.$^{16,17}$ Decrease in maternal blood pressure in the supine position results in decrease in venous return to the heart and thus decrease in cardiac output. The resultant hypotension may adversely affect the foetus by compromising placental blood flow. Parturients may be symptom free or may complain of distressing symptoms of fainting or nausea and vomiting.$^{16}$ Displacing the uterus to the left or by elevating the right hip restores maternal pressure to normal level in up to 90% of patients$^{17}$. Hence the routine uses of the wedge for uterine displacement in obstetrics care.

Engorgement of the epidural vasculature makes puncture of an epidural vein more likely. The decrease in the epidural space by the engorged vessels leads to decreased local anaesthetic drug requirement during spinal anaesthesia.$^{18}$

The mechanics of respiration is another important area in the parturient; the expanding uterus displaces the diaphragm cephalad,
decreasing the functional residual capacity, while the vital capacity and the inspiratory capacity remain unchanged because of an increase in antero posterior thoracic diameter. Although tidal volume increases by 40% and respiratory rate by 15% resulting in an increase in alveolar ventilation by 70%, rapid desaturation occurs during apnoea due to reduced functional residual capacity and increased oxygen consumption.\textsuperscript{12}

High spinal anaesthesia that involves paralysis of the intercostal muscle will reduce the contribution of the rib cage to breathing. Spinal anaesthesia for Caesarean section requires a block up to the level of T5 and as a consequence there are reductions in maternal peak expiratory flow rate, forced vital capacity and forced expiratory volume. Despite these reductions oxygen saturation is maintained. This seems to show that the level of block alone may not be an important factor in the development of desaturation and respiratory depression during spinal anaesthesia; other factors are the baseline saturation and age of patient.\textsuperscript{19} Oxygen is used during spinal anaesthesia in obstetric practice as part of the management of tissue hypoxia secondary to post spinal hypotension.\textsuperscript{20}
SPECIAL ASPECTS OF SPINAL ANAESTHESIA IN OBSTETRICS

Spinal anaesthesia adequate for Caesarean section will provide sympathetic nerve blockade up to T5 causing a fall in systemic vascular resistance. The arterial and venous vasodilatation reduce cardiac preload which in turn limit cardiac output. The blockade of cardiac efferent sympathetic fibers from T1-T4 results in loss of chronotropic and inotropic drive with resultant bradycardia and fall in cardiac output.\textsuperscript{12}

The decrease in systemic vascular resistance precedes the onset of hypotension, spinal induced hypotension usually develops rapidly. When hypotension occurs during spinal anaesthesia, it usually develops within 5 –20 minutes. For this reason the first half hour of a spinal anaesthesia is considered to be its most vulnerable period.\textsuperscript{21}

This mandates close monitoring of maternal vital signs and a prompt attention to complaints of nausea, vomiting or dizziness.\textsuperscript{22}

The degree of spinal induced hypotension that should be regarded as significant and requires intervention is universally accepted as decrease in a patient’s systolic blood pressure of more than 20% - 30% of the preanaesthetic value. A decrease in systolic blood pressure below 90 - 100mmHg or a decrease in mean arterial pressure to 80-85mmHg from the baseline values are also accepted
Smaller doses of local anaesthetics produce higher block in pregnant than in non-pregnant women. Because of the lower requirement for local anaesthetic, the amount of anaesthetic agent used for spinal anaesthesia in obstetrics should be reduced.

The major factor in the development of hypotension is the level of block, the propensity for parturients at term to develop unusually high level of block during spinal anaesthesia is probably best explained by the following reasons.

1. The cerebrospinal fluid in the spinal subarachnoid space of women at term is considerably less than in non-pregnant women. The reduction in CSF volume is due to venous engorgement in the epidural and subarachnoid spaces.

2. The CSF concentration of progesterone increases during pregnancy and there is a correlation between the increasing CSF progesterone and decreasing dose of the lidocaine required to produce equivalent segment of spinal anaesthesia as proposed by Datta et al.

3. Other factors such as lordosis of pregnancy may contribute to the higher level of spinal anaesthesia seen in pregnant women. Reduction in capacity of the subarachnoid space leading to changes in spinal fluid volume, increased inferior
vena caval pressure and increased nerve sensitivity to local
anaesthetic probably constitute the most important factors.

SPINAL ANAESTHESIA AND THE FOETUS

Spinal anaesthesia may affect the foetus directly, through the
effect of drugs, (the local anaesthetic agents or vasopressor) or
through the physiological changes caused by sympathetic blockade
in the mother which results in hypotension.

The uterine vasculature lacks an autoregulatory mechanism.
Therefore, uteroplacental blood flow correlates directly with
perfusion pressure and inversely with uterine vasculature
resistance.\textsuperscript{12} The oxygen content of foetal blood is normally low,
therefore any interference with placental blood flow may have
immediate and adverse effects on foetal oxygenation. One of the
consequences of poorly managed hypotension at Caesarean
section is foetal distress. It has been suggested that a maternal
systolic pressure of less than 100mmHg may be responsible for
foetal bradycardia\textsuperscript{25,26} and acid base abnormalities and if prolonged
may lead to neurobehavioural changes in the newborn.\textsuperscript{27} Although it
has been suggested that the duration of the period of hypotension is
as important as the actual numerical value and, if transient may be
of little consequence, this concern indicates that it should be
avoided or promptly treated.\textsuperscript{28}

The direct effects of spinal anaesthesia on the foetus by direct drug action are mild and transient. Subarachnoid administration of drug results in low/undetectable maternal plasma concentration. These extremely low plasma concentrations are not expected to cause any foetal adverse effect. In a study by Ngan Kee and workers\textsuperscript{29} foetal tachycardia developed in 13\% of the foetuses, possibly as a result of ephedrine crossing the uteroplacental barrier after intravenous administration, while Ayorinde and co-workers\textsuperscript{30} did not notice any chronotropic impact on the foetuses in their study of preemptive intramuscular phenylephrine and ephedrine therapy of spinally induced hypotension although phenylephrine does not cross the uteroplacenta barrier.

A desirable vasopressor for use in obstetric is one with no uterine vasoconstriction property because uterine vessels possess only alpha receptor and respond to sympathomimetic agent. Therefore, a vasopressor with alpha agonist property may have potential vasoconstrictive effect on the uteroplacental vasculature with worsening of foetal condition.
HYPOTENSION AND SPINAL ANAESTHESIA

Hypotension is the most common side effect of neuroaxial block in obstetrics. Over the last decade several interventions such as pelvic tilts, prophylactic preventive administration of fluid and the use of vasopressors have been employed to reduce the incidence of maternal hypotension.

In 1967, Wollman and Marx introduced the concept of preloading. These authors proposed that intravenous volume expansion should be instituted as a prophylactic rather than therapeutic measure in response to hypotension. They reported prehydration to be successful in all 14 patients receiving prophylactic volume expansion after spinal anaesthesia and a complete failure to prevent hypotension in non prehydrated parturients. Although, Clark et al reported similar results in 1976, the remarkable success of 100% prevention of hypotension was never reproduced.

There are lots of issues concerning prehydration regimens in terms of fluid characteristics, for example crystalloids versus colloid, volume quantity and timing of the fluid have all been discussed.

Rout et al also discovered that even large volume of crystalloid (greater than 1 litre) does not appear to confer additional
benefit over smaller volumes (250 millilitre) and may be detrimental in patients with limited cardiopulmonary reserve. This may be explained by the short half life of crystalloids. However, the use of colloids such as 4% Succinylated gelantin, Hydroxyethylstarch and Albumin solutions may be helpful in reducing the incidence of hypotension because colloids remain longer in the intravascular space. Ueyema and workers\textsuperscript{34} in a study on preloading compared crystalloids with colloids, and found 58% and 75% incidence of hypotension in patients given 0.5 litre of 6% Hydroxyethylstarch and 1.5 litre of Ringers lactate respectively. It would appear that a higher volume of colloid may be more effective in preventing hypotension but Rout and Rocke\textsuperscript{56} cautioned against the risk of pulmonary oedema, allergy and higher cost.

Aortocaval compression is present to some degree in all women at Caesarean section\textsuperscript{36}. The degree of compression is probably a major factor in the incidence and severity of hypotension, important hypotension seldom persists beyond delivery in the absence of major blood loss. Hypotension which is resistant to treatment often responds to turning to a full lateral position. Carrie\textsuperscript{36} has proposed the maintenance of the lateral position until the moment of skin preparation and Stoneham \textit{et al}\textsuperscript{37} have published research suggesting that haemodynamic stability is greater with
Carrie´s technique. With close attention to positioning, preloading, and the use of vasopressor, most parturients have minimal problems with hypotension.

Vasopressors are the mainstay in the treatment of subarachnoid – block – associated hypotension. Early pharmacologic treatment of hypotension is necessary to prevent adverse effects to the mother and the baby.

Vasopressors raise the blood pressure, usually by vasoconstriction and also by increasing cardiac output. The most commonly used are sympathomimetic agents, they exert their effect via the adrenergic receptors. They may act directly on the receptor or indirectly by causing the release of norepinephrine. Because of their mode of action, the indirectly acting drugs may exhibit tachyphylaxis on repeated administration.

The adrenergic receptors can be divided into alpha and beta which are further divided into sub types 1 and 2. Alpha 1 receptor stimulation causes vasoconstriction while alpha 2 receptor stimulation causes sedation and analgesia. Beta 1 receptor stimulation produces positive inotropic and chronotropic effect whereas beta 2 receptor stimulation relaxes the bronchus, vascular smooth muscle and the myometrium.

There was initially a great reluctance to use vasopressors in
obstetrics due to their effect on the uterine artery.\textsuperscript{39} Crawford et al\textsuperscript{40} thought that the maintenance of maternal blood pressure by vasopressor was responsible for foetal asphyxiation. Ephedrine remains one of the most extensively studied vasopressor used to treat hypotension in obstetric population.\textsuperscript{39} Evidence supporting the use of ephedrine came in 1974 by Ralston and Shnider\textsuperscript{41}, in which uteroplacental blood flow and fetal acid base status were measured in pregnant ewes following the administration of equipotent doses of ephedrine, metaraminol, mephentermine and methoxamine. The result showed that ephedrine had little effect on uteroplacental blood flow and foetal arterial pH whereas the other alpha agonists caused a marked reduction in uteroplacental blood flow.\textsuperscript{41} This result led clinicians to make ephedrine the drug of choice in the treatment of hypotension in obstetrics for many years.\textsuperscript{42}

Further study on pregnant ewes demonstrated that a gradual occlusion of the uterine arteries failed to produce foetal acidosis until blood flow was reduced over 60\%.\textsuperscript{43} Utero placental perfusion pressure should therefore be dependent on the systemic arterial pressure.\textsuperscript{44} Both ephedrine (alpha and beta agonist) and phenylephrine (alpha agonist) will correct the fall in arterial pressure and maintain cardiac output, ephedrine will achieve this by increasing the heart rate while phenylephrine will do so by
increasing the systemic vascular resistance.\textsuperscript{44}

Moran and colleagues\textsuperscript{11} compared phenylephrine and ephedrine and found that phenylephrine produces higher umbilical artery pH than ephedrine. Ephedrine induced beta adrenergic stimulation of the foetus is a possible mechanism for the foetal acidemia. In human, ephedrine given to the mother has foetal effect; it can increase foetal heart rate and foetal catecholamine level so the authors concluded that increase in metabolic rate due to ephedrine induced beta adrenergic stimulation was the most likely cause of increased incidence of foetal acidosis in the ephedrine group.\textsuperscript{11} Phenylephrine does not affect the foetal circulation although it may cause a reflex bradycardia in the mother.\textsuperscript{31}

Prophylactic intramuscular ephedrine has been described by Rout and colleagues.\textsuperscript{45} They compared intra muscular injection of ephedrine 25mg and 50mg and found that 50\% and 90\% of the patients developed reactive hypertension respectively. The intramuscular absorption reported to be unpredictable. Furthermore, neonatal acid base status was impaired in the ephedrine 50mg group with umbilical pH lower than the control group. They concluded that prophylactic administration of intra muscular ephedrine prior to spinal anaesthesia is associated with unacceptably high incidence of maternal hypertension should spinal
anaesthesia fail. Hence this method is not recommended.

In comparison, the advantages of intravenous ephedrine include the ability to withhold its administration until after the onset of anaesthesia is confirmed and better timing of drug effect to the onset of sympathetic block.\textsuperscript{46}

Magness and Rosenfield\textsuperscript{47} concluded that the relationship between phenylephrine dose and uterine vascular resistance is not linear and dramatic increase in uterine vascular resistance is seen with doses greater than 100ug. Furthermore, comparative studies have suggested that the use of ephedrine may be associated with greater foetal acidosis compared with phenylephrine.\textsuperscript{8,11,47}

These data\textsuperscript{8,11} suggest that contrary to common practice, ephedrine should not be the only ideal drug for management of spinal anaesthesia induced hypotension in obstetric patient.

**PHARMACOLOGY OF COMMONLY USED VASOPRESSORS**

**EPHEDRINE**

Ephedrine is a sympathomimetic amine\textsuperscript{38} similar in structure to the synthetic derivative amphetamine and methamphetamine. It is an alkaloid derived from a plant in the genus Ephedra. Ephedrine exhibits optic isomerism and has two chiral centers.

Its principal mechanism of action relies on its indirect action on
the adrenergic receptor system, it has agonist activity at both alpha and beta adrenergic receptors, its principal mechanism is to release norepinephrine from storage vesicle in presynaptic neurons. Ephedrine may be administered orally or intravenously. The oral bioavailability in man is 60%. It is degraded by monoamine oxidase at a lower rate than adrenaline because it does not contain catechol moiety, small amount is metabolized in the liver and its metabolites include p-hydroxylephedrine, norephedrine and conjugates of these compounds. The drug and its metabolites are excreted in the urine and the elimination half life of the drug is 3-6 hours.

Intravenous preparation of the drug is an aqueous solution containing either hydrochloride or sulphate compounds. It comes in either 30mg or 50 mg preparation per ml. The peak effect is 2-5 minutes.

Ephedrine is a weak base and its excretion can be accelerated by acidification of urine. Intravenous injection of ephedrine produces a prompt rise in blood pressure within seconds.

It is used in the treatment of hypotension in spinal and epidural anaesthesia and is considered the drug of choice in obstetric regional anaesthesia because the placenta and uterine blood flow are maintained. It is can also be use as a topical decongestant and as a bronchodilator in the treatment of asthma due to its beta
agonist action. Cardiovascular side effects include cardiac arrhythmia, angina, tachycardia and hypertension while in the central nervous system it may cause restlessness, confusion, insomnia, euphoria and nausea. In the respiratory system it may cause pulmonary oedema.

Ephedrine should not be used with antidepressant or in patients with closed angle glaucoma and in phaeochromocytoma.

Doses commonly used are 3-10mg intravenous bolus injection, 15-30 mg can be given intramuscularly\(^\text{47}\). Net price 3mg/ml at 10ml/ampoule is £ 2.70. The shelf life is 2 years.

PHENYLEPHRINE

Phenylephrine is a sympathomimetic vasoconstrictor\(^\text{38}\). It has one chiral center and can exist as either S or R enantiomer. It is a pure alpha adrenergic receptor. It is available in oral, nasal spray and intravenous forms. The L isomer is the active form.

Phenylephrine is a direct selective alpha adrenergic receptor; it does not cause the release of endogenous norepinephrine like ephedrine. It does not cause central nervous system stimulation, insomnia, anxiety, irritability and restlessness. Responses are more sustained than norepinephrine lasting 20 minutes after intravenous administration and as long as 50 minutes after subcutaneous
injection. Penetration of the brain is minimal and it does not cross the placenta.

It is metabolised by monoamine oxidase, an enzyme which is present in the liver and gastrointestinal tract, the principal route of metabolism are sulphation and glucoronidation of the 3 hydroxyl group to 3 hydroxyl mandelic acid and 3 hydroxyl phenyl glycol. Sulphate conjugations are formed from the metabolites. Excretion is via the kidneys.

The intravenous preparation is an aqueous colourless solution and comes in 10mg per 1 ml ampoule, the peak effect of intravenous route is 1 minute.

It counteracts the hypotensive effect of epidural and spinal anaesthesia. It causes vasoconstriction and uterine vasoconstriction. It can be used as nasal decongestant.

Bradycardia results from baroreceptor activation vasoconstriction. If tachycardia is undesirable phenylephrine is better than ephedrine. It causes hypertension and bradycardia.

The dose by intramuscular route is 2-5mg while the intravenous dose is 80-200ug, it can also be given by infusion at the dose of 30-60ug /min. Net price 10mg/ml at 1 ml/ampoule is £ 2.64. The shelf life is 2 years.
METARAMINOL

This sympathomimetic drug acts on both alpha and beta 1 receptor but has no effect on beta 2 receptor. It causes peripheral vasoconstriction, has positive inotropic effects with consequent increase in the systemic blood pressure. It is used in acute hypotensive states and also counteracts the hypotensive effect of spinal and epidural anaesthesia. Bradycardia, arrhythmias and hypertension are some of its side effects. Intravenous injection is 0.5-5 mg while 2-10mg by intramuscular injection.

METHOXAMINE

Methoxamine is sympathomimetic agent with direct action at the alpha 1 receptor. It thus produces a rise in blood pressure, with minimal effect on myocardiac contractility. Sinus bradycardia occurs as a result of vagal stimulation, it has no effect on bronchial smooth muscle and does not stimulate the respiratory or central nervous system, the intramuscular injection dose is 10mg -15mg.

EPINEPHRINE

Epinephrine is the predominantly natural catecholamine secreted from the adrenal medulla forming 80% of the total
catecholamine content in adults and the remaining 20% is norepinephrine. It has both alpha and beta stimulating properties causing both arteriolar and venous constriction, it also has chronotropic and inotropic actions on the heart.

Epinephrine\textsuperscript{39} is used for the maintenance of blood pressure in the critical care situation. In low doses the beta effect predominates causing increase in cardiac output and a fall in systemic vascular resistance, as the dose increases the alpha 1 activity leads to a rise in blood pressure. This predisposes the patients to cardiac arrhythmia and the beta 2 effects may cause a reduction in uterine tone.

Epinephrine is therefore not a particularly suitable drug for the maintenance of maternal blood pressure but may be used when other appropriate vasopressors are not available. The effect is dose dependent and may be given by slow intravenous injection but the effect is short lived, the drug should be titrated to effect and may be injected in 0.3-0.5ml aliquots of 1:10,000.
CHAPTER THREE
RESEARCH DESIGN

SAMPLE SIZE

The sample size was calculated using the formula for proportions since the outcome measures are qualitative.

\[ n = \frac{(Z\alpha + Z\beta)^2 \left( \pi_1 (1 - \pi_1) + \pi_2 (1 - \pi_2) \right)}{\delta^2} \]

- \( n \) = Sample Size
- \((Z\alpha + Z\beta)^2 = 7.849\) its power is 80%
- \(\pi_1\) = Proportion in expected group (55%)
- \(\pi_2\) = Proportion in control group (80%)
- \(\delta\) = Smallest clinically important difference to be detected
- \(\delta = \pi_1 - \pi_2\)

Therefore:

\[ n = \frac{7.849 (0.55) (0.45) + 0.80 (0.20)}{(0.25)^2} \]

\[ n = 31 \]

Sample size in each group is 31

PATIENTS AND METHODS

SITE OF STUDY

The study was a prospective comparative study. It was carried out at the University College Hospital, Ibadan.
INCLUSION CRITERIA

The study was carried out on healthy parturients ASA I or II at term with singleton foetus undergoing elective Caesarean Section under spinal anaesthesia.

EXCLUSION CRITERIA

Exclusion criteria included patient refusal, coagulopathy, raised intracranial pressure, sepsis at the injection site or systemic, antepartum haemorrhage, patients with haemoglobinopathy; pregnancy induced hypertension, multiple pregnancy, diabetes mellitus, renal impairment, maternal weight greater than 100kg and history of allergy to any of the local anaesthetic agent.

SAMPLING PROCEDURE

Pregnant women that fulfilled inclusion criteria were counselled on the Prenatal Ward a night before the surgery and after consenting they were eligible to be included in this study. The patients were randomised into 2 groups, group A and group B in a double blind fashion using a coded sealed envelope technique. The patients were unaware of the identity of the drug belonging to the coded group chosen.
After picking a code, the chief resident mixed the study drug into one millilitre of each drug. It would have been ideal for the pharmacy to code and mix the drug but such protocol is not yet available in our institution.

The drug was later handed over to the attending anaesthetist who then administered the drug. Both patients and the attending anaesthetists were unaware of the identity of the study drug, hence double blindness is ensured.

METHODOLOGY

The hospital institutional review committee approved this double blind randomised study, (Appendix IV). After obtaining written informed consent, 62 patients with American Society of Anesthesiologists physical status 1 and 2 scheduled for elective Caesarean section under spinal anaesthesia were recruited.

The patients were seen on the ward on the evening before the day of surgery. The study was explained to each patient and written consent was obtained using a consent form, Appendix 1. The patients were premedicated with oral Ranitidine 150mg for the night and on the morning of the surgery with a preoperative fasting instruction of 6 hours.

The patients were all transported to the operating room in the left
lateral position. In the Labour Ward theatre, data on patient characteristics was obtained by the investigator using the study form, Appendix 2.

The baseline heart rate, blood pressure, respiratory rate and oxygen saturation were taken and recorded. Anaesthetic machine, drugs and other intubating equipments were also checked. The blood pressure was taken with non invasive automated oscillometry while the oxygen saturation and the heart rate were measured with a pulse oximeter using NONIN comprehensive monitor. A 16 gauge intravenous cannula was sited in the non dominant hand, and a preload of 10ml/kg of Normal saline or Ringers lactate was infused over 15 to 20 minutes before instituting the spinal anaesthesia, the infusion rate was thereafter set to administer about 100ml/hour to give maintenance fluid.

Under aseptic condition, spinal anaesthesia was induced by the investigator with the parturients in the sitting position using a suitable spinal inter space between L3 and L5 vertebral surface marking. After identifying the spinal inter space, the skin and the inter spinous ligaments were infiltrated with 2 ml of 1% lidocaine. The subarachnoid space was entered with 25 guage Quincke spinal needle through a 20 guage introducer (Portex) after free flow of cerebrospinal fluid was observed 2.5 ml of hyperbaric 0.5%
Bupivacaine was injected. The end of the spinal injection was taken as time 0.

After induction of spinal anaesthesia, the patients were placed in the supine position with a left lateral wedge for uterine displacement while a pillow supported the head and the shoulder to limit the cephalad spread of the block. The height of block was tested with pin prick along the mid axillary line.

The mean time from subarachnoid block to incision time and the surgical incision to delivery time were recorded. The blood pressure, the heart rate, oxygen saturation and respiratory rate were measured every two minutes for the first 10 minutes and then at 5 minute intervals until the end of the procedure.

Hypotension was defined as a decrease in systolic blood pressure more than 30% below baseline or below 100mmHg while hypertension was an increase in systolic blood pressure of more than 30% above baseline.

Whenever there was hypotension, the randomised drug was administered intravenously and could be repeated if hypotension persisted. Atropine 0.5mg was to be given whenever the pulse rate was <60 beats /minute. The oxygen saturation and the presence or absence of nausea and vomiting were all recorded.

Supplemental oxygen at 3L/min was administered via nasal cannula
to all mothers and after the delivery of the baby 10 IU of oxytocin was given and another 10 IU of oxytocin was added to 500ml of Normal saline or Ringers lactate to sustain the uterine contraction.

The APGAR Scores of the babies were recorded at 1 and 5 min. Any hypotension that developed in the recovery room was to be treated with another dose of vasopressor and intravenous fluid. The study period was continued till the recovery room.

STATISTICS

Data analysis was performed using SPSS 11.0 computer based statistical software. The results were presented in tables and figures. Comparison of means and proportions were done using chi square $X^2$ with $p< 0.05$ considered as significant.
CHAPTER FOUR

RESULTS

A total of 62 healthy parturients, 31 in each group of American Society of Anesthesiologists (ASA) 1 and 2 physical status were studied. The two study groups were matched for age, weight, height, gestational age, volume of preload fluid transfusion, the birth weight of babies and their Apgar scores (TABLE 1).

INDICATION FOR CAESAREAN SECTION

Previous Caesarean section accounted for the highest indication for Caesarean section in the study population group with 19 patients (61.3%) in the Ephedrine group and 20 patients (64.5%) in the Phenylephrine group. Other indications for Caesarean section included abnormal presentation, post datism, recurrent mid trimester abortion and foetal macrosomia. (Table 2)

CHARACTERISTICS OF SPINAL ANAESTHESIA AND SURGICAL TIMES

All the patients had adequate level of anaesthesia before surgical incision was made.

The median levels of sensory block to pin prick were similar in the two groups of study, T5 (T4-T5) in group A and T5 (T4- T5) in group
B, p value of 0.40. The sensory block levels in those parturients that developed hypotension were above T4.
The mean time from subarachnoid block to incision was $5.16 \pm 0.24$ minutes in ephedrine and $5.2 \pm 1.42$ minutes in the phenylephrine group with p value of 0.50, while the surgical incision to delivery time was $6.20 \pm 1.36$ minutes in ephedrine group and $6.6 \pm 1.45$ minutes in the phenylephrine group with p value of 0.10. (TABLE 3) both were not significantly different.

**HYPOTENSION**

Table 3 also shows that the baseline blood pressure values for group A were comparable to group B and 7 patients (22.5%) and 8 patients (25.8%) in the Ephedrine and Phenylephrine groups respectively had a decrease of greater than 30% from their baseline systolic blood pressure with p value of 0.876. The incidence of hypotension in the 62 patients was 24.2%.
The mean time of the onset of hypotension after the subarachinoid was 4.4 min in ephedrine group and 6.5 min in the phenylephrine group with p value of 0.097.

**EFFECTS OF THE STUDY DRUG**

Changes in systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation and respiratory rate for the first 35
minutes after the spinal anaesthesia was administered are shown in figures 1,2,3,4 and 5 respectively. Changes in the systolic blood pressure after the vasopressor was administered were higher in the phenylephrine group than in the ephedrine group but became significant in the 15th minute of the procedure with p value of 0.04 and afterward the systolic blood pressures became higher in the ephedrine group but these were not significant. Figure 1

The mean baseline diastolic blood pressure was 74.84±7.04 for ephedrine group while the phenylephrine group was 77.26±8.55 and the p value was 0.23. Also, the intra operative diastolic blood pressures were higher in the phenylephrine group compared to the ephedrine group and became significant in the 15th and the 20th minutes of the procedure with p value of 0.03 and 0.04 respectively. Figure 2

The mean baseline heart rate was 84±8.31 for Ephedrine group while for Phenylephrine group was 87±8.72 with p value of 0.73. However, there was statistical difference in the two groups from the 8th minute of the procedure to the 30th minute, analysis showed a higher heart rate in ephedrine group compared to phenylephrine group which showed a downward trend in the heart
rate although no heart rate was below 60 beats per minutes, this was statistically significant in the 8th to 30th minute intraoperatively with p values ranging from 0.01-0.04. Figure 3

Figure 4 shows that the mean oxygen saturation values of the two groups were similar. The mean baseline oxygen saturation of the ephedrine group was 97.80±0.44 compared to 98.00±0.00 for the phenylephrine group. Intraoperatively oxygen saturation was above 98%, although all patients had oxygen routinely in this study so the effect of the vasopressor or spinal anaesthesia could not be ascertained.

Patients in phenylephrine and ephedrine groups had similar mean respiratory rate at baseline of 17.40±1.67 and 17.12± 1.64 respectively with p value of 0.77. Changes in the respiratory rates in the first 35 minutes after the bolus dose of the study were shown, with no statistical difference between the two groups as there were no recorded episode of respiratory depression in any parturient and respiratory rate was above 12beats/min throughout the study.

INTRA OPERATIVE SIDE EFFECTS

The incidence of intraoperative side effect in the two groups is presented on TABLE 5.
There was no recorded episode of bradycardia or tachycardia in either ephedrine or phenylephrine group.

One patient (3.2%) developed hypertension in the Ephrine group. After spinal anaesthesia, four patients (12.9%) and 3 patients (9.6%) developed nausea in the ephedrine group and phenylephrine group respectively and no patient had vomiting in the study groups, nausea were noticed in the hypotensive patients.

There was no need to repeat ephedrine or phenylephrine because no patient developed refractory hypotension.

No patient also developed shivering from spinal anaesthesia and no intraoperative visceral pain was noticed in the 62 parturients studied.

The 1st and 5th minute median APGAR scores were similar for the two groups. The median APGAR score in 1 minute for ephedrine group was 8.0 and for phenylephrine group was 9.0. None of the new born infants required tracheal intubation or admission into the special care unit in the immediate post delivery period. TABLE1
TABLE 1

Patients characteristics

Data expressed as mean ± SD, Apgar score expressed as median

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 31)</th>
<th>Group B (n = 31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.77±3.32</td>
<td>31.23±5.71</td>
<td>0.23</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.96±10.19</td>
<td>63.19±11.89</td>
<td>0.31</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.45±5.41</td>
<td>157.71±7.34</td>
<td>0.17</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>40.71±2.4</td>
<td>39.94±2.58</td>
<td>0.20</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.82±3.26</td>
<td>27.28±4.39</td>
<td>0.64</td>
</tr>
<tr>
<td>Volume of preloading (ml)</td>
<td>649.93±338.</td>
<td>642.74±286</td>
<td>0.19</td>
</tr>
<tr>
<td>Infant birth weight (g)</td>
<td>3325.8±199.9</td>
<td>3339±490</td>
<td>0.20</td>
</tr>
<tr>
<td>APGAR score 1min</td>
<td>8.0±0.56</td>
<td>9.0±0.72</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>10.0±0.36</td>
<td>10.0±0.17</td>
<td>0.41</td>
</tr>
</tbody>
</table>
### TABLE 2

**Indication for Caesarean Section**

Expressed as numbers and percentage

<table>
<thead>
<tr>
<th>Indication</th>
<th>Group A (n = 31) Ephedrine</th>
<th>Group B (n = 31) Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Caesarean section</td>
<td>19(61.3%)</td>
<td>20(64.5%)</td>
</tr>
<tr>
<td>Breech presentation</td>
<td>9(29%)</td>
<td>5(16.1%)</td>
</tr>
<tr>
<td>Transverse lie</td>
<td>3(9.7%)</td>
<td>0%</td>
</tr>
<tr>
<td>Postdatism</td>
<td>0%</td>
<td>1(3.2%)</td>
</tr>
<tr>
<td>Recurrent mid trimester abortion</td>
<td>0%</td>
<td>1(3.2%)</td>
</tr>
<tr>
<td>Fetal macrosomia</td>
<td>0%</td>
<td>4(12.9%)</td>
</tr>
</tbody>
</table>
TABLE 3

CHARACTERISTICS OF SPINAL ANAESTHESIA AND SURGICAL TIMES

Data expressed as mean ± while hypotension as figure and percentage

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=31) Ephedrine</th>
<th>Group B (n=31) Phenylephrine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum level of sensory block median range</td>
<td>T5 (T4-T5)</td>
<td>T5 (T4-T5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Subarachnoid block to incision time (min)</td>
<td>5.16±0.24</td>
<td>5.19±1.42</td>
<td>0.50</td>
</tr>
<tr>
<td>Surgical incision to delivery time (min)</td>
<td>6.20±1.36</td>
<td>6.22±1.45</td>
<td>0.10</td>
</tr>
<tr>
<td>Time of onset of hypotension (min)</td>
<td>4.4±1.51</td>
<td>6.5±2.26</td>
<td>0.097</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (22.5 %)</td>
<td>8 (25.8%)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4

**Cardiorespiratory Values at Baseline**

Data expressed as mean ± SD,

<table>
<thead>
<tr>
<th></th>
<th>Group A (n= 31) Ephedrine</th>
<th>Group B (n=31) Phenylephrine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean baseline systolic blood pressure</strong></td>
<td>121.42 ± 6.18</td>
<td>125.35 ± 5.88</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Mean baseline diastolic blood pressure</strong></td>
<td>74.84 ± 7.04</td>
<td>77.26 ± 8.55</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Mean baseline heart rate</strong></td>
<td>84.80 ± 8.31</td>
<td>87.50 ± 8.72</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Mean foetal heart rate</strong></td>
<td>139.6 ± 7.04</td>
<td>137.50 ± 7.07</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Mean baseline oxygen saturation</strong></td>
<td>97.80 ± 0.44</td>
<td>98.00 ± 0.00</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Mean baseline respiratory rate</strong></td>
<td>17.40 ± 1.67</td>
<td>17.12 ± 1.64</td>
<td>0.77</td>
</tr>
</tbody>
</table>
FIGURE 1

Intraoperative Mean Systolic Blood Pressure

Mean Systolic Blood Pressure

Time in Min

Ephedrine
Phenylephrine
FIGURE 2

Intraoperative Diastolic Blood Pressure

Mean Diastolic Blood Pressure

Time in Min

Ephedrine
Phenylepine
FIGURE 3

Intraoperative heart rate

![Graph showing intraoperative heart rate comparison between ephedrine and phenylephrine over time.](image_url)
FIGURE 4

INTRAOPERATIVE OXYGEN SATURATION

Error! Objects cannot be created from editing field codes.
FIGURE 5

INTRAOPERATIVE RESPIRATORY RATE.

Mean respiratory rate.

TIME IN MINUTES.

- Ephedrine
- Phenylephrine
TABLE 5
Intraoperative side effects

<table>
<thead>
<tr>
<th></th>
<th>Group A n = 31 Ephedrine</th>
<th>Group B n = 31 Phenylephrine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>7(22.5%)</td>
<td>8(25.8%)</td>
<td>0.349</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1(3.2%)</td>
<td>0%</td>
<td>0.31</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Desaturation</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4(12.9%)</td>
<td>3(9.6%)</td>
<td>0.16</td>
</tr>
<tr>
<td>vomiting</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Shivering</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Intraoperative visceral pain</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER FIVE

DISCUSSION

Hypotension remains a major concern of the anaesthetist whenever spinal anaesthesia is performed especially in obstetric patients. The main cardiovascular effect of spinal anaesthesia which is hypotension, is due to the fact that the local anaesthetic drug which is injected into the subarachnoid space blocks not only the sensory and motor fibers but also the preganglionic fibers. The hypotension is caused by blockade of the vasoconstrictor fiber which results in vasodilatation of resistance and capacitance vessels.\textsuperscript{12}

Fifteen patients in all (24.2\%) developed hypotension in this study. Desalu and Kushimo\textsuperscript{48} reported 70\% of their patients had hypotension in prehydrated group and 40\% in the ephedrine group, while Alahufita et al reported 60\%\textsuperscript{49} but Ngan Kee et al\textsuperscript{29} reported 80\% of hypotension despite prophylactic bolus of ephedrine. The reason for the low incidence of hypotension in this study may be due to the definition of hypotension used in this study. Hypotension was defined in this study as a decrease in systolic blood pressure of more than 30\% below baseline or below 100mmHg. Hypotension is
defined arbitrarily in most studies, with values ranging from a 20 - 30% reduction from baseline systolic blood pressure to absolute values less than 90-100mmHg. The incidence of hypotension clearly depends on its definition. Moderate hypotension was defined by Desalu and Kushimo as a decrease in systolic blood pressure of > 20% from the baseline value while severe hypotension was a decrease of > 30% from the baseline value. Therefore their incidence was higher because of inclusion of mild to moderate hypotension in their study.

Another reason may be due to the level of sensory block, in this study as there was no patient that had sensory block above T4, if a higher level of block observed in this study, this would have constituted a reason for higher incidence of hypotension. There is a relationship between the level of sensory block and the occurrence of hypotension during spinal anaesthesia, and the cephalad extent of a spinal anaesthesia at the end of Caesarean section may remain in the region of the upper thoracic dermatome with resultant adverse haemodynamic effect. Mojica and workers found that the peak block height above T5 was associated with an increase risk of hypotension. They also demonstrated an increase of 25% in the incidence of hypotension for each incremental of one segment above the peak sensory height. The sensory block level in
all the parturients that developed hypotension in this study were between T4-T5.

Equal doses of hyperbaric Bupivacaine were used for all the parturients based on previous study. Hyperbaric 0.5% bupivacaine was favoured rather than isobaric to minimise the risk of excessive rostral spread and high spinal following the use of isobaric bupivacaine. Finally, the low incidence of hypotension in this study may be attributed to strict adherence to prophylactic measures used (left lateral displacement, intravenous preloading with crystalloid and the use of pillow under the head and shoulders of the parturients).

All of the parturients in this study received a crystalloid preloading. The aim of prehydration before spinal anaesthesia is to increase venous return and preserve central blood volume. Despite the claims from the study of Wollman and Marx\textsuperscript{31} that crystalloid prehydration totally prevented spinal anaesthesia-induced hypotension, the use of crystalloid preloading does not always prevent hypotension after spinal anaesthesia for Caesarean section but reduces the incidence.

The onset of hypotension following injection of local anaesthetic in this study was 4.4 minutes in Ephedrine group and 6.5 in the
phenylephrine group which was however comparable to the 5 minutes recorded in the study by Desalu and Kushimo.\textsuperscript{40}

When hypotension occurs during spinal anaesthesia, it usually develops within 5 –20 minutes. For this reason the first half hour of a spinal anaesthesia is considered to be its most vulnerable period.\textsuperscript{21}

This study is in agreement with other studies on the role of vasopressor in the treatment of hypotension. Vasopressors have been shown to be more effective at limiting spinal hypotension than other treatment of hypotension like prehydration\textsuperscript{48} and left uterine displacement. Ephedrine has been the gold standard for the treatment of hypotension during spinal anaesthesia for more than 50 years. Vasopressors which have a predominantly alpha adrenergic effect such as phenylephrine are more effective at restoring maternal blood pressure than ephedrine which has both alpha and beta effect. However, alpha adrenergic drugs mediate increase in uterine artery resistance and may reduce placental blood flow despite effective treatment of maternal hypotension hence they are not favoured by many anaesthetists.

However, phenylephrine is rapidly becoming the vasopressor of choice in obstetrics anaesthesia. It has been shown to effectively increase maternal blood pressure during spinal-induced
hypotension without any detrimental effect to the mother or the baby. Neonatal acid base status is better with phenylephrine than with ephedrine, when they are given in equipotent doses.\textsuperscript{8,43,44} The dose at which phenylephrine causes increase in uterine artery resistance tend to be dose dependent according to Magness and Rosenfield\textsuperscript{47} who found the dose to be greater than 100ug hence the anaesthetists that frown at phenylephrine should consider lower doses.

Patients with pre-eclampsia, diabetic or hypertensive often have utero-placental insufficiency and may require caesarean delivery but Phenylephrine for the treatment of spinal induced hypotension is controversial which require further study.

This study revealed that the two vasopressors ephedrine 5mg and phenylephrine 100ug effectively restored systolic and diastolic blood pressure above the baseline. However, the mean systolic blood pressures were higher in the phenylephrine group than in the ephedrine group up to the 25\textsuperscript{th} minute of the procedure. Thomas et al\textsuperscript{8} tested bolus ephedrine 5mg and phenyephrine 100ug and concluded that phenylephrine 100ug was as effective as 5mg ephedrine in restoring maternal arterial pressure during spinal anaesthesia and did not have detrimental effect on the foetus or umbilical pH.
Dinesh Sahu\textsuperscript{51} compared three vasopressors, ephedrine, phenylephrine and mephentermine in 60 patients undergoing elective and emergency Caesarean section under spinal anaesthesia. He noticed that the three vasopressors maintained arterial blood pressure within 20\% limit of the baseline and that phenylephrine maintained it better in the first 6 minutes of the bolus dose as compared to ephedrine. This was explained by the peak effect of phenylephrine which is 1 minute and that of ephedrine is 2-5 minutes.

Ramanthan and colleagues\textsuperscript{52} studied 127 patients undergoing elective Caesarean section under epidural anaesthesia. They concluded that ephedrine and phenylephrine increase the blood pressure and that phenylephrine did not cause foetal acidosis when used in treating maternal hypotension.

The reduction in heart rate observed in the phenylephrine group is consistent with the finding from other studies. Pure alpha agonist will cause an increase in systemic vascular resistance and consequent blood pressure increase and will cause a slowing of the heart.

Hall et al\textsuperscript{10} encountered bradycardia as low as 40 beats/ minutes in 2 out of 10 patients studied and atropine was given.
All patients showed an increase in heart rate with ephedrine use due to its beta adrenoreceptor activity and one patient (3.2%) developed hypertension in this study probably the dose was too large for the patient. Hypertension also occurred in two patients and four patients had tachycardia following ephedrine use in a study by Desalu and Kushimo. Therefore, if tachycardia is undesirable phenylephrine may be better than ephedrine also if there is mitral stenosis, phenylephrine may have advantage over ephedrine.

Cooper and colleagues compared ephedrine and phenylephrine for the treatment of maternal hypotension and consistent with finding of other studies found that ephedrine caused more acidosis in the foetuses. Cooper and colleagues study showed a strong correlation between ephedrine use and an increase in the pCo2 (artery-vein). They concluded that ephedrine may be stressing the foetus and may have contributed to the foetal acidosis. They however found no correlation between phenylephrine dose and an increase in pCO2 (artery–vein). Although, it was not possible to analyse the umbilical pCO2 of the foetuses in this study due to lack of facilities however the mean APGAR scores of these babies can give a reflection of foetal outcome. In this study there was no difference in the mean APGAR
Scores of the babies between the two groups at one and five minute.

The current evidence support APGAR score as a better predictor of neonatal outcome than measurement of umbilical pH. In 1953, Virginia Apgar reported that neonatal survival through 28 days of life was related to the condition of the infant in the delivery room. Analysis of the relation of five minute APGAR scores to neonatal survival indicates that the APGAR score is just as useful today as it was 60 years ago.

Casey and colleagues carried out a retrospective study on singleton live infants delivered at 26 weeks or later and compared their APGAR scores and umbilical artery blood pH values to predict neonatal death during the first 28 days after birth. The five minute APGAR score was noticed to be a better predictor of neonatal outcome than measurement of umbilical artery pH even for newborn infant with severe acidosis. APGAR score is a good index of immediate survival while foetal blood gas analysis is a sensitive indicator of adequate placental perfusion.

Desalu and Kushimo studied hypotension in parturients undergoing Caesarean section under spinal anaesthesia and they attributed low APGAR scores < 7 at one minute in some neonates in their study to the frequency at which the blood pressures were
taken which was at 5 minutes interval and stated blood pressure readings should be every 1-2 minutes after subarachnoid block to follow the trend in changes and allow prompt treatment of any decrease in blood pressure. In this study the parturients were monitored every 2 minutes for the first 10 minutes then at 5 minutes interval until the end of the procedure. None of the newborns in the study required tracheal intubation, ventilation or admission into the special care baby unit.

None of the 62 parturients studied showed signs of respiratory depression (respiratory rate of less than 12/minute) during the study period. Respiratory depression may be due to high spinal anaesthesia that involved paralysis of the intercostal muscle which reduces the contribution of the rib cage to breathing. Spinal anaesthesia for Caesarean section requires a block up to the level of T5

Oxygen is administered during spinal anaesthesia in obstetric practice as part of the management of tissue hypoxia secondary to post spinal hypotension. All the parturients in this study had oxygen supplementation via nasal cannula to prevent desaturation. Crawford wrote in 1984⁵⁶ that it is advisable to provide the mother with supplemental oxygen until the time of delivery. His opinion was widely accepted through his writings and this established the
practice of oxygen at Caesarean section but solely for foetal reasons. Increasing the inspired maternal oxygen fraction increases oxygen delivery to the foetus. Although all patients had oxygen routinely in this study via nasal cannula, the effect of the vasopressor or spinal anaesthesia on oxygen delivery could not be ascertained and there was no difference in the oxygen saturation between the two group of study.

Kelly and colleagues\textsuperscript{19} did not notice any desaturation despite deterioration in respiratory mechanism and administration of 35\% of oxygen did not improve UV PaO2. However, Khaw and colleagues\textsuperscript{57} noticed that giving 60\% of FiO2 to parturients undergoing spinal anaesthesia resulted in a modest increase in umbilical vein (UV) PaO2 but cautioned against higher FiO2 above 60\% as it was associated with increased risk of free radical activity in both the mother and the foetus.

Maternal nausea and vomiting is also a significant problem during spinal anaesthesia for Caesarean section. Four patients (12.9\%) in the ephedrine group had nausea while 3 patients (9.6\%) in the phenylephrine group had nausea and no patient vomited in this study. Intraoperative hypotension is associated with the onset of emetic symptoms.\textsuperscript{58}
The physiological and anatomical changes of late pregnancy predispose parturients to emetic sequelae.\textsuperscript{59} Factors attributed to the high incidence of nausea and vomiting include hormonal changes in pregnancy, intraoperative pain, fundal pressure during difficult delivery and anaesthetic drugs.

From this study, the occurrence of nausea was mainly in hypotensive patients. Most of the nausea coincided with the onset of maternal hypotension, nausea is considered to be a premonitory sign of hypotension because of the associated brain stem hypoxaemia.

Previous studies have shown that hypotension is associated with intraoperative emetic symptoms during Caesarean section under spinal anaesthesia.\textsuperscript{46,59}

Hypotension, as a cause of nausea and vomiting should be anticipated and treated before administering antiemetic therapy. Datta et al\textsuperscript{46} reported that the incidence of emetic symptoms correlate with the presence of arterial hypotension. However phenylephrine has been noticed to prevent nausea and vomiting better than ephedrine. Cooper et al\textsuperscript{53} suggest a possible explanation which might be due to an increase in vagal tone following reduction in preload.
LIMITATION OF STUDY

Among the weaknesses of this study is the failure to measure umbilical pCO2, which is used to calculate the umbilicus arterial minus venous (A-V) pCO2 difference, this would have helped to support the idea of increased foetal metabolic rate following ephedrine use.

There is still debate about the ideal dose of ephedrine to correct maternal hypotension.

There is problem of availability of these vasopressors in this environment, phenylephrine in particular had to be ordered while ephedrine was not routinely available. Phenylephrine comes in 10mg per millilitre and the dose to be given was 100ug hence the need to be careful during dilution to prevent over dosage while ephedrine comes in 30mg and 5mg was given hence the risk of over dosage is minimal. It is therefore advised that efforts should be made that both drugs are available in all hospitals.
CONCLUSION

The results from this study showed that 24.2% of patients developed hypotension and that hypotension remains a common complication during Caesarean section performed under spinal anaesthesia.

Phenylephrine and ephedrine were found to equally maintain the arterial blood pressure in parturients undergoing Caesarean section under spinal anaesthesia although phenylephrine gives a higher blood pressure value than ephedrine but the availability and the ease of sourcing and mixing ephedrine makes it to be favoured and widely used in our environment.

Phenylphrine gave a lower heart rate while ephedrine gave a higher heart rate however oxygen saturation, neonatal outcome as assessed by Apgar scores were good and similar in the two groups.
RECOMMENDATION

Maternal hypotension remains a common complication during spinal anaesthesia for caesarean section. All preventive measures (volume preloading, left uterine displacement, the use of pillow to support the head and shoulder) should be used. Whenever there is a need to treat hypotension in obstetrics under spinal anaesthesia phenylephrine could be considered if available. Careful dilution of phenylephrine is necessary to prevent over dosage. Further studies are necessary, to determine the effective dose of phenylephrine to treat maternal hypotension.
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PATIENT INFORMED CONSENT

My name is Dr. Adigun Tinuola Abiodun. I am a resident Doctor at the Department of Anaesthesia, University College Hospital, Ibadan.

I am conducting a study titled “Comparison of Ephedrine with Phenylephrine for the maintenance of arterial blood pressure during elective Caesarean section under spinal anaesthesia”.

Low blood pressure (Hypotension) is a recognised effect of spinal anaesthesia and this can be treated with either Ephedrine or Phenylephrine. Either of these drugs will be administered to you should you develop low blood pressure.

These drugs should not have any side effect on you or your baby. You are free to refuse to take part in this study. You have the right to withdraw at any time if you choose to.

I will greatly appreciate your help in responding and taking part in this study.

------------------------------------------------------------------
Signature of Patient and date      Signature of Investigator and date
APPENDIX II

DATA COLLECTION FORM

STUDY TITLE; COMPARISON OF INTRAVENOUS PHENYLEPHRINE WITH EPHEDRINE FOR THE MAINTENANCE OF ARTERIAL BLOOD PRESSURE DURING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA

Name - (Initials)
Age -
Hospital number-
Weight (kg)
Height (cm)
Gestational age (weeks)
Indication for Caesarean section
Time of Subarachnoid block.
Time of skin incision
Time of onset of Hypotension
Time of delivery of baby
Fluids given -
Blood given -
Infant Birth weight (g)
Apgar score -
At 1min -
5min
Preanaesthetic Baseline Vital Signs

- Blood pressure
- Maternal Heart Rate
- Foetal heart rate
- Maternal Oxygen Saturation
- Maternal Respiratory Rate

Complications of drug / procedure

- Hypertension            YES  OR  NO
- Nausea but no vomiting  YES  OR  NO
- Nausea with vomiting    YES  OR  NO
- Bradycardia             YES  OR  NO

If yes treat with 0.5mg Atropine

- Other complication please state

**MATERNAL HEAMODYNAMIC PARAMETERS**

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APPENDIX III

ETHICAL CONSIDERATION

1. STATEMENT OF CONFIDENTIALITY

Patient participation in the clinical research is confidential. Only the investigator will have access to the patient’s identity and to information that can be associated with his /her identity. In case of publication of this research no personal identifying information will be disclosed.

2. STATEMENT OF TRANSLATION TO LOCAL LANGUAGE

The content of the consent form will be translated to patient’s own language for better understanding, and if there is language barrier, an interpreter will be used for this purpose.

3. BENEFICENCE TO PARTICIPANTS

The patients will not be required to pay for the study drugs, this will be provided by the investigator.

4. NON MALEFFICENCE TO PARTICIPANTS

The study will not expose the patients to any drug that has not been used safely in the past.

5. VOLUNTARY PARTICIPATION

The choice to participate in this study shall be voluntary, the patients have the right to withdraw at any stage of the study. This will not affect the patient’s statutory rights as a patient.
UI/UCH INSTITUTIONAL REVIEW COMMITTEE

CERTIFICATION LETTER

Principal Investigator: Dr. Adigun Tinuola Abiodun

IRC Protocol No: UI/IRC/05/0035

Protocol Title: COMPARISON OF INTRAVENOUS PHENYLEPHRINE WITH EPHEDRINE FOR MAINTENANCE OF ARTERIAL BLOOD PRESSURE DURING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA.

STATUS: APPROVED

The UI/UCH Institutional Review Committee has reviewed your protocol titled: “Comparison of Intravenous Phenylephrine with Ephedrine for Maintenance of Arterial Blood Pressure during Elective Caesarean Section under Spinal Anaesthesia.”

The study aims at comparing the efficiency of ephedrine with phenylephrine in maintaining maternal arterial blood pressure during caesarean section under anaesthesia. The outcome of the study would contribute to future study on the topic.

THE RESEARCH PROTOCOL DESCRIBED ABOVE HAS BEEN REVIEWED BY THE UI/UCH IRC WITH THE RESULTS AS INDICATED.

[Stamp: UI/UCH IRC APPROVED 21 JUL 2005]

F. A. Adeniyi
Professor/Chair, UI/UCH IRC
E-mail: uiiuchirc@yahoo.com

International Regulations require that any severe drug reactions and unexpected adverse occurrence to subjects during the conduct of this research be reported to the UI/UCH IRC Secretariat promptly. Any changes to this protocol must be submitted for review to the UI/UCH IRC.