PROPHYLACTIC PHENYLEPHRINE BOLUS VERSUS INFUSION FOR PREVENTION OF MATERNAL HYPOTENSION DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION AT WINDHOEK-BASED TEACHING HOSPITALS, NAMIBIA

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBRIVIATIONS AND ACRONYMS

ACE	Angiotensin Converting Enzyme
ADH	Antidiuretic Hormone
ASA	American Society of Anesthesiologists
CO	Cardiac Output
CS	Caesarean Section
CSF	Cerebrospinal Fluid
IONV	Intraoperative Nausea and Vomiting
NIBP	Non- Invasive Blood Pressure
PB	Phenylephrine Bolus
PE	Phenylephrine
PI	Phenylephrine Infusion
RCT	Randomized Control Trial
SPSS	Statistical Package for Social Sciences

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DEDICATION

This research is dedicated to my family; especially my husband, Mr Teofilus Shiimi and my daughters for your continuous support and words of encouragement. You were my sources of strength during my weakness. Thank you for being my pillar of strength. May God bless you abundantly.

DECLARATIONS

I, Ebba Panduleni Shaanika, hereby declare that this study is my work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree to any other institution.

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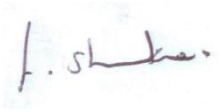

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ABSTRACT

Background: Maternal hypotension is a common complication of spinal anaesthesia during caesarean delivery. Injection of vasopressors with non-pharmacological measures have been investigated for prevention of martenal hypotension as well as the foeto-maternal effects of treatment.

Aim: The primary aim of the study was to compare prophylactic 50 mcg phenylephrine bolus (PB) with a fixed continuous 25 mcg/min phenylephrine infusion (PI). The secondary aim was to assess the side effects and neonatal outcomes of the two treatments.

Settings and design: A prospective, randomised, controlled double-blinded study was conducted in the maternity theatres of Windhoek Central Hospital and Katutura Intermediate Hospital.

Methods and Materials: Ninety-two eligible parturients, ASA I and II, scheduled for elective caesarean section under spinal anaesthesia were recruited and randomised into two groups. PB group received a prophylactic 50 mcg phenylephrine (PE) bolus immediately after spinal anaesthesia whereas PI group received prophylactic 25 mcg/min PE infusion. Maternal blood pressure, heart rate and side effects were recorded every minute for the first 20 minutes while neonatal outcome was assessed with Apgar score at the 1st and 5th minute.

Statistical Analysis: Categorical variables were presented in numbers and percentages. Normally distributed continuous variables were presented as mean standard deviation (±SD) and compared using t-test. Non normally distributed continuous variables were compared with Mann-Whitney test. A p-value of $p< 0.05$ was considered significant.

Results: Parturients in the PI group had a significantly lower incidence of hypotension than PB group (32% vs 71% $p = 0.0001$). Nausea and vomiting was lower in PI group than PB group

(13% vs 31% p = 0.033). Reflex bradycardia was comparable between groups (p= 0.489). No parturient in the PB group had reactive hypertension whereas 11% of participants in PI group did (p=0.024). Participants in the PI group received about 36% more phenylephrine than the PB group (p=0. 0277). Apgar scores between the two groups showed good neonatal outcomes.

Conclusion: There was better control of blood pressure in the PI group than PB group. Both groups had similar incidence of reflex bradycardia as well as good neonatal outcomes. Intraoperative nausea and vomiting (IONV) was higher in the PB group than PI group, whereas no reactive hypertension experienced in PB group.

Keywords: Spinal induced hypotension; Spinal anaesthesia; Prevention; Caesarean section; phenylephrine prophylaxis; phenylephrine bolus; phenylephrine infusion

CHAPTER 1

1.0 INTRODUCTION

1.1 Background

Spinal anaesthesia has become a technique of choice for uncomplicated caesarean section over the years globally.[1] Caesarean delivery is defined as a surgical procedure used for the delivery of the baby through incision in the abdomen and uterus.[2] The Royal College of Obstetricians and Gynaecologists classified caesarean delivery (CS) under four broad categories depending on the maternal and foetal condition at the time of the procedure.[2] Categories I – III are emergencies of different timelines in relation to decision to delivery interval while category IV are caesarean deliveries carried out electively at the time suited for the patient and the medical team.[2-4]

Worldwide spinal anaesthesia is promoted in uncomplicated operative deliveries as it has notable advantages over general anaesthesia such as allowing the mother to be awake during the procedure hence the birthing process becomes meaningful. It is simple, cost effective and efficient technique that provides complete sensory and motor block as well as postoperative analgesia with a high success rate.[3-5] It avoid risks associated with airway interventions as well decreases the incidence of deep venous thrombosis and lesser amount of haemorrhage.[3-5]

Despite these advantages, there are drawbacks to spinal anaesthesia. The most common adverse effect for the mother is hypotension with the incidence as high as 70-80% when pharmacological prophylaxis are not used.[3-5] There are controversies surrounding the definition of spinal induced hypotension (SIH) during spinal anaesthesia. A study by Klöhr and colleagues found fifteen different definitions of hypotension in studies carried out between 1999 and 2009. Definitions used

in these studies were looking at the systolic blood pressure within the range of 80-100mmHg or a decrease from the reference blood pressure ranging from 0-30% or the combination of both values. Many studies concluded on two commonly used definitions: a decrease of blood pressure by ≥20% from the baseline (prior to spinal anaesthesia) or a drop of systolic blood pressure to ≤100mmHg or a combination of both values as per international consensus.[3-5] A drop in blood pressure may initiate intraoperative nausea and vomiting which may induce undesired conditions for the patient and surgical staffs.[3-5]

Different strategies have been employed to prevent hypotension with varying success such as avoidance of supine hypotension syndrome via left uterine tilt, crystalloid or colloid preload/co-loading and pharmacological agents.[3-5] No single intervention has been proven to eliminate spinal induced hypotension.[6-8] Among the vasopressors, ephedrine (a mixed α and β agonist) was previously recommended as the drug of choice in obstetrics, but there is now increasing evidence that this agent has the propensity to decrease foetal pH and increase base excess.[9-11] Phenylephrine, a pure α-agonist, is currently considered as a preferred drug in uncomplicated pregnancies.[9-11] The international consensus recommends the use of ephedrine or phenylephrine for management of spinal induced hypotension during caesarean section.[12]

The aim of vasopressor in spinal-induced maternal hypotension is to return the systemic vascular resistance to normal or closer to physiological values and an agent with predominantly α-agonist activity is recommended.[12]

1.2 Problem statement

Hypotension following spinal anaesthesia during caesarean section is a frequent complication when pharmacological prophylaxis are not used.[3-5] Avoiding spinal induced hypotension is

important for maternal and foetal safety as well as maternal comfort since even minor degrees of hypotension may be associated with an increased incidence of intraoperative nausea and vomiting. Okudaira et.al reported that Spinal induced hypotension of more than two (2) minutes was associated with poor neonatal neurobehavioral outcome as this prolonged period of hypotension resulted in trivial rise in oxypurines and lipid peroxides in the umbilical vein and these chemicals are associated with ischaemic-reperfusion injury, hence the necessity to institute prophylactic measures during caesarean section.[12-15]

1.3 Rationale of the study

Studies are lacking on the prevention and management of spinal induced hypotension in parturients in Namibia. The current practice in Katutura Intermediate Hospital and Windhoek Central Hospital is the administration of fluid, ephedrine or phenylephrine boluses following a drop of more than 20% in systolic blood pressure from the baseline or any drop in systolic blood pressure associated with nausea and vomiting. The goal of prophylactic phenylephrine bolus or infusion is to offer a more effective method of preventing spinal hypotension, nausea and vomiting with fewer clinical interventions. This is the first study in our hospitals which could provide evidence for the prevention of spinal induced hypotension in parturient undergoing caesarean section in line with the International consensus guidelines for the use of vasopressors routinely and preferably prophylactically.

1.4 Objectives of the study

Overall objectives

The primary objective of this study was to investigate bolus injection of 50 mcg phenylephrine versus a dose of 25 mcg/min phenylephrine as continuous infusion in the prevention of spinal induced maternal hypotension.

Specific objectives:

- To compare the incidence of intraoperative nausea and or vomiting (IONV)(defined as nausea and or vomiting experienced post citing spinal anaesthesia) between the patients who received bolus injection of 50 mcg phenylephrine versus a dose of 25 mcg/min phenylephrine as continuous infusion over the first 20 minutes after citing the spinal block
- To compare the incidence of reactive hypertension (defined as blood pressure $\geq$ 140 mmHg) between the two groups
- To compare the incidence of maternal bradycardia (defined as a heart rate < 60 beats/min) between the two groups
- To compare the total phenylephrine dose administered between the two groups
- To compare the Apgar score at 1 min and 5 min post-delivery between the two groups.

1.5 Hypothesis testing

Null hypothesis: There is no difference between 50 mcg bolus injection of phenylephrine and 25 mcg/min continuous infusion of phenylephrine in the prevention of spinal-induced maternal hypotension

Alternate hypothesis: There is a difference between 50 mcg bolus injection of phenylephrine and 25 mcg/min continuous infusion of phenylephrine in the prevention of spinal-induced maternal hypotension

1.6 Study Limitations

Umbilical cord blood gas estimation could not be used in this study for neonatal status evaluation due to unavailability of blood gas machine in the two maternity units. Patients had various degrees of hydration when they presented to theatre for caesarean delivery.

1.7 Delimitations

Apgar scores was used for neonatal status evaluation. All patients were co-loaded with a 1000 ml of Ringer's lactate.

1.8 Summary

In this chapter, the background of the study, problem statement, rationale, study objective, hypothesis testing, limitations and delimitations are discussed. The next chapter provides a review of the relevant literature to enhance a better understanding of the problem.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1. Introduction

This literature review gives an overview of the pathophysiological changes occurring in parturients in general, it also looks at its association to the development of maternal hypotension during caesarean delivery conducted under spinal anaesthesia. However, the main overview of this review would centre on the prophylactic use of phenylephrine infusion versus phenylephrine bolus in the prevention of SIH, other methods such as fluid loading, positioning protocols has been included as the use of vasoactive agents could not efficiently prevent SIH as a sole method. The review mainly focused on phenylephrine use in parturients, furthermore other vasoactive agents such as ephedrine, norepinephrine were covered as well. Studies on the dosing, method of administration and popular methods of dosing were mentioned. In general, the literatures reviewed presented a multimodal approach to prevent SIH.

2.2 Spinal anaesthesia

2.2.1 Definitions

Spinal anaesthesia: The neuraxial technique whereby local anaesthetics are injected into the cerebrospinal fluid (CSF) to produce sensorimotor block. [13-15]The injection is performed below L2 vertebrae, where spinal cord ends in adults.[13-15]

Spinal induced Hypotension: The two common definitions used in this study are either a decrease of reference blood pressure by ≥20% prior to spinal anaesthesia or a drop of systolic

blood pressure to ≤100mmHg or a combination of both values based on the findings by Klöhr and colleagues as well as the international consensus.

Bradycardia: Heart rate < 60mmHg

Hypertension: A blood pressure of ≥ 140/90 mmHg

2.2.2The significances and Pathophysiological effects of spinal induced hypotension in pregnancy

Pregnancy causes diverse physiological changes on various body organs. These changes are attributed to the effect of the maternal hormone balance, biochemical shifts in response to large metabolic demands required by a growing foetus and the placenta plus the expanding forces of the gravid uterus.[13-15] The physiological changes on the cardiovascular system have significant anaesthetic implications during spinal anaesthesia.[13-15] Among the hormonal changes are increment of progesterone, nitric oxide, and prostacyclin which causes a reduction in systemic vascular resistance accompanied by a decline in response to norepinephrine and angiotensin, and as a result the renal artery and aorta dilates. [13-15] The elevated cardiac output is attributed to the physiological increase in heart rate and the role of the renin-angiotensin system.[13-15] Renin-angiotensin stimulates conversion of angiotensin I to angiotensin II by the effect of angiotensin-converting enzymes (ACE) and the net effect is increased blood volume. Angiotensin II results into vasoconstriction and increased antidiuretic hormone (ADH) and aldosterone and this results into an increased blood pressure. [13-15]

The causes of spinal induced hypotension are multifactorial .[13-15]The cardiovascular system changes are of significance in the prevalence of hypotension during pregnancy. Increased serum levels of progesterone mediates increased neuronal sensitivity.[13-15] It explains why there is an

increased sensitivity to local anaesthetics during pregnancy hence an exaggerated response of hypotension.[13-15] The hormonal effects also engender peripheral vasodilation and the net result is a decrease in systematic vascular resistance. Furthermore, the compensatory mechanisms such as a rise in heart rate, vasoconstriction to normalise the cardiac output and return the blood pressure to physiological reference values are impaired during spinal anaesthesia.[13-15] The combination of impaired compensatory mechanisms, hormonal effects and aortocaval compression due to the gravid uterus are among the important reasons for a high prevalence of hypotension in parturients in comparison to normal population.[13-15]

Nausea and vomiting during spinal anaesthesia occurs via the following pathophysiological mechanisms which is a result of hypotension.[13-15] Firstly, hypotension results into decreased brain perfusion which causes transient brain ischaemia, and this activates the vomiting centres.[13-15] Secondly, spinal anaesthesia results in overall reduction of splanchnic blood flow by 20%. [13-15] Reduction in splanchnic blood flow stimulates the splanchnic system to release emetogenic substances from the gastrointestinal tract which induces nausea and vomiting. [13-15]

2.2.3 Different methods employed in prevention of spinal induced hypotension

Untreated spinal induced hypotension may be of critical consequences involving both mother and foetus, hence prevention and treatment during caesarean delivery has been a subject ever since spinal anaesthesia has been applied.[16-19] No single intervention has been proven to eliminate spinal induced hypotension.[16-19] Different studies and practical experiences proposed that effective prevention and treatment of hypotension needs different approaches and this includes administration of crystalloids during anaesthesia, restriction of aortocaval compression in a gravid uterus and management with vasopressors.[16-19]

2.2.3.1 Fluid loading

Different studies has been carried out on the influence of crystalloid and colloid preloading and/ or coloading to prevent hypotension. Preloading with crystalloids 500 – 1500 ml did not prove to be effective due to prompt spreading of administered fluids in the extravascular space, hence co-loading (immediate fluid administration concurrently with spinal block) has been shown to enhance the outcome of this method.[18-21] Further investigations on co-loading, has concluded that there may be minimal fluid re-distribution because of instantaneous vasodilation .[18-21] In comparison with preloading and co-loading it has been discovered that co-loading is more effective to preloading when two methods are applied using the same types of fluids, hence Crystalloid co-loading is greater to crystalloid preloading [18-21] and alike to colloid preloading .[18-21] Furthermore, the use of colloid fluids has been associated with higher cases of anaphylactic reactions.[22-24] Several studies compared different types of fluids and the conclusion was crystalloid co-loading was alike to colloid co-loading.[22-24] In terms of fluid volume to be administered, the amount required for colloids is lesser than crystalloids.[22-24] Overall for optimum controlling of blood pressure during spinal anaesthesia for caesarean delivery, it was proposed to combine co-loading of 1000 – 2000 ml of crystalloids with a vasoactive agent.[22-24] The aim is to maintain the SAP drop of ≤ 10% from the baseline and/or avoid a drop of >20%.[25-26] In conclusion, the existing data encourage the use of fluid co-loading than preloading.

2.2.3.2 Vasopressors

Choice of vasopressor

Several studies on have shown that the non-pharmacological methods alone are ineffective in preventing spinal hypotension during caesarean delivery hence it was considered crucial to add a

vasoactive agents. The use of vasopressors is broadly acknowledged as an efficient method for prevention of SIH in addition to fluid loading.[27-32] The first drug studied in parturients in the prevention of SIH is dopamine, followed by ephedrine, and of recent phenylephrine and norepinephrine are receiving attention.[27-32]

Phenylephrine is principally used as an alternative to ephedrine as ephedrine is associated with the tendency to cause fetal acidosis.[8,33-35] Studies have encouraged the use of a prophylactic phenylephrine dose as the preferred method to inhibit a decline in blood pressure in healthy women.[8,33-35]

Phenylephrine (PE) is a pure alpha-1 adrenergic agonist.[8,33-35] Even though its chemical structure is related to adrenaline and ephedrine, its mechanism of action differs as it causes intense peripheral vasoconstriction resulting in a rise in systemic vascular resistance. Its effect on cardiac output and end-organ perfusion are variable depending on coexisting patient factors such as the mode of administration, hydration status and the patient's reference heart rate, to mention a few. [8,33-35]. The common side effect of phenylephrine is a reflex bradycardia. It commonly occurs with high doses during phenylephrine infusion.[8,33-35] Its effect on cardiac output is variable based on the population.[8,33-35]

During caesarean section, phenylephrine is commonly administered intravenously either by infusion or in the form of bolus injections, doses ranging from 50-100mcg.[37-42] The bolus administration may require repeated administration as phenylephrine has a short duration of action ranging from 5 -20 minutes.[8,35-38] Phenylephrine can be safely administered without the fear of tissue necrosis in comparison to other vasoactive agents.[8,35-38]

In addition, studies have shown that phenylephrine has a low prevalence of foetal acidosis, low transplacental transfer and low prevalence of maternal nausea and vomiting.[8,35-38]

Ephedrine is a non-selective sympathomimetic amine and it acts directly both on alpha and beta receptors. It works primarily indirectly by inhibiting neuronal norepinephrine reuptake and by replacing more norepinephrine from storage vesicles.[39-40] The characteristic above explains its slow onset of action as well as longer duration of action in comparison with phenylephrine. Stimulation of cardiac beta1- adrenergic receptor results into an increased heart rate and heart contractility.[39-40] Higher levels of ephedrine has been detected in the foetal blood with median umbilical venous/ maternal ratios of 1.13 in comparison to phenylephrine which had a median umbilical venous/maternal ratios of 0.17.[39-40] Recent studies have discovered that neonates born to mothers on higher doses of ephedrine either had a component of acidosis, higher serum lactate as well as higher levels of serum catecholamines.[39-40]

Ephedrine is still considered a drug of choice in a fewer conditions, such as: [39-40]

- Patients with a low heart rate either a pre-existing low heart rate or a low heart rate resulting from spinal induced hypotension[29--33]
- Patient with impaired cardiac function.[33]
- Patients with impaired placental perfusion as a reduced cardiac output by phenylephrine will further impairs placental blood flow. [33] Mohta et.al's randomised control study on parturient with foetal compromise concluded that there was no discrepancy between ephedrine and PE concerning foetal Apgar scores and umbilical pH.[33] In addition to that study, Sen et al concurred that neither agent was superior with regard to acute foetal compromise in relation to foetal acidosis.[17]

- Pre-eclampsia: These patients have a higher baseline systemic vascular resistance, hence administration of an alpha agonist might decrease uteroplacental perfusion in this population.[33]

  Noradrenaline is a potent alpha-1 adrenergic agonist, with comparative modest beta-agonist activity, administration results in higher heart rates than with comparable doses of phenylephrine. Studies on noradrenaline use in the prevention of SIH are still at an infant stage.[33]

Dose of vasopressor

Different studies carried out during caesarean delivery looked at two forms of administration (infusion or bolus) and doses were administered based on whether phenylephrine was given by means of an infusion or a bolus. Studies investigated a wide range of doses ranging from 50-150mcg, when administered in the form of a bolus.[19,8,34-39]

Outcome on investigation of prophylactic phenylephrine infusion versus prophylactic phenylephrine bolus or therapeutic bolus showed satisfactory blood pressure control in the prophylactic group, but Doherty et al reported more haemodynamic stability with bolus regimen as there were decreased incidence of hypertension and bradycardia.[6]

The study done by George and colleagues on phenylephrine bolus dosage, suggested a 150mcg bolus for therapy and this has shown to be associated with rewarding outcome in prevention of SIH.[8] Tanaka et.al regarding phenylephrine prophylaxis reported 122mcg as 95% effective dose in prevention of SIH during caesarean delivery.[34] A randomised control trial (RCT) by Lee et al

discovered that 1.5mcg/kg was superior to a dose of 1mcg/kg and 2mcg/kg as prophylactic bolus for inhibition of SIH.[35]

When phenylephrine was administered as an infusion, doses ranging from 10 – 100 mcg/min were investigated.[8,19,34-35] The most investigated dosages were ranging from 25-50 mcg/min.[8,19,34-35] Investigations on the low dose (25mcg/min) had higher prevalence of hypotension.[8,19,34-36] The two studies by Allen et al and Stewart et al reported a high incidence of SIH with a lower dose of (25 mcg/min) in comparison with a higher incidence of Hypertension and bradycardia in administration of higher dose (50mcg/min).[19,36]

In conclusion various studies have been carried out to evaluate the optimum dose of phenylephrine (10 – 100 mcg) while a dose of 10 mcg has been found infective, doses as high than 100 mcg were found to result into reactive hypertension and a reflex maternal bradycardia. The goal of continuous prophylactic infusion is for a more effective method in inhibiting spinal induced hypotension and its associated side effects.[42,44]

2.2.3.3 Positioning protocols

The positioning protocols in the parturient patient lying down have the following objectives; relieving aortocaval compression and increasing venous return.[37-42]

A study done by Lee and colleagues, stated that a 15° left tilting during caesarean section under spinal delivery resulted into an increased cardiac output.[40] Secondly Kundra et. al., concluded in their study that positioning a full-term parturient from a left lateral position inhibited aortocaval compression efficiently in comparison with a parturient moving directly from supine to 15 ° left-tilt position.[41] In addition, a study by Higuchi et al demonstrated no improvement in cardiac output (CO) except with 45° left tilting.[42]The major drawback to these studies is the fact that all the study

population were non-anaesthetised full-term parturients. Lastly, studies on comparisons of parturients with wedge placement and left lateral table tilt position has demonstrated a higher incidence of hypotension, higher blockade level as well as increased interventions in terms of administration of vasopressors. [41-42,46] More studies are needed to scrutinise the haemodynamics change associated with parturient tilting after sitting a spinal block.

2.3 Summary

The current findings advocate a multimodal approach to the prevention and treatment of SIH as no single method has been proven to be effective on its own. Fluid loading is preferred to no-fluid protocol with the addition of vasoactive agents prophylactically in the prevention of SIH. At present, phenylephrine is the favoured drug in healthy parturients. Ephedrine is preferred in parturient with cardiac conditions such as; bradycardia, hypertensive disorders and uteroplacental insufficiency. Norepinephrine is currently under investigation as a substitute to phenylephrine in healthy parturients. Lastly, caesarean section is a common procedure executed in most hospitals worldwide and dealing with SIH is a common challenge facing anaesthetists. Future studies should emphasise on the use of simple and rapid regimen that can be easily applied by anaesthetists without expensive medications and drug delivery devices.

CHAPTER 3

3.0 RESEARCH METHODOLOGY

3.1 Introduction

This chapter provides an outline on how this clinical study was carried out. It highlights the materials and methods employed. The main purpose of the study was to investigate the impact of prophylactic intermittent boluses versus continuous infusion of phenylephrine on spinal induced hypotension during caesarean delivery at the two Windhoek based-teaching hospitals: Katutura Intermediate hospital and Windhoek Central hospital. The focus was on the study population, sampling techniques, sample size, data collection methods and the ethical considerations.

3.2 Study location

The study was conducted at the two Windhoek-based teaching hospitals: Katutura Intermediate Hospital and Windhoek Central Hospital, which are the two state referral hospitals in Windhoek, Namibia. Katutura Intermediate Hospital antenatal ward has eighteen beds in total of which four are High Care beds, whereas Windhoek Central Hospital has twenty-eight beds of which four are High Care beds.

3.3 Study design

The study was conducted as a prospective randomised controlled double-blinded study in which eligible participants were allocated to two treatment groups after obtaining written informed consent

3.4 Study population

The study was done on parturient aged 18 – 45 years who had completed thirty-seven weeks of pregnancy, belonging to American Society of Anaesthesiologists' [ASA] physical class I or II, with a singleton pregnancy and scheduled for Category IV caesarean section under spinal anaesthesia.

3.4.1 Inclusion Criteria

The inclusion criteria for this study were parturient aged 18 – 45 years, ASA I and II at term (37-week gestation), with singleton pregnancy, category IV caesarean section under spinal anaesthesia and who gave written informed consent.

3.4.2 Exclusion criteria

The following groups of patients were excluded based on review of their antenatal medical records:–

- contraindications to spinal anaesthesia
- Pre-existing medical conditions like pregnancy induced hypertension, pre-eclampsia/eclampsia
- CS Category I-III
- Patient who refused to give consent or lacked the capacity to give consent
- History of allergy to local anaesthetic agents (lidocaine and bupivacaine) and study drug: phenylephrine.
- Multiple pregnancy

3.5 Sampling method and Recruitment of subjects

3.5.1 Power Analysis

To obtain an adequate sample size and the appropriate statistical power, a power analysis was conducted. In testing the hypotheses, four variables were addressed namely the power of the statistical test, the alpha level of significance, the effect size and the sample size. Ellis reported that the effect size measures the strength of the relationship between two variables to determine whether the difference is real or due to other factors. [43] Effect size is usually measured as standard mean difference, odds ratio or correlation coefficient. Alpha level of significance denotes to the probability of obtaining a Type 1 error (α) (probability of rejecting the null hypothesis when it is true. The alpha significance criterion is usually set at 0.05 and below.[43] Furthermore, Ellis states that p-value are sensitive to sample size when the sample is not biased.[43] Sample size relates to the level of sampling error present in the analysis whereas the statistical power determines the Type II error rate (β) of the test and if the acceptable level is 0.2 then the desired power = 0.8. [43]

3.5.2 Sample size determination

The sample size estimation was determined using Epitools - Epidemiological calculator to detect significant differences between two proportions. Allen et al, reported a proportion 15% of patients had hypotension following prophylactic phenylephrine 50 mcg/min infusion and Choudhary et al, observed 44% of patients had hypotension following phenylephrine 50 mcg bolus injection.[5,19] Taking these two values as references, the minimum required sample size at 95% and assuming a type-1 error of 0.05 is 40 patients in each group. Adding 10% attrition increased sample size to 90 (45 patients per group).

3.5.3 Sampling technique

Consecutive patients who fulfilled the eligibility criteria were recruited and subsequently allocated into one of the two groups: Bolus (group A) or Infusion (group B). The patients were randomly allocated into either of the two groups using a computer generated table of random numbers prepared by a statistician. The allocation numbers were marked on temper-evident, identical, opaque and well-sealed envelope with a questionnaire labelled group A or B inside. The statistician, responsible for generating the allocation numbers was not directly involved in recruiting patients. After obtaining informed consent from the patients, they were requested to pick an envelope and hand it to a medical intern. Based on the allocation in the envelope, the medical intern prepared and administered the treatment according to the protocol drawn up for the study which was either a bolus treatment or continuous phenylephrine infusion. Patients' demographics and haemodynamic parameters where recorded on a pre-designed sheet (Appendix 5) by an anaesthetist nurse. The participants and the outcome assessor (anaesthetist nurse) were blinded with regard to the two groups. The allocation process was concealed from the anaesthetist responsible for recruiting patients into the trials. The statistician kept a randomisation register containing records of contents of the envelopes along with the date and time of randomisation. In the event of a medical emergency such as any adverse reaction (unexpected anaphylactic reaction to local anaesthetic or study drugs) the outcome assessor was unblinded and the subject was replaced accordingly.

3.6 Method of data collection

The study ran consecutively from one centre to the other as elective caesarean sections occurred on different days: Windhoek Central Hospital on Mondays, Wednesdays, and Fridays, while

Katutura Intermediate Hospital on Tuesdays and Thursdays. A pre-anaesthetic evaluation was carried out on every patient and relevant laboratory investigation were ensured as per hospital protocol. Before setting up the spinal anaesthesia, the anaesthetic machine, equipment, and medications for resuscitation were checked and kept ready. Each patient had two intravenous lines and Drager multiparameter monitors connected prior to spinal block**.** Non-invasive blood pressure (NIBP) was recorded from time zero when the test drug was given which was either bolus injection or infusion and every 1 min till delivery of the baby, the outcome measures were concluded after the delivery of the baby. A medical intern allocated to work with the principal investigator (Registrar), prepared the treatment based on the allocation, identical 20 ml syringes were used to administer the treatments: either 50 mcg/ml of phenylephrine or saline for the intermittent bolus group; 25 mcg/min phenylephrine or saline for the continuous infusion group as per the study protocol. Group A patients were treated prophylactically with 50 mcg bolus of phenylephrine immediately after inducing spinal block. The dose was repeated every minute after the NIBP measurement if there was any drop in systolic blood pressure of ≤100 mmHg or a drop exceeding ≥20% of the baseline. A saline infusion was run in this group via a syringe driver, in addition to the phenylephrine bolus, this was done to keep the patient and outcome assessor blinded. Group B received a prophylactic phenylephrine infusion, at a rate of 25 mcg/min with a syringe driver (Becton Dickinson CareFusion, East Rutherford, New jersey), and it was started immediately after performing a spinal block. A drop in systolic blood pressure ≤100 mmHg or a drop exceeding ≥20% of the baseline in this group, was treated with a bolus injection of 25 mcg phenylephrine repeatedly every minute after the NIBP measurement until the blood pressure normalises. All the participants received a standard spinal block, consisting of 0.5% hyperbaric bupivacaine 10 mg plus 10 mcg fentanyl performed by the principal investigator.Post citing spinal block, all patients

were tilted at 15° left lateral position using an electronic remote controlled theatre table. All patients were co-loaded with 1000 ml of Ringer's lactate. Patients who developed a bradycardia (heart rate < 60 beats/min), were given atropine 0.25 mg. The dose was repeated if bradycardia persisted. The outcome assessor ensured that the data obtained are entered in the proforma designed for the study.

3.7 Data collection

Data were collected by means of a questionnaire designed for the study; by the outcome assessor (anaesthetic nurse), through observation.

3.8 Data analysis

After completion of data collection, data were checked for errors plus coding. The coded data were entered into Statistical Package for Social Sciences (SPSS for windows 24.0, SPSS, Inc, Chicago, IL, USA) for analysis with the help of a statistician. A t-test was used to find the significance between the two groups for continuous variables. The data for incidence of hypotension and occurrence of nausea and or vomiting was compared using the chi-square test. Data for serial BP measurement and heart rate were analysed using a t-test. Results were expressed as a mean ± standard deviation and a p-value < 0.05 was considered statistically significant.

3.9 Ethical consideration

A written informed consent was obtained during pre-anaesthetic consultation to eligible patients, before surgery as per hospital protocol in the language of their choice. The nature and objective of the study was explained to each patient. Patients not willing to participate or not eligible for the study were excluded. Serial numbers were used for data collection to ensure anonymity.

Participants' names were not used in the study at any point. All information obtained from the patients were treated strictly confidential. Data collected remained in the custody of the principal investigator and data collected were only used for this study. Ethical clearance was obtained from UNAM ethical committee and the Ministry of Health and Social Services (MoHSS).

3.8 Withdrawal from the study

Patients were allowed to withdraw from the study at any point without any loss of benefit or extra risk.

3.11 Summary

This chapter provided an overview of the population studied, the sampling methods, data management and analysis

CHAPTER 4

4.0 RESULTS

4.1 Introduction

This chapter presents the results of the study involving two groups, one received prophylactic phenylephrine bolus of 50mcg and the other, an infusion dose of 25mcg/min continuous phenylephrine infusion for the prevention of maternal hypotension and associated side effects. The results focused on the demographic characteristics of the subjects such as age, gestational age, weight, height and body mass index. Furthermore, outcomes such as hypotension, reactive hypertension, and maternal bradycardia between the two groups that were investigated are presented as well as the total dose of phenylephrine administered between the two groups and the Apgar scores.

4.2 Demographic characteristics of the participants

One hundred and twenty (120) patients were screened for eligibility, and twenty-eight patients were excluded because they did not meet the inclusion criteria. Ninety-two subjects were randomised into either phenylephrine bolus (PB) group (n = 45) or phenylephrine continuous infusion (PI) (n = 47) group. According to Figure 1, 92 subjects completed the study and were available for the final analysis. The subjects in both PB and PI groups were comparable in their demographic characteristics in respect of age, gestational age, height, weight and body mass index, as shown in Table 1. Overall, there was no statistical significance in demographic data between the two groups, $p>0.05$.

The mean age (±SD) of PB group was 31.2 (±6.0) years and for PI group was 30.0 (±6.0) years, which indicated that the PB group subjects were older but this difference was not significant (p =0.282). The PB group mean gestational age was 38.5 (±3.0) weeks and for PI group, the mean gestational age was 39.0 (±1.5) weeks, (p=0.870). The mean height was 1.62 (±0.1) metres and 1.61 (±0.1) metres for the PB and PI groups respectively, (p= 0.552). Lastly, the mean weight was 78.3 (±15.0) kg for the PB group and 76.2 (±14.0) for the PI group, which was comparable being not statistically significant (p= 0.475).

All the subjects were American Society of Anesthesiologists [ASA] physical status class I and II who received a standard local anaesthetic dose, consisting of 0.5% hyperbaric bupivacaine 10 mg plus 10 mcg fentanyl injected intrathecally for spinal anaesthesia.

Enrolment:

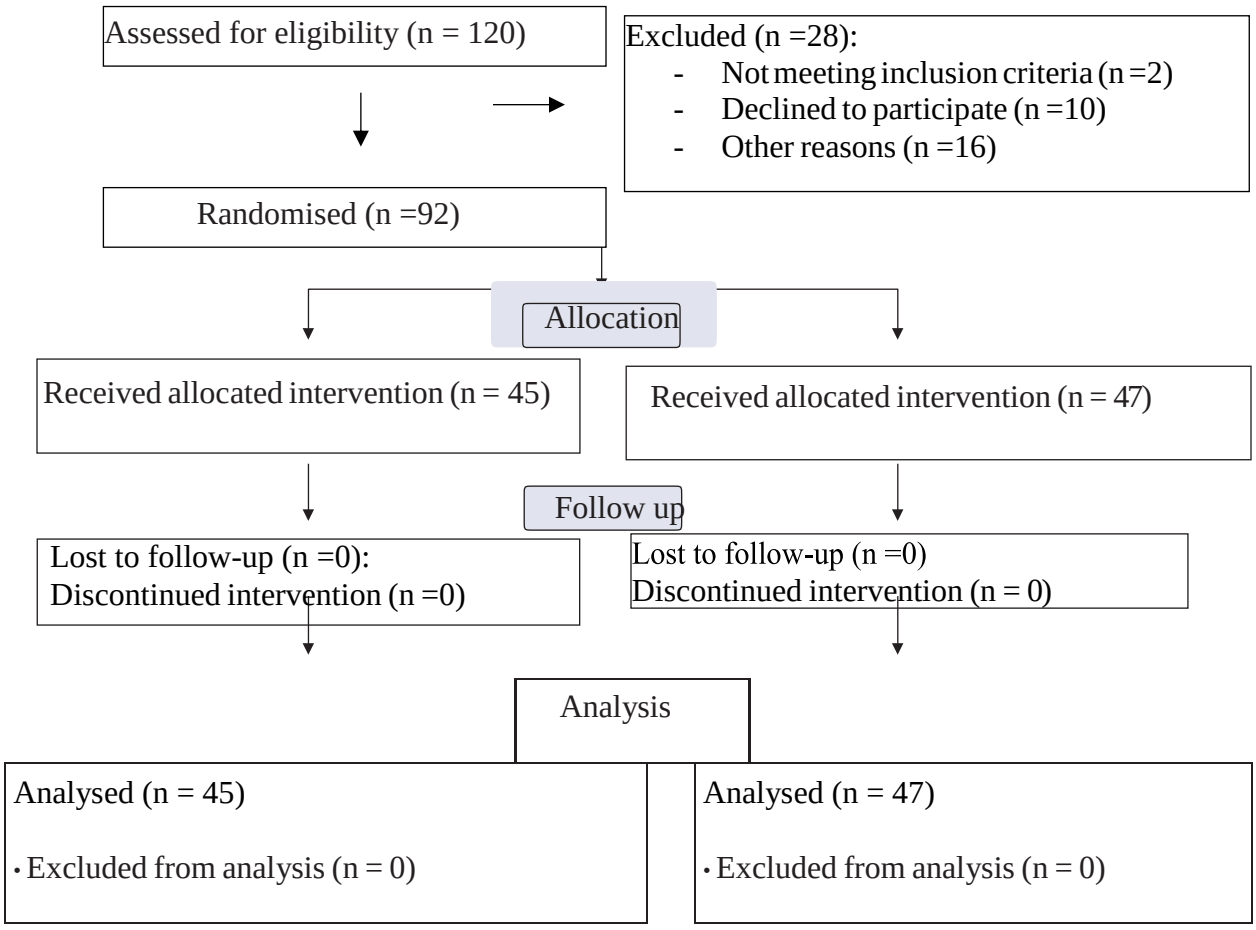

Figure 1: CONSORT flow diagram for patient enrolment..

Table 1: Demographic characteristics of the patient

Variable	**PB group**			**PI group**			**P value**
	Mean	**SD**	**median (range)**	**Mean**	**SD**	**median (range)**	
Age (years)	31.2	6.0	30.0 (20 – 44)	30.0	6.0	30.0 (18 – 43)	0.282
Gestational age (weeks)	38.5	3.0	39.0 (37 – _41)	39.0	1.5	39.0 (37– 41)	0.870
Weight (kg)	78.3	15.0	79.0 (52 – 110)	76.2	14.0	13.9 (44– 115)	0.475
Height (m)	1.62	0.1	1.60 (1.5 –1.7)	1.60	0.1	1.60 (1.5–1.8)	0.552
BMI (kg/m^2)	30.4	5.3	30.0 (21– 44)	30.0	29.0	29.0 (19– 45)	0.631
ASA II Physical status	45			47			

BMI = Body mass index, PB = phenylephrine bolus, PI = phenylephrine infusion, ASA= American Society of Anesthesiologists'

4.3 The study outcomes in the parturients: PB group versus PI group

4.3.1 Maternal hypotension

As shown in Table 2, the incidence of hypotension was significantly higher in PB group (71 %) than the PI group (32 %), p=0001.

Table 2: Incidence of hypotension between the two groups

Variable	Treatment type		χ^2	p-value
	PB group	PI group		
Hypotension				
Yes n (%)	32(71.1)	15(31.9)	14.134	0.0001*
No n (%)	13(28.9)	32(68.1)		

* Significant $p < 0.05$

4.3.2 Incidence of intraoperative nausea and or vomiting (IONV)

The parturients in the PB group experienced a higher incidence of intraoperative nausea and vomiting (IONV) than the PI group (Table 3). The association between maternal IONV and the administration of prophylactic phenylephrine bolus versus infusion was significant, (p=0.033).

4.3.3 Maternal bradycardia

This index study indicated in Table 3 that maternal bradycardia was slightly higher in the PI group (17%) compared with the PB group (16%), but there was no statistical significance (p= 0.489).

4.3.4 Reactive hypertension

Table 3 showed that the incidence of reactive hypertension was significantly higher in the PI group with 11% compared with PB group where no parturient experienced this outcome, (p= 0.024).

Table 3: Incidence of IONV, bradycardia and reactive hypertension between groups

Variable	Treatment type		χ^2	p-value
	PB group	PI group		
IONV				
Yes n (%)	14 (31.1)	6(12.8)	4.548	0.033*
No n (%)	31 (68.9)	41(87.2)		
Bradycardia				
Yes n (%)	7 (16)	8 (17)	0.036	0.849
No n (%)	38 (84)	39 (83)		
Reactive hypertension				
Yes n (%)	0(0)	5 (10.6)	5.062	0.024*
No n (%)	45(100)	42 (89.4)		

*significant p< 0.05

IONV= intraoperative nausea and vomiting

4.4 Total dose of phenylephrine administered

As shown in Table 4, the results of the total phenylephrine dose administered between the two groups was not normally distributed, so a two-sample Wilcoxon Rank-sum (Mann-Whitney) test was applied. The parturients in PI group received a significantly higher total phenylephrine dose (about 36% more) than the PB group parturients, (P<0.0277).

Table 4: Total phenylephrine dose administered between the two groups

Variable	Treatment type				P-value
	PB group		PI group		
	Rank-sum	Expected	Rank-sum	Expected	
Total phenylephrine dose (mcg)	1811.5	2092.5	2466.5	2185.5	0.0277

4.5 Apgar scores

According to Table 5, the Apgar score at the 1st minute was higher in the PI group compared to the PB group, however this difference was not significant (p=0.177). At the 5th minute, the overall the Apgar score was higher the PB group compared with the PI group, (p=0.045).

Table 5: Neonatal Apgar scores at 1 minutes and 5 minutes

Variable	Treatment type		χ^2	p-value
	PB group	PI group		
APGAR Score in 1 minute				
8 n (%)	8(17.8)	14(29.8)	1.822	0.177*
9 n (%)	37(82.2)	33(89.1)		
APGAR Score in 5 minutes				
9 n (%)	0(0)	4((8.5)	4.004	0.045*
10 n (%)	45(100)	43(91.5)		

*significant p<0.05

CHAPTER 5

5.0 DISCUSSION

5.1 Introduction

In this chapter, the main findings are discussed. Comparisons are made with the findings from published studies on preventative strategies on spinal anaesthesia-induced hypotension. Furthermore, limitations, conclusions and recommendations are made based on the objectives of the study.

5.2 Discussion

This prospective randomised controlled double-blinded study investigated the effectiveness of prophylactic phenylephrine infusion (PI) versus prophylactic phenylephrine bolus (PE) injections in the prevention of spinal induced hypotension in parturients who underwent category IV caesarean section.

5.2.1 Maternal hypotension

In this present study, parturients in the PI group had significantly lower incidence of hypotension than the PB group (p= 0.0001). The frequency of maternal hypotension was more than two-folds in the PB group compared to the PI group. The implication is that prophylactic phenylephrine infusion was more effective at achieving a better control of the blood pressure within 20% of the baseline than intermittent bolus injections. This result was comparable to studies by Choudhary and Bajaj, and Sen et al, in which prophylactic infusion of 50 mcg/ml phenylephrine were administered during spinal anaesthesia for caesarean section.[5,17] There are researchers who have divergent reports about bolus phenylephrine and have expressed the opinion that phenylephrine

infusion has no clinical merit.[6] The common factor with these studies is that a much higher bolus dose of phenylephrine than the 50 mcg administered in this study. Doherty et al used 120 mcg, George et al used between 80 – 180 mcg, Tanaka et al used as much as 120 mcg.[6,8,34] Lee et al advocated a bolus phenylephrine dose of 1.5 mcg/kg as suitable instead of 1 mcg/kg or 2 mcg/kg.[40]

Kinsella et al observed that in clinical practice; administering a bolus injection only when blood pressure falls from baseline might lead to a delay in the effect of treatment hence hypotension might ensue.[13] For this reason, it is advisable to administer phenylephrine at a variable prophylactic infusion rate 25-50 mcg/min after intrathecal injection. They recommended the use of smart pumps to achieve stable maternal haemodynamic profile.[13] Results have shown that high bolus doses of phenylephrine increase the incidence of reflex bradycardia and reactive hypertension, so caution must be exercised.[8,34] The goal of treatment is to maintain BP within 20% of baseline with regular prophylactic phenylephrine administration, lateral uterine displacement and crystalloid co-loading thereby optimising patient outcomes and minimising side effects. This index study was carried out with this goal in view.

Other vasopressors have been studied, ephedrine was previously the vasopressor of choice in obstetrics; however, phenylephrine has replaced it being a pure α-agonist has shown greater efficacy, lower transplacental transfer and less likelihood to depress foetal pH. Recent researches are emerging on the use of a low dose norepinephrine in parturients undergoing caesarean section under spinal anaesthesia.[26, 30- 31]

5.2.2 Incidence of intraoperative nausea and vomiting (IONV)

In this index study, the PB group had 31% parturients who experienced IONV in relation to 13% in the PI group, which was significant (p=0.033). This finding was comparable with the findings

by Ngan Kee et al and das Neves et al.[7,22]However, the studies by Allen et al did not find any difference in the incidence and severity of IONV in four phenylephrine groups despite variable infusion rates 25, 50, 75 and 100 mcg /min.[19] It is hard to explain this given that hypotension does engender cerebral hypoperfusion and brain ischaemia resulting in the activation of the vomiting centre.[31] In addition, hypotension causes gut hypoperfusion with subsequent release of emetogenic substances such as serotonin.[30]Other factors with emetogenic potential are exteriorisation of the uterus, visceral manipulation, and administration of uterotonics, such as oxytocin.[30]

5.2.3 Maternal bradycardia

The incidence of reflex bradycardia was more or less the same between the two groups 16% and 17% in the PB group and PI group respectively. There was no statistical significance p= 0.849. Some studies used high dose of phenylephrine infusion (100-120mcg/min) in conjunction with cohydration and reported low incidence of hypotension (as low as 0%) but the incidence of bradycardia was more than 30%[19,35] The action of phenylephrine on alpha one receptor results in vasoconstriction with an increased preload and systemic vascular resistance hence a resultant reflex bradycardia.[30-, 31] The absence of reflex bradycardia in the index study could be explained by the relatively low dose used in contrast to studies in which doses up to 100 – 120 mcg of phenylephrine were investigated.[8,19]

5.2.4 Reactive hypertension

There was statistical significance in the incidence of reactive hypertension in the PI group versus the PB group (p= 0.024). No parturients in the PB group experienced reactive hypertension whereas 11% of participants in PI group did. This result was comparable with the findings by Kumar et al , who compared a weight-based prophylactic phenylephrine infusion with a weight-

based bolus.[50] Allen et al showed that a dose of 25 mcg/min was found to have low incidence of reactive hypertension in comparison to high doses (100 mcg/min).[19] However, this study compared this outcome between bolus injection and infusion. Other studies have suggested that reactive hypertension with intravenous prophylactic infusion may be prevented by administering a weight-based phenylephrine infusion[43-45] It would however be challenging to adjust the vasopressor dose according to weight in an effort to deliver personalised treatment regimen.[44] Veeser et al observed that the use of prophylactic infusions was likely to expose parturients not prone to hypotension to phenylephrine unnecessarily, with no evidence that hypertension, bradycardia or neonatal end point were affected.[28] The issue of deciding who is prone to hypotension remains controversial as the literature has reported a high incidence of spinal induced hypotension up to 80% without vasopressor prophylaxis. [41-45] Deciding on the parturients who belonged to the 20% of the non-vulnerable population could be another subject of research.

5.2.4 Total dose of phenylephrine administered

In terms of the total dose, the parturients in a PI group had a higher total phenylephrine dose of 2466.5 mcg versus 1811.5 mcg in a PB group, (0.0277). This finding was comparable with Allen et al and Kumar et al, where the phenylephrine infusions resulted in relatively higher doses with resultant decreased side effects such as hypotension and IONV.[19,45] However, Doherty et al reported high doses of phenylephrine with no clinical maternal benefits in their study. They further reported that infusion regimen required a higher total dose of phenylephrine to maintain maternal arterial blood pressure at baseline during the pre-delivery period.[6]

5.2.5 Apgar scores

Lastly, the Apgar scores between both groups showed a good neonatal outcome overall, with all babies scoring ≥ 8. Other studies has pointed out that predicting neonatal outcome using the Apgar scores does not give enough evidence of hypoxia that might results in neurological damage.[2] Furthermore, Apgar score does not give a true reflection of uteroplacental perfusion.[29] Umbilical cord blood gas and pH might be more sensitive to reveal foetal condition when assessing perfusion and the impact of vasopressor on the foetus.

5.3 Conclusions

This present study supports the hypothesis that phenylephrine as a prophylactic infusion leads to a significantly better control of post spinal hypotension than intermittent bolus injections during caesarean section under spinal anaesthesia. When used in the dose of 25 mcg/min, it does not lead to reflex bradycardia and has a relatively low incidence of reactive hypertension. However, participants in the PI group received about 36% more phenylephrine than the PB group. The Apgar scores between groups showed good neonatal outcomes.

5.4 Limitations

- The study was carried out in healthy parturients, singleton pregnancy, category IV caesarean section
- This findings may not be applicable to parturients with cardiovascular diseases such as hypertension
- Only non-invasive methods of monitoring of arterial blood pressure was used which might not detect the transient haemodynamic changes such as maternal cardiac output

5.5 Recommendations

At Katutura Intermediate Hospital and Windhoek Central Hospital, although phenylephrine is readily available, there is no protocol as to what dose or mode of administration should be administered. Most anaesthesia providers administer bolus phenylephrine in response to spinal induced hypotension. The index study suggest the following recommendations:

1. The Hospitals are encouraged to invest in equipment that would ensure tight blood control in parturients as well assessment of neonatal outcomes
2. The Hospitals to come up with protocols for routine, prophylactic phenylephrine infusion immediately after setting up spinal anesthesia to prevent maternal hypotension and its foeto-maternal effects. Anaesthesia providers should undergo a training period and should demonstrate competence in the prevention and management of SIH based on Hospital protocol.

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APPENDIX 1

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Date: 15 February 2021

Dr. Ebba P. Shaanika
PO Box 1868
Windhoek

Dear Dr. Shaanika

***Re:* Prophylactic phenylephrine bolus versus infusion for prevention of maternal hypotension during spinal anaesthesia for caesarean section at Windhoek-Based teaching Hospitals, Namibia.**

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;
3.2 No other data should be collected other than the data stated in the proposal;
3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
3.4 A quarterly report to be submitted to the Ministry's Research Unit;
3.5 Preliminary findings to be submitted upon completion of the study;
3.6 Final report to be submitted upon completion of the study;
3.7 Separate permission should be sought from the Ministry for the publication of the findings.

4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

BEN NANCOMBE
EXECUTIVE DIRECTOR

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

"Your Health Our Concern"

APPENDIX 2

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13215
Windhoek
Namibia

Harvey Street
Windhoek

Tel. No: (061) 203 3024
Fax No: (061) 222886

Enquiries: Mrs. S. Iipinge **Ref. 17/3/3EPS** **Date: 01 June 2021**

OFFICE OF THE CHIEF MEDICAL SUPERINTENDENT
WINDHOEK CENTRAL HOSPITAL

Dr Ebba P Shaanika
PO Box 1868
Windhoek
0814997636

Dear Dr. Shaanika

SUBJECT: PERMISSION TO CONDUCT A RESEARCH STUDY ON THE PROPHYLACTIC PHENYLEPHRINE BOLUS VERSUS INFUSION FOR PREVENTION OF MATERNAL HYPOTENSION DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION AT WINDHOEK CENTRAL HOSPITAL.

1. Reference is made to your application to conduct the above-mentioned study.

2. This letter serves to inform you that permission has been granted for you to conduct a study at Windhoek Central Hospital, on the above mentioned subject as you have requested and does not include any remuneration.

3. Patient/Client's information should be kept confidential at all times.

4. Preliminary findings to be submitted to Customer care office, Windhoek Central Hospital upon completion of the study.

Thank you for your kind gesture.

Yours sincerely

Dr. D.I.UIRAB
CHIEF MEDICAL SUPERINTENDENT

MINISTRY OF HEALTH AND SOCIAL SERVICES
Private Bag 13215
02-06-2021
Windhoek Namibia
WINDHOEK CENTRAL HOSPITAL

"Your Health, Our Concern"

APPENDIX 3

Republic of Namibia

Ministry of Health and Social Services

Private Bag 13215
WINDHOEK
Namibia

Intermediate Hospital Katutura
Independence Avenue
WINDHOEK

Telephone (061) 203 4004/5
Telefax (061) 222706

Enquiries: Dr. F. M. Shiweda

Date 31 May 2021

OFFICE OF THE CHIEF MEDICAL OFFICER

Dr. Ebba P. Shaanika
P. O. Box 1868
Windhoek

Dr. E. P. Shaanika

RE: **PROPHYLACTIC PHENVLEPHRINE BOLUS VERSUS INFUSION FOR PREVENTION OF MATERNAL HYPOTENSION DURING SPINAL ANAESTHESIA FOR CEASAREAN SECTION AT WINDHOEK-BASED TEACHING HOSPITALS, NAMIBIA**

The above mentioned subject refers:

This office hereby grants you permission to do a research on Prophylactic Phenvleprhine Bolus versus infusion for prevention of maternal hypotension during spinal anaesthesia for Caesarean Section at Katutura Hospital, Khomas Region, MoHSS.

Please provide this office with a copy of your findings.

Thank you

Yours in health,

1/6/2021

DR. F. M. SHIWEDA
CHIEF MEDICAL OFFICER

MINISTRY OF HEALTH
AND SOCIAL SERVICES
P/BAG 13215
WINDHOEK NAMIBIA
01-06-2021
INTERMEDIATE HOSPITAL KATUTURA

APPENDIX 4

INFORMED CONSENT FORM

Project title: A comparative study of prophylactic phenylephrine bolus versus infusion for prevention of maternal hypotension during spinal anaesthesia for caesarean section at Windhoek-based teaching hospitals, Namibia.

Principal Investigator: Ebba P. Shaanika

Contact number: +264813171845

IRB Research approval number:

Sponsor of the research: None

Purpose of the research: The aim is to obtain evidence based medicine for our Windhoek-based teaching hospitals which will enable us to adopt recommended guidelines of administering vasopressor prophylactically

Procedure of the research: You are being selected to participate in the study because you met the following criteria: you are 18 years old and above, and you are scheduled for caesarean section under spinal anaesthesia. The research will involve managing maternal hypotension during spinal anaesthesia by administering phenylephrine using two methods (infusion or bolus). You will be requested to pick a number and hand it to the medical intern who will pick a set of temper-evident, identical, opaque and well-sealed envelope with a number which correlates to the number you picked. Based on allocation in the envelope, the medical intern will prepare and administer the treatment according to the protocol drawn up for the study. The anaesthetist nurse will peruse your medical records to enter into the data collection form these parameters: age, weight, height,

gestational age, type of anaesthesia and surgery, complications during and how these complications were treated.

Potential risks: The potential risks are those for every caesarean section done under spinal anaesthesia such as a fall in blood pressure, fast or slowing down of the heart rate, nausea and vomiting, failure of spinal block to provide adequate anaesthesia for which general anaesthesia is a remedy. However, these aforementioned effects of surgery and anaesthesia are treatable and the care-givers would make sure that you and your baby are managed throughout the procedure according to the hospital guidelines.

Potential benefits: The survey would provide useful data, which would provide the basis for evidence-based changes which would improve on the day-to-day obstetric anaesthesia service in our study centres.

Financial implication for joining the research: Your participation in this research will not cost you anything outside the usual charges for registration, investigation and services; such as, surgery, etc.

Confidentiality: You will be assigned a number and your name would not be written on the form to ensure confidentiality. The information and data obtained will be stored in files under lock and key. The access will be available only to the principal investigator.

Voluntariness: Your participation is entirely voluntary. You are free to decline participation in this study but we will greatly appreciate your help in taking part in this survey.

APPENDIX 4

Alternatives to participation: Your refusal to participate in this research will not affect your treatment in the hospital in any way. You have a right to withdraw at any given time, if you choose to.

Due inducement: You will not be paid any fees for participating in this research. There would be no waiver of prescribed fees for any service.

Consequences of participants' decision to withdraw from the research and procedure for orderly termination of participation: You can choose to withdraw from the research at any point in time. However, some of the information obtained about you before this withdrawal may have been analysed and used in reports and publications. These cannot be removed anymore. However, we promise to make good faith to comply with your wishes as much as is practicable.

What happens to participants/community at the termination of the research: The outcome of this research will be made available to the Office of Research and Development.

AUTHORIZATION

You are making a decision whether or not to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to participate.

_____ _____

Name of Research Participant (please print) **Date**

_____ _____

Signature of Staff Obtaining Consent **Date**

APPENDIX 4

(Optional)

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research participant; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Office of Research, Ministry of Health and Social Services, Windhoek.

APPENDIX 5

Data collection Questionnaire

Date & time

Serial No ☐

ASA category: ☐

Gestational age: ☐

Level of SA Block (sensory & Motor): ☐

Caesarean section indication:……

Age: ☐ years

Weight: ☐ Kg

Height: ☐

BMI_____kg/m^2

Tachycardia Yes ☐ No ☐

Bradycardia Yes ☐ No ☐

Hypotension Yes ☐ No ☐

Nausea/Vomiting Yes ☐ No ☐

Apgar score: 1min ☐ 5min ☐

Blood pressure (every min till delivery): Baseline 1min 2min 3min 4min 5min 6min 7min 8min 9min 10min 11min 12min 13min 14min 15min 16min 17min 18min 19min 20min

Time from skin incision to delivery:

Total amount of bolus test drug injected _____ ml

Total amount of test drug via syringe driver _____ ml

APPENDIX 6

FACULTY OF HEALTH SCIENCE

FEEDBACK FROM UPGSC HELD 26/11/2020

FROM: DR L N LUKOLO, HOD, PGS, FACULTY OF HEALTH SCIENCES

Matters arising from previous meeting:

APPROVAL OF SUPERVISOR

6.4.1.1 STUDENT: C MBAPAHA

Dr H. Amukugo were approved to be the supervisor of student C Mbapaha

1. **PROPOSALS FOR NOTING AND APPROVAL OF SUPERVISORS**

Student name and number /Topic	**Recommended Supervisors**
1.Loini Talishi Shivolo, 200505769, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: A Survey On End Of Life Care In The Intensive Care Units In Three Government Teaching Hospitals , Namibia	Recommended supervisor: DR KINGSLEY TOBI Approved
2.Salomon Namupolo, 200111442, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: Paediatric pain assessment with face leg activity cry (FLACC) in post anesthetic care unit (PACU), Windhoek central hospital : an observational, and quality improvement study	**Recommended Supervisors**: Dr JM Mumba Approved

APPENDIX 6

3.Shigwedha, 200404229, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: The Effect Of Oxytocin On Uterine Tone During Elective Caesarean Section At Windhoek state Hospitals	**Recommended supervisor:** DR KINGSLEY TOBI Approved
4. Murakwani 218241564, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) Topic: A comparison of intrathecal morphine with fentanyl on the duration of postoperative analgesia at Namibian teaching hospitals in Windhoek	**Recommended supervisor:** Prof Rukewe Approved
5.Shaanika E P , 200110373, MMED (ANAESTHESIOLOGY, CRITICAL CARE AND PAIN MANAGEMENT) **Topic:** Prophylactic Phenylephrine Bolus Versus Infusion For Prevention Of Maternal Hypotension During Spinal Anaesthesia For Caesarean Section At Windhoek-Based Teaching Hospitals, Namibia	**Recommended supervisor:** Prof Rukewe Approved

1. **MARKS FOR DISCUSSION AND RECOMMENDATION TO AEC FOR APPROVAL**

1.1 Julia Amunime, MPH, 200410733, (recommended to AEC for approval)
1.2 O Ikeakanam, Doctor of Nursing science (recommended to AEC for approval)
1.3 Harriet Kagoya, PhD in Public Health (recommended to AEC for approval)
1.4 Roswitha Mahalie, PhD, Public Health (recommended to AEC for approval)
1.5 Adenuga B Aderemi, PhD in Pharmacy (recommended to AEC for approval