ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

DEPARTEMENT OF ANESTHESIA

COMPARISON OF HEMODYNAMIC RESPONSE AND FETAL OUTCOME FOLLOWING SPINAL ANESTHESIA, BETWEEN NORMOTENSIVE AND SEVERELY PREECLAMPTIC PARTURIENTS UNDERGOING ELECTIV CESAREAN SECTION: A PROSPECTIVE STUDY

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A THESIS TO BE SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF ANESTHESIA FOR PARTIALFULFILMENT OF THE REQUERMENT OF THE MSC IN ANESTHESIA

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Declaration

I, the undersigned, declare that this thesis is my original work in partial fulfillment of the requirements for the degree of MSc in Anesthesia. I understand that plagiarism will not be tolerated and all directly quoted material has been appropriately referenced

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Date of Submission: _____

This thesis work has been submitted for examination with my/our approval as Advisors and Tutors on the MSc in Anesthesia course

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Abstract

Background: Maternal hypotension is a common complication after spinal anesthesia resulting in adverse maternal and fetal outcomes. Theoretical knowledge claims that it is more common in severely preeclamptic parturients.

Objective: To compare hemodynamic changes and neonatal outcome in normotensive and severe preeclamptic parturients undergoing elective cesarean section under spinal anesthesia.

Methodology: A prospective cohort study was conducted at St. Paul's Millennium Medical College hospital from July 1 to December 20, 2019 on 84 American Society of Anesthesiologists (ASA) II and III parturients divided in to two groups (42 severely preeclamptic group and 42 normotensive group) who underwent elective Cesarean delivery under spinal anesthesia were involved in the study. After preloading with crystalloids, a 0.5% isobaric bupivacaine of 12.5 mg was used for spinal anesthesia. At the completion of the block, vital signs were recorded every three minutes till 20 minutes after spinal anesthesia and every five minutes then after. Hypotension was defined as a 30% decrease in mean blood pressure in both groups. Vasopressors, total fluids taken intraoperatively, neonatal Apgar scores were recorded. Chi-square test was used to calculate the incidence of hypotension between groups; both paired and unpaired t-tests were also used to calculate the percent fall of both blood pressure and heart rate from corresponding baselines of each group and intergroup respectively, after checking the distribution of data using Shapiro wilks test and histogram inspection in SPSS version 20 software.

Results: After induction of spinal anesthesia; systolic blood pressure, diastolic blood pressure and mean blood pressure decreased in both groups, but more in the normotensive groups as compared to the preeclamptic one, in the first 9 minutes. The incidence of hypotension (over a period of 30minutes after spinal anesthesia) in the preeclamptic patients (31%) was less than that of the healthy parturients (59.5%), despite the former receiving smaller volumes of intravenous fluids. There was no statistically significant difference in heart rate of both groups before and after the induction of spinal anesthesia. The 5^{th} minute Apgar score recordings were also comparable between the groups.

Conclusion: Our study showed that the incidence and magnitude of spinal anesthesia-

induced hypotension was less in severely preeclamptic parturients than healthy parturients who underwent elective cesarean delivery under spinal anesthesia.

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List of Acronyms

ASA = American Society of Anesthesiologists

Ug= Microgram

CS = Caesarean Section

DBP = Diastolic Blood Pressure

HR = Heart Rate

IV = Intravenous

MAP = Mean Arterial Pressure

SA = Spinal Anesthesia

SBP = Systolic Blood Pressure

SVR = Systemic Vascular Resistance

SPHMMC= Saint Paul's Hospital Millennium Medical College

ICU = Intensive Care Unit

SAB = Sub-Arachnoid Block

APGAR= Appearance, Pulse, Grimace, Activity and Respiration of a baby

NIBP= Non-invasive blood pressure (measurement)

Chapter One: Introduction

1.1 Background: Pregnancy induced hypertension constitutes major cause of morbidity and mortality in developed and developing countries, and it is 5–10% of all pregnancies(1). Pre-eclampsia is a hypertensive disorder of pregnancy that occurs after 20 weeks of gestation.

The reported incidence of preeclampsia in obstetrics practice is 5-7% worldwide (2), and in Ethiopia it holds 5.47% , which accounts for 19% of maternal deaths(3).

Preeclampsia is a principal cause of fetal morbidity and mortality, also the leading reason of maternal ICU admissions, and responsible for 15–20% of maternal deaths worldwide(4,5).

The exact cause is not known yet, but endothelial cell dysfunction has been implicated in its pathogenesis(8).Compared to a normal pregnancy, characterized by an increased plasma volume and a decrease in systemic vascular resistance (8,9), preeclamptic women are characterized by a lower plasma volume and an increase in systemic vascular resistance in addition to hypertension and proteinuria.

Women with preeclampsia have an increased rate of cesarean section consequent upon the high incidence of intrauterine growth restriction, fetal distress, and prematurity (10). Caesarean delivery poses a challenge to maternal hemodynamics and might predispose the parturient to harmful cardiovascular complications. The available choices of anesthesia are general anesthesia or regional blocks, but each has its own unwanted effects on the maternal hemodynamics and consequently on the fetus. spinal anesthesia -associated hypotension may occur in up to 64% - 100% of pregnant women undergoing cesarean delivery (11).

Spinal-induced maternal hypotension produces unpleasant symptoms such as nausea, vomiting, and light-headedness. It may also cause a decrease in uteroplacental blood flow and result in fetal acidosis(12). Because of the risks related to airway edema, difficulty with the airway or failed intubation, hypertensive response to direct laryngoscopy, and aspiration pneumonitis, general anesthesia is associated with more

untoward outcomes in this particular group of patients (13–16).But, risk-benefit considerations strongly favor neuraxial techniques over general anesthesia for cesarean delivery in cases of severe preeclampsia according to recent studies(17,18).

Therefore, the present study was carried out in an effort to compare the hemodynamic changes and newborn well-being in patients with severe preeclampsia and healthy parturients undergoing spinal anesthesia for elective cesarean section.

1.2. Statement of the problem

The reported incidence of sp

Severely preeclamptic patients have been considered to be at higher risk of profound maternal hypotension when they undergo cesarean section under spinal anesthesia (10). Maternal hypotension causes low cardiac output resulting in unpleasant symptoms such as nausea, vomiting, light-headedness, placental hypo perfusion and poor perinatal and maternal outcomes (10,17,19–21) and was the most frequent complication associated with maternal morbidity and mortality during cesarean section (22).

Although controversial, some studies have shown the effectiveness of colloid and crystalloid loading on reducing the incidence of spinal anesthesia induced hypotension in normotensive parturients (13,23), but vasopressor agents and volume loading, which are commonly used to manage spinal anesthesia-induced hypotension, could put the preeclamptic patients at increased risk of hypertension and iatrogenic pulmonary edema (18,24,25). Intraoperative pulmonary edema may occur in up to approximately 3% of women with pre-eclampsia, with 70% of cases occurring after birth(25).

Minimal hemodynamic effects from spinal anesthesia in healthy pregnancy have been demonstrated when using a low dose of bupivacaine (less than 10 mg bupivacaine) but this has not been sufficiently investigated in pre-eclamptic toxemia. But, low dose spinal (bupivacaine between 5 and 7 mg) may result in inadequate level of analgesia and anesthesia and necessitate conversion to general anesthesia(26).

Conventional dose of local anesthetics for spinal anesthesia with crystalloids preloading at 10ml/kg over 10-15 minutes was associated with less incidence of

hypotensive episodes in recent studies using hyperbaric bupivacaine(1,17,18),but most of these studies used vasopressors as both bolus and continuous infusions for treatment and as prophylactic for hypotension, which are not available in our setting.

Although the relative safety of the subarachnoid block in these patients has been demonstrated in the studies above (the availability of vasopressors at hand), there is no study that compared the differences in the hemodynamic changes and newborn well-being after single-shot spinal anesthesia between preeclamptic and healthy parturients in settings like in ours.

Hyperbaric bupivacaine was used in previous studies, but only isobaric bupivacaine is available in our setting. Baricity of local anesthetics has an important role on spinal block effects and there are controversial results on the degree of hemodynamic changes and incidence of hypotension between hyperbaric and isobaric bupivacaine (27–29).

Furthermore, the incidence of spinal anesthesia-induced maternal hypotension showed inconsistency across different studies, which makes it almost difficult to set standard targets and develop a local management protocol (10,30,31)and other studies did not find any differences in incidence of hypotension, magnitude of hemodynamic changes and neonatal outcome between severely preeclamptic and healthy parturients(32,33).

There were also inconsistent findings on the 1st minute Apgar scores assessments between severely preeclamptic and normotensive parturients on previous studies. In addition, most of the studies were done in settings where the recommended drugs and vasopressors used for treatment of spinal induced hypotension are available.

We want to conduct this in our setting in using 0.5% isobaric bupivacaine, where the recommended drugs or vasopressors for prophylactic and treatment of spinal induced hypotension are not available.

1.3. Significance of the study

In severe preeclampsia, chronic placental hypo perfusion is often significant. Since the uteroplacental circulation is not auto regulated, further decreases in perfusion may be poorly tolerated by the fetus. Primary peripartum goals in the severely preeclamptic parturient are the optimization of maternal blood pressure, cardiac output, and uteroplacental perfusion and the prevention of seizures and stroke(19). Better control of the perioperative hemodynamic changes can lead to reduction in perioperative morbidity and mortality in obstetric patients (34). Therefore, the present study was carried out in an effort to compare the hemodynamic changes and newborn well-being in patients with severe preeclampsia and healthy parturients undergoing spinal anesthesia for cesarean section. The present study is also initiated to further validate the safety of spinal anesthesia in pre-eclamptic patients. Spinal anesthesia can provide reliable and fast anesthesia, especially in busy setups like in our institution.

As far as my knowledge, there is no published data on the same topic in the country, so it can serve as baseline data for other similar topics to be studied for the future. There is also variability of anesthetists' interest on choosing better anesthetic technique for severely preeclamptic patients i.e. some use general anesthesia by the fear that spinal anesthesia could cause severe hypotension and others abandon using general anesthesia for its complications. This study will contribute its role on mediating these controversies.

Chapter Two: Review of Literature

When one considers the cardiovascular pathophysiology of severe preeclampsia, including decreased intravascular volume and markedly raised SVR (35), the optimal anesthetic method for Cesarean delivery remains unsettled. There has been an understandable caution as regards regional anesthesia, due to the theoretical possibility of precipitous hypotension, decreased cardiac output and associated placental hypo perfusion. But, current clinical experience demonstrated relative safety of regional technique over general anesthesia (5,15,36,37), and, among regional anesthesia, epidural anesthesia has been traditionally the method of choice. However, spinal anesthesia has not yet been popular due to the common belief that the sudden and extensive sympathetic blockade following subarachnoid block (SAB) will result in severe hypotension that will endanger maternal and fetal safety(1).Several studies (both prospective and retrospective) have been done for validating its use in those patients, comparing with their healthy counterparts(normotensive parturients).

2.1 Spinal Anesthesia for severe preeclampsia

A retrospective study of 202 cases by Shrestha and Sharma in 2012 (Nepal), using hyperbaric bupivacaine 0.5% for spinal anesthesia for cesarean section in preeclampsia recommended spinal anesthesia as a preferred method taking into account the relatively stable and better hemodynamic stability, convenience in procedure and rapid and predictable anesthesia and no risks of sudden critical hypotension(38). The study was a retrospective and the vital signs were measured every five minutes in which hypotension could result in physiological derangement in between the given intervals.

A prospective study by Saha *et al*. in 2013 (India) compared the hemodynamic response and neonatal outcome following spinal anesthesia between normotensive and severe preeclamptic women undergoing caesarean section on a total of 60 parturients(30 healthy and 30 severe pre-eclamptic. In this study, the drug used was 12.5 mg of 5% bupivacaine (hyperbaric) in both groups. They concluded that severely pre-eclamptic parturients experienced less hypotension following spinal anesthesia than normotensives and required less phenylephrine with comparable fetal Apgar scores. But, percentage fall of DBP, HR and MAP from the baseline was not statistically

significant between the two groups(1). In this study, the gestational age of the fetuses was comparable.

Other prospective cohort study by Khatri and his colleagues (India) in 2014, administered spinal anesthesia with the same dose of the above drug(12.5mg) to sixty patients, of which thirty were severe preeclamptics and thirty of them normotensive parturients to compare the hemodynamic response, fetal Apgar score and vasopressor requirements between the groups. Hypotension and vasopressor requirements were less in the severe preeclamptic parturients and comparable fetal Apgar scores, despite the fetuses from severely preeclamptics had smaller gestational age. The mean intra-operative crystalloid requirement in both groups were not statistically significant)(34). In this study hyperbaric bupivacaine was used.

Another prospective study by Farrukh et al.in 2014(Pakistan), compared the incidence of spinal anesthesia induced hypotension in severely preeclamptic and normotensive parturients undergoing elective caesarean section (two hundred patients) using 0.75% 15mg hyperbaric bupivacaine(relatively high dose). Patients were preloaded with 1litre of Ringer lactate. The incidence of hypotension was 17.0% in the severely preeclamptic patients and 42.0% in the normotensive parturients(39).In this study the gestational age of newborns was not identified , which could affect the given results between groups.

Ashok V.Despande and colleagues in the same year conducted a prospective cohort study, they compared the incidence and severity of spinal anesthesia associated hypotension in pre eclamptics undergoing caesarean delivery (using hyperbaric bupivacaine, 0.5% (2.5ml to 2.8 ml)). It was found that, the magnitude of decrease in SBP was similar in both groups, whereas that of decrease in DBP and MAP was significantly smaller in preeclamptic patients and HR was comparable. Preeclamptic patients had significantly less incidence of clinically significant hypotension that made use of IV ephedrine necessary than normal patients (10).The neonatal outcome was not assessed in the 1st minute and gestational age was lower in the preeclamptic group, which may affect the hemodynamic parameters.

Mitra et al.(India) by 2016 concluded that subarachnoid block in preeclampsia patients

was associated with better perioperative hemodynamic stability, less hypotension, less vasopressor consumption and more gradual blood pressure changes(40). In this study, the authors found significant differences in SBP, DBP and MAP at different point of times (immediately after volume preload, immediately after SAB, 4 minutes, 6 minutes, 8 minutes, 10 minutes, after skin incision, after uterine incision, after newborn delivery, after placental delivery, immediately after oxytocin administration and at the end of surgery) in both the groups(40). They used invasive arterial blood pressure monitoring in place of noninvasive monitoring unlike other studies. The gestational age at the time of surgery was significantly lower in the preeclampsia group and 2.5 ml of 0.5% hyperbaric bupivacaine was used.

Mendes et al. (Brazil) conducted a prospective study on hemodynamic effects and neonatal outcomes of spinal anesthesia on forty parturients of both severely preeclamptic and normotensive groups using 2.2 mL of 0.5% hyperbaric bupivacaine with 0.1 mg of preservative–free morphine for spinal anesthesia after preloading with 500 mL of crystalloid. The mean drop in systolic blood pressure was 27.5% in the severely preeclamptic group and 24, 2% in the normotensive group and diastolic blood pressure decreased by 33.1% and 35.9% respectively and this was not statistically significant in their study. They did not find statistically significant difference between the two groups regarding the occurrence of hypotension, ephedrine use or total ephedrine dose and APGAR scores in 1st and 5th minutes (32). This study followed standardized protocols for hypertension management and spinal anesthesia, but they claimed small sample size was used in their study.

Leena Goel et al.(2018) compared the intraoperative requirement of phenylephrine after spinal anesthesia, between severe pre-eclamptic and normotensive parturients for elective caesarean section on a total of 50 parturients with 12.5mg of hyperbaric bupivacaine, and they found that the mean requirement of phenylephrine was higher in normotensive , the baseline heart rate and subsequent changes remained comparable, but the minimum observed readings of SBP, DBP and MAP were lower than that of pre-eclamptic group and were statistically significant and the Apgar score at 1 and 5 minutes were equal in both the groups(2).

The explanations for less hypotension being, as observed by Smith et al (41) and Saha et

al (1), damaged vascular endothelium, as seen in severe PE, produces increased amount of endogenous vasopressor ¬like thromboxane and endothelin, resulting in persistent vasoconstriction, which is not altered even after SAB, resulting in less hemodynamic alterations; this contrasts with normal pregnancy, where altered balance of vascular tone, reduced response to endogenous pressor and increased synthesis of vasodilator prostaglandins and nitric oxide, make them very sensitive to spinal anesthesia, producing hypotension after subarachnoid block.

Hyperbaric bupivacaine was used in the above studies, but only isobaric bupivacaine is available in our setting. Baricity of local anesthetics has an important role on spinal block effects and there are controversial results on the degree of hemodynamic changes and incidence of hypotension between hyperbaric and isobaric bupivacaine (27–29).

There were also inconsistent results on the 1st minute Apgar scores assessments between severely preeclamptic and normotensive parturients on studies above. In addition, most of the studies were done in settings where the recommended drugs and vasopressors used for treatment of spinal induced hypotension are available.

2.2 Hypothesis

HO1: Severely preeclamptic patients who undergo spinal anesthesia for cesarean sections have the same degree of hypotension with that of healthy patients. (BP, HR) i.e. u1=u2

HA1: Severely preeclamptic and healthy parturients who undergo spinal anesthesia for cesarean delivery have different degrees of hypotension. i.e. u1≠u2

HO2: There is no difference in fetal outcomes between severely preeclamptic and healthy parturients who undergo cesarean delivery under spinal anesthesia. (Apgar score) i.e. u1= u2

HA1: There is a difference in fetal outcomes between severely preeclamptic and healthy parturients who undergo cesarean delivery under spinal anesthesia. i.e. u1≠u2

Chapter Three: Objective of the study

3.1 General objective

To compare hemodynamic changes and neonatal outcome in normotensive and severe preeclamptic parturients undergoing elective cesarean section under spinal anesthesia

3.2 Specific objectives:

- To compare blood pressure (the incidence of hypotension) between groups
- To compare heart rate between groups
- To compare the 1^{st} and 5^{th} minutes APGAR scores between the groups

Chapter Four: Methods and Materials

4.1 Study area

This study was conducted at St. Paul's Millennium Medical College (SPHMMC), the second largest public hospital in Ethiopia, located in Addis Ababa. SPHMMC has been designated a national specialized hospital as well as a training Centre for obstetrical care by the Federal Ministry of Health.

4.2 Study design and period

An Institutional based prospective study was conducted from July 1, to December 20, 2019(5months duration).

4.3 Source population

All patients who underwent caesarean section delivery under spinal anesthesia within the study period at St. Paul's Millennium Medical College hospital

4.4 Study population

All parturients who fulfilled the inclusion criteria that underwent caesarean section delivery under spinal anesthesia within study period

4.5 Study variables

4.5.1 Dependent variables

- Blood Pressure
- Heart Rate
- Apgar score(1^{st} and 5^{th} scores)

4.5.2 Independent variable

- Socio demographic characteristics: age, weight, height
- ASA status
- Preoperative surgical diagnosis
- Duration of surgery
- Base line heart rate, blood pressure

- Total amount of fluid
- Blood loss
- Utero-tonic agent

4.6 Inclusion and exclusion criteria

4.6.1 Inclusion criteria:

- Non-laboring parturients of ASA (physical status II, III)
- Age above 18 years old
- Weight 45–70 kg
- Carrying a singleton pregnancy
- Elective cesarean section

4.6.2 Exclusion Criteria:

- Patients in labor
- ASA grade IV V
- Patients with chronic hypertension
- Renal or cardiac disease
- Multiple gestations
- Eclamptic patients
- Has any contraindication for spinal anesthesia
- BMI >35 kg/m2
- Abruption placentae or placenta Previa

4.7 Operational definitions

Severe preeclampsia: is defined as systolic blood pressure (SBP) 160 mm Hg, diastolic blood pressure (DBP) 110 mm Hg, or both using noninvasive blood pressure measurement (NIBP) and are taking antihypertensive drugs as recorded from patient chart.

Hypotension : more than a ≥ 30% decline in mean arterial blood pressure (MAP) below the baseline in both groups(18). We defined spinal hypotension as fall of greater than 30% mean arterial pressure (MAP) from baseline, considering that a decrease of 20% in MAP is usually a therapeutic goal in severe hypertension as explained by previous study(11).

The percentage falls of blood pressure (SBP, DBP, MAP) and HR between two measurements and it was calculated as:

Percentage fall = (baseline value- current value/ baseline value)*100

Negative (-) values: indicate the percent fall of a parameter (SBP, DBP, MAP) from its corresponding baseline value (in figures of the result section) and higher than baseline values of heart rate (HR) on some intervals after spinal anesthesia (table 3).

Bradycardia: Pulse rate below 60 using pulse oximetry.

Three Minutes time interval: Early detection of hypotension and prompt targeted treatment may effectively reduce the risk of hypotension after anesthesia and improve the safety and comfort of parturients undergoing cesarean section. There is no evidence or clinical guideline on the optimal NIBP cycle. Based on previous studies, intervals between 2 min and 5 min are used in clinical practice(13,42). Repeated NIBP measurements too often lead to increased discomfort of the patient, and an inappropriate interval time may prevent clinicians from timely detection of hypotension. So, we used 3minutes interval for the first 20 minutes after spinal anesthesia (more likely time to detect the hemodynamic effects of spinal anesthesia with bupivacaine), then after every 5minutes till the end of surgery.

Vasopressor: a drug which produces vasoconstriction and results in rise in blood pressure.

APGAR score=a score used to assess neonatal condition at 1st and 5th minutes out of 10, after delivery. Appearance (color), Pulse (heart rate), Grimace (reflex), Activity (muscle tone) and Respiration of a baby

	Score 0	Score 1	Score 2
Colour	Blue or pale	Peripherally blue, centrally pink	Pink
Heart rate	Absent	<100 beats/min	>100 beats/min
Reflex irritability	No response	Grimace	Cry or active withdrawal
Muscle tone	Limp	Some flexion	Active motion
Respiration	Absent	Weak cry: hypo-ventilation	Good, crying

Fig.I APGARE Score

4.8 Sample Size and Sampling technique

4.8.1 Sample size

Aim of the study was to compare hemodynamic changes and vasopressor requirements in normotensive and severe preeclamptic parturients undergoing cesarean section under spinal anesthesia. Two independent sample size formula based on the mean difference of SBP, DBP,MAP,HR neonatal Apgar score and the incidence of hypotension(proportion) between the two groups from the previous study was used to calculate sample size for each group and each objective. The larger result taken from each group (mean difference of DBP) was taken to calculate the required sample size. The lowest decrease of DBP in healthy groups was 29.4 ±15.3 % and lowest decrease of DBP in severe pre-eclamptic groups was 21.01±11.5% (43). Using G*power version 3.1.9.2 sample size was computed using a priori difference between two independent means (two groups). (Power =80, α=0.05, β=0.20)

t tests - Means: Difference between two independent means (two groups)

Analysis: A priori: Compute required sample size

Input: Tail(s) = Two

Effect size d = 0.6206577

α err prob = 0.05

Power (1-β err prob)= 0.8

Allocation ratio N2/N1 = 1

Output: Noncentrality parameter δ = 2.8442109

Critical t = 1.9893186

Df = 82

Sample size group 1 = 42

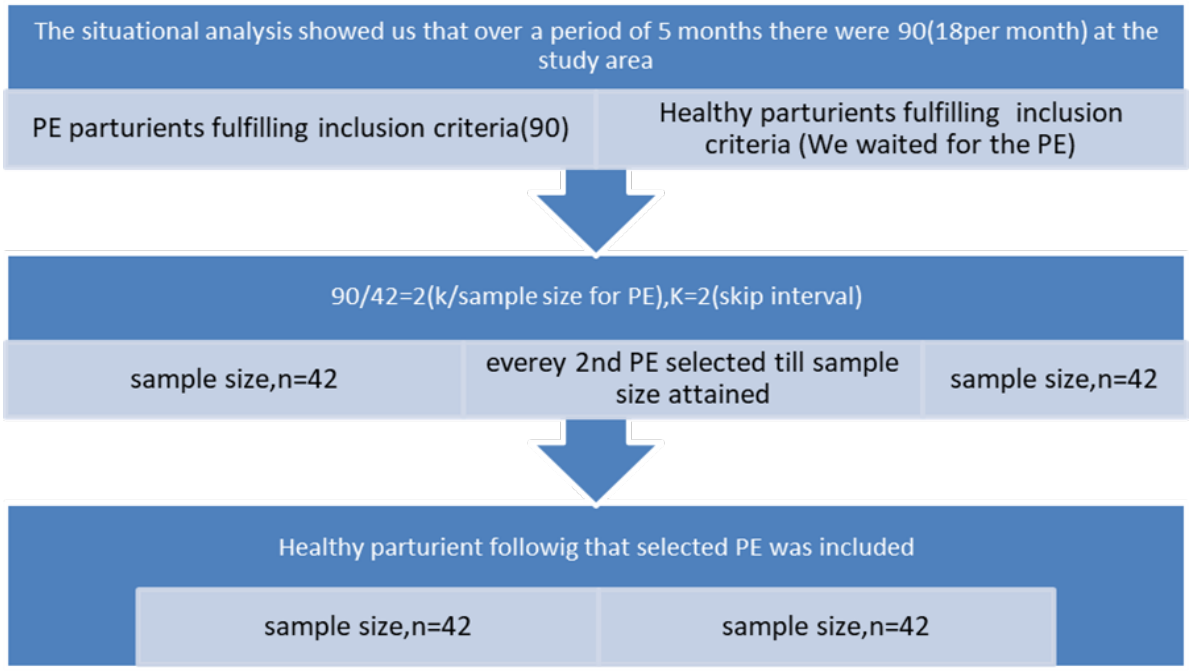
Sample size group 2 = 42

Total sample size = 84

Actual power =0.8025575 (using G*power version 3.1.9.2 sample size was computed using a priori difference between two independent means (two groups).So that the sample size was 42 for each group.

4.8.2 Sampling Technique

Each severely preeclamptic was chosen using systematic random sampling technique, and the healthy parturient next to that was included. The daily operation schedule list was used as a sampling frame. The situational analysis showed that 18 severe preeclamptics who fulfilled our inclusion criteria were operated in SPHMMC per month. According to this data, we had 90 patients in our study period (five months duration) from whom we collected data from only 42 severe preeclamptics. So, the skip interval (k) was calculated as K=90/42= 2, from the daily operation schedule list of data collection was included. The skip interval was used only for parturients who satisfied the inclusion criteria.



PE=preeclamptic

Fig.II: Sampling technique

What is routinely done for parturients who undergo elective cesarean delivery (those who fulfilled our inclusion criteria) under spinal anesthesia at the study area?

Patients are given 10 mg of IV metoclopramide at the morning of the surgery. After receiving the patient in the operating room, patient charts are checked and reviewed (antihypertensive agents were recorded), a brief clinical examination is done and standard ASA monitors are attached including ECG, pulse oximetry, NIBP. Parturients are preloaded with normal saline or lactated Ringer's solution, of at least 500 ml over 15 -20 minutes before the anesthesia, with patient in left lateral position. Baseline SBP,

DBP, MAP and HR were calculated as mean of 2 consecutive measurements 2 minutes apart (we did). After proper aseptic precaution, spinal anesthesia is administered, with patient in sitting position, after skin infiltration with 2ml of 2% lidocaine, with a 24 or 25 gauge spinal needles (Quincke) in L3-4 or L4-5 vertebral interspaces through a midline approach. After observing the free flow of cerebrospinal fluid, isobaric bupivacaine, 0.5% (2.5ml or 12.5 mg) is injected intrathecally and the patient returned to supine position with left uterine displacement and slight (10-15^0) head up position. Surgery is allowed after adequate sensory block has been confirmed. Patients were followed till the conclusion of surgery (we did).

4.9 Data collection methods

Two BSc anesthetists as principal data collectors and one nurse as assistant of them were involved for data collection process. After providing training for the data collectors, data was collected using pretested questionnaires. All patients selected for the study were asked for their consent and instructed on how to self-report pain for pinprick stimulation. Patients were followed till the conclusion of surgery.

4.10 Data quality control

To assure the reliability and validity of the data, structured questionnaire was pretested on 5% of the sample size before actual data collection. Training and orientation about the objectives and relevance of the study, each items included in the study tools and the whole process of data collection was provided for data collectors and supervisors. Data quality control included in the study tools and the whole process of data collection was provided for data collectors and supervisors. During data collection, regular supervision and follow up was undertaken. Supervisors checked each questionnaire daily with further cross check by principal investigator for completeness and consistency of data.

4.11 Data Processing and Analysis

The data was analyzed on Statistical Package for the Social Sciences (SPSS) version 20 computer program after it was cleaned and coded. Mean and standard deviation were used to summarize data, tables and figures to display results. Chi-square test was used to calculate the incidence of hypotension between groups; both paired and unpaired t-tests were used to calculate the mean differences of both blood pressure and heart rate

from their corresponding baselines of each group and intergroup respectively, after checking the distribution of data using Shapiro wilks test and histogram inspection in SPSS version 20 software.

→% of fall from baseline of all parameters (SBP, DBP, MAP and HR) was calculated as = (baseline value-current value/baseline value)*100. P value less than 0.05 ($p < 0.05$) was considered as significant.

4.12 Ethical Considerations

Approval of ethical research committee was mandatory to commence or carry out the study. Permission was obtained from medical director of St. Paul's Millennium Medical College hospital to conduct the research. The study was undertaken on the basis of the patients' wish that in all circumstances it was planned to obtain informed written consent. There was no coercion, and or no incentives to be involved in the study.

4.13 Dissemination plan

The result will be presented for the fulfillment of master's degree in science of anesthesia. The result will be submitted to anesthesia department in soft and hard copy. It will also be given to St. Paul's Millennium Medical College hospital. Finally, it will be published on journals, and on the official website of Addis Ababa university.

Chapter five: Results

Eighty four patients (severe preeclampsia=42 and healthy=42) were studied. Demographic data, the times from skin incision to delivery, the sensory blocked levels at the time of incision, the volumes of estimated blood loss, the volume of IV fluid administered preoperatively and the surgical durations were similar between the two groups (Table 1). All the preeclamptic parturients had taken magnesium sulphate 4gm loading dose and hydralazine of 20mg (daily dose).

After delivery, oxytocin 20 IU was started as infusion and fetus wellbeing was assessed using Apgar scores at 1^{st} and 5^{th} minutes.

The mean gestational age and mean one-minute Apgar scores in the patients with severe preeclampsia were significantly lower than those of the healthy parturients. Baseline values of heart rate were comparable in both groups. Peak sensory block level was similar in both groups and no patients complained of intraoperative pain and required supplemental analgesics. The mean intra-operative crystalloid requirement in PE group was 1353.6±284 ml, while in normotensive group it was 1716.7±431ml (P-value < 0.05, statistically significant). Hypotension was treated promptly by increasing the rate of fluid administration. Only two patients from the normotensive group took 10ug IV bolus adrenaline for hypotension treatment and none of the severely preeclamptic group.

After induction of spinal anesthesia; SBP, DBP and MAP decreased in both groups, but more in the normotensive groups as compared to the preeclamptic one in the first 9 minutes (Table 2). There was no statistically significant difference in heart rate of the groups after the induction of spinal anesthesia (Table 2).

The incidence of hypotension (as measured on 10 time intervals after spinal anesthesia) the preeclamptic patients (31%) was less than that of the healthy parturients (59.5%) (Table 2), despite the former receiving smaller volumes of intravenous fluids (Table 1), (1716.7±431ml versus 1353.6±284 ml) (P = 0.001).

Table 1: Baseline characteristics of variables between groups

Variable	Normotensive (n=42)	Preeclamptic (n=42)	P-value
Age, year(mean ±SD)	29.3±4	30.8±3.8	0.09
Weight, kilograms(mean ±SD)	68.8±8.6	72.2±8.1	0.06
Height, meters(mean ±SD)	1.64±0.6	1.64±0.5	0.94
Gestational age, week(mean ±SD)	39±1.07	35.5±1	0.01**
Baseline SBP, mmHg(mean ±SD)	125.8±11.8	161.3±10.1	0.001**
Baseline DBP, mmHg(mean ±SD)	75.8±11.4	104.6±9.5	0.001**
Baseline MAP, mmHg(mean ±SD)	91.3±10	123.5±7.9	0.001**
Baseline HR, b/min(mean ±SD)	92±10.6	91.8±10.5	0.95
IV fluid preloaded, ml(mean ±SD)	481.7±177	446.4±164	0.348

Legends; **= statistically significant, mean±standard deviation (unpaired T-test was used for analysis)

From table 1: Baseline characteristics were statistically similar in both groups ($P>0.05$), but the baseline SBP, DBP, MAP, and gestational age ($P<0.05$), in parturients with preeclampsia than the corresponding values among the non-preeclamptic parturients. As the baseline blood pressure was statistically different between the groups, we

classified them as two cohorts: severely preeclamptic parturients as one cohort and the normotensive as another cohort. So, in calculating the magnitude of decrement from consequent measurements after induction of spinal anesthesia (was expressed as % decrease from baseline) in blood pressure was calculated at each given time intervals(immediately after SA,3min,6,9,12,15,18,21,26,31 and at the end of surgery) in each group using paired t-test(not in the table) then after the magnitude of decrement in both groups were compared according to a common criteria i.e. a 30% decrease from baseline of each group(for incidence of hypotension), using unpaired test(table 1).

Table 2: Intraoperative Measures

Variable	Normotensive(n=42)	S.preeclamptic(n=42)	P-value
Upper level of sensory block(*)	T4(T4-T6)	T4(T4-T6)	0.601
APGAR score, 1stmin(*)	8(8-9)	8(7-8)	0.004**
APGAR score, 5thmin. (*)	9(9-10)	9(9-10)	0.737
Intraoperative crystalloid, ml	1716.7±431	1353.6±284	0.001**
Estimated blood loss, ml	443.6±80	473.8±74	0.078
Duration of surgery, min.	30.1±3	29.8±2	0.588

Legends;* Mann Whitney u-test →median (interquartile range), **=statistically significant, mean ±standard deviation (unpaired T-test) →Values were expressed as median (interquartile range) for the Mann Whitney u-test and mean ±standard deviation for unpaired T-test.

From table 2: Estimated intraoperative blood loss, duration of surgery and 5th minute Apgar scores were statistically nonsignificant between the groups (p>0.05), but

intraoperative fluid administered were more in the severely preeclamptic groups ($p<0.05$).1st minute Apgar score was also lower in the severely preeclamptic patients.

Table 3: Mean % changes of mean arterial pressure and heart rate (from baseline) between successive period analysis after spinal anesthesia between the groups

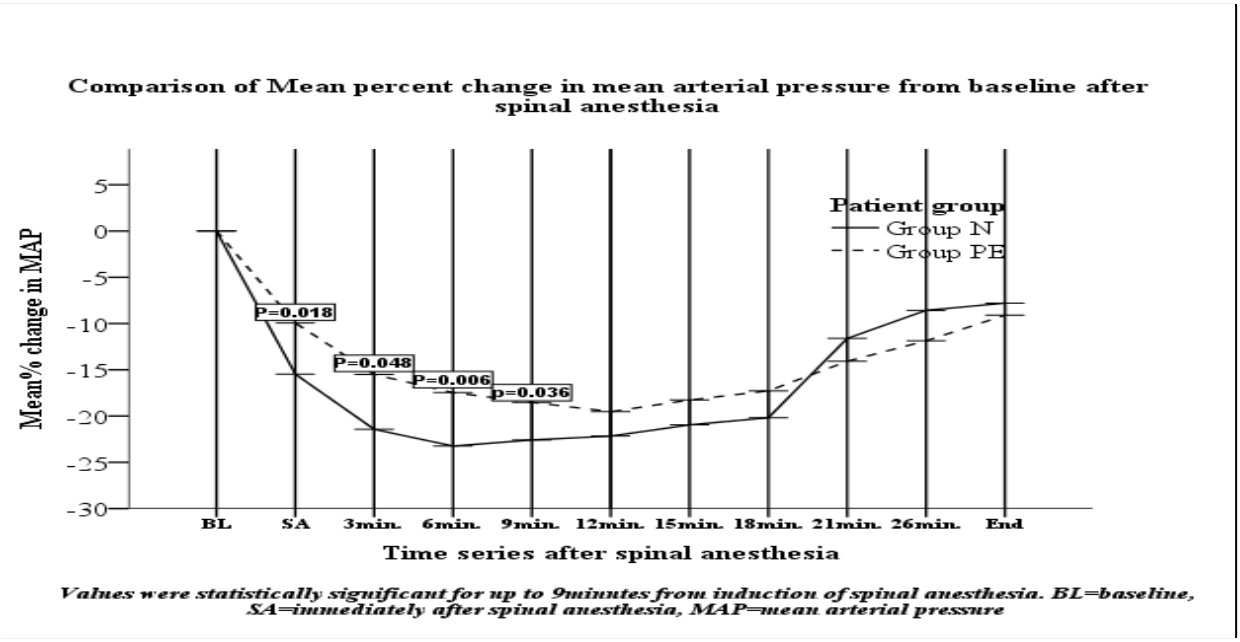
Variables over time series		Normotensive(n=42) →group N	Preeclamptic(n=42) group PE	P-value
After preload	MAP (%)	0.2±4	1 ±4	0.109
	HR (%)	-4±8	-4±6	0.738
After spinal	MAP	16±13	10±6	0.018**
	HR	-3±13	-8±7	0.07
3 minutes	MAP	21±12	15±7	0.048**
	HR	5±13	8±9	0.180
6 minutes	MAP	23±12	17±5	0.006**
	HR	3±13	2±10	0.637
9 minutes	MAP	23±10	18±8	0.036**
	HR	5±14	7±10	0.56
12 min.	MAP	22±13	19±8	0.263
	HR	5±11	7±11	0.425
15 min.	MAP	21±13	18±7	0.259
	HR	6±10	7±11	0.600
18 min.	MAP	20±14	17±7	0.232
	HR	-4±10	-6±10	0.125
21 min.	MAP	12±8	14±6	0.128

	HR	-3±11	-5±9	0.45
26 min.	MAP	9±7	11±5	0.068
	HR	-5±10	-8±8	0.155
At the end of surgery	MAP	8±8	9±6	0.403
	HR	-4±11	-5±10	0.353
Incidence of hypotension		59.5% (25/42)	31% (13/42)	0.015*

** Statistically significant values, Unpaired t-test used for analysis; Parameters were expressed as Mean± Standard deviation, MAP=mean arterial pressure, HR= heart rate, * Chi-square test (has the patient developed hypotension according to the definition of MAP? →yes/no), the (-) of heart rate indicates for values that were higher than their corresponding baseline levels, as calculated as % mean fall= ((baseline HR-HR(higher) at the given time interval after spinal anesthesia, example at 18min)/baseline HR)*100.

From Table 3: The magnitude of changes (mean) in MAP of the normotensive group (group N) were higher ($p<0.05$); in the early 9minutes after spinal anesthesia, and the incidence of hypotension (59.5%) was higher in the normotensive groups (N) than in the severely preeclamptic group (PE) i.e.31% . The magnitude of changes(mean) in heart rate of both groups were not statistically significant throughout all time intervals after the induction of spinal anesthesia($p>0.05$).

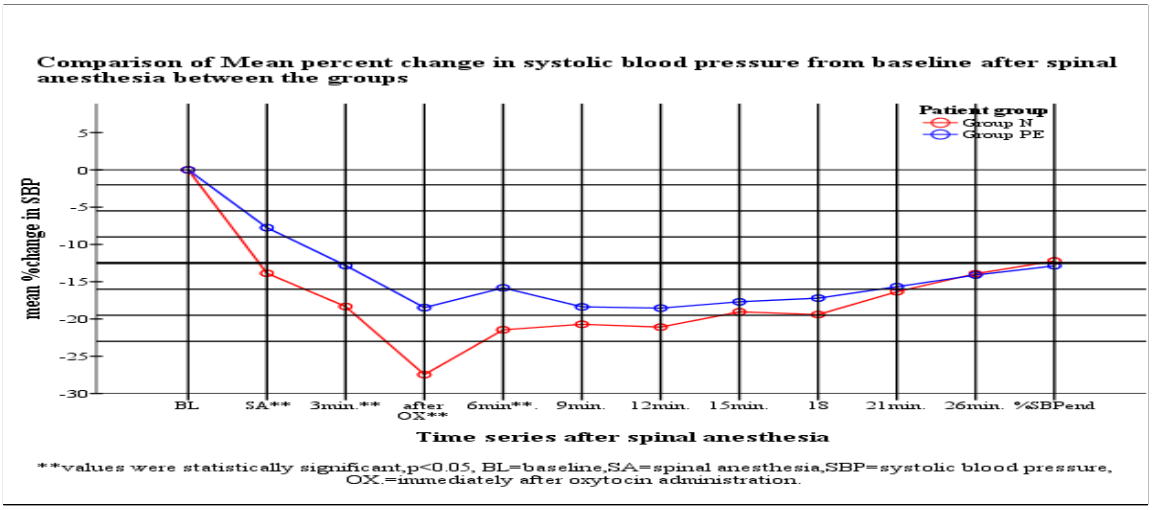
Figure III: Mean % fall of mean arterial pressure (from baseline) between successive period analysis after spinal anesthesia between the groups



Values were expressed as mean% compared to their corresponding baseline MAP (mean arterial pressure) and was calculated as % mean fall= ((baseline MAP-MAP at the given time interval after spinal anesthesia, example at 3min)/baseline MAP)*100. We expressed the mean as percentage (%) of its baseline value, because we wanted to categorize the results according to the definition of hypotension (in our study) as ≥30% decrease of the baseline MAP of each group. The negative (-) indicates the percent of decrement from its baseline level.

From figure III: The percent fall in MAP of the normotensive group(group N) were higher($p<0.05$); immediately after induction of spinal anesthesia,3minutes,6 minutes and 9minutes after spinal anesthesia and then after, there were no statistically significant changes between the groups till the conclusion of surgery(only statistically significant values are shown in fig. I).

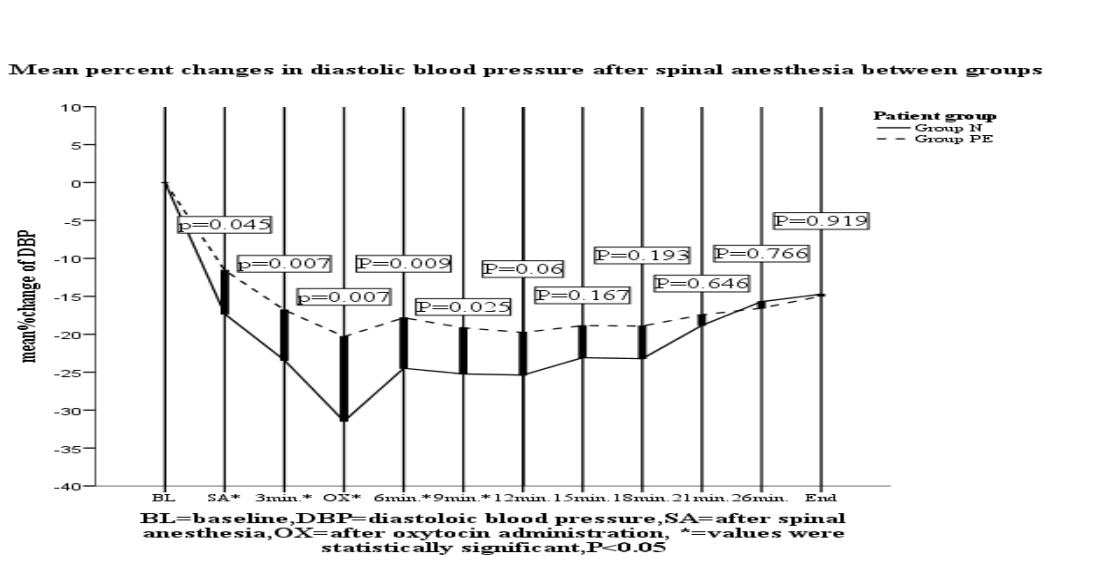
Figure IV: Comparison of percent fall (from baseline) in systolic blood pressure from baseline after spinal anesthesia between the groups



*=statistically significant values, unpaired T test was used for analysis of SBP between the group, Values were expressed as mean% compared to their corresponding baseline SBP (systolic blood pressure) and was calculated as % mean fall= ((baseline SBP-SBP at the given time intervals after spinal anesthesia, example at 3min)/baseline SBP)*100. We expressed the mean as percentage of its baseline value.

From figure IV: The % mean fall in SBP of the normotensive group(group N) were higher($p<0.05$); immediately after induction of spinal anesthesia, at 3minutes and 6 minutes after spinal anesthesia and then after, there were no statistically significant changes between the groups till the conclusion of surgery.

Figure V: Comparison of mean % change (from baseline) in diastolic blood pressure from baseline after spinal anesthesia between the groups



*=statistically significant values, unpaired T test was used for analysis of DBP between the group, Values were expressed as mean% compared to their corresponding baseline DBP (diastolic blood pressure) and was calculated as % mean change= ((baseline DBP-DBP at the given time intervals after spinal anesthesia, example at 3min)/baseline DBP)*100. We expressed the mean as percentage of its baseline value. The negative (-) indicates the percent of decrement from its baseline level.

From figure V: The magnitude of changes(mean) in DBP of the normotensive group(group N) were higher($p<0.05$); immediately after induction of spinal anesthesia,3minutes,6 minutes and 9minutes after spinal anesthesia and then after, there were no statistically significant changes between the groups till the conclusion of surgery.

Chapter six: Discussion

The reported incidence of spinal anesthesia-induced maternal hypotension is varied due to inconsistent definition among several studies, claimed to be between 7% and 89.2% (18,19).

Our study revealed that, after induction of spinal anesthesia; SBP, DBP and MAP decreased in both groups, but more in the normotensive groups as compared to the severely preeclamptic one in the first 9 minutes. There was no statistically significant difference in heart rate of the groups after the induction of spinal anesthesia. The incidence of hypotension (as measured on 10 time intervals after spinal anesthesia) the preeclamptic patients (31%) was less than that of the healthy parturients (59.5%), despite the former receiving smaller volumes of intravenous fluids (Table 1), (1716.7±431ml versus 1353.6±284 ml) (P = 0.001). The mean one-minute Apgar scores in the patients with severe preeclampsia were significantly lower than those of the healthy parturients (8(7-8) vs 8(8-9) with p=0.004, but the 5^{th} minute Apgar score recordings were comparable between the groups (p=0.737).

A prospective study by Sivevski et al. in Republic of Macedonia found that, the blood pressure(SBP,DBP and MAP) falls (%) from baseline were significantly greater in the healthy parturients compared to those with severe preeclampsia and the incidence of hypotension in the preeclamptics was 25% compared to 53% in healthy parturients(18).This study was consistent with our finding.

A prospective comparative study of sixty parturients by Aya et al. showed that, the incidence of hypotension in the severely preeclamptic parturients was16.6% and 53.3% in normotensive groups, in spite of receiving less crystalloid fluids and higher dose of 0.5% bupivacaine. Significant hypotension was defined as systolic BP decrease to less than100 mm Hg in healthy parturients or 30% decrease in mean BP in both groups(11).The percent decrease(from baseline) of mean diastolic and mean arterial pressures after spinal anesthesia were higher in the normotensive groups. The slight differences in the incidence of hypotension may be partly, due to low dose of bupivacaine in their study (10mg vs. 12.5mg).

Another study by Chowdhury et al. found that minimum SBP, DBP and MAP recorded

were always higher in the preeclamptic group, in comparison to the normotensive group. The percentage fall in MAP calculated from baseline was also less in the preeclamptic group(16). This was comparable with our study.

In their study, Ishrat and Raja concluded that, preeclamptic patients experienced less hypotension than healthy parturients following spinal anesthesia and fall in DBP and MAP were
significantly higher in healthy parturients(43). Our study results were also similar to their study. Nikoosersht et al.(prospective) in Iran, reported that the incidence of hypotension in severely preeclamptics was found to be significantly lower in comparison to the rate among healthy parturients (55% vs 89%),despite the normotensive received more volumes of intravenous fluids (2.5 versus 2.4 lit.). Despite differences, this study found high incidence of hypotension in both groups. They defined (hypotension ≥ 25% decline to baseline MAP vs. ≥ 30% in our study) might explain why the incidence of hypotension was higher in their study.
Karuna and Pallavi on their prospective study, did not find a difference between normotensive and preeclamptic groups regarding the occurrence of hypotension, decrement of blood pressure, vasopressor use, or newborn well-being after spinal anesthesia using 0.5% hyperbaric bupivacaine 2 ml (10 mg).This was in contrary to our study, and the reason could be the small dose of the drug(33).
The mean values of HR did not change significantly in both groups throughout all time intervals after the induction of spinal anesthesia, but intraoperative values were slightly higher than their baseline values in both groups (the negative values in table 3).

This finding was in line with studies done by Khatri et al., Ishrat and Raja, and Sivevski et al(18,34,43).

In terms of vasopressor use, only two patients from the normotensive group were treated with 10mcg of adrenaline, and this was not adequate for comparison.

Several factors might have contributed to less incidence of hypotension in the severely preeclamptic patients. An obvious factor is the large difference in gestational age between the study groups. Indeed, healthy parturients carrying a larger fetus may be at

increased risk of aortocaval compression (higher gestational age in the normotensive would correspond to large fetal weight).

In addition, by dilating epidural blood vessels, the aortocaval compression could facilitate the cephalad spread of local anesthetics, leading to a higher upper level of spinal blockade in healthy parturients. Although the upper sensory levels were similar in both groups, the aortocaval compression may, at least partly, account for the increased incidence and severity of hypotension in the healthy parturients in our study.

Another explanation could be partly the results of a study by Smith et al and Saha et al, in which damaged vascular endothelium, as seen in severe PE, produces increased amount of endogenous vasopressor ¬like thromboxane and endothelin, resulting in persistent vasoconstriction, which is not altered even after SAB, resulting in less hemodynamic alterations; which contrasts with normal pregnancy, where altered balance of vascular tone, reduced response to endogenous pressor and increased synthesis of vasodilator prostaglandins and nitric oxide, make them very sensitive to spinal anesthesia, producing hypotension after spinal anesthesia(1,41).

In terms of fetal outcome, the mean one-minute Apgar scores in the patients with severe preeclampsia were significantly lower than those of the healthy parturients (8(7-8) vs 8(8-9) with p=0.004, but the 5^{th} minute Apgar score recordings were comparable between the groups (p=0.737).

The cause of the lower mean one-minute Apgar scores in newborns from severely preeclamptic women may be that they had lower gestational age (35.5±1 vs 39±1.07 ,P< 0.001) and chronic uteroplacental insufficiency, which results in intrauterine growth restriction.

But studies (Khatri et al.) and Leena Goel et al. (2018) found comparable 1^{st} and 5^{th} minute Apgar score results in both severely preeclamptic and normotensive groups. The explanation for this could be advanced antenatal care and use of vasopressor intraoperatively(2,34).

Regarding fetal well-being, it had been theorized that the sympathectomy attributable

to spinal anesthesia could significantly decrease uteroplacental blood flow in preeclamptics and, thereafter, lead to worse neonatal outcomes. Conversely, several studies supporting the safety of spinal anesthesia in these patients have been published, and neuraxial anesthesia for labor pain relief has even been shown to increase placental blood flow in patients with severe preeclampsia (32).

6.1 Limitation of the study

Anti-hypertensive agents were not protocolled and oxytocin drip was not strictly controlled, which may affect our results.

Chapter seven: Conclusion and Recommendations

7.1 Conclusion

Our study showed that the incidence and magnitude of spinal anesthesia-induced hypotension was less in severely preeclamptic parturients than healthy parturients who underwent elective cesarean delivery under spinal anesthesia.

7.2 Recommendations

- ✓ **For anesthetists in SPMMMC**

Spinal anesthesia is safe for severely preeclamptic parturients.

- ✓ **For further researcher**

We recommend further studies with the antihypertensive and uterotonic agents controlled (protocoled) on the study setting.

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9. Annexes

9.1 Annex I: English version Consent form

Dear participant:

My name is Meles; I am attending a postgraduate program in the field of Anesthesia at Addis Ababa University. I am conducting my thesis on comparing the effects of spinal anesthesia on maternal hemodynamic changes and fetal outcome between normotensives and severe preeclamptic parturients undergoing elective cesarean sections from July 1, to August 30, 2019.

The information going to be obtained will help the government and other responsible bodies to

reduce the incidence of hypotension which helps to reduce maternal and neonatal morbidity and

mortality. As a chance you were included in the study. So, we kindly request your involvement in the study and honest response to achieve the objective of the study. Your response will be completely confidential and you have full right either to refuse a single question or leave the study. However, your honest response to those questions will help us to asses and understand the effect. So, we are requesting you to give honest response and keep participation.

Would you willing to participate in the study please? YES/NO

Thanks for taking part in the study!!!!

For further question ask investigator

Tele - +251914584531

Email - melesmd@gmail.com

9.2 Annex II: Amharic version consent form

የመጠይቅ ፈቃድ

የተከበራችሁ የጥናቱ ተካፋዮች

ጤና ይስጥልን እኔ _____ እባላለሁ። በአዲስ አበባ ዩኒቨርሲቲ በእንስቴዚያ ትምህርት ክፍል ተመራማሪ ነኝ። በቀዶ ጥገና ወሊድ የእንስቴዚያ መድሀኒት በሚሰጥበት ግዜ የሚከሰቱ የደም ግፊት እና የልብ ምት ለውጦች ላይ የሚሰራ ጥናት በጋንዲ መታሰቢያ ሆስፒታል እየተመራመርኩኝ ሲሆን: ጥናቱ ለእርሶ ምንም አይነት የገንዘብ ጥቅም አያስገኝም ነገርግን የጥናቱ ውጤት በህክምና ዘርፍ ላይ ያሉትን ችግሮች ለመቅረፍ እና የታካሚዎችን ደህንነት የሚያረጋግጡ ህጎች እንዲሰተካከሉ እና ሥራ ላይ እንዲውሉ የበኩሎን አስተዋፅዖ ያበረክታሉ። ስምዎ በዚህ ጥናት ላይ አይፃፍም። ስለዚህም የእርሶ ምላሽ ሚስጥራዊነቱ የተጠበቀ ነው::በዚህ መጠይቅ ላይ ለመሳተፍ መስማማትም ሆነ አለመስማማት ይችላሉ። ባለመስማማቶ ምንም የሚጎዱት ነገር የለም።

ምንም አይነት ጥያቄ ካለዎት ቀጥሎ በተፃፈው አድራሻ ተመራማሪውን ማግኘት ይችላሉ።

ጥያቄዉን ለመቀጠል ፍቃደኛ ኖት?

አዎ ____ አይደለሁም_____ (ስለረዱገኝ በድጋሚ አመሰግናለሁ)

መለሰ ደስታ (ዋና ተመራማሪ):

ስልክ +251-914-58-45-31

የመረጃ ሰብሳቢ ስምና ፊርማ

ስም ፊርማ _____ቀን_____

9.3 Annex III: Data capturing tool (Questionnaire)

Part I. Sociodemographic data

S.No	Question	Response
101	Age	
102	Weight	
103	Height	
104	BMI	

Part II. Preoperative Assessment and Baseline vital signs

S.No	Question	Response
201	Gestational age	
202	Parity	
203	Indication for C/S	Preeclampsia(Severe/mild/moderate)
		CPD
		Previous c/s
		Malpresentation
		Other: (Specify)
204	Other coexisting disease	
205	ASA Status	I

		II	
		III	
206	Systolic BP	1st measurement	2 minutes later
		_____mmHg	_____mmHg
207	Diastolic BP	_____ mmHg	_____mmHg
208	Mean Arterial Pressure		
209	Heart Rate	_____Beats/m	_____b/min
210	Magnesium sulphate	_____mg	
211	Anti-Hypertensive	Hydralazine_____ mg	
		Methyldopa_____ mg	
		Other:	

212	Antiemetic(Premedication)	Metoclopramide
		Cimetidine
		Other:
213	Fluid preloaded/coload	Ringer's Lactate _____ ml.
		Normal Saline _____ ml.

Part IIIa: Intra-operative Assessment

S.No	Question	Response
301	Dose of local anesthetic	_____mg
302	Vertebral Interspace drug administered(Circle one)	L_3/L_4
		L_2/L_3
		L_4/L_5
303	Local anesthetic administered time	
304	Level of Sensory block(Circle one)	T5

		T7
		T6
		T4
305	Skin incision time	
306	Delivery time	
307	Utero-tonic agent	Oxytocin_____ IU
		Ergometrine_____ mg
308	Vasopressor used	Ephedrine_____ mg
		Adrenaline_____ ug.
		Phenylephrine_____ ug.
		Other:
309	Atropine	_____mg
310	APGAR Score	1st minute_____
		5th minute_____

311	Total fluid used intraoperatively	_____ml.
312	Estimated blood loss	_____ml

Part IIIb. Intraoperative Vital Signs

S.No	Time	Systolic BP	Diastolic BP	MAP	Heart Rate
401	Immediately after volume preload(2nd baseline)				
402	Immediately after Spinal Anesthesia				
403	3 minutes after SA				
404	6 minutes after SA				
405	9 minutes after SA				
406	12 minutes after SA				
407	15 minutes after SA				
408	18 minutes after SA				
409	21 minutes after SA				
410	26 minutes after SA				
411	31 minutes after SA				
412	Immediately after oxytocin administration				
413	At end of surgery				

414	Duration of Surgery				