COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE

DEPARTMENT OF ANESTHESIA

EFFECT OF PROPHYLACTIC ONDANSETRONE ON PREVENTION OF SPINAL INDUCED HYPOTENSION AMONG WOMEN UNDERWENT ELECTIVE CESAREAN SECTION AT YEKATIT-12 HOSPITAL, ETHIOPIA, 2019: PROSPECTIVE COHORT STUDY

INVESTIGATOR: AHMED HAMU (B.SC.)

ahmedhamu84@gmail.com

ADVISORS: 1. BETELIHEM G. (B.SC. M.SC. LECTURER OF ANESTHESIA)

2. SIRYET. (B.SC. M.SC. LECTURER OF ANESTHESIA)

June, 2020

ADDIS ABEBA, ETHIOPIA

Addis Ababa University

College of health science school of medicine

Department of anesthesia

A Thesis Submitted to Addis Ababa University school of Medicine Department of Anesthesia for requirement of partial fulfillment of Degree of Masters of Science in Advanced Clinical Anesthesia.

Name of investigator	**Ahmed Hamu**
Title of the thesis	**Effect of prophylactic Ondansetron on prevention of spinal anesthesia induced hypotension among women undergoing elective cesarean section at Yekatit-12 hospital, Ethiopia, 2019: Prospective cohort study**
Duration of project	**October 30 to January 2019/2020**
Study area	**Yekatit-12 hospital, Ethiopia**
Address of investigator	**Phone:+251924823790** **Email:** ***ahmedhamu84@gmail.com***
Proposal submission date:	**May, 2019**
Thesis submission date:	**June, 2020**

DECLARATION

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

Name: Ahmed Hamu

Signature: _____

Submission to MSc Tutor, Department of Anesthesia, Addis Ababa University

Date of Submission: _____

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

Name	Signature	Date
1. BETELIHEM G.	_____	_____
2. SIRYET T.	_____	_____

ACKNOWLEDGEMENT

First of all I would like to express my greet thanks to Department of Anesthesia School of Medicine College of Health Science Addis Ababa University for giving this opportunity to perform this research thesis.

I would like to express my heart-full gratitude and thanks to my advisors Ms. Betelihem Girma and Mr. Siryet Tesfaye for their invaluable support and comments. And my data collectors for your dedication and precious work in collecting data.

I would like to express my heart-full gratitude and thanks to Mr.Fetene Seyoum for his invaluable comments and endless support.

Additionally I would like to extend my great gratefulness towards those authors and researchers of articles and on-line information for the valuable works I have read and cited in my research thesis.

Table of Contents

List of Figure

List of Table

ABBREVIATIONS/ACRONYM

ASA	American Society of Anesthesiologists
BJR	Bezold-Jarisch reflex
BP	Blood pressure
BMI	Body mass index
CI	Confidence Interval
CS	Cesarean Section
CSE	Combined spinal epidural
DBP	Diastolic blood pressure
EC	Ethiopian Calendar
ECS	Elective Cesarean Section
EDHS	Ethiopia Demographic and Health Survey
5HT3	Five Hydroxytryptamine receptor three
G.C	Gregorian calendar
HEENT	Head,ear,eye, nose and throat
HR	Hear Rate
IV	Intra-venous
IU	International unit
mg	milligram
NIBP	Non-Invasive Blood Pressure
NPO	Nothing per oath
PSH	Post Spinal Hypotension
RCT	Randomized control trial
SBP	Systolic blood pressure
SAB	Sub Arachnoid block
SA	Spinal Anesthesia
SIH	Spinal induced hypotension
T	Thoracic vertebrae
WHO	World Health Organization

ABSTRACT

Background: Hypotension is a common side effects after spinal anesthesia which associate with both maternal and fetal morbidity. Many interventions have been suggested to prevent this clinical problem. A commonly used antiemetic, ondansetron, can be used as an alternative to prevent hypotension after spinal anesthesia. The action believed to inhibit Bezold-Jarisch reflex.

Objective: To assess effect of prophylactic ondansetron on spinal anesthesia induced hypotension among women undergoing elective cesarean section at yekatit-12 hospital, from Oct, 2019 –Jan, 2020, Addis Ababa, Ethiopia.

Methodology: In this prospective cohort study 100 patients with American Society of Anesthesiologists (ASA) status class-II, age≥18 and BMI 18 -30 kg/m2 who underwent cesarean section under spinal anesthesia were included. Prophylactic group (n=50) receive 4mg ondansetron, while Non-prophylactic group (n=50) did not receive ondansetron. The outcomes of the study were the incidence of hypotension, nausea, vomiting and the need of rescue vasopressor. Comparisons of variables between study groups were done using student t test and Chi square test. Significance was determined at P value <0.05. Table and graph were used to show result of the study.

Result: The incidence of hypotension is 13(26.5%) in prophylactic group compared to non-prophylactic group 36(75% with (p=007). There was a statistically significant difference in mean systolic blood pressure, mean heart rate and mean arterial pressure between the groups at all-time point with p<0.05. The incidence of nausea and vomiting was higher in non-prophylactic group when compared with prophylactic group with (p=0.003 & 0.001) respectively. There was not significant difference in total need of rescue vasopressor between groups (6.1% in prophylactic and 10.4% in non-prophylactic group with (p=0.17).

Conclusion and Recommendation: prophylactic use of 4mg intravenous ondansetron 5 minutes before spinal anesthesia significantly reduces the incidence of hypotension; nausea and vomiting in parturient undergoing elective cesarean section. We recommend the use prophylaxis ondansetron for prevention of spinal anesthesia induced hypotension in parturient undergo elective cesarean section under spinal anesthesia.

CHAPTER ONE: INTRODUCTION

1.1 Background

Spinal anesthesia is the injection of local anesthetics into the subarachnoid space for the purpose of blunting autonomic, sensory and motor nerve transmission. It has been practicing for obstetric anesthesia since the beginning of the 20th century .It's advantages over general anesthesia was less nausea and vomiting, less urinary retention, reduced opioid requirement, greater mental awareness, less intraoperative blood loss, decreased incidence of thrombotic events, and less risk of developing a post-op ileus. Additionally, patients have improved respiratory and cardiac stability, and are quicker to drink, eat, and ambulate post-operatively(1).

Now a day's spinal anesthesia technique is practiced for treatment of post-operative pain due to co-administration of LA with opioids that allows post-operative analgesia, improving maternal comfort in the post-operative period. Spinal blocks also have the advantage of being more cost-effective when compared with epidural anesthesia(2).

Regional anesthesia has become the most preferred anesthesia technique for cesarean section because due to its simplicity, rapid onset of action, maternal comfort and safety when compared with general anesthesia (2, 3).

Before spinal anesthesia was emerged general anesthesia was the only option for cesarean section but now a day the proportion was significantly decreased due to new emerged and sophasticated techniques for regional anesthesia, such as the combined spinal epidural (CSE) anesthesia and the continuous spinal anesthesia.The practice of spinal anesthesia in Ethiopian hospitals are increasing and most of the mothers are choosing this regional technique due to many advantage and for both mother and fetus(4).

Spinal block –induced sympatholytic leads to vasodilatation and hence, causes maternal hypotension which leads to a attenuation in systolic arterial blood pressure and can compromise uterine blood flow and fetal circulation which results in hypoxia and fetal acidosis(5).

Hypotension is a common clinical problem faced by patients on spinal anesthesia and if severe it can lead to both maternal and fetal morbidity. Hypotension for less than two minutes did not affect neonatal neurobehavioral outcomes whereas more than four minutes of maternal hypotension was associated with neonatal neurobehavioral outcomes changes at four up to seven days of life(6)

Severe hypotension poses serious risks to mother (such as loss of consciousness, aspiration and even cardiac arrest) and baby (such as lack of oxygen and brain damage(7, 8). The physiological mechanism of spinal induced hypotension (SIH)is mostly being rapid onset of sympatholytic due to increased sensitivity of nerve fibers to local anesthetics during pregnancy which related to the Sympathectomy that results in a reduction of the tone of splanchnic vasculature and the lower limbs and Higher sensitivity to local anesthetics combined with aortocaval compression of the pregnant uterus are the main reasons for increased incidence and higher levels of hypotension in pregnant women, compared to non-obstetric patients. This decrease in systemic vascular resistance leads to venous pooling and therefore results a reduction in venous return. The consequence reduction in preload, thus affects the cardiac output(9).

Pregnant women also exhibit an increased level of sympathetic activity compared to parasympathetic activity.Sympatholysis therefore leads to a higher degree of peripheral vasodilatation and a predominance of parasympathetic activity, consequently reducing the venous return and cardiac pre-load, and resulting in bradycardia, nausea and vomiting. The reduced pre-load in turn results in reduced cardiac output (CO), leading to systemic hypotension. This state is further aggravated by aortocaval compression and Higher sympathetic block proportionally reduces the occurrence of compensatory mechanisms via baroreceptors and increases the risk of cardio inhibitory reflexes such as the Bezold-Jarisch reflex and, ultimately, cardiac arrest and death(7).

The occurrence of hypotension is decrease in vascular resistance caused by sympathetic blockade which in turn causes vasodilatation and finally leads to drop in arterial pressure(10, 11). For the sympathetic blockage the main cause is blockage of nerve pathway by inhibition of Na influx at Na channel that resulted in activation of Bezold Jarisch reflex (BJR),and increased baroreceptor activity may lead to hypotension and bradycardia. BJR is triggered by chemoreceptors and mechanoreceptors which are serotonin sensitive. Serotonin is an additive trigger for BJR in hypovolemic patients(12).Bezold Jarisch reflex activation can lead to activation ventricular receptor by nociception or stretch that result in decrease HR & MAP (10).

To prevent post spinal hypotension, mechanical techniques, volume preloading and loading and vasopressor drugs have been tried in several studies with variable results(13-17). In a systematic review done by Pamela in 2011 showed that Colloid is more reliable than crystalloid in preventing hypotension but it is not available in different hospitals and it is coasty(13).

Ondansetron is a serotonin receptor subtype 3 (5-HT3) antagonist. It is commonly used as an antiemetic, working to block 5-HT3 receptors in the GI system and in the chemoreceptor trigger zone of the brain. It has a rapid onset of action(18). Aside from its central action in the brain, ondansetron will bind to 5-HT3 receptors peripherally, including those within the cardiac ventricles and on the vagus nerve, which help to mediate the BJR Binding these receptors prevents induction of the BJR and decreases parasympathetic dominance, lessening the degree of bradycardia and hypotension brought about by spinal anesthesia(11).

We have commonly used ondansetron as anti-emetic in obstetric anesthesia for prevention or treatment of nausea and vomiting in different private and governmental hospital. The price of 4mg ondansetron is 25 Ethiopian birr but in different Ethiopian hospital this drug is not available and not practiced as prophylactic in prevention of spinal induced hypotension after this study if prophylactic ondansetron is effective in prevention of spinal induced hypotension we will change the practice of all anesthesia provider to use this drugs due to it have minimum effects on both mother and fetus

1.2 Statement of the problem

Spinal anesthesia has the potential to produce several undesirable problems; the main one being is hypotension the expected level sensory block during spinal anesthesia is T4 (thoracic vertebrae 4) needed for cesarean section(1).

Hypotension is a common clinical problem faced by patients on spinal anesthesia and if severe it can lead to both maternal and fetal morbidity. Severe hypotension poses serious risks to both mother (such as loss of consciousness, aspiration and even cardiac arrest) and baby (such as lack of oxygen and brain damage(7, 8).Maternal hypotension is the most common complication during CS under spinal anesthesia with a reported incidence greater than 80% if not prevented(13).Retrospective study done in America on pregnant mother undergoing elective delivery under spinal anesthesia found that 46.5% of those mothers have encountered decrease in blood pressure more than 30% from the base line mean arterial blood pressure and 7.6% of pregnant mothers encountered a decrement of greater than 50% from base line mean arterial blood pressure(19).

Other study also showed that the incidence of hypotension was reported to be 92% in the control group during cesarean section with spinal anaesthesia(20) while in the nonobstetric patient was 33%(21).

A Study in Nigeria in 2010 by Adigun et.al, which compare the effects of phenylephrine and ephedrine the reported incidence of SIH in obstetrics was 24.2%(22).

Study done in South African showed that 79% of anesthesia related deaths were because of spinal anesthesia. It is specifically stated that two thirds (2/3) of the deaths were directly related to spinal anesthesia induced hypotension(23).

Another study done in Ethiopia by Ashebir Nugussie in 2016 found that the incidence of hypotension among mothers who undergone cesarean section after spinal anesthesia was (80%)(24).

Cross sectional study done at 2013 in Ethiopia on pregnant mothers who underwent cesarean section by spinal anesthesia showed that the incidence of hypotension is 36.6%(4).

Mothers with pre delivery hypovolemia may be at risk of cardiovascular collapse because the sympathetic blockade may severely decrease venous return. As a consequence, prevention of

spinal hypotension has been a key research area within the field of obstetric anesthesia(25). Hypotension is treated with either large amounts of fluid therapy or vasopressors. Fluid therapy has been shown to provide positive outcomes in helping to reduce hypotension, but it can also lead to fluid overload and urinary retention(1).

Now a day hypotension during obstetric spinal anesthesia can been managed by fluid preloading, or co-loading by double iv line, atropine prophylaxis, positioning to avoid aortocaval compression after spina positioning of the patient (Lower limb compression and elevation techniques) and the use of vasoconstrictors, However, in the anesthesia practice, prevention and management of hypotension related to spinal anesthesia remains a difficult problem and there was no consensus on its optimal management (1).

study done in Ethiopia comparing on timing of fluid administration for prevention of hypotension after spinal anesthesia, the number of mothers who develop hypotension in preload group was statistically significant, suggesting co-loading was better than preloading in the prevention of hypotension after spinal anesthesia but if you give too much fluid there may be fluid overload and leading pulmonary edema and if not treated it may lead to death(26).

Based on recent evidences and meta-analysis that showed crystalloid pre-hydration has poor efficacy for preventing hypotension, probably because it undergoes rapid distribution. As an alternative, administration of a fluid bolus starting at the time of intrathecal injection (co-hydration and several authors are now suggesting that a preload is unnecessary. As well Lower limb compression techniques may also have unintentional effects such as localized ischemia, nerve injury or unacceptable maternal discomfort(7). However, the incidence of Post Spinal Hypotension (PSH) is still high with all fluid loading protocols; thus, the use of fluid loading as a sole method for prophylaxis might be not satisfactory for many anesthetists

Vasopressor administration was another method used for prevention of spinal induced hypotension in either as loading dose or as prophylactic dose. Ephedrine is typically administered in doses ranging from five to twenty-five milligrams intravenously to treat acute decreases in blood pressure but the cardiovascular effects varies with each dose and repeated administration can cause tachyphylaxis and decrease the effectiveness of the drugs(27).

However , most of the study done in abroad showed that, there is a trend of using prophylactic measures to reduce the incidence of hypotension after induction of spinal anesthesia for caesarean sections. Due to drug constriants and expensiviness in our country it is not common to use prophylactic vasopressor to reduce incidence and severity of spinal induced hypotension.

Despite many research have been done in the past on the prevention of SIH, like fluid preloading or co-loading which have side effect like fluid overload that result in pulmonary edema and may lead to maternal death the other was atropine prophylaxis, vasopressor administration like ephedrine and phenylephrine is also used after the patient become hypotension but repeated administration can cause irregular heart beat additionally vasopressor like phenylephiniprine may also cause decreased uterine blood flow and it may lead to fetal hypoxia as well as in many of our hospital this vasopressor is not available which makes new options to prevent this side effect appealing for the prevention of this incidence in obstetrics(7)

1.3 Significance of the study

Hypotension during Spinal anesthesia is a common problem that occurs for the patients underwent elective cesarean section after spinal anesthesia. Prevention of hypotension improves safety and satisfaction for both patients and anesthesia provider. Many research have been tried to reduce the incidence of hypotension; but there is no single best research have been found .Ondansetron is serotonin receptor antagonist that we have commonly used as anti-emetic in obstetric anesthesia for prevention or treatment of nausea and vomiting and many resent studies showed that ondansetron is used in prevention of spinal induced hypotension after spinal anesthesia but this practice was not common in many of Ethiopian hospital and health sectors(28).

The high incidence of post spinal hypotension (PSH) in obstetric patients who underwent spinal anesthesia has been tried either pharmacological or non-pharmacological. Different studies suggests the need for multimodal protocols for prevention and management of this problem. Post spinal hypotension in obstetrics population underwent cesarean section was common daily situation that all anesthesia provider is facing; thus, research should be needed on these area. Best prophylaxis in prevention of hypotension after spinal anesthesia is still controversial(29).

In most health institution and hospital in Ethiopia, practice of prevention of hypotension is done by preloading the patient with 10-20 ml/Kg of crystalloid fluid before spinal anesthesia and adrenaline and other vasopressor was is given as IV boluses for treatment of hypotension after spinal anesthesia

Some study showed that ondansetron prophylactic does not prevent hypotension after spinal anesthesia for obstetrics and in contradiction to these, there were other studies which support the use of prophylactic ondansetron has attenuate maternal blood pressure after spinal anesthesia. Our study was to found this contradictory result and to use ondansetron prophylaxis for the prevention of spinal induced hypotension because the drug was available, cost effective and minimum side effects for both mother and fetus(30, 31).

Hypotension during spinal anesthesia is a common complication following caesarian Section which results in decrease in uterine blood flow with a potential compromise of fetal oxygenation and may lead to fetal hypoxia. Thus, prevention of severe hypotension during caesarean section is much more important than that in normal population for a favorable maternal and fetal

outcome. Therefore, it is very important to prevent this incidence before it can be happened. The result of the study will also be helpful for governmental and non-governmental organizations who have strategies to reduce maternal morbidity and mortality undergoing cesarean section. There is no study conducted on this topic in our country so that it can be used as a base line data for further researchers.

It can also be used as a sole input to the literature.

CHAPTER TWO: LITERATURE REVIEW

Incidence of spinal induced hypotension

Spinal anesthesia is a type of regional anesthesia where conduction block of nerve roots is achieved by administering local anesthetic agent into the subarachnoid space through a lumbar puncture. It produces complete analgesia with profound muscle relaxation (31). A Survey undertaken in Europe by Lirk et al. in 2012 showed the incidence of spinal induced hypotension was up to 42%(32). In a Cross sectional study done in Germany with 503 mothers who underwent cesarean delivery under spinal anesthesia also showed the incidence of hypotension was 56.5%(33).

Study done at 2008 in Thailand, Chulalongkorn University Bangkok among seven hundred seventy two who underwent elective cesarean section under spinal anesthesia is found the incidence of hypotension is 52.6% whereas, a study done at 2011 in Iran which compared crystalloid, colloid and prophylactic ephedrine with lower extremities bandage showed the incidence of SIH as 54%,64%, and 36% respectively(34, 35).

According to research done at 2018 in India with 502 mothers who underwent cesarean delivery under spinal anesthesia the incidence of hypotension vary with three category of hypotension mild, moderate, and severe were 20%,35% and 40%(36) In a research undertaken at 2008 in Siriraj Hospital, Mahidol University, Bangkok the incidence of hypotension after spinal anesthesia was 65.1%(37)

A Study in Nigeria in 2010 by Adigun et.al, which compare the effects of phenylephrine and ephedrine the reported incidence of SIH was 24.2%(37) In South Africa there was dramatic increase in cesarean section being performed is associated with high incidence of SIH. It contributes for spinal related deaths rate by 42%(38)

Cross sectional study done at 2013 in Ethiopia with pregnant mothers who underwent cesarean section by spinal anesthesia the incidence of hypotension is 36.6%(4)

Mechanism of Spinal Anesthesia-Induced Hypotension

When local anesthetic agents are introduced into the subarachnoid space, the drug spreads from the injection site and its concentration gradient decreases as it moves further. A differential blockade results as only the most local anesthetic susceptible neurons will be blocked in the areas of this decreased concentration gradient. Type B autonomic nerve fibers (sympathetic fibers) are of the most susceptible neurons as they are relatively small in diameter and lightly myelinated. Because of this, sympathetic neurons tend to be blocked up to six spinal segments above somatic sensory fibers, which are generally larger in diameter and more heavily myelinated. The cardiovascular effects of spinal anesthesia is due to sympathetic blockage that causes arterial vasodilation, decreased systemic vascular resistance, venous pooling, and reduction in venous return. These changes cause a redistribution of blood that often results in hypotension if the block reaches the cardiac accelerator fibers, at levels T1 to T4, this hypotension can be amplified by the development of bradycardia and decreased cardiac output(1)

Ondansetron

Spinal anesthesia is affected by baroreceptor reflexes, volume receptor reflexes, and the activation of Bezold-Jarisch. The Bezold-Jarisch reflex is a cardiovascular inhibitory reflex that produce hypotension after spinal anesthesia when it is activated(1).There may be cardiovascular collapse if hypotension severe and not treated early(39).Serotonin (5HT3) (5-hydroxytriptymine is a neurotransmitter which have different effects in different ways throughout our body by binding to a different of receptors. On the cardiovascular serotonin have an effect of inducing vasoconstriction(40, 41) by binding 5 HT2 receptors .The effects after binding was both a positive inotrope and positive chronotropic effects on heart (41). After binding to 5-HT3 receptors it can activate the BJR reflex which can cause hypotension as well as low heart rate (40).

Effect of ondansetron prior to spinal anesthesia

A retrospective study on chart review of (N=114) that conducted at University of North Dakota in 2016 showed that administration of ondansetron prior to spinal anesthesia in elective cesarean section was reduced the incidence of hypotension. There was no significant association between ondansetron and hypotension but they found a significant association between ondansetron and decreased vasopressor use(42).

Randomized control trial done in china in 2014 on optimal dosage of ondansetron for preventing maternal hypotension for elective cesarean delivery on a sample of 150 patients women scheduled for elective cesarean section the patients were randomly allocated to five groups (n=30) in each group. Five minutes prior to spinal anesthesia, women were given ondansetron with 5 ml of normal saline (S), 2 mg (O2), 4 mg (O4), 6 mg (O6), or 8 mg (O8) of ondansetron was given respectively five minute before subarachnoid block. The study found that the incidence of hypotension was significantly lower in those group who have taken 4mg and 6 mg ondansetron groups with ($P < 0.05$) and insignificant those have taken 8mg ($p > 0.05$). There was minimal changes SAP,DAP,MAP were observed in group O4 ($P < 0.05$(43).

In A study done by Rout CC showed that even though volume preload in the elective cesarean section is advocated, hypotension associated with spinal anesthesia for cesarean section did not eliminated by volume preloading allone(13).Another study found that colloids were more effective than crystalloids in prevention of spinal induced hypotension following sub arachoid block(44).

An Observational Study done in Virginia, Common Wealth University in 2015 the effects of Ondansetron on QT Interval in Adult Emergency Department Patients. The study showed that Ondansetron caused a mean prolongation of the QT by 20 micro second (95% confidence interval [CI] = 14 to 26 micro second), with a mean proportion change from baseline of 5.2% (95% CI = 3.8% to 6.6%). There were (95% CI = 0 to 13%) showed that serious adverse cardiac electrical events and QT interval prolongation does occur in adult ED patients receiving intravenous ondansetron prior to surgery(45).

A meta-analysis done on the timing of fluid administration for prevention of spinal anesthesia found that fluid co-loading is preferred to preloading because it carries more success or at least the same results in prevention of PSH with the advantage of being less time consuming(46).

Prospective, double‐blind RCT done in Saudi Arabia on 2017 which included 265 healthy pregnant women scheduled for elective cesarean delivery under SA on the Effect of prophylactic ondansetron and continuous infusion of phenylephrine. Women was randomly assigned into four groups to receive either placebo (control), ondansetron (O) 8 mg , phenylephrine infusion (50 mcg/min) (P) and ondansetron plus phenylephrine (OP) variables that were evaluated included blood pressure, heart rate, oxygen saturation, nausea, vomiting, ECG changes, pruritus, and vasopressor requirements. The study found that differences (P = 0.0001) in the number of patients with hypotension (50.8% control, 44.6% O, 20.9%P, 25.0% OP), the percentage of time points (P = 0.0001) with systolic hypotension per patient ,(17.4% control, 8.7% Ondansetron ,2.1% Phenylephrine, 6.7% Ondansetron and phenylephrine) and the number of patients requiring supplementary boluses of ephedrine was (P = 0.003), phenylephrine (P = 0.017) or atropine (P = 0.0001(47).

RCT study done in Poland on dose dependent study on 72 patients Undergoing elective Caesarean section was randomly assigned to ondansetron group (group O) or placebo group (group P).the study found that ondansetron group have 35 patients administered ondansetron 8 mg intravenous whereas group P consisted of 34 patients 10 mg ondansetron. The study found that Hypotension was observed in 14 group O patients (39%) and in 15 group P patients (44%); the difference was not statistically significant. Bradycardia was found in 1 group O patient (3%) and in 2 group P patients (6%) the difference was not statistically significant in reduction of blood pressure following subarachnoid anesthesia for Caesarean section after the administration of 8 mg of ondansetron was not confirmed(48).

Double blinded randomized controlled trial study done Pakistan in 2014 on One hundred patients. The patient was randomly divided in two groups of 50 each. Both groups have been preloaded with Ringer's lactate with a dose of 10-20 milliliters per kilogram. Group A received 04 mg of IV ondansetron 5 min prior to spinal anesthesia, whereas Group B received 5ml normal saline 05 minutes before administration of Spinal Anesthesia. Hypotension was found in 21 patients in group A (42%), while it was observed in 34 Patients in Group B (68%) (P= 0.009). Bradycardia was noted in 9 patients in Group A (18%) and 19 patients in Group B (p=0.026) the study found Intravenous administration of 04 mg of intravenous ondansetron, 05 minutes prior to subarachnoid block, is effective in decreasing frequency of hypotension(49).

RCT Study done in Africa (Egypt) in 2018 on comparisons of the use of Ondansetron alone with combined vasoconstrictors and fluid preload to decrease the incidence of spinal hypotension on 90 patients. The patients were randomly allocated into two groups of 45 each. Group I patients (ondansetron group) received 4 mg ondansetron in 5 ml normal saline (IV) 5 minutes before induction of spinal anesthesia. Group II patients received preloading with 5 ml of normal saline over 5 minute period preceding the spinal block followed by intravenous bolus of 2.5 mg ephedrine in the first and second minute and 2.5 mg ephedrine every 5 minutes for the next 20 minutes after the injection of spinal anesthetic drug. The study found that incidence of hypotension after SA in Group I (ondansetron group) was 17.6% while group II (combination group) was 13.3%, there is no statically significant difference between group (P = 0.082).The use of Ondansetron alone versus combined vasoconstrictors(17) with fluid preload significantly reduces the incidence of post-spinal hypotension (PSH) with no significant difference between two groups(31).

A prospective, double-blind RCT done in Egypt in 2018 on 100 patients to evaluate the effect of prophylactic ondansetron on spinal anesthesia-induced hypotension and bradycardia among patients undergoing elective cesarean deliveries. Patients were randomized to receive intravenous ondansetron 4 mg in 10 mL of saline or 10 mL of saline. The Patient was grouped into two groups which included 50 patients in each group. The study showed that there is Decreased in systolic blood pressure among patients receiving ondansetron at all-time points (P 0.05) and diastolic blood pressure did have different between groups (P= 0.05).those patients who received ondansetron arterial pressure was higher immediately and 30 minutes after spinal anesthesia (P 0.05), higher heart rates were found immediately,20 minutes, and 50 minutes after anesthesia (P 0.05), and the incidence of nausea (P = 0.020) and vomiting (P=0.031) were lower and they found that Prophylactic intravenous ondansetron significantly reduced hypotension and heart-rate fluctuations among patients undergoing elective cesarean deliveries under spinal anesthesia(50).

A Prospective randomized Double blind RCT done in Africa (Tunisia) in 2014 on the Effect of Ondansetron on the Occurrence of Hypotension and on Neonatal Parameters during Spinal Anesthesia for Elective Caesarean Section on 90 patients. The groups was classified into ondansetron and placebo. The study found that there are fewer patients in the O group

experienced hypotension as compared to those of placebo group with 15 (37.5%) and 31 (77.5%) ($P < 0.001$) respectively. Thus, the average consumption of ephedrine intra operatively was 5.10 ± 7.78 mg in group O while it was 12.90 ± 9.24mg in placebo group with a significant difference (P <0001(11).

A Prospective Double-Blind, Placebo-Controlled, Randomized Trial done in 2015 by American society of regional anesthesia and pain medicine on Eighty-six patients undergoing elective cesarean delivery were recruited and randomly allocated to receive either 8 mg intravenous ondansetron (group O; n = 44) or placebo (group P; n = 42) then (SBP), MAP), (DBP), and (HR) were measured at baseline and every 3-minute intervals from the time of administration of SA until delivery of fetus. The study found that there was no significant different in SBP (P = 0.78), MAP (P = 0.89), DBP (P = 0.82) and HR (P = 0.18) between groups. Phenylephrine requirements to treat hypotension were 350 μg (175–700 μg) in group ondansetron and 450 μg (300–700 μg) in group Placebo (P = 0.30) group. Pruritus was found in 63% in ondansetron group and 56% in group P (difference, 0.08 [95% confidence interval,−0.23 to 0.41], P = 0.59). There was no significant difference in the incidence of nausea and vomiting was found between groups. The study found that Ondansetron prophylaxis does not have any change on hemodynamics of the patients after spinal anesthesia. There is also no significant difference between groups in vasopressor use, pruritus, or nausea and vomiting(30).

There are many research was done on hypotension, but hypotension is still common problem that obstetric population was facing after spinal anesthesia. If it was not treated early it have bad effects on both mother and fetus like nausea vomitting fetal acidosis.The prevention and treatment of maternal hypotension associated with spinal anesthesia for C-section remains a problem. Protocols that aim to prevent hypotension during spinal anesthesia for CS may result better outcomes than protocols of treatment after the hypotension occurred(51).

CHAPTER THREE: OBJECTIVES

3.1 General Objective

To assess effect of prophylactic ondansetron for prevention of spinal induced hypotension during elective cesarean section at yekatit 12 hospital from Oct to Jan 2019/2020.

3.2 Specific Objective

- To compare the occurrence of hypotension after spinal anesthesia between group
- To compare occurrence of nausea and vomiting between groups
- To compare the needs for rescue vasopressor between group

Research hypothesis

H_O1: There is no difference in the incidence of hypotension between prophylactic and non-prophylactic group

H_A1: There is difference in the incidence of hypotension between prophylactic and non-prophylactic group

H_O2: There is no difference in the incidence of nausea and vomiting between prophylactic and non-prophylactic group

H_A2: There is difference in the incidence of nausea and vomiting between prophylactic and non-prophylactic group

H_O3: There is no difference in the incidence of need for rescue vasopressor between prophylactic and non-prophylactic group

H_A3: There is difference in the incidence of need for rescue vasopressor between prophylactic and non-prophylactic group

2.3 conceptual frame work

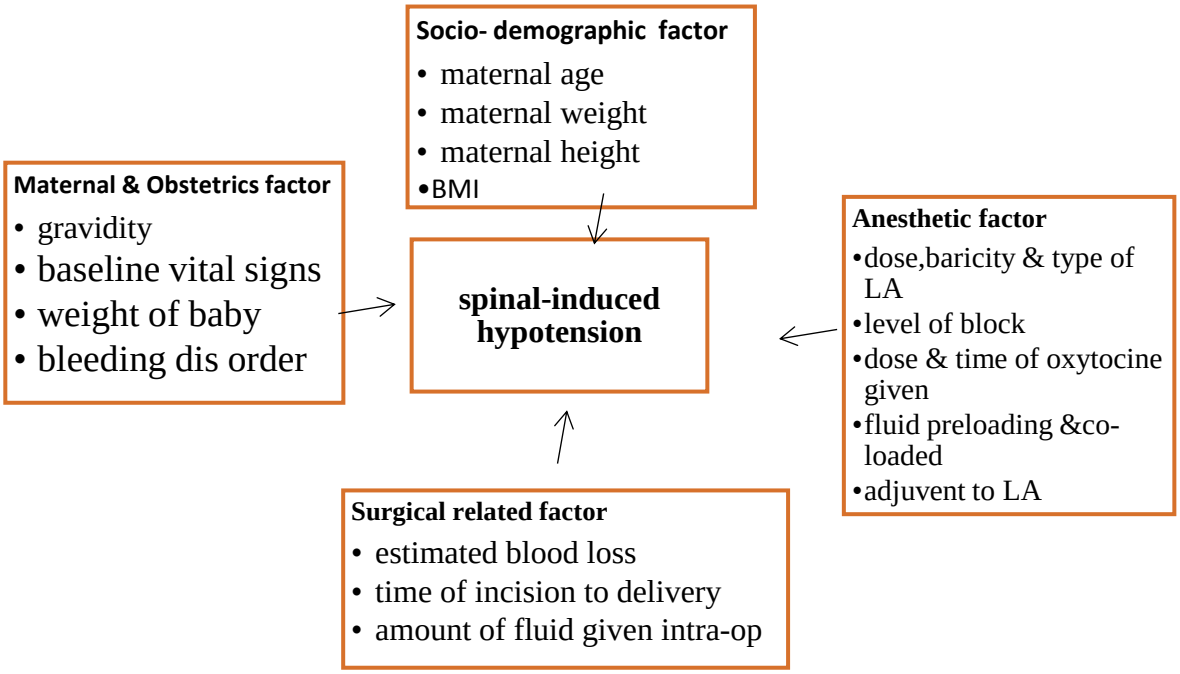

Figure 2 Conceptual frame work for major factor affecting spinal induced hypotension

CHAPTER FOUR: METHODOLOGY AND MATERIALS

4.1 Study Area

The study has been conducted at yekatit 12 hospital located in Addis Ababa capital city.It is one of the thirteen governmental hospitals found in Addis Ababa which is under admnistration of Addis Ababa city Health Bureau. The Hospital primarily gives services for diffirent speciality like general surgery ,pediatrics,internal medicine,gynecology and obstetrics,maxillo facial surgery,ENT surgery .The hospital has many beds and an average of 10 new borns delivered each day.The hospital has many operation table and it have only one operation table for C/S.In this hospital there is an average of 10 delivery per day. Out of these one fourth are delivered by elective cesereal.

4.2 Study design and Study period

Institutional based Prospective cohort study design from Oct 30 –Jan 30, 2019/20

4.3 Population

4.3.1 Source population

All pregnant mothers who gave birth by elective cesarean section at Yekatit 12 Hospital,

4.3.2 Study Population

Pregnant mothers who gave birth by elective caesarian section under spinal anesthesia in the study period that fulfilled inclusion criteria.

4.4 Study Variables

4.4.1 Dependent Variables

- occurrence of post spinal hypotension
- occurrence of nausea and vomiting
- Need of rescue vasopressor

4.4.2 Independent variable

Socio-demographic variables

- Age
- Weight
- Height
- Body mass index of mother

Maternal and obstetrics characteristics

- Parity
- Previous history of cesarean section
- Indication for cesarean section
- Maternal hemoglobin level
- Anesthesia related variables
- Amount of fluid colloded
- Type, bariciyt and dose of local anesthesia
- Level of block
- Weight of baby

Vital Signs of the mother

- Systolic blood pressure
- Diastolic blood pressure
- Mean arterial blood pressure

4.5 Eligibility Criteria

4.5.1 Inclusion Criteria

- Elective caesarean section under spinal anesthesia.
- ASA class II
- Age > 18 years
- BMI 18 -30 kg/m2

4.5.2 Exclusion criteria

- Mother on anti serotogenic medication or migraine headache
- Known allergy to LAs/opioids/non-steroidal anti-inflammatory drugs
- mothers with Preoperative hypotension or hypertension
- mothers with diabetes mellitus
- mothers with Cardiovascular disease
- mother with pulmonary disease
- mother with renal or liver disease
- Body mass index < 18 or >30Kg/m2
- Failed spinal block
- Hypersensitive for ondansetron
- Mother with neurologic problem
- Mothers with bleeding disorder (placenta previa,abraption and any bleeding dis order)
- Mother with major bleeding intra operatively

4.6 Sample size and sampling technique

4.6.1 Sample size determination

Sample size was determined by using Epi info version 7 stat calc program(46) and re checked by manual calculation. By considering A power of 80%, confidence interval 95% and ratio of unexposed to exposed 1:1, and incidence of hypotension in unexposed =77.5% and incidence of hypotension in exposed = 37.5%, which is estimated from previous study done in Africa, Tunisia. A sample size of 45 patients per group will be necessary(11).

$$n_1 = \frac{(Z_{\alpha/2} + Z_{1-\beta})^2 \; p\, q\, (r+1)}{r\,(P_1 - P_2)^2} \quad \ldots\ldots\ldots \quad \ldots n_2 = r\, n_1$$

$$p = \frac{p_1 + r p_2}{r+1} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad q = 1-p$$

n_1 = number of exposed

n_2 = number of unexposed

$Z_{\alpha/2}$= 1.96 = value of the standard normal distribution corresponding to a significance level of α (1.96 for a 2-sided test at the 0.05 level)

Z_{β}= 0.84 = value of the standard normal distribution corresponding to the desired level of power (0.84 for a power of 80%)

P_1= proportion of exposed with disease and $q_1 = 1-p_1$

P_2= proportion of unexposed with disease and $q_2 = 1-p_2$

r = ratio of unexposed to exposed

$p_1 = 0.775$ and $p2 = 0.375$ r=1

$p = 0.775 \text{ x } (1\text{x}0.375) = 0.1453$

$1 + 1$

$q = 1-0.1453 = 0.8547$

$n_1 = \frac{(1.96+0.84)^2 * 0.856 * 0.145\ (1+1)}{1(0.775-0.375)^2 \ / \ 0.16} = \frac{7.15}{} = 44.68 = 45$

$n_1 = 45 \qquad n_2 = 45$

After adding 10% attrition rate the total sample size was =100 patients.

4.6.2 Sampling procedure

A three-month reports showed 200 patients undergo elective C/S. Ninety participants were recruited with the probability of 50%. Considering the sequential patients scheduled for C/S (sampling frame), one number (starting point) selected by lottery method. Data collection was made on one patient for every two patients who underwent C/S in both groups until the required sample size is reached.

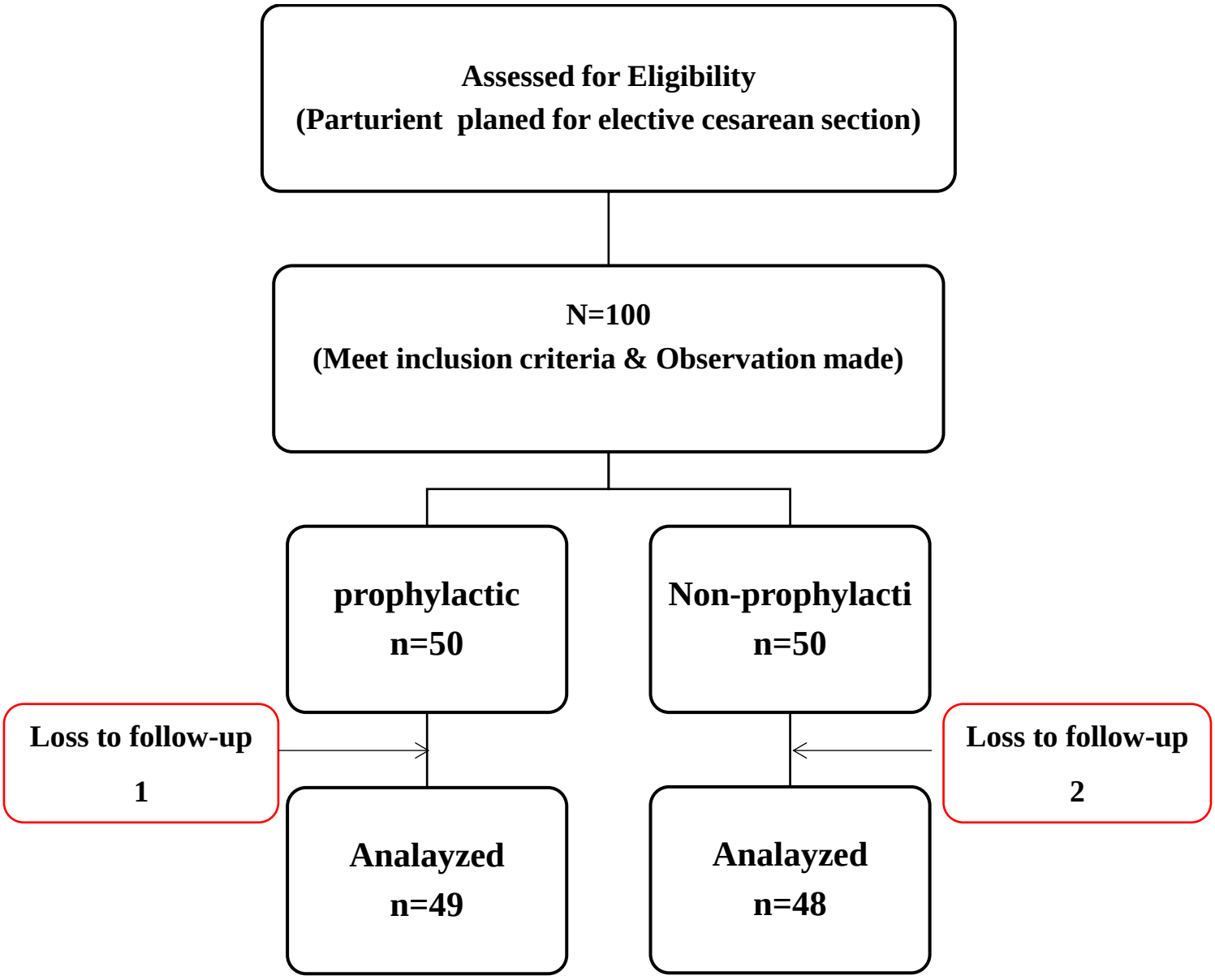

Figure 3: Flow chart

4.7 Data collection tools and procedure

Data was collected from selected study participants using pretested questionnaire. Data would be collected from Oct 30, 2019 - Jan 30, 2020.

Anesthesia management for elective CS in the study hospital is carried out by B.Sc. and M.Sc. anesthesia professional. Patients having American Society of Anesthesiology (ASA) status-II and BMI <30 kg/m2 status and presenting for elective cesarean section were included in the study. Patients having contraindication to spinal anesthesia, cardiovascular disease, pulmonary disease, and renal disease, liver disease, morbidly obese and failed spinal block; were excluded from the study. When patients arrived in operation theatre, they were weighed and standard monitoring was applied before start of procedure. Prophylactic group was given 4 mg of intravenous ondansetron in 5 minutes before spinal administration while non-prophylactic group was not. Base line Heart rate and blood pressure were recorded. Then spinal anesthesia was administered in sitting position, using a 23-25 G spinal needle in L2-L3 & L3-4 space 2-2.5 ml of 0.5% bupivacaine was used for subarachnoid blockage and they were immediately placed in supine position while the level of sensory block was be evaluated with cold sensation 5 min after spinal anesthesia and intra operative data were collected by assigned anesthetist.

4.8 Data processing and analysis

Data was coded and then entered and cleaned using Epi Info version 7 and exported to Statistical package for Social Sciences (SPSS) software version 20.0. Using SPSS Numeric have been described in terms of mean ± SD for symmetric and median (Interquartile range) for asymmetric numeric data. Comparison of numerical variables between study groups was done using unpaired student t- test and Manny Whitney U test for symmetric and asymmetric data respectively. Frequency and percentage has been used to describe categorical variable and statistical difference between groups was tested using Chi square. Significance was determined at P value <0.05 .The result is presented by using text, tables, charts and graphs.

4.9 Data quality assurance

To assure the quality of data, training on the objectives and relevance of the study and brief Orientations on the assessment tools was be provided for data collector. During data collection, each questioner was be revised by the investigator for being complete and appropriate. The data collectors was instructed to write card number on the questionnaire during the data collection if further cross check is needed.

4.10 Ethical consideration

The study was conducted after approval by Addis Ababa University, Ethical review board to conduct the study. A legal letter would also be submitted to yekatit 12 Hospital, where the study will take place. Verbal informed consent would be obtained from all parturient after full explanations of the goals and procedures of the study. After permission was taken from the hospital and study participant the data collection would be conducted

4.11 Dissemination plan

The result of the study will be submitted to the collage of medical and health science of Addis Ababa University, yekatit12 hospital, Addis Ababa city health bureau, Ethiopian Anesthetist Association and other responsible bodies. The result would be presented at collage of medical and health science in different seminars, meeting, conferences and workshops. Moreover, efforts would be done to publish the findings of the study and disseminated through different journals and scientific publications

4.12 Operational Definition

Prophylactic group: Patients that received prophylactic intravenous 4 mg ondansetron five minute before spinal anesthesia

Non-prophylactic group: patients those do not premeditated with ondansetron

American Society of Anesthesiologists (ASA) physical status classification: developed by the ASA taskforce which classify patients according to their physical status (systemic well-being) **(52)**

ASA class I: normal healthy patient except the surgical compliant he had

ASA class II: a patient with a mild systemic disease without substantive functional limitation

ASA class III: a patient with severe systemic disease with substantive functional limitation

ASA class IV: a patient with severe systemic disease that is a constant threat to life

ASA class V: moribund patient who is not expected to survive without the operation

Baseline value: measurement taken before induction or spinal anesthesia given

Hypotension: defined as a decrease in SBP >20% of baseline, or SBP <90 mmHg(53-55)

Severe hypotension: SBP less than 80 mmHg are considered as severe hypotension(54).

Hypertension: defined as an increase of SBP >20% of baseline(54).

Tachycardia: an increase in heart rate of ≥20% of the baseline value or heart rate less than 120(54).

Bradycardia: a decrease in heart rate ≥30% from baseline value or heart rate less than 60(54).

Failed spinal: is implying that a spinal anesthesia was attempted, but no block resulted and inadequacy relating to the extent, quality, or duration of local anesthetic action for the proposed surgery.

Co loading: giving crystalloyd fluid while at the same time performing spinal anesthesia

Post spinal hypotension: is hypotension occurs immediately after administration of intratechal local anesthetics.

The level of sensory block: is loss of cold sensation and will be recorded bilaterally in the anterior axillary line or mid-clavicular line.

CHAPTER FIVE: RESULTS

5.1 Socio Demographic and clinical characteristics

One hundred parturient were enrolled in this study three participant were lost, two of them from non- prophylactic and one parturient from prophylactic group. There was no significant difference among the two groups with regard to age, BMI, duration of surgery, mean time from SA to delivery of the fetus (min), Intra operative fluid(ml), Estimated intra operative blood loss(ml) ,weight of baby(kg),oxytocin(IU) used and level of blocks (p value > 0.05) (Table-1).

Table 1: Socio demographic characteristics and clinical characteristics:

	Prophylactic group(n=49)	Non-prophylactic group(n=48)	p-value
Age (years)	31.36 ± 5.149	29.72 ±5.077	.719
Body Mass Index(kg/m2)	23.75 ± 2.974	23.70 ± 2.739	.935
L2-L3/L3/L4	6 (10.2)/43 (89.8%)	8/ (16.7%)/40 (83.3%)	.652
Gravidity (weeks)	3±1.32	3 ±1.43	.982
Base line systolic blood pressure	126.61±13.017	123.12 ±16.964	.067
Base line diastolic blood pressure	76.98 ± 10.615	80.72 ±11.572	.438
Base line mean arterial blood pressure	89.39 ±11.987	94.05 ±11.462	.259
Base Line Heart Rate(bpm)	90.45 ± 10.727	88.10 ±11.567	.767
Weight of delivered baby(kg)	2.7 ±1,67	2.8 ±1.47	.243
Gravidity: One Two Three Above	11 (22.45%) 13 (26.5%) 12 (24.5%) 13 (26.55%)	13 (27.1%) 14(29.2%) 12 (25%) 9 (18.7%)	.736
Blood loss (ml)	328.63± 81	332.63 ± 70.68	.381
Dose of bupivacaine in mg 10/12.5	21(42.85) / 28(57.15%)	25 (52.1%) / 23 (47.9%)	.343
Level of Block1. T4-T5 T6-T7 T8-T9	11(22.5%) 24(48.98%) 14(28.52%)	13 (27%) 19 (39.6%) 16 (33.4%)	.756
Amount of intra-op fluid used	2.003 ± 0.38	2.083 ± 0.33	.900
Dose of oxytocin(IU)	37.14 ±2.16	36.17 ± 2.14	.089
skin incision to delivery(min)	4.90 ± 1.74)	5.25±1.446	.059
Duration of surgery(min)	40.95± 8.3	38.9 ± 6	.444

Values are presented as: number (%):chi-square test, mean ±standard division: independent T test and p < 0.05 is statistically significant

5.2 occurrence of hypotension

The occurrence of spinal anesthesia induced hypotension analyzed by using chi square test shows there was statically significant lower incidence in patient receiving prophylactic ondansetron. The proportions of patients with hypotension is lower 13(26.5%) in prophylactic group compared to non- prophylactic group 36(75%) with an X2 (1, N= 97) =9.842 P=0.007

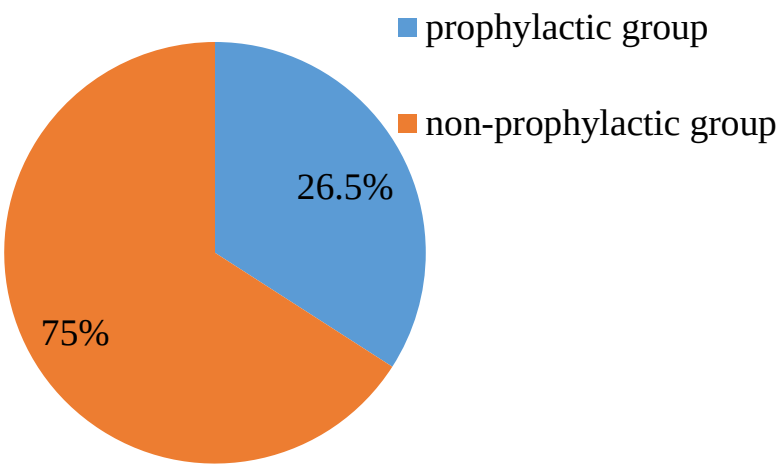

Figure 4: incidence of hypotension between two groups

5.3 occurrence of nausea –vomiting

There are 12(24.5%) patients in prophylactic group and 28(58.3%) patient in non-prophylactic group who have experienced Nausea (p=0.004*)* and 5(10.2%) patients in prophylactic group and 25(52.1%) patients in non-prophylactic group experience vomiting (p=0.001*)*

Table 2: Incidence of nausea and vomiting distribution in two groups of patients

	Prophylactic group(49)	**Non-prophylactic group(48)**	**p-value**
Nausea	12(24.5%)	28(58.3%)	(*p=0.004)*
Vomiting	5(10.2%)	25(52.1%)	(*p=0.001)*

5.4 Need for rescue vasopressor

There was no statistically significant different in the need for rescue vasopressor between groups in which three (6.1%) in prophylactic and five (10.4%) in non- prophylactic group respectively required vasopressor with p =0.17.

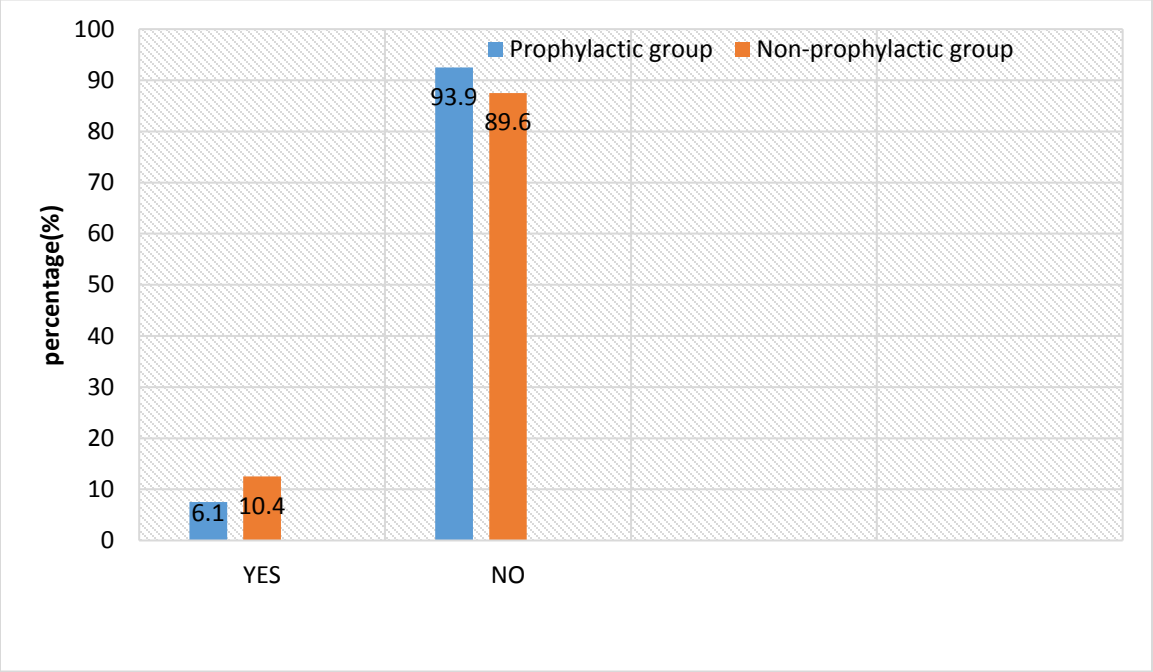

Figure 5: Need of rescue vasopressor between two groups

5.5 Intra operative SBP, DBP AND MAP between groups

There is statically significant difference in SBP, DBP and MAP between prophylactic and non-prophylactic group at all point of 5 min interval in span of 50 min. *P* <0.05 was found at all-time intervals.

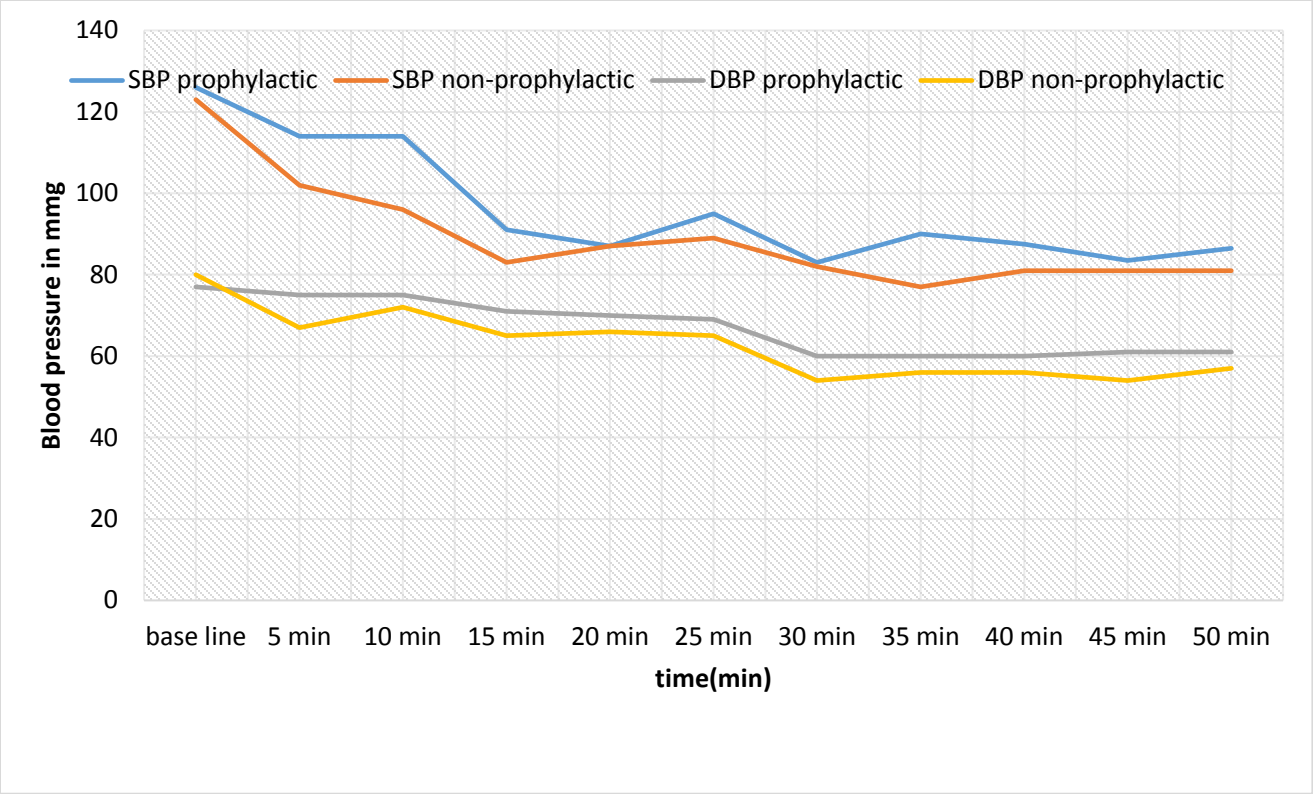

Figure 6: Comparison of systolic and diastolic blood pressure change between two groups

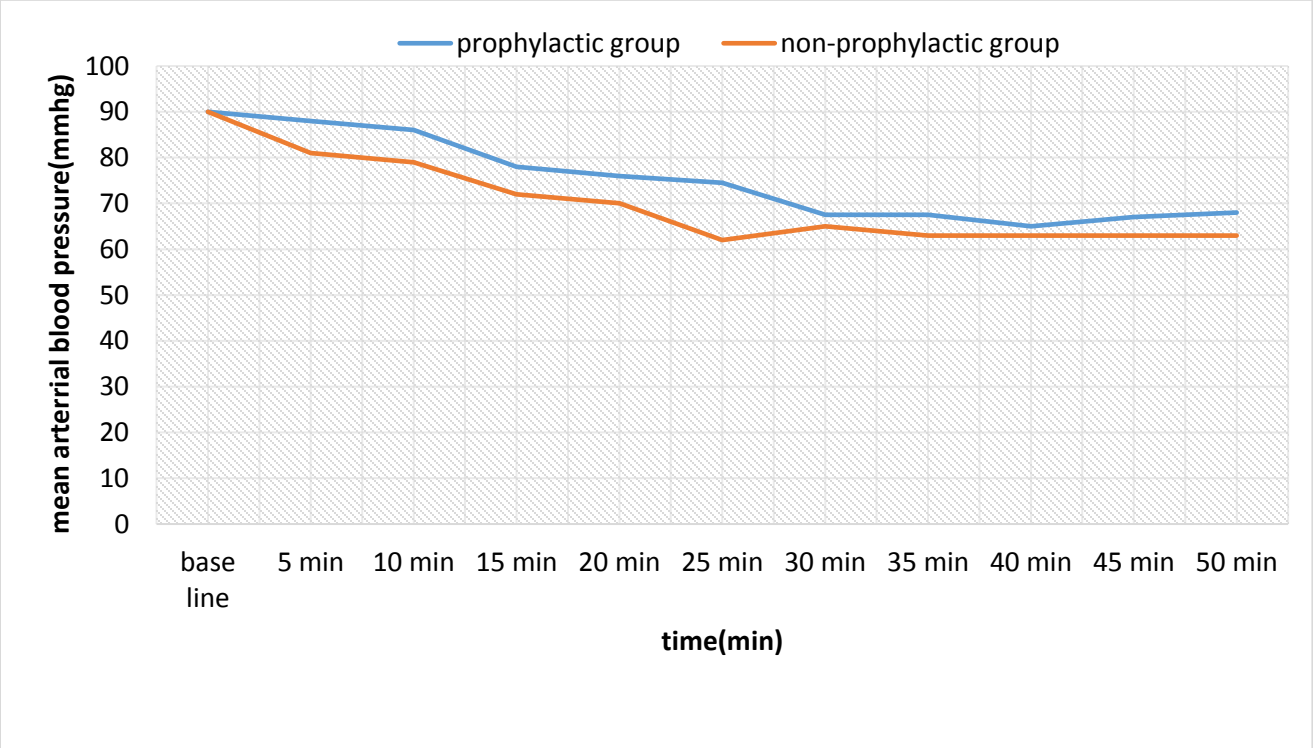

Figure 7: Comparison of mean arterial blood pressure changes between two groups

CHAPTER SIX: DISCUSSION

Hemodynamic change after spinal anesthesia have serious complications on both mother as well as fetus because maternal hypotension can lead to decreased placental perfusion that can cause intra uterine fetal hypoxia which is manifested as abnormal fetal heartbeat. One of the important issues regarding anesthesia in pregnant women underwent spinal anesthesia is prevention of spinal induced hypotension(25).Different techniques and methods are evaluated to prevent the occurrences of spinal induced hypotension Such as preloading or co-loading fluid, administration of atropine prophylaxis ,Trendelenburg position and vasopressors(7).Intra venous administration of ondansetron is one of the methods currently used treat severe nausea and vomiting after spinal or general anesthesia because it can block 5HT3 receptor that can cause sympathetic blockage(56).

We assessed the effect of prophylactic ondansetron on spinal anesthesia induced hypotension in 97 parturient who undergone cesarean section. Our study showed statically significant lower incidence of spinal anesthesia induced hypotension in prophylactic 13(26.5%) group compared to non- prophylactic group 36(75%) (p=0.007).The result of this study is in line with study done in Tunisia by Walid Trabelsi et al, that assessed Effect of ondansetron on the occurrence of hypotension and on neonatal parameters during spinal anesthesia for elective caesarean section showed that, the incidence of hypotension was 15 (37.5%) in prophylactic and 31 (77.5%) non-prophylactic group ($P < 0.001$)(11).

Another study done in Pakistan by Naseem Abbas et al, on Role of prophylactic ondansetron for prevention of spinal anesthesia induced hypotension in lower segment caesarean section found that the incidence of hypotension was 21(42%) patients in ondansetron group and 34 (68%) in non-ondansetron group (*p*-value= 0.009)(49).

This results is also comparable with the study done in china by Wang et al ,A dose dependent study on Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension for cesarean delivery:, showed that the incidence of hypotension was 18(60%) in prophylactic group and 9(30%) in non-prophylactic group p< 0.05)(43).

This study is in line with study done in Rawalpindi at Family Hospital by Baiq et al, on the Use of Ondansetron for Prevention of Spinal Induced Hypotension found that the incidence of hypotension occurred in7.5% cases in prophylactic group compared to 28.3% in non-prophylactic group (p=0.005)(57).

Similarly the study done in India is in line with study done in India by Raghu et al that assessed the Effect of ondansetron in the prevention of spinal anesthesia-induced hypotension showed that that the incidence of hypotension occurred in 34(60.7% in prophylactic group compared to 22(39.3%) non-prophylactic group p=0.0359)(58).

A meta‐analysis conducted by Gao et al that assessed the Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension. They found that prophylactic administration of intra venous ondansetron reduces the incidence of spinal anesthesia‐induced hypotension(59).

In contrary to this results a study done in Poland by owczuk et al, found hypotension was observed in 14(39%) in ondansetron prophylactic group and 15(44%) in none ondansetron prophylactic group(p>0.005)(12).The observed difference was due to they have used 8 mg of ondansetron as prophylaxis because in dose dependent study in china by Wang et al found that those mother who have took 4mg and 6 mg were statistically significant(p<0.005) but those who had taken 2mg and 8mg was not statically significant(p>0.005)(43).

There is also study done in United State of America by Terkawi et al, that compared 8mg ondansetron with normal saline, they found that there is no statically different between groups (p>0.05(30).

In contrary to this results the study done in India by Andrzej et al, they found that Hypotension was observed in 14(39 %) in prophylactic and 15(44 %) in non- prophylactic group(p=0.84)(48).

The observed difference was due to they have used 8 mg of ondansetron as prophylaxis but in our study we have used 4 mg ondansetron, because study done by Terkawi et al and Wang et al showed that those mother who have taken 8 mg ondansetron prophylaxis when compared with control group have no significant effect in prevention of hypotension(p > 0.05)(30, 43).

The results of this study shows significant difference in incidence of Nausea and vomiting 24.5% patients in prophylactic group and (58.3%) patient in non-prophylactic group were experience Nausea (p=0.004*) and* 5(10.2%) patients in prophylactic group and 25(52.1%) patients in non-prophylactic group experience vomiting (p=0.001).

The result of this study is in line with study done in Egypt by Nabih et al, that compared ondansetron and placebo for the reduction of spinal anesthesia-induced hypotension for elective cesarean section found that the incidence of nausea and vomiting were (12% vs 30%) and (4% vs 18%) in prophylactic and non-prophylactic groups respectively(p=0.02,p=0.031)(50).

The result of this study is in line with study done in china by Wang et al, A dose dependent study on ondansetron ,Showed that the incidence of nausea and vomiting were (10.3% vs 33.3%) and (3.4% vs 3.3%) in prophylactic and non-prophylactic groups respectively ($p<0.05$)(43).

This finding is also in line with study done in Iran by Hajian et al, that assessed on the Efficacy of Intravenous Ondansetron on Hemodynamic Complications in Women Undergoing Spinal Anesthesia for Cesarean Section showed that the incidence of nausea vomiting were 7.8% in prophylactic group and 33.3% in non-prophylactic group(p=0.001)(56).

Similarly a study done in India by sahoo et al, that assessed Reduction in spinal-induced hypotension with ondansetron in parturient undergoing caesarean section found that the incidence of nausea was 1% in prophylactic group and 7% in non-prophylactic group(p=0.049)(60).

Another study is in line with study done in Tunisia by Trabelsi et al, that assessed Effect of ondansetron on the occurrence of hypotension and on neonatal parameters during spinal anesthesia for elective caesarean section also showed that nausea and vomiting were compared to those in prophylactic group (22.5%) and (62.5%) in non-prophylactic group respectively($P < 0.001$)(11).

In contrary to in this results a study done in Poland by Andrez j et al, found that the incidence of nausea and vomiting were (11 % vs 12 %) and (0 % vs 1 %) in prophylactic and non-prophylactic groups respectively(48).The observed difference was due to they administer 30 ml of 0.3 M of sodium citrate to prevent aspiration pneumonia during surgery(48).

In this study we found that three (6.1%) patients and 5(10.4%) patients in prophylactic and non-prophylactic group respectively required vasopressor with ($p =0.17$).The results of this study is in line with study done in Egypt by Rashad et al that assessed the Effects of ondansetron on hemodynamic changes for mother undergoing elective cesarean section under spinal anesthesia, found that prophylactic group require lower vasopressor compared to non-prophylactic group(61).

In this study we found that significant difference in intra operative SBP, DBP and MAP between groups. The result of this study is in line with study done in Egypt by Nabih et al that compared ondansetron and placebo for the reduction of spinal anesthesia-induced hypotension during elective cesarean found that there is Significant differences in SBP,DBP and MAP were observed between lumber puncture and 2 hours in both groups ($P < 0.05$) for all comparisons(62).

A study done in Poland by sahoo et al, the effect of ondansetron in Reduction of spinal-induced hypotension for parturient undergoing caesarean section showed that ,there is significant differences in SBP, DBP and MAP between groups($p<0.05$)(60).

The result of this study is in line with study done in china by Wang et al, showed that there is significant differences between prophylactic group and non-prophylactic group ($p< 0.05$) (43)

In contrary to this result a study done in India by Tatikonda et al, found that there was no significant difference in SBP, DBP, and MAP between groups at any point of 3 min interval intra operatively. $P > 0.05$ was found at all time intervals in the span of 30 min(63).

The observed difference is due to they have used higher dose (15 mg) 0.5% hyperbaric bupivacaine for all parturient compared to 10 mg or 12.5 mg in our study. The other probability may be due to they have used atropine and ephedrine for those mother whose heart rate decreased 20% from base line(63).

Limitation and Strength

Strength: We have tried to make comparable study groups in terms of socio demographic distribution, perioperative and clinical factor that affect study outcome so that the difference observed may be due to exposure factors.

Limitation This study has certain limitations, including: there is no any study done in Ethiopia on this topic and during comparisons I have used the study done in other countries and most of studies I have used for comparison was randomized control trials.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

Conclusion

The results of this study shows that 4mg ondansetron prophylaxis given intravenously 5 minutes prior to spinal anesthesia is decreased the incidence of spinal induced hypotension, nausea and vomiting for parturient undergoing elective cesarean section.

Recommendation

According to the finding of the study, we recommend the use 4mg prophylaxis ondansetron for all elective cesarean section undergoing spinal anesthesia to prevent spinal induced hypotension except those who are contraindicated.

Hospital: we recommend to give training on the ondansetron prophylaxis on prevention of spinal induced hypotension for all anesthetist in different hospital.

For Ministry of Health/ Regional Health Bureau

Providing ondansetron for all hospitals and health institution for better maternal care undergoing surgery.

For researchers

Considering this study as a baseline a further long term multicenter study is recommended.

REFERENCE

1. Nagelhout J, Plaus K. Nurse Anesthesia. St Louis, MO: Saunders. Elsevier; 2014.
2. Yeoh SB, Leong SB, Heng AST. Anaesthesia for lower-segment caesarean section: Changing perspectives. Indian journal of anaesthesia. 2010;54(5):409.
3. Abdissa Z, Awoke T, Belayneh T, Tefera Y. Birth outcome after caesarean section among mothers who delivered by caesarean section under general and spinal anesthesia at Gondar University teaching hospital north-west Ethiopia. 2013.
4. Marye A, Mesfin E, Endris B. SPINAL ANESTHESIA FOR CESAREAN DELIVERY AT TWO TEACHING HOSPITALS IN ADDIS ABABA, ETHIOPIA.
5. Corke B, Datta S, Ostheimer GJA. Hypotension during spinal anesthesia for cesarean section: its influence on infant outcome. 1982;37:658-62.
6. Hollmen AI, Jouppila R, Koivisto M, Maatta L, Pihlajaniemi R, Puukka M, et al. Neurologic activity of infants following anesthesia for cesarean section. 1978;48(5):350-6.
7. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane database of systematic reviews. 2006(4).
8. Shahzadi I, Hanif S, Afridi Y. ROLE OF EPHEDRINE INFUSION IN SPINAL ANAESTHESIA INDUCED HYPOTENSION. Pakistan Journal of Physiology. 2016;12(4):12-5.
9. Hofhuizen C, Lemson J, Snoeck M, Scheffer G-J. Spinal anesthesia-induced hypotension is caused by a decrease in stroke volume in elderly patients. Local and regional anesthesia. 2019;12:19.
10. Kinsella S, Tuckey J. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold–Jarisch reflex. British Journal of Anaesthesia. 2001;86(6):859-68.
11. Trabelsi W, Romdhani C, Elaskri H, Sammoud W, Bensalah M, Labbene I, et al. Effect of ondansetron on the occurrence of hypotension and on neonatal parameters during spinal anesthesia for elective caesarean section: a prospective, randomized, controlled, double-blind study. Anesthesiology research and practice. 2015;2015.
12. Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszułowicz R, Dylczyk-Sommer A, et al. Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: a double-blind, placebo-controlled study. 2008.
13. Rout C, Rocke D, Levin J, Gouws E, Reddy D. A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective cesarean section. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1993;79(2):262-9.
14. Jackson R, Reid J, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at caesarean section. BJA. 1995; 75 (3): 262-5.
15. Vercauteren M, Hoffmann V, Coppejans H, Van Steenberge A, Adriaensen H. Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section. British journal of anaesthesia. 1996;76(5):731-3.
16. Gajraj NM, Victory RA, Pace NA, Van Elstraete AC, Wallace DH. Comparison of an ephedrine infusion with crystalloid administration for prevention of hypotension during spinal anesthesia. Anesthesia & Analgesia. 1993;76(5):1023-6.
17. Critchley L, Short T, Gin T. Hypotension during subarachnoid anaesthesia: haemodynamic analysis of three treatments. BJA: British Journal of Anaesthesia. 1994;72(2):151-5.
18. Ootaki C, Stevens T, Vargo J, You J, Shiba A, Foss J, et al. Does general anesthesia increase the diagnostic yield of endoscopic ultrasound-guided fine needle aspiration of pancreatic masses? Anesthesiology: The Journal of the American Society of Anesthesiologists. 2012;117(5):1044-50.

19. Maayan-Metzger A, Schushan-Eisen I, Todris L, Etchin A, Kuint J. Maternal hypotension during elective cesarean section and short-term neonatal outcome. American journal of obstetrics and gynecology. 2010;202(1):56. e1-. e5.
20. CLARK RB, RB C, DS T, CH T. Prevention of spinal hypotension associated with Cesarean section. 1976.
21. Arndt JO, Bomer W, Krauth J, Marquardt B. Incidence and time course of cardiovascular side effects during spinal anesthesia after prophylactic administration of intravenous fluids or vasoconstrictors. Anesthesia & Analgesia. 1998;87(2):347-54.
22. Adigun TAJFoA. Comparison of intravenous ephedrine with phenylephrine for the maintenance of arterial blood pressure during elective caesarean section under spinal anaesthesia. 2018.
23. Rout CC, Farina Z. Anaesthesia-related maternal deaths in South Africa Chapter Seven of the 5th Saving Mothers Report 2008-2010. Southern African Journal of Anaesthesia and Analgesia. 2012;18(6).
24. Nigussie A. The Prevalence and Risk Factors of Post Spinal Hypotension Among Pregnant Mothers who Delivered by Elective Caeserean Section from January to February At Gandhi Memorial Hospital, Addis Ababa, Ethiopia. Cross Sectional Study Design: Addis Abeba University; 2016.
25. Butwick A, Columb M, Carvalho B. Preventing Spinal Hypotension During Cesarean Delivery: What is the Latest? Obstetric Anesthesia Digest. 2015;35(4):176-7.
26. Tiruneh A. Prospective Cohort Study on Effect of Timinig on Fluid Administration for Prevention of Spinal Anesthesia Induced Hypotension in Obstetric Mothers at Ghandi Memorial Hospital, December 2016 to February 2017 Addis Ababa, Ethiopia: Addis Abeba University; 2017.
27. Nivatpumin P, Thamvittayakul V. Ephedrine Versus Ondansetron in the Prevention of Hypotension During Cesarean Delivery: A Randomized, Double-blind, Placebo-controlled Trial. Obstetric anesthesia digest. 2017;37(2):102-3.
28. Friedly C, Simmons S, Riddle DJIJoE-BH. Prophylactic ondansetron for prevention of maternal hypotension following spinal anesthesia in women undergoing cesarean section: A systematic review. 2016;14(4):196-7.
29. Simon L, Provenchère S, de Saint Blanquat L, Boulay G, Hamza J. Dose of prophylactic intravenous ephedrine during spinal anesthesia for cesarean section. Journal of clinical anesthesia. 2001;13(5):366-9.
30. Terkawi AS, Tiouririne M, Mehta SH, Hackworth JM, Tsang S, Durieux ME. Ondansetron does not attenuate hemodynamic changes in patients undergoing elective cesarean delivery using subarachnoid anesthesia: a double-blind, placebo-controlled, randomized trial. 2015.
31. Mohamed SA, Hussam AM, Abdallah SA, Sarhan KA, Shaban AM. Ondansetron Is an Effective Alternative to Decrease the Incidence of Postspinal Hypotension in Healthy Subjects Undergoing Infra-Umbilical Surgeries Compared To Combined Volume Loading and Vasoconstrictors: Randomized Controlled Trial. Open access Macedonian journal of medical sciences. 2018;6(12):2363.
32. Mazda Y, Tanaka M, Terui K, Nagashima S, Inoue RJJoa. Postoperative renal function in parturients with severe preeclampsia who underwent cesarean delivery: a retrospective observational study. 2018;32(3):447-51.
33. Brenck F, Hartmann B, Katzer C, Obaid R, Brüggmann D, Benson M, et al. Hypotension after spinal anesthesia for cesarean section: identification of risk factors using an anesthesia information management system. 2009;23(2):85.
34. Somboonviboon W, Kyokong O, Charuluxananan S, Narasethakamol AJMjotMAoT. Incidence and risk factors of hypotension and bradycardia after spinal anesthesia for cesarean section. 2008;91(2):181.
35. Ali M, Iqbal AJPAFMJ. A COMPARATIVE STUDY OF TWO DIFFERENT DOSES OF 0.75% HYPERBARIC BUPIVACAINE FOR SPINAL ANAESTHESIA IN ELECTIVE CAESAREAN SECTION. 2019;69(1):154-59.
36. Fakherpour A, Ghaem H, Fattahi Z, Zaree SJIJoA. Maternal and anaesthesia-related risk factors and incidence of spinal anaesthesia-induced hypotension in elective caesarean section: A multinomial logistic regression. 2018;62(1):36.

37. Ohpasanon P, Chinachoti T, Sriswasdi P, Srichu SJMjotMAoT. Prospective study of hypotension after spinal anesthesia for cesarean section at Siriraj Hospital: incidence and risk factors, part 2. 2008;91(5):675.
38. Rout CC, Farina ZJSAJoA, Analgesia. Anaesthesia-related maternal deaths in South Africa Chapter Seven of the 5th Saving Mothers Report 2008-2010. 2012;18(6).
39. Tubog TD, Kane TD, Pugh MA. Effects of ondansetron on attenuating spinal anesthesia-induced hypotension and bradycardia in obstetric and nonobstetric subjects: a systematic review and meta-analysis. AANA J. 2017;85(2):113-22.
40. Terkawi AS, Mavridis D, Flood P, Wetterslev J, Terkawi RS, Abdulhak AAB, et al. Does ondansetron modify sympathectomy due to subarachnoid anesthesia? Meta-analysis, meta-regression, and trial sequential analysis. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2016;124(4):846-69.
41. Shields SH, Holland R. Pharmacology of Vasopressors and Inotropes.
42. Phipps LE. Reducing Hypotension in Elective Cesarean Section Patients with Administration of Ondansetron Prior to Spinal Anesthesia: A Retrospective Chart Analysis. 2016.
43. Wang M, Zhuo L, Wang Q, Shen M-K, Yu Y-Y, Yu J-J, et al. Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension during cesarean delivery: a dose-dependent study. International journal of clinical and experimental medicine. 2014;7(12):5210.
44. Ge M, Wang S, Dai Z, Li Y, Xie L, Liu X, et al. Effect of ephedrine combined with bupivacaine on maternal hemodynamic and spinal nerve block in cesarean delivery. Biomed Rep. 2017;6(3):295-9.
45. Moffett PM, Cartwright L, Grossart EA, O'Keefe D, Kang CS. Intravenous ondansetron and the QT interval in adult emergency department patients: an observational study. Academic Emergency Medicine. 2016;23(1):102-5.
46. Hasanin A, Mokhtar AM, Badawy AA, Fouad R. Post-spinal anesthesia hypotension during cesarean delivery, a review article. Egyptian Journal of Anaesthesia. 2017;33(2):189-93.
47. Ortiz-Gómez JR, Palacio-Abizanda FJ, Morillas-Ramirez F, Fornet-Ruiz I, Lorenzo-Jiménez A, Bermejo-Albares ML. Reducing by 50% the incidence of maternal hypotension during elective caesarean delivery under spinal anesthesia: Effect of prophylactic ondansetron and/or continuous infusion of phenylephrine-a double-blind, randomized, placebo controlled trial. Saudi journal of anaesthesia. 2017;11(4):408.
48. Marciniak A, Owczuk R, Wujtewicz M, Preis K, Majdyło K. The influence of intravenous ondansetron on maternal blood haemodynamics after spinal anaesthesia for caesarean section: a double-blind, placebo-controlled study. Ginekologia polska. 2015;86(6).
49. Abbas N, Shah SAR, Naqvi SS. Role of prophylactic ondansetron for prevention of spinal anaesthesia induced hypotension in lower segment caesarean section. Pakistan Armed Forces Medical Journal. 2016;66(6):790-94.
50. El Khouly NI, Meligy AM. Randomized controlled trial comparing ondansetron and placebo for the reduction of spinal anesthesia-induced hypotension during elective cesarean delivery in Egypt. International Journal of Gynecology & Obstetrics. 2016;135(2):205-9.
51. Iqbal MS, Ishaq M, Masood A, Khan MZ. Optimal dose of prophylactic intravenous ephedrine for spinal-induced hypotension during cesarean section. Anaesthesia, Pain & Intensive Care. 2019:71-5.
52. Keats AS. The ASA classification of physical status–a recapitulation. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1978;49(4):233-5.
53. Shitemaw T. Effect of prophylactic ephedrine on blood pressure changes during cesarean section under spinal anesthesia at Tikur Anbesa specialized hospital, Ethiopia, 2018: prospective cohort study: Addis Ababa Universty; 2018.
54. Desalu I, Kushimo O. Is ephedrine infusion more effective at preventing hypotension than traditional prehydration during spinal anaesthesia for caesarean section in African parturients? International journal of obstetric anesthesia. 2005;14(4):294-9.

55. Nivatpumin P, Thamvittayakul V. Ephedrine versus ondansetron in the prevention of hypotension during cesarean delivery: a randomized, double-blind, placebo-controlled trial. International journal of obstetric anesthesia. 2016;27:25-31.
56. Hajian P, Malekianzadeh B, Davoudi M. Efficacy of Intravenous Ondansetron on Hemodynamic Complications in Women Undergoing Spinal Anesthesia for Cesarean Section: A Randomized Placebo Controlled Clinical Trial. Galen Medical Journal. 2016;5(1):13-8.
57. Baig R, Shah AA, Khurshid T, Abid L, Tariq Z. Use of Ondansetron for Prevention of Spinal Induced Hypotension. Journal of Islamabad Medical & Dental College. 2017;6(4):208-13.
58. Raghu K, Kumar S, Rajaram G, Nikhil N, Damodar P. Effect of ondansetron in the prevention of spinal anesthesia-induced hypotension. Journal of the Scientific Society. 2018;45(3):125.
59. Gao L, Zheng G, Han J, Wang Y, Zheng J. Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: a meta-analysis. International journal of obstetric anesthesia. 2015;24(4):335-43.
60. Sahoo T, SenDasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: a double-blind randomised, placebo-controlled study. International journal of obstetric anesthesia. 2012;21(1):24-8.
61. Rashad MM, Farmawy MS. Effects of intravenous ondansetron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in parturients undergoing cesarean section. Egyptian Journal of Anaesthesia. 2013;29(4):369-74.
62. El Khouly NI, Meligy AMJIJoG, Obstetrics. Randomized controlled trial comparing ondansetron and placebo for the reduction of spinal anesthesia-induced hypotension during elective cesarean delivery in Egypt. 2016;135(2):205-9.
63. Tatikonda CM, Rajappa GC, Rath P, Abbas M, Madhapura VS, Gopal NV. Effect of intravenous ondansetron on spinal anesthesia-induced hypotension and bradycardia: A randomized controlled double-blinded study. Anesthesia, essays and researches. 2019;13(2):340.

ANNEXES

Annex: I Assurance of principal investigator

I undersigned and agree to accept responsibility for the scientific ethical and technical Conduct of the research project and for provision of required progress reports as per terms and conditions of the Research Publications Office in effect at the time of Grant is forwarded as the result of this Application.

Name of the principal investigator:

Date. October, 2019 Signature _____

Name of the advisor:

Date. . January, 2019 Signature _____

Annex: II Information sheet

Hello.

My name is _____. I

Am a researcher and I have been attending postgraduate program in the field of Anesthesia at Addis Ababa university. I am going to conduct research on effectiveness' of prophylactic ondansetron for prevention of spinal induced hypotension among women undergoing elective cesarean section at yekatit 12 hospital,ethiopia,2019,prospective cohort study from October to January 2019/2020. The information going to be obtained will help the government and other responsible bodies to decrease in morbid adverse events after surgery and patient satisfaction. Your participation is very valuable for the success of this project. Also be mindful that whatever we will get here is for research purposes only and the information will not be used by any other person apart from this research and therefore, confidentiality can be guaranteed. However, your names will not be mentioned or be attached to anything that you say.

Do you want to continue yes---------- No---------- (Thank you in advance for your help!)

Name and contact address of investigators

Ahmed Hmu.ahmedhamu84@gmail.com,0924823790/0986294177

Identification card no. ----------

Annex IV Questionnaire

Questioner developed for collection of data for the study on effectiveness' of prophylactic ondansetron for prevention of spinal induced hypotension among women undergoing elective cesarean section at yekatit 12 hospital,ethiopia,2019,prospective cohort study from October to January 2019/2020.

Section: 1 Socio demographic factors

S.N	Question	Response	Code
	Patient card no		
	Patient age(yrs.)		
	Body Weight (k/g)		
	Height		
	BMI		
	NPO Time----------hrs		

	Gestational age(weeks)	< 34 wks.	
		34 – 37wks	
		37 – 40 wks.	
	Gravidity	One	
		Two	
		Three	
		Four	
		Above specify	
	Allergy to any of the following drugs	Local anesthetics	
		Ondansetron	
		Unknown	
		Others specify_____	
	Previous History of CS		
	Indication for CS		
	Initial HCT, Hgb,Plts		

Section 2. Procedure related variables:

Duration of incision to delivery time	**…… minutes**	
Blood loss during surgery		
Type of utero genic agent used	Oxytocin Yes dose……. no	
	Ergometrine **Yes dose** **No**	
Type of local anesthetics	**Lidocaine** **Yes. Dose…….** **No** **Bupivacaine** **Yes dose……**	

	No	
Baricity	**Hyperbaric** **Hypobaric** **Isobaric**	
Level of blocks **T4-T5** **T6-T7** **T8-T9** **T10**		
Duration of surgery		
Amount of fluid coloaded		
Weight of the baby		

Section 3.Data during peri-operative period

S.no	Question	Response	Code
	Base line Heart rate	_____ bpm	
	Base line Blood pressure(MAP)	SBP____(____) mmhg DBP____(____) mmhg MAP____(____) mmhg	
	Base line RR & spo2	_____br/m &_____%	
	Does the patient receive any premedication?	Yes	
		No	
	If Yes specify type and dose	1. _____(_____mg) 2. _____(_____mg)	
	Dose of 0.5% bupivacaine used for SA	_____ mg	
	Site of spinal administration b/n L2 &L3 b/n L3 & L4		
	Additives to local anesthetics	Yes	
		No	
	If yes, specify type and dose	_____ (_____mg/mcg)	

	Any additional analgesic drug required and given intraoperative?	Yes	
		No	
	If Yes .specify type, time and dose of drug given	_____ (____mg	
	Premedicated with ondansetron	Yes Dose ……..mg	
		No	

Section 4: Intra operative Hemodynamic status of the patients

V/S	**5 min**	10 min	15 min	**20 min**	**25 min**	**30 min**	**35 min**	**40min**	**45min**	**50min**
SBP										
DBP										
MAP										
PR										
SPO2										

Section 5: Any Intra/post-operative events

	Yes	**No**
Hypotension		
Bradycardia		
Nausea		
Vomiting		
If other specify _____		

Section 6: requirement of rescue vasopressor

	Yes	**No**
Vasopressor used		

Data collector

Name signature

_____ _____