An-Najah National University

Faculty of Graduate studies

Prophylactic Ephedrine versus Phenylephrine for Preventing Maternal Hypotension in Women Undergoing Spinal Anesthesia for Cesarean Section- a Clinical Trial

By

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Dedication

I dedicate this thesis to my precious daughter, Joud, and to all my family members.

I also dedicate this work to the spirit of the martyrs of Palestine and to prisoners of freedom in Israeli jails, and for every anesthesiologist and every CRNA nurse who has taught me as a CRNA student.

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I am grateful to God for the good health and well being that was necessary to complete this thesis.

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الاقرار

انا الموقع ادناه مقدم الرسالة التي تحمل العنوان

Prophylactic Ephedrine versus Phenylephrine for maternal hypotension in women undergoing spinal anesthesia for Cesarean section

أقر بأن ما اشتملت عليه هذه الرسالة انما هي نتاج جهدي الخاص، باستثناء ما تم الإشارة اليه حيثما ورد، وان هذه الرسالة ككل، أو أي جزء منها لم يقدم لنيل أي درجة أو لقب علمي أو بحثي لدى أي مؤسسة تعليمية أو بحثية أخرى .

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work and has not been submitted elsewhere for any other degree or qualification.

Student name الاسم:

Signature: التوقيع:

Date: التاريخ: ٢٠١٦/٥/٢٩

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List of Abbreviations

ASA	American Society of Anesthesiologists
Bp	Blood Pressure
Cm	Centimeter
C-S	Cesarean section
ECG	Electrocardiogram
ERC	Ethics and research committee
HR	Heart rate
IV	Intravenous
Kg	Kilogram(s)
Mg	Milligram(s)
Min	Minute
Ml	Milliliter(s)
Spo2	Percentage of arterial oxygen saturation
UOP	Urine output
µg	Microgram (s)
PMC	Palestine Medical Complex
PHCI	Palestinian Health Information Center
CRNA	Certified Registered Nurse Anesthetist

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Abstract

This study was presented in the 6th Palestinian Forum for Medical Research (PFMR), Biomedical Research Symposium April 9th, 2016. Bethlehem University, Palestine.

This study received an award from the conference for Scientific Excellence

Background

Hypotension during spinal anesthesia for cesarean section is secondary to the sympathetic blockade and aorto-caval compression by the uterus and it can be deleterious to both the fetus and the mother.

Ephedrine and phenylephrine improve venous return after sympathetic blockade during the spinal block.

Aims

The aims of the present study are to compare the efficacy of ephedrine and phenylephrine in the prevention and treatment of maternal hypotension during spinal block, to evaluate the side effects of ephedrine and phenylephrine, and to assess fetal changes as measured by Apgar scores.

Methods

Fifty five women, American Society of anesthesiologist (ASA) Grade I and II, undergoing spinal anesthesia with Bupivacaine and Fentanyl for cesarean section were randomly divided into two groups to receive prophylactic ephedrine (n = 27, dose = 10 mg, i.v.) or Phenylephrine (n = 28, dose = 80 µg, i.v.) immediately at the time of providing the subarachnoid block. Mean (SD) age of Ephedrine group was 30.48 ± 5.5 vs. the Phenylephrine group, which was 31.64 ± 3.3. Hypotension was defined as a decrease in systolic arterial pressure of >20% from baseline values and was treated with bolus administration of the vasopressors at 50% of the initial dose. Maternal arterial pressure (BP) and heart rate (HR) were measured every 3 minutes by automated oscillometry. Ringer's lactate (RL) solution (20 ml/kg) was infused 30 minutes before spinal injection for all participants. Vital signs (blood pressure, heart rate, and arterial oxygen saturation) were recorded throughout the surgery. Maternal and neonatal perioperative complications were also controlled and recorded. The incidence of hypotension, reactive hypertension, bradycardia, tachycardia, nausea and vomiting, and Apgar scores on the 1st and 5th minutes were evaluated.

Results

There was an insignificant difference in demographic data between the groups. The mean (±SD) dose of ephedrine used was 19.81 mg (±5.46) and phenylephrine was 125.71 µg (±35.64). Changes in systolic and diastolic

pressure were comparable in the two groups. There were significant differences in the incidence of reactive hypertension episodes (Ephedrine group: 48 (14.5%) vs. Phenylephrine group: 26 (7.7%) P < 0.005). There were no differences in the incidence of bradycardia (Ephedrine group: 3(11.1%) vs. Phenylephrine group: 6 (21.4%) P > 0.301). There were significant differences in the incidence of nausea and vomiting (Ephedrine group: 10 (37%) vs. Phenylephrine group: 3 (10.7%); P> 0.018). There were no significant differences in the incidence of hypotension, with an incidence of 18(66.7%) in the Ephedrine group and 17(60.7%) (P <0.646) in the Phenylephrine group. Maternal arrhythmias were more common in the Ephedrine group at 10(37%) than in the Phenylephrine group at 7 (25%), but the difference is not significant (P=0.334).Additionally, maternal restlessness was more common in the Ephedrine group:8 (30.8%) than the Phenylephrine group: 3 (10.7%), but with an insignificant difference (P=0.068).

Differences in the Apgar score in the 1st and 5th minute were not observed. Number of patients who required rescue dose in the Ephedrine group was 24 (88.9%), which was significantly higher than the Phenylephrine group at 20 (71.4%), P < 0.005). There are significant differences in the number of rescue doses of the two drugs. In the Phenylephrine group there was only one patient (3.6%) that had the rescue dose 3 times, and for the Ephedrine group there were 9 patients (33.3%) that had the rescue dose 3 times each, (P = 0.033).

Conclusion

We conclude from this study that phenylephrine 80μg has a similar vasopressor effect to that of ephedrine 10 mg for the prevention or treatment of maternal hypotension during spinal anesthesia for elective cesarean section, and that there is no difference in neonatal clinical outcomes as measured by the Apgar score. The applicability of the results is limited to healthy women with term fetuses. The clinical significance of bradycardia, reactive hypertension and intraoperative nausea and vomiting should not be overlooked. Giving Phenylephrine immediately at the time of providing the subarachnoid block is superior to ephedrine to reduce reactive hypertension, nausea, vomiting and requirements for vasopressors rescue medication. The results of this study support the use of phenylephrine for the maintenance of maternal arterial pressure during spinal anesthesia for elective cesarean section.

Nurse Anesthetist Implications

In view of maternal complications, the most important and noticeable complication was brief bradycardia (reflex bradycardia), which was transient and only occurred in a few cases (HR<60 per minute) that needed treatment with 0.5 mg intravenous Atropine based on policies and procedures for anesthesia clinic supervised by an anesthesiologist. Nausea and vomiting that responded rapidly to antiemetic medication was slightly high in the ephedrine group. None of the observed complications were

serious enough to have a significant impact on either the mothers or newborns according to the Apgar score.

Keywords: phenylephrine, ephedrine, spinal anesthesia, maternal hypotension, cesarean section.

Chapter One

Introduction

1. Introduction

Spinal anesthesia (SA) is often selected for cesarean delivery because of its fast onset, reliable sensory and motor blockade, and reduced risk of local anesthetic toxicity, as well as for the various advantages for the mother and fetus (Clark, et al., 1976; Macarthur, 2007). However, hypotension is a frequent intra-operative complication that occurs following SA.

Hypotension during spinal block for cesarean section is secondary to the sympathetic blockade, and it can be harmful to both the fetus and the mother. The harmful effects that can happen are a reduction in uterine and placental blood flow, disruption of fetal oxygenation and fetal acidosis, and maternal symptoms of reduced cardiac output. Other side effects, such as nausea, vomiting or altered consciousness may also occur (Rout and Rocke, 1994).

The incidence of hypotension after spinal anesthesia for cesarean section can be as high as 80% if the precautionary prevention steps such as previous hydration, moving the uterus to the left, and vasopressors, have not been taken into account (Riley et al., 1995).

Ephedrine has been considered the sole choice of vasopressor for treatment of spinal hypotension despite the lack of a confirmation of its superiority over other vasoconstrictors. Previous studies have reported that increased blood pressure caused by ephedrine is related to the preservation of the uterine and placental blood flow, especially because of its beta-

adrenergic action (James et al., 1970; Ralston, et al., 1974). However, other studies have suggested that ephedrine can reduce umbilical pH without affecting Apgar scores (Magalhães, et al., 2009; Ngan Kee, 2009).

Phenylephrine has been used for the prevention or treatment of spinal-induced hypotension in cesarean delivery. Studies have shown that phenylephrine maintains uterine and placental blood flow and higher umbilical blood pH than ephedrine, which has a similar effect in controlling hypotension, but with a lower risk of fetal acidosis (Taylor, et al., 1991; Morgan, 1994).Standard choices of vasopressor agents such as ephedrine and phenylephrine for treatment of spinal hypotension in cesarean sections is still a controversial issue (Moran,et al., 1991). It is, therefore, important to compare the efficacy of ephedrine and phenylephrine in the prevention and treatment of maternal hypotension during spinal block in order to evaluate the side effects of ephedrine and phenylephrine, and to assess fetal changes after using either ephedrine or phenylephrine using an Apgar score.

1.2. Background

1.2.1 Definition of cesarean section:

Cesarean delivery is a surgical procedure to terminate pregnancy through removing the fetus from the mother's uterus by an incision opening abdominal layers and the uterus in a full-term pregnancy. It may be elective or emergency. The most common indications for elective cesarean include(i) a previous cesarean section; (ii) genital herpes in the

mother; (iii) pregnant with twins;(iv) mother with HIV to decrease chance of transmission of infection to the baby; and (vi) fetal mal−presentation (Hannah, 2004).

The most common indications for emergency cesarean include (i) fetal distress; (ii) maternal distress due to bleeding caused by placenta previa, abruptio, or accretta; and (iii) dystocia (Naeem, et al., 2015; Haghighi and Ibrahimi, 2000).

The most common complications of cesarean section include: (i) wound infection; (ii) heavy blood loss; (iii) nausea and vomiting; (iv) injury to another organ such as the bladder; (v) neonatal tachypnea of the newborn (James, 2011; Cunningham and Leveno, 2012; Rajasekar and Hall, 1997; Ghahiri and Khosrav, 2015).

1.2.2 Regional anesthesia

Regional anesthesia is undoubtedly the most popular technique of anesthesia for cesarean section. In 2002 in the UK, 95% of elective sections and 87% of emergency operative deliveries were performed under regional anesthesia (Mvan de Velde, 2006).

Regional anesthesia is an anesthesia procedure and technique which involves the correct placement of a needle or catheter adjacent to nerve plexus that innervate the region of the body where surgery is to be performed; it is a safe procedure and an effective method to provide good anesthesia and analgesia during intra and post operative, which include: (i)

spinal anesthesia; (ii) epidural anesthesia; and (iii) peripheral nerve block (Morgan, 2013**)**. We are just concentrating on spinal anesthesia.

1.2.3 Spinal anesthesia (SA)

Spinal anesthesia is preferred for cesarean section. It is simple to perform, economical and introduces rapid onset of anesthesia and muscle relaxation. It provides high efficiency, lower drug doses, low neonatal depression, a conscious mother, and it decreases the incidence of aspiration pneumonitis. On the other hand, SA produces a fixed duration of anesthesia, post dural puncture headache, hypotension, and less control over block height (Caplan et al, 1998).

The benefits of spinal anesthesia in obstetrics were first recognized in July 1900, when the obstetrician Oscar Kreis administered spinal cocaine to six parturient women in labor. However, these pain relief methods in obstetrics initially fell into disrepute, since inadequate training and monitoring led to high morbidity and mortality. In a study by Moran, it was found that the mortality after SA was 1 in 1,000 surgical patients prior to 1944, and as high as 1 in 139 in obstetrics (Moran, 1991).

SA is an invasive anesthetic procedure. A site entails insertion of a spinal needle between lumbar vertebrae (3-4 or 4-5) to inject local anesthetic such as Bupivacaine in to the intrathecal, subarachnoid space. The local anesthetic is used to block sensory and motor nerves from fourth thoracic to fourth sacral dermatomes, which leads to sympathetic block out flow. Its earliest possible complication is hypotension due to vasodilatation

of the vessels, so patients should receive bolus intravenous fluids (mostly crystalloids) at 20 ml/kg before the procedure (Laporta et al.,1995; Nagelhout, 2010).

Regarding mechanism of bradycardia after subarachnoid block

Most patients do not experience a significant change in heart rate after spinal anesthesia. The mechanism responsible for bradycardia is not clear, but in young (age < 50), healthy (ASA class 1) patients there is a higher risk of bradycardia. Beta-blocker use also increases the risk of bradycardia. The incidence of bradycardia in the nonpregnant population is about 13%. Blockade of the sympathetic nervous system causes arterial vasodilation, decreased SVR, venous pooling, and a reduction in venous return. These changes cause a redistribution of blood that often results in hypotension. If the block is high enough, the sympathetic nerve fibers that innervate the heart, known as the cardioaccelerators (T 1 to T 4), become anesthetized, An imbalance occurs between vagal fibers, and the heart rate often slows, further contributing to hypotension, Intracardiac stretch receptors have been shown to reflexively decrease heart rate when filling pressures fall. The heart rate may decrease because of a fall in right atrial filling which decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins.(Barash,2013).

1.2.4 Drug used in spinal anesthesia-Bupivacaine

Bupivacaine is a mide local anesthetic that has a mechanism of action to block the sodium channel. It is a potent local anesthetic and has a long duration of action (3- 4 hours). It is often used with adjuncts like fentanyl to improve its effect and increase the duration of action to six

hours. It is widely used for cesarean section delivery. Spinal bupivacaine 0.5% 10-15 mg is an adequate dosage (Datta, 2006).

The incidence of hypotension after spinal block for cesarean section can be as high as 80% if prophylactic measures, such as prior hydration, moving the uterus to the left side, and vasopressors, are not instituted (Morgan, 1994; Husaini, 1998).

Hypotension is defined as a decrease in blood pressure that leads to inadequate tissue perfusion and oxygenation (Jackson et al., 1995). Blood pressure decrease below 20% of the baseline can lead to organ damage and myocardial ischemia, or a mean arterial pressure of less than 50 mmHg (Heitmiller, 2010).

Hypotension during spinal block for cesarean section is secondary to the sympathetic blockade and aorto-caval compression by the uterus and it can be deleterious to both the fetus and the mother. Ephedrine and phenylephrine improve venous return after sympathetic blockade during the spinal block (Cyna et al., 2006).

1.2.5 Phenylephrine, the study drug

Phenylephrine is considered a pure α_1-adrenergic agonist. It promotes dose-dependent vasoconstriction, which is more pronounced in the venous than in the arterial bed, improving venous return after the sympathetic blockade during spinal block. Studies have shown that phenylephrine maintains uterine and placental blood flow and higher

umbilical cord blood pH than ephedrine, while having similar efficacy to that of ephedrine in controlling hypotension, but with a lower risk of fetal acidosis (Morgan, 1994; Lee, 2002).

Phenylephrine is used for the treatment of acute hypotension with a dosage of 0.1 – 0.5 mg intravenously; the main side effects are reflex bradycardia due to increased cardiac output. Other side effects of phenylephrine are headache, excitability, anxiety, restlessness, high blood pressure,and rarely abnormal heart beats (Calvey & William, 2008).

Pharmacodynamics of phenylephrine. Interaction of phenylephrine with α1-adrenergic receptors on vascular smooth muscle cells causes activation of the cells and results in vasoconstriction. Following phenylephrine hydrochloride intravenous administration, increases in systolic and diastolic blood pressures, mean arterial blood pressure, and total peripheral vascular resistance are observed. The onset of blood pressure increase following an intravenous bolus phenylephrine hydrochloride administration is rapid, typically within minutes. As blood pressure increases following intravenous administration, vagal activity also increases, resulting in reflex bradycardia.

Phenylephrine has activity on most vascular beds, including renal, pulmonary, and splanchnic arteries (Bennett, 2010)

Pharmacokinetics of phenylephrine hydrochloride. The observed effective half life was approximately 5 minutes. The steady-state volume of distribution of approximately 340 L suggests a high distribution into organs and peripheral tissues. The average total serum clearance is approximately

2100 ml/min. The observed phenylephrine plasma terminal elimination half-life was 2.5 hours. Phenylephrine is metabolized primarily by monoamine oxidase and sulfotransferase. After intravenous administration of radiolabeled phenylephrine, approximately 80% of the total dose was eliminated within first 12 h and approximately 86% of the total dose was recovered in the urine within 48 h. The excreted unchanged parent drug was 16% of the total dose in the urine at 48 h post intravenous administration. There are two major metabolites, with approximately 57 and 8% of the total dose excreted as m-hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are considered not pharmacologically active (Bennett, 2010)

1.2.6 Ephedrine, the study drug

Ephedrine is a non-catecholamine sympatho-mimetic agent that stimulates alpha and beta adrenergic receptors directly and predominantly indirectly, producing its effects by releasing norepinephrine from nerve endings in the autonomous nervous system, which leads to an increased heart rate, blood pressure, cardiac output, and systemic vascular resistance. It crosses the blood brain barrier and produces central nervous system stimulation. Traditionally, it is the vasopressor of choice in obstetric anesthesia despite the lack of confirmation of its superiority over other vasopressors (Rout, 1993; Ralston et al., 1974). The intercurrences of epinephrine include maternal supraventricular tachycardia, tachyphylaxis, and fetal acidosis (Burns, et al., 2001; James, et al., 1970).

Prior studies report that the increase in blood pressure caused by ephedrine is related to preservation of uterine and placental blood flow, especially due to its beta-adrenergic action (Burns, et al., 2001; James, et al., 1970). However, other scholars have suggested that ephedrine can reduce umbilical cord pH without affecting Apgar scores (Kang et al., 1982; Ratcliffe, 1993).

Ephedrine can be given in increments of 3-6 mg every 3-4 minutes intravenously to treat hypotension produced by sympathetic block during spinal anesthesia and it has a half life of 3-6 hours. The side effects of ephedrine that may occur are nervousness, dizziness, headache, nausea, loss of appetite, and trouble sleeping (Calvey & William, 2008).

Pharmacodynamics of Ephedrine. Ephedrine is indirect sympathomimtic action that resemble those of adrenaline peripherally. stimulate heart rate ,cardiac output, and increases peripheral resistance , so it is usually as a result increase blood pressure, centrally in adults it produces increase alertness, anxiety , tremors, nausea and insomnia. The α-adrenergic receptors of smooth muscle cells in the bladder base stimulation may increase the resistance to the outflow of urine. Activation of ß-adrenergic receptors in the lungs promotes bronchodilation. More over cardiovascular effect from ephedrine is the result of a balance among α-1 adrenoceptor-mediated vasoconstriction, ß-2 adrenoceptor-mediated vasoconstriction, and ß-2 adrenoceptor-mediated vasodilatation. Stimulation of the ß-1 adrenoceptors results in positive inotrope and chronotrope action. Tachyphylaxis to the pressor effects of ephedrine may occur with repeated administration,

Pharmacokinetics of ephedrine half time is 6 hours approximately when it is given orally and one hour if administered intravenous. Its onset Immediate of (IV). More than 20 min (subcutaneous), 10 to 20 min (IM) and 15 to 60 min (oral). It is metabolized into norephedrine. However, well absorbed when given orally, first pass metabolism in the liver and excreted largely by the kidney. Both the parent drug and the metabolite are excreted in urine. Ephedrine crosses the placental barrier (Harvey, 2012).

1.3 Problem statement

In recent years, spinal anesthesia has become one of the most acceptable anesthetic techniques globally (Lin,et al., 2012) as well as in Palestine due to its rapid onset, intensity, symmetric sensory and motor block; it has been successfully used for cesarean section. In Palestine, the prevalence of cesarean section has doubled from 6% in 1996 to 14.8% in 2006. In 2014, the cesarean section rate in the West Bank was 23.7% and in the Gaza Strip was 21.3% (PHCI, 2014). These rates are higher than the optimal rates of cesarean section according toWorld Health Organization recommendations that indicate that the best outcomes for women and babies appear to occur with cesarean section rates of 5% to 10 % (Fernando et al., 2006).

Spinal anesthesia causes fewer complications than that of general anesthesia in both the mother and the fetus (Eriksson,et al., 2010; Chestnut, 2009; Riberio, 2007). However, despite these advantages, hemodynamic complications, especially hypotension of the mother, which is related to

sympathetic blockade, is up to 80% if prophylactic measures are not used (Clark, et al., 1976; Macarthur & Riley, 2007).

Maternal hypotension can have adverse maternal effects (nausea, vomiting, dizziness, and decreased consciousness) and fetal effects (decreased utero-placental blood flow, impaired fetal oxygenation, and fetal acidosis) (Clark et al., 1976).

Historically, ephedrine was the vasopressor recommended in obstetrics, but evidence suggests that ephedrine causes a reduction in fetal pH and base excess (although without affecting the Apgar Score) when compared to other vasopressors such as phenylephrine (Magalhães et al., 2009; Ngan Kee, 2009). The administration of a prophylactic phenylephrine significantly reduces the incidence of hypotension associated with spinal anesthesia (Cooper, et al., 2002; Ngan Kee, 2004). However, concerns have been raised about the safety of this technique in terms of the frequent incidence of reactive hypertension and bradycardia (Beilin, 2006).

In Palestinian hospitals, phenylephrine and ephedrine are both used to maintain maternal arterial blood pressure (BP) during spinal anesthesia for cesarean delivery but differ in their hemodynamic effects and their effects on the utero-placental circulation and umbilical cord gases (Alahuhta, et al., 1992; Thomas, et al., 1996; Lee, et al., 2002).

Anesthetists in Palestine have different aspects using phenylephrine and ephedrine, most of them declared they preferred the use of ephedrine because of its ease of use and it is more practical in its dilution.

1.4 Significance of the study

In elective cesarean section under spinal anesthesia, hypotension has been reported in as many as 85% of patients. Hypotension may be detrimental to the mother and the resulting placental hypo perfusion to the fetus. Careful positioning and volume preloading with crystalloid or colloids have been used to prevent it, but these are not comprehensive measures and a vasopressor is required to correct hypotension quickly. Prevention and treatment of this complication with special medical agents for optimal preservation of the mother's blood pressure and fetal circulation has been an important issue. Several studies have compared different medications in the prevention and treatment of decreased blood pressure following spinal anesthesia in pregnant women. However, experimental data are rather controversial and there is no general agreement about a special drug group.

In Palestine, there are different regimens to treat maternal hypotension with vasopressors in different hospitals either by giving phenylephrine or ephedrine. Both of these drugs have effects and side effects. There is strong interest in using vasopressors (ephedrine or phenylephrine) during spinal anesthesia for cesarean section delivery to prevent or treat hypotension.

Based on research, when prophylactic ephedrine is given, fetal acidosis, tachycardia, and reactive hypertension can occur, but hypotension can be prevented. When prophylactic phenylephrine is given in doses that significantly reduce maternal nausea and hypotension, the incidence of fetal acidosis is relatively low, but bradycardia can be a side effect. Research suggest that there is likely to be an overall benefit from giving prophylactic phenylephrine compared to giving ephedrine to treat hypotension as it occurs. However, further studies are required to test this hypothesis. We have studied bolus phenylephrine and ephedrine for maintenance of arterial pressure during spinal anesthesia in cesarean section.

1.5 Aims of the study

The aims of the present study are to compare the efficacy of ephedrine and phenylephrine in the prevention and treatment of maternal hypotension during spinal block, to evaluate the side effects of ephedrine and phenylephrine, and to assess fetal changes as measured by Apgar scores.

1.6 Hypothesis

H1: There are no significant differences at (α=0.05) between the effect of ephedrine and phenylephrine on the vitality of the newborn baby during spinal anesthesia in cesarean section using an Apgar score.

H2: there are no significant differences at (α=0.05) in Reactive hypertension between Phenylephrine and Ephedrine.

H3: there are no significant differences at (α=0.05) in Nausea and vomiting between Phenylephrine and Ephedrine.

H4: there are no significant differences at (α=0.05) in Restlessness between Phenylephrine and Ephedrine.

H5: there are no significant differences at (α=0.05) in Heart Rate (Tachycardia episodes, Bradycardia (episodes) between Phenylephrine and Ephedrine.

H6: there are no significant differences at (α=0.05) in vomiting between Phenylephrine and Ephedrine.

H7: there are no significant differences at (α=0.05) in Systolic blood pressure intraoperatively between Phenylephrine and Ephedrine.

H8: there are no significant differences at (α=0.05) in Systolic blood pressure intraoperatively between Phenylephrine and Ephedrine.

Chapter Two

Literature review

2. Literature Review

This chapter provides an overview of previous studies of patients undergoing elective cesarean section under spinal anesthesia and being administered either phenylephrine or ephedrine for maintenance of the mother's blood pressure. It also includes the effect of these two vasopressors on the Apgar score of the baby and the other negative effects on the mother.

In a randomized, double-blind study, conducted by Moran, et al.(1995) sixty women planning for elective cesarean section in spinal anesthesia randomly received either ephedrine (n = 29) at a dose of 10 mg intravenous bolus, or phenylephrine (n = 31) at 80 μg IV bolus doses to maintain systolic blood pressure of ≥ 100 mmHg. Umbilical arterial blood gases were measured and the neonatal Apgar score and early neonatal neurobehavioral scale points were evaluated. There were significant differences between groups in the mean umbilical artery pH, PCO2, and base deficit in favor of phenylephrine. There were no significant differences between the groups in the neonatal Apgar score, early neonatal neurobehavioral scale score, or the presence of maternal nausea and vomiting. The authors concluded that phenylephrine is as effective as ephedrine in the treatment of maternal hypotension when used in small additive bolus injections (Moran, et al., 1991).

A study was conducted in the United States by Laporta, et al. (1995). In this study, the authors compared the maternal and neonatal

catecholamine concentrations, followed by the use of either phenylephrine or ephedrine to treat a drop in maternal blood pressure after spinal anesthesia for cesarean section. Forty women were randomized into two groups: Group 1 (n = 20) were treated with ephedrine that was given as 5 mg i.v. bolus injections; Group II (n = 20) were treated with phenylephrine, which was given in 40µg i.v. bolus injections, both to keep the mother's systolic blood pressure at or above 100 mmHg. Maternal vein (MV), umbilical vein (UV), and umbilical artery (UA) blood samples were taken at the time of delivery. Samples were assayed for catecholamine concentrations and blood gas. When they compare the blood gas values between the two groups, catecholamine concentrations in UA, UV and MV (upon delivery) samples were significantly higher in the ephedrine group compared to the phenylephrine group. No significant differences in maternal characteristics were noted, such as acid-base values, nausea and vomiting, and Apgar scores between the groups. The authors concluded that phenylephrine is as safe and effective as ephedrine in the treatment of low blood pressure in healthy women undergoing cesarean delivery. The use of phenylephrine was also accompanied by significantly lower norepinephrine concentrations in both the mother and the newborn.

An experiment was conducted in the USA, in which 38 women undergoing elective cesarean section under spinal anesthesia were randomized to receive either phenylephrine boluses (100 mcg doses), or ephedrine (5 mg doses) for the maintenance of the mother's blood pressure. The purpose of the administration of vasopressors was a slope of systolic

pressure to ≤ 90% of baseline values. Maternal blood pressure (BP) and heart rate (HR) were measured every minute. Cardiac output (CO) was measured by cross-sectional and Doppler echocardiography before and after giving 1500 ml of Ringer lactate fluids and after every 2 min after administration of bupivacaine. The umbilical artery pulsatility index (PI) was measured using Doppler before and after spinal anesthesia. The results showed that the median (range) number of boluses of phenylephrine and ephedrine was similar. Maternal systolic blood pressure and CO results were the same in both groups, but the mean [95% CI] maximum percentage change in the mother's HR was greater in the phenylephrine group than in the ephedrine group. This study supports the use of phenylephrine for the maintenance of maternal arterial pressure in patients undergoing cesarean section electively during spinal anesthesia (Thomas et al., 1996).

A quantitative systematic review was conducted in China, in which the authors compared the efficacy and safety of ephedrine with phenylephrine for the prevention and treatment of hypotension under spinal anesthesia for cesarean section delivery. Seven randomized controlled trials (n=292) were recognized. Variables that were assessed were maternal hypotension, hypertension and bradycardia, as well as neonatal umbilical cord blood pH values and Apgar scores. The study found that there was no difference between phenylephrine and ephedrine for the management (prevention and treatment) of maternal hypotension, but, they showed that maternal bradycardia was more likely to happen with phenylephrine than with ephedrine. Also, the results showed that women who were given

phenylephrine had neonates with higher umbilical arterial pH values than those women given ephedrine. In fact, there was no difference between the two vasopressors in the incidence of true fetal acidosis or Apgar scores of7 at 1 and 5 min. The authors concluded that the present systematic review does not support that ephedrine is the preferred drug for the management of maternal hypotension during spinal anesthesia for elective cesarean delivery in healthy, non-laboring women **(**Lee et al., 2002**).**

A study conducted in India by Sahu et al. (2003) included sixty women undergoing elective and emergency caesarean section in spinal anesthesia who developed hypotension after subarachnoid block. Women were randomly assigned to three groups, Group P (receiving a phenylephrine dose of 100 µg, I.V (n = 20)), group E (receiving an ephedrine dose of 6 mg, I.V (n = 20)) and group M (receiving a mephentermine dose of 6 mg IV (n = 20)). Hypotension was defined as a decrease in systolic arterial pressure of >20% of baseline values. The authors concluded that elevation of systolic arterial pressure in the phenylephrine group was significantly higher for the first six minutes out of the bolus dose when compared with the ephedrine and mephentermine groups. There was a significant reduction in heart rate in the phenylephrine group. Neonatal Apgar scores were >7 in all three groups.

A systematic literature study was conducted in China to compare the effect of ephedrine and phenylephrine for the treatment of spinal anesthesia-induced hypotension during cesarean section. A total of 15 trials and 742 mothers undergoing elective C-sections were analyzed. When used

to prevent hypotension, patients who received ephedrine and phenylephrine did not change significantly in the presence of hypotension, umbilical artery pH or venous pH values. In the treatment of hypotension, patients who received ephedrine and phenylephrine had a comparable incidence of intraoperative hypotension, whereas mothers who received phenylephrine had newborns with higher umbilical arterial pH and venous pH values than those who had received ephedrine. The authors conclude that the use of prophylactic ephedrine and phenylephrine were both effective in preventing maternal hypotension during C-section under spinal anesthesia. Phenylephrine was superior to ephedrine to treat hypotension, evidenced by higher cord blood pH (Lin et al., 2012).

Gunda, et al., (2010) conducted a study of 100 ASA I and II patients scheduled for elective cesarean section with spinal anesthesia. Each patient was randomized to one of the two double-blind study groups. Group E received an ephedrine dose of one ml (5 mg / ml) with normal saline for hypotension if present (n = 50). Group C received one ml of phenylephrine (100ug / ml) with normal saline for hypotension if present (n = 50). Heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure were compared between and within groups to the basal values at 0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, and 60 minutes from the start of the operation. The occurrence of side effects and neonatal results were studied between the groups. This study showed that all patients had treatment for hypotension. Provision of phenylephrine was with considerable slope in HR. Variance in SBP, DBP, and MAP was analogous

in both groups for the most common times. The incidence of nausea, vomiting and tachycardia were significantly higher in the ephedrine group. The authors concluded that phenylephrine and ephedrine are allowable options to counter maternal hypotension associated with spinal anesthesia in elective cesarean section. They also found that complications of intra-operative nausea and vomiting, tachycardia and bradycardia should be considered when making a choice of vasopressors, which suggests that phenylephrine may be more relevant in promoting maternal well-being.

A study was conducted in Iran by Moslemi & Rasooli (2015). The aim of the study was to compare the effect of prophylactic infusion of phenylephrine compared to ephedrine in the prevention of hypotension women undergoing spinal anesthesia in elective cesarean section. Eighty-three patients were included in the study and were divided randomly into three groups. Group Ph got phenylephrine infusion; Group E got ephedrine infusion while Group P was delivered as placebo. Any decrease in BP around 20% from the baseline was treated with 50-100 µg of phenylephrine in the Ph group, or 5-10 mg of ephedrine in the E and P groups. This was repeated as necessary. These drugs were prepared in numerical marked syringes and given to nurses (blind to medication) who were asked to monitor patients. They were instructed to administer one ml of this drug solution if hypotension was higher than 20% from baseline (each 1 ml of phenylephrine was prepared as 50 micrograms and each one cc of ephedrine was 5 mg). Vital signs (blood pressure, heart rate and arterial oxygen saturation) were registered in time. Mother and newborn

perioperative complications were monitored and recorded. Systolic and diastolic blood pressures were higher in the phenylephrine group of recipients than the control group, but no higher than in the ephedrine group. Maternal rhythm disorders were more common in the ephedrine and phenylephrine groups than the control group. Vomiting was more common in the ephedrine group ($P < 0.05$). Further, five minute Apgar scores were higher in newborns in the phenylephrine and ephedrine groups than in the placebo group ($P < 0.05$). The newborn phenylephrine group had less acidosis than the other groups. They concluded that prophylactic infusion of phenylephrine can effectively reduce spinal anesthesia-related hypotension without any significant complication for the mother or her fetus (Moslemi & Rasooli, 2015).

In a randomized double-blind study in India, women received either doses of ephedrine bolus of 6 mg (group 1, n = 30) or 100µg of phenylephrine (group 2, n = 30) when the mother's systolic pressure was 80% of baseline. The study showed that differences in systolic pressure were comparable in the two groups. There were no differences in the incidence of bradycardia, nausea and vomiting. Umbilical artery pH and venous pH was significantly greater in the phenylephrine group than in the group of ephedrine. The base excess of the umbilical artery was significantly less in group E than in group P. Apgar scores at 1, 5 and 10 minutes and neurobehavioral score of 2-4 hours, 24 hours and 48 hours were similar in the two groups. They concluded that 100 µgof phenylephrine and 6 mg of ephedrine have similar efficacy in the treatment

of maternal hypotension during spinal anesthesia for elective cesarean section. Newborns in group P had significantly higher umbilical artery pH and base excess values than those in group E (Prakash et al., 2010).

A study was conducted in India by Nazir ,et al. (2012). A total of 100 patients undergoing elective cesarean section under spinal anesthesia with a normal pregnancy were randomly allocated into two groups of 50 each. Group I received a prophylactic bolus dose of ephedrine10 mg i.v. at the time of intrathecal block with rescue boluses of 5 mg. Group II received a prophylactic bolus dose of phenylephrine 100 μg at the time of intrathecal block with rescue boluses of 50μg. Hemodynamic variables such as blood pressure and heart rate were recorded every two minutes up to the delivery of the baby and then every 5 minutes. Neonatal outcome was assessed using Apgar score at 1 and 5 minutes and neonatal umbilical cord blood pH values. The authors found that there was no difference in managing hypotension between the two groups. Incidence of bradycardia was higher in the phenylephrine group. The differences in umbilical cord pH, Apgar score, and birth weight between the two groups were found to be statistically insignificant. The author concluded that phenylephrine and ephedrine are equally efficient in managing hypotension during spinal anesthesia for elective cesarean delivery. There was no difference between the two vasopressors in the incidence of true fetal acidosis. Neonatal outcome remained equally good in both groups.

A study from Finland conducted by Alahuhta, et al. (1992) researched the effects of i.v. vasopressors on19 healthy parturient women

undergoing elective cesarean section. Doppler velocimetry of maternal uterine, placental arcuate arteries and fetal umbilical cords, and kidney and middle cerebral arteries were studied during spinal anesthesia. Fetal cardiac muscle function was investigated simultaneously by M-mode echocardiography. Patients were randomized into two groups given either ephedrine or phenylephrine as a prophylactic infusion supplemented with smaller bolus doses if systolic arterial pressure decreased by more than 10 mmHg from the control value. Both the vasopressors restored maternal arterial pressure effectively. Ephedrine group showed no significant differences in any of the Doppler velocimetry recordings in relation to the fundamental values, but during phenylephrine infusion, indices of blood flow velocity waveform of uterine and placental arcuate arteries increased significantly and vascular resistance decreased significantly in the fetal renal arteries. Healthy fetuses seemed to tolerate these changes in uteroplacental circulation well. However, the Apgar score for newborns and acid-base values in the umbilical cord was within the normal range in both groups. The results suggest that caution is required when selecting the specific vasoconstrictor drug, dosage and route of administration for treatment of maternal hypotension resulting from spinal anesthesia for cesarean section.

In a systematic review study that was conducted in Germany by Veeser et al. (2012), the combined data available for defining the maternal and neonatal effects of the two vasopressors phenylephrine and ephedrine was analyzed. Hypotension, hypertension and bradycardia of the mothers;

fetal acidosis defined as a pH <7.20; continuous variables base excess (BE); and arterial pCO2 of newborns were registered. The eligibility criteria were met by 20 trials including 1,069 patients. Risk ratio (RR) of true fetal acidosis was 5.29 (95% CI 1.62 - 17.25) for ephedrine versus phenylephrine (P = 0.006). BE values for ephedrine use was significantly lower than after phenylephrine. Umbilical Artery pCO2 did not differ. Mothers treated with ephedrine had a lower risk of bradycardia (P = 0.004). No differences between vasopressors were observed for hypotension and hypertension. The authors conclude that there is a reduced risk of fetal acidosis associated with the use of phenylephrine. In addition to the results of BE, this suggests a beneficial effect of phenylephrine on fetal outcome parameters.

A study was conducted in Brazil by Magalhães, et al. in (2009). The purpose of this study was to compare the effect of ephedrine and phenylephrine in the prevention and treatment of maternal hypotension during spinal anesthesia for patients undergoing cesarean surgery and to assess their side effects and fetal changes. Sixty patients undergoing spinal anesthesia with bupivacaine and sufentanil were randomly divided into two groups to receive prophylactic ephedrine (group E, n = 30, dose = 10 mg) or phenylephrine (group P, n = 30, dose = 80 μg). Hypotension (blood pressure equal to or lower than 80% of baseline) was treated with bolus administration of the vasoconstrictor with 50% of the initial dose. The incidence of hypotension, reactive hypertension, bradycardia, vomiting, and Apgar scores at the 1st and 5th minutes, and blood gases in umbilical

cord blood were evaluated. The authors found that the mean dose of ephedrine used was 14.8 ± 3.8 mg and phenylephrine was 186.7 ± 52.9 micrograms. Demographic parameters and the incidence of vomiting, bradycardia, and reactive hypertension were similar in both groups. Hypotension had an incidence of 70% in group E and 93% in Group P ($p < 0.05$). The mean arterial pH of umbilical cord blood and Apgar score in the 1st minute were lower in Group E ($p < 0.05$). Differences in the Apgar score in the 5th minute were not observed. The author concluded that ephedrine was more effective than phenylephrine in the prevention of hypotension. Both drugs had a similar incidence of side effects. Fetal repercussions were less frequent with phenylephrine and were transitory with the use of ephedrine.

A study was conducted in Brazil to compare the efficacy of phenylephrine, metaraminol, and ephedrine in the prevention and treatment of hypotension after spinal anesthesia for cesarean section. Ninety pregnant women undergoing cesarean section were randomized into three groups to receive a bolus followed by continuous infusion of vasopressors as follows: phenylephrine group (50μg+50μg/min); metaraminol group (0.25 mg + 0.25 mg / min); ephedrine group (4 mg + 4 mg / min). The infusion dose was doubled when the systolic blood pressure dropped to 80% of the baseline and a bolus was given when the systolic blood pressure dropped to below 80%. The infusion dose was divided in half when the systolic blood pressure increased to 120% and was stopped when it became higher. The incidence of hypotension, nausea and vomiting, reactive hypertension,

bradycardia, tachycardia, Apgar scores and umbilical arterial blood gases were assessed at the 1st and 5th minute. There was no difference in the incidence of hypotension, bradycardia, reactive hypertension, infusion discontinuation, atropine or Apgar. Rescue boluses were higher only in the ephedrine group compared with the metaraminol group. The incidence of nausea and vomiting and fetal acidosis was greater in the ephedrine group. The three drugs were effective to prevent hypotension, but fetal effects were more common in the ephedrine group (Aragãoa, et al., 2014).

Chapter Three

Methodology

3. Methodology

This chapter presents an overview of the research methodology used for this study. It includes: study design, study sample (study population, sample size, and sampling process), setting, ethical consideration, data collection, and data analysis procedures.

3.1Study Design: A prospective, randomized, double-blind study**.**

3.2 Study Population

The target population is full-term pregnant women with age from 18 to 40 years old and planned for elective cesarean delivery with ASA Classification I & II.

3.3 Study Setting

The study was conducted in specialized gynecological centers at the Palestine Medical Complex (PMC) and Palestinian Red Crescent society Hospital in the city of Ramallah, Palestine.

3.4 Participants

Sixty parturient women, ranging in age from 18-40 years old, with American Society of Anesthesiologists (ASA) physical status I or II (Appendix 4) who were scheduled for elective cesarean delivery under spinal anesthesia.

3.5 Sample and sampling

To determine the optimal sample size for a study that assures an adequate power to detect statistical significance, calculating power of the study at 80%, and the level of alpha as $p<0.05$, the sample size was calculated as 20 women for each group (Table B12 Appendix 9) .To increase the power of our study we have taken 30 in each group as has been performed in previous studies (Kunter, 2005; Lee et al., 2002). In summary, the determination of sample size was based on calculation of the sample size and based on prior studies.

3.6 Pre-enrollment assessment

Every patient that was recruited in the study must have done a complete blood count to check hemoglobin levels and platelet counts to exclude any patient that had a low platelet count (less than 100×10^{3}). Low platelet count is very important for spinal anesthesia because low count increases the probability of epidural hematoma, so spinal anesthesia is contraindicated if the patient has thrombocytopenia.

3.7 Randomization

Patients were randomly divided into two groups using sequential, sealed envelopes with random numbers previously prepared by a person who was not involved with the study in any way. Patients who met the inclusion criteria were randomized in double-blind fashion to receive either:

Group (1) (n=27), Ephedrine: 10 mg i.v. bolus simultaneously with subarachnoid block.Group (2) (n=28), Phenylephrine: 80 µg i.v. bolus simultaneously with subarachnoid block. The study drugs were prepared in identical 10-mL syringes by an anesthesiologist not involved with data collection.

After Enrollment, 27 patients were assigned to ephedrine group out of thirty because one of them return consent to participate (n = 1) and two of them (n = 2) were converted to general anesthesia. Regarding phenylephrine group, 28 patients were assigned to the intervention out of thirty, two of 30 patients (n = 2) return their consent to participate in the study (Figure 1).

3.8 Blindness

Both pregnant women and anesthesiologists who participated in the surgeries were blinded to group allocation.

3.8.1 Preparation of vasopressors

A second anesthetist, who did not attend the surgery, prepared the vasopressor agents. The solutions were prepared in a syringe of 10 mL as follows:

Group P: phenylephrine 80µg

Group E: ephedrine 10mg

3.9 Study period

February 2015 to July 2015.

3.10 Inclusion criteria

(1) Physical status ASA I or II (Appendix 4); (2) Term pregnancy of a single fetus; (3) Elective indication for cesarean section; (4) 18-40 years old.

3.11 Exclusion criteria

(1) Refusal to participate in the study; (2) Patients younger than 18 years of age; (3) Pre-existing or pregnancy-induced systemic hypertension; (4) Presence of cardiovascular or cerebrovascular diseases; (5) fetal abnormalities; (6) history of allergy to the drugs used in the study, and contraindications to spinal block; (7) Parturient woman who has blood pressure of 135/ 95 mmHg; (8) Parturient woman who has chronic hypertension; (9) Parturient woman who has a heart rate <60 beats per minute and > 120 beat per minute.

3.12 Study Measures (Variables)

(a) Dependent variables: maternal hypotension

(b) Independent variables: Ephedrine, Phenylephrine, Spinal anesthesia

3.13 Conceptual definition of the terms

Hypotension was defined as a decrease in systolic arterial pressure >20% of baseline values and it was treated with a bolus of 50% of the initial dose of the vasopressor. Reactive hypertension was characterized as blood pressure 20% higher than baseline levels after the use of the vasopressor. Heart rate below 60 bpm was characterizedas bradycardia when accompanied by hypotension, and it was treated with 0.5 mg of atropine. Apgar scores on the first and fifth minutes for all newborns were determined and a score below eight was considered low. Tachycardia was considered at a heart rate greater than 100 beats per minute (Neves et al., 2010).

3.14 Follow up with patients

Each patient in the two groups included in the study received follow-up intraoperatively and in the post-anesthesia care unit (PACU) to control blood pressure, heart rate and other issues every three minutes in the operating room and on arrival at the PACU and every 15 minutes until discharge from PACU. Blood pressure, heart rate and other symptoms for each mother were recorded from the patient file as documented by nurses.

3.15 Procedure

After obtaining the study approval by the Institutional Review Board (IRB) of An-Najah National University, written informed consent was obtained from all parturient women after full explanations of the goals and procedures of the study. Sixty parturient women with American Society of

Anesthesiologists (ASA) physical status I or II who were scheduled for elective cesarean delivery under spinal anesthesia were recruited.

A data sheet containing the following information was filled out for each woman: name, age, height, weight, place of residence, body mass index, gestational age, blood pressure, heart rate, respiratory rate, ECG rhythm, and Spo2 as baseline.

A physical assessment was performed for all patients. The patient was assessed for weight measurement, and the non-invasive blood pressure, pulse and respiration were controlled and recorded. Laboratory tests were assessed (complete blood count, specifically the platelet count). Intravenous cannula 16 Fr G was inserted. Ringer's lactate (RL) solution (20 ml/kg) was infused 30 minutes before spinal injection for the all participants.

The anesthesia machine was checked and anesthesia equipment was also prepared for an emergency. Equipment for spinal anesthesia and drugs were prepared. Standard monitoring according to the American Society of Anesthesiologists that includes continuous electrocardiogram, non-invasive blood pressure, and pulse oximetry was followed.

Patients were placed in dorsal decubitus, or a sitting position, for a few minutes and blood pressure and heart rate were measured three times at 3-minute intervals and the arithmetic average of the values was calculated, which was considered the basal pressure of pregnant women and recorded on the data collection form.

Ephedrine or phenylephrine was administered at the same time of the spinal block. Patients in Group (1) received a prophylactic intravenous bolus of 10 mg of ephedrine immediately at the same time of the spinal block.

Patients in Group (2) received a prophylactic intravenous bolus of 80 µg of phenylephrine at the same time of the spinal block.

In the current study, the dose of 80 µg of phenylephrine was selected based on a previous study by Lee et al. (2012) in which this dose was the effective dosage when administered as an intravenous bolus, without severe side effects. The dose of 10 mg of ephedrine was selected based on a previous study by Magalhães et al. (2009) in which this was the effective dose when administered as an intravenous bolus, without severe side effects.

The syringes with the study drugs were prepared by an anesthesiologist who was not being involved in the collection of the data and analysis of the results.

Spinal puncture was done with a spinal needle by an anesthesiologist (pencil point spinal needle G 27 Fr) between L3-4 or L4-5 when the patient was in left lateral decubitus, and a Crawford wedge was placed under her right hip to obtain left uterine displacement. A solution containing Marcaine (0.5%, 2ml and 10 Mcg Fentanyl) was administered. Patients were placed at the same time of the spinal block in a supine position immediately after injection. The development of the block was recorded,

then oxygen therapy was administered to all patients; 6 L/min was delivered via a face mask until delivery. Heart rate and blood pressure were recorded immediately from the time of induction of spinal anesthesia then every 3 minutes until skin closure.

The number of spinal puncture trials and level of block were recorded. All patients were observed for block parameters by an anesthesiologist, as well as hemodynamic changes and complications following SA. Assessing dermatome levels after administering a subarachnoid block (SAB) every minute after the puncture by using a swap soaked in alcohol was undertaken. The use of the alcohol sponge to test the level of a block was determined by Rocco et al. (1985). Authorization for the surgical procedure was given only when the level of the blockade reached T_5.

The time from the blockade to the incision of the skin, incision of the uterus, and removal of the fetus were recorded. The incidence of maternal hypotension, reactive hypertension, bradycardia, nausea and vomiting, and the total dose of vasopressor were also analyzed. Apgar at the first and fifth minutes of all neonates was determined and a score below eight was considered low.

3.16 Rescue medication for hypotension

Maternal hypotension was defined as a blood pressure equal to or lower than 20% of baseline values and it was treated with a bolus of 50%

of the initial dose of the vasopressor (5 mg of ephedrine for group (1); 40 µg of phenylephrine for group (2).

3.17 Rescue medication for bradycardia

Atropine was administered in 0.5-mg increments whenever bradycardia (heart rate <60 beats/min) was associated with a systolic pressure less than baseline or if the heart rate was <45 beats/min irrespective of arterial pressure.

3.18 The incidence of maternal tachycardia and reactive hypertention

The incidence of maternal tachycardia (heart rate >100 beats/min) and reactive hypertension (increase in systolic pressure above baseline by 20% after the use of the vasopressor) were recorded. The number of vasopressor doses required, total dose of vasopressor administered, time of first administration of vasopressor, and requirement for atropine and its relation to vasopressor administration were noted.

3.19 Data Collection

We were interested in what side effects the patients experienced and to get an estimate of their incidence after giving the ephedrine and phenylephrine drugs. To discover what had been reported previously we ran a search on MedLine of studies reporting the most common side effects of ephedrine and phenylephrine ,. This was used as a base when developing the data collectrion sheet. This data collection sheet was validated with experts group that including, two anesthesiologists, two CRNA, one postoperative

nurse and statistician. Small comments had been the feedback from the experts which had been taken in concern at the final version of the data colletion sheet (Appendix 2).

Vital signs observations (BP, Pulse, Spo2, ECG rhythm, and RR) were recorded on arrival and every 15 minutes in the PACU until discharge from PACU., and the Apgor score was assessed by a pediatrician and asked for every baby score at the first minute and at 5 minutes. All variables were recorded (nausea, vomiting, headache, shivering, restlessness, arrhythmias and it is type, reactive hypertension, back pain, pain at the surgical incision, atropine needed, time from spinal puncture to skin incision, time to uterine incision, time from uterine incision to fetal delivery, and rescue dose of ephedrine and phenylephrine).

3.20 Data Analysis Plan

SPSS Version 20 was used for data analysis. The results were conducted only for patients who were included in and completed the study. Descriptive statistics (frequency, percentage) were used. The student t-test for continuous data, Mann-Whitney test for ordinal data, and Chi-square test for nominal data were used to analyze the results. A $p < 0.05$ was considered significant.

3.21 Ethical Considerations

The study presented in this thesis was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board (IRB), Palestinian Red Crescent Hospital and Ministry of Health. Consent formswere obtained from the patients prior to participation. Randomization of the treatment poses an ethical dilemma, as the patient is not allowed to

decide her treatment. Nevertheless, all patients were given both verbal and written information about the aim and objectives of the study before considering participation in the study. It was made clear that participation was voluntary, could be terminated at any time and that confidentiality was guaranteed. For that reason, the ethical dilemma was deemed to be small. However, all patients were given prophylactic treatment of hypotension and all the patients received rescue medication when required, regardless of which group the patients were randomised to.

The patients´ anonymity may have been threatened when performing continuous data collection. The results were presented in a way that ensured that it was not possible to identify any of the individuals. The study protocol concentrates on the patients' health and well-being.

Chapter Four

Results

4.1 Data Analysis:

The student t-test for continuous data, Mann-Whitney test for ordinal data, and Chi-square test for nominal data were used to analyze the results. The means and standard deviations were used to describe the continuous and the ordinal data, while the frequencies and percentages were used to describe the nominal data. A $p < 0.05$ was considered significant.

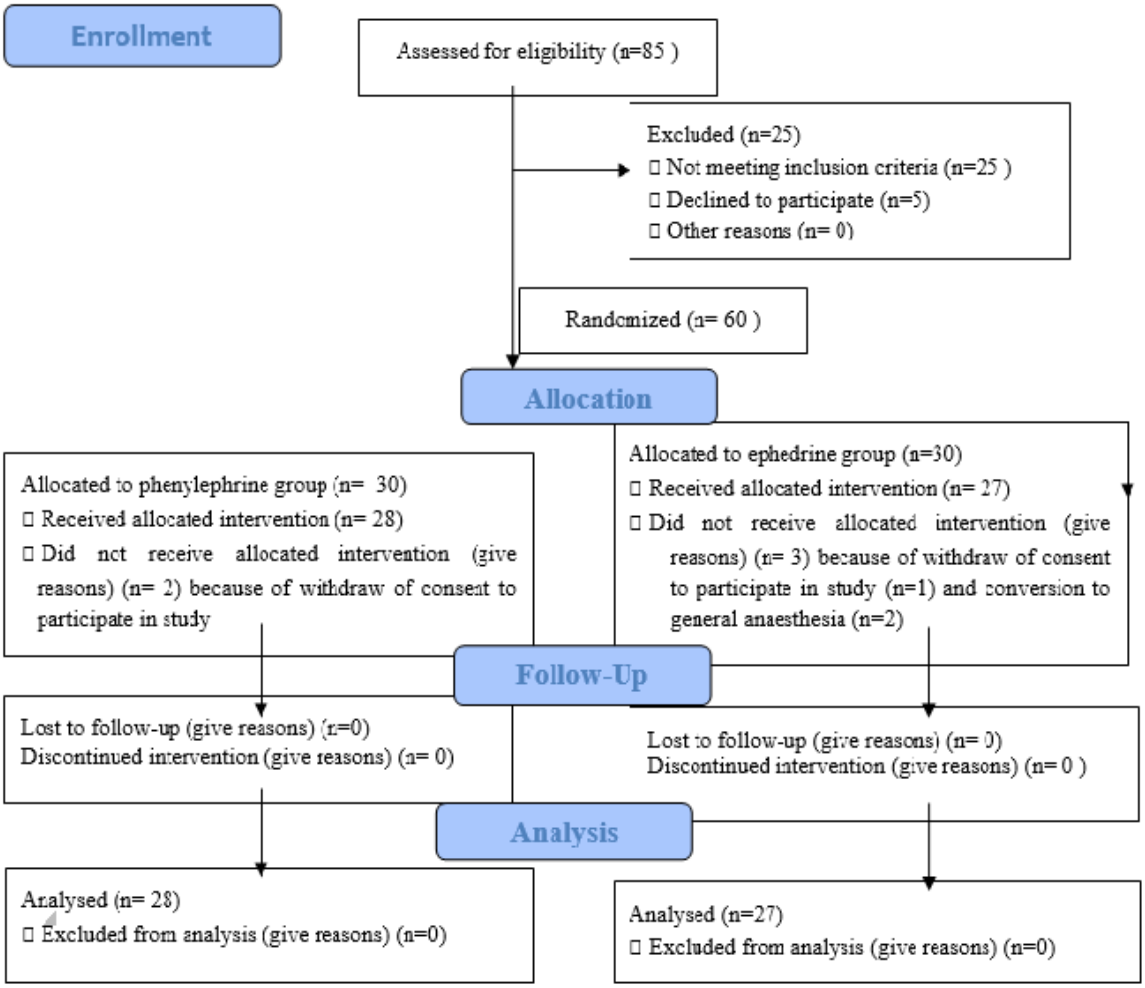

Figure (1): CONSORT FLOW DIAGRAM

Table 1: Demographic data of the patients in both phenylephrine and ephedrine groups

General characteristics	Phenylephrine (n=28)	Ephedrine (n=27)	P-Value
Age (years)	31.640± 3.369	30.48± 5.550	0.403
Weight (kg)	78.2± 14.38	80.27± 12.3197	0.613
Height (cm)	164.14± 7.347	161.70± 5.075	0.151
Body mass index ($kg.m^2$)	28.696± 5.0004	30.978± 4.5249	0.081
Gestational age (weeks)	38.586± 1.819	39.011 ± 1.1768	0.128
Baseline systolic pressure (mmHg)	123.29±9.63	120.56±9.4	0.255
Baseline heart rate (beats/min)	89.18±10.86	88.37±12.2	0.919

**Significant at 0.05 level. Data are Mean±SD with P-values derived from Mann-Whitney U test or Frequencies and Percentages (%) with P-values derived from Chi Square test.*

Table (1) above shows that there are no significant differences between the phenylephrine group and the ephedrine group in all general characteristics of patients exhibited in the table above at the 0.05 level (the p-values >0.05).

Table (2): Anesthetic and surgical parameters in phenylphrine and ephedrine groups

Anesthetic – surgical parameters	Phenylephrine (n=28)	Ephedrine (n=27)	P-Value
Time from blockade to skin incision (min) (Mean ± SD)	5.46± 2.912	5.89± 2.439	0.244
Time from blockade to uterine incision (min) (Mean ± SD)	11± 3.432	12.67± 4.243	0.110
Time from blockade to fetal delivery (min) (Mean ± SD)	13.54± 3.469	15.33± 4.566	0.124
Time from uterine incision to fetal delivery (min) (Mean ± SD)	2.46± 1.374	2.67 ± 1.414	0.507
Level of the block L3-4 (n (%)	26 (92.9%)	24 (88.9%)	0.609
Level of the block L4-5 (n (%)	2 (7.1%)	3 (11.1%)	0.609
Total dose of vassopressors (Mean ± SD)	125.71 µg±35.64	19.81 mg±5.46	------
Number of patients who required rescue dose	20 (71.4%)	24 (88.9%)	0.005*
Number of rescue doses:			
0	8(28.6%)	3(11.1%)	0.033*
1	9(32.1%)	6(22.2%)	
2	10(35.7%)	8(29.6%)	
3	1(3.6%)	9(33.3%)	
4	0(0.0%)	1(3.7%)	
Number of rescue drug combinations	0 (0 %)	6 (22.2 %)	———
Total intravenous fluids given (20 ml /kg)	1494.21 ± 361.570	1605.56± 246.395	0.337
Total urine output (ml) during operation	137.50 ± 51.379	124.07 ± 49.858	0.266
Total estimated blood loss (ml)	625± 143.049	666.67± 159.928	0.388
Anesthesia time (min) From spinal block to PACU	38.07 ± 13.379	42 ± 7.937	0.566
Surgical time (min) From surgical incision to PACU	33.25± 11.844	36.63± 7.088	0.493

*Significant at $p < 0.05$ level. Data are Mean±SD with P-values derived from Mann-Whitney *U* test or Frequencies and Percentages (%) with P-values derived from Chi Square test.

The table (2) above shows that there is a significant difference at the 0.05 level between the phenylephrine group and the ephedrine group in the number of patients who required rescue doses (phenylephrine n= 20/28 (71.4%), ephedrine n= 24/27 (88.9%), p-value = 0.005 < 0.05. This indicates that the number of patients who required rescue medication in the ephedrine group is significantly more than the number of patients in the phenylephrine group; results are in favor of phenylephrine. The table shows also that there are a significant difference in the number of rescue doses between the two drugs; for the phenylephrine group there is only one patient (3.6%) that received 3 rescue doses, which is less than the expected number, and for the ephedrine group, there are 9 patients (33.3%) that received 3 rescue doses, which is more than the expected number; the p-value = 0.033 < 0.05.

On the other hand, the table shows that there are no significant differences between the phenylephrine group and the ephedrine group in the other parameters and variables exhibited in the table above at the 0.05 level (the p-values>0.05).

Table (3): The percentage and number of episodes of side effects in phenylphrine and ephedrine groups

Side effects	Phenylephrine (n=28)	Ephedrine (n=27)	P-Value
Hypotension episodes	53 (15.7%)	48 (14.5%)	0.993
Hypotension patients (number)	17(60.7%)	18(66.7%)	0.646
Reactive hypertension patients (number)	15(53.6%)	11(40.7%)	0.341

Reactive hypertension (episodes)	26 (7.7%)	48 (14.5%)	0.005*
Arrhythmias	7 (25%)	10(37%)	0.334
Tachycardia (episodes)	101(29.9%)	100(30.1%)	0.845
Tachycardia patients(numbers)	21(75.0%)	21(77.8%)	0.808
Bradycardia (episodes)	6(1.8%)	5(1.5%)	0.345
Bradycardia (number)	6(21.4%)	3(11.1%)	0.301
Vomiting	0 (0%)	4(14.8%)	0.034*
Nausea	3 (10.7 %)	6 (22.2%)	0.249
Nausea and vomiting (together)	3(10.7%)	10(37%)	0.018*
Headache	4(14.3%)	4 (14.8%)	0.956
Shivering	3(10.7%)	2 (7.4%)	0.670
Restlessness	3 (10.7%)	8 (30.8%)	0.068
Patients needing Atropine because of bradycardia	4(14.3%)	2(7.4%)	0.413
Number of trials of spinal needle insertion of more than one time	1.64±0.826)	1.56±0.847)	0.574
Number of patients that have been stuck with spinal needle more than one time	13(46.4%)	10(37.03%)	0.480
Back pain	0(0%)	0(0%)	------
Pain at the surgical incision n(%)	0(0%)	1(3.7 %)	0.304

*Significant at 0.05 level. Data are Mean±SD with P-values derived from Mann-Whitney *U* test or Frequencies and Percentages(%) with P-values derived from Chi Square test.

The table (3) above shows that there is a significant difference at the 0.05 level between the phenylephrine group and the ephedrine group in the reactive hypertension episodes variable (phenylephrine =7.7%, ephedrine =14.5%); the p-value = 0.006 < 0.05 (Figure 2). This means that patients in the ephedrine group have significantly more reactive hypertension than the patients in the phenylephrine group; results are in favor of phenylephrine

The table above also shows that there is a significant difference at the 0.05 level between the phenylephrine group and the ephedrine group in the vomiting variable (phenylephrine=0.0%, ephedrine=14.8%); the p-value = 0.034 < 0.05 (Figure 3). This indicates that the patients in the ephedrine group experienced significantly more vomiting than the patients in the phenylephrine group; results are in favor of phenylephrine.

The table above shows that there is a significant difference at the 0.05 level between the phenylephrine group and the ephedrine group in the nausea and vomiting variable (phenylephrine=10.7%, ephedrine=37%); the p-value = 0.018 < 0.05 (Figure 5). This illustrates that the patients in the ephedrine group had significantly more episodes of nausea and vomiting than the patients in the phenylephrine and the results are in favor of phenylephrine.

On the other hand, the table shows that there are no significant differences between the phenylephrine group and the ephedrine group in the other variables exhibited in the table above at the 0.05 level(the p-values>0.05).

The percentage of side effects (hypotension, reactive hypertension, tachycardia, and bradycardia) in phenylphrine and ephedrine groups is summarized in Figure (2) and the percentage of side effects (nausea, vomiting, headache, shivering, restlessness, atropine needed and arrhythmias) in phenylphrine and ephedrine groups are summarized in Figure (3).

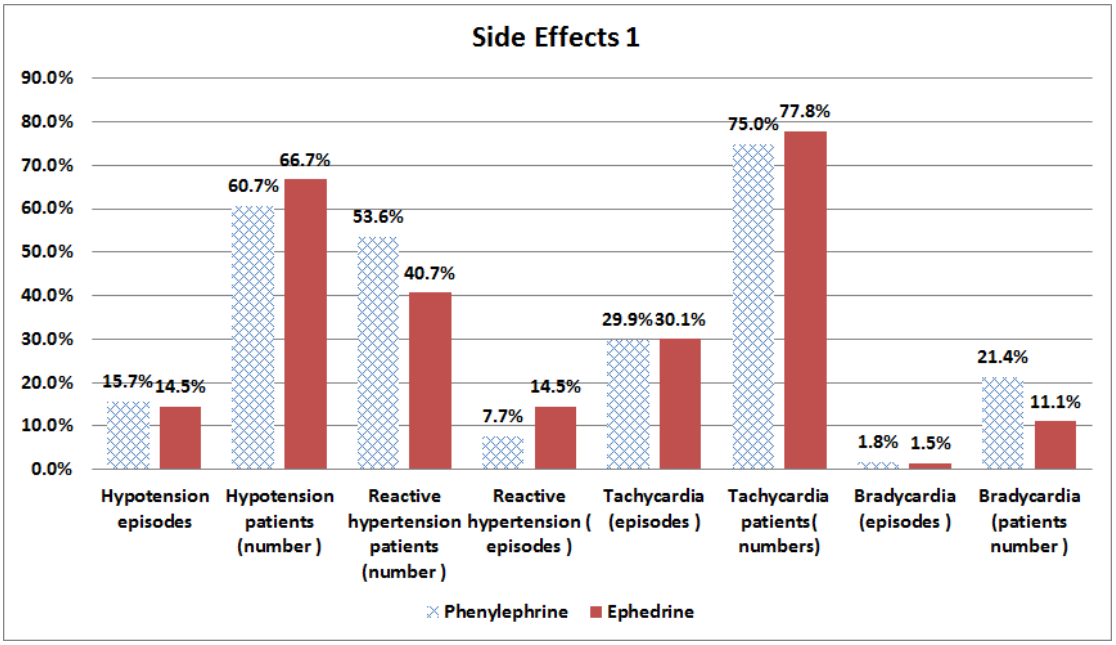

Figure (2). The Percentage of side effects (hypotension, reactive hypertension, tachycardia, bradycardia), in phenylphrine and ephedrine groups.

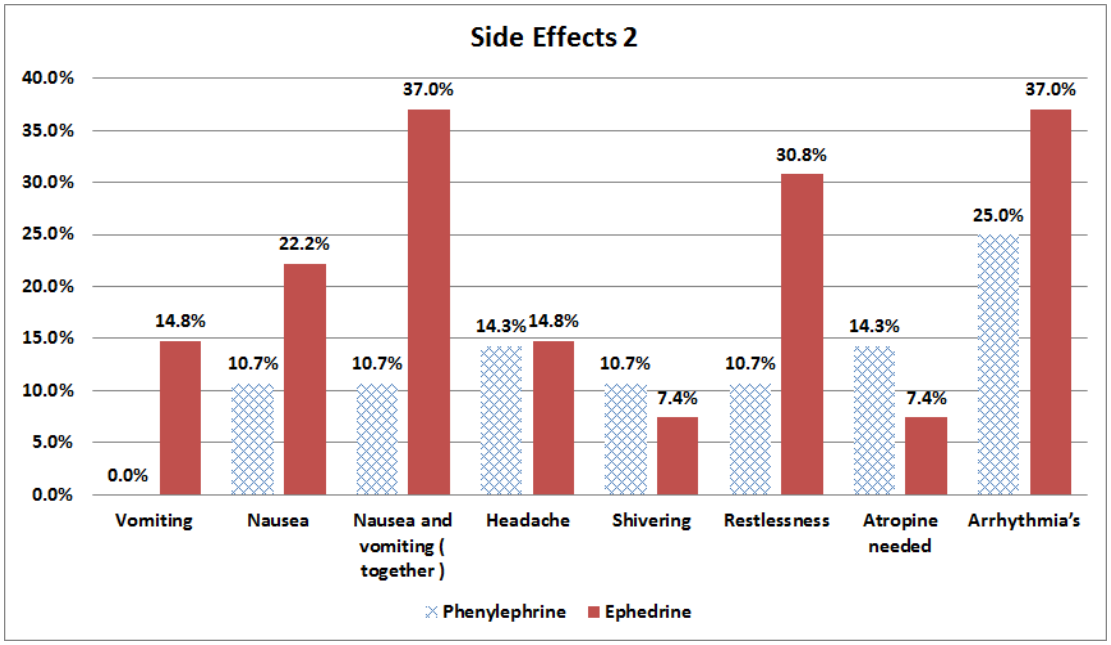

Figure (3). The Percentage of side effects (nausea, vomiting, headache, shivering, restlessness, atropine needed and arrhythmias), in phenylphrine and ephedrine groups.

Table (4): Fetal Apgar Score at 1 minute and 5 minutes

ABGAR score	Phenylephrine (n=28)	Ephedrine (n=27)	P-Value
1 minute	8.1±0.10	8±0.08	0.466
5 minutes	9.7±0.08	9.8±0.05	0.960
Apgar score < 8 at 1 min	6(21.4%)	6(22.2%)	0.943
Apgar score < 8 at 5 min	1(3.6%)	0(0.0%)	0.322

*Significant at 0.05 level. Data are Mean±SD with P-values derived from Mann-Whitney *U* test or Frequencies and Percentages (%) with P-values derived from Chi Square test.

The table (4) above shows that there are no significant differences between the phenylephrine group and the ephedrine group in the two measurements of Apgar score at 1 minute and 5 minutes exhibited in the table above at the 0.05 level(the p-values are>0.05).

Table (5): Parameters of systolic blood pressure (BPS), diastolic blood pressure (BPD), heart rate (HR), peripheral capillary oxygen saturation(SPO2) before (pre), after drug administration and post operatively (post)

Parameters	Phenylephrine (n=28)	Ephedrine (n=27)	P
BPS_pre	123.29±9.63	120.56±9.4	0.255
BPD_pre	73.14±9.59	73.3±8.47	0.781
HR_pre	89.18±10.86	88.37±12.2	0.919
RR_pre	23.18±4.23	21.82±4.1	0.294
SPO2_pre	98.04±0.96	98.19±0.96	0.511
BPS (after drug administration)	112.35±8.71	114.96±12.5	0.501
BPD (after drug administration)	57.57±8.5	57.23±9.77	0.692
HR (after drug administration)	91.33±11.88	92.99±13.63	0.511
RR (after drug administration)	19.97±3.01	20.77±4.2	0.511
SPO2 (after drug administration)	99.79±0.31	99.86±0.36	0.182
SBP post	111.31±9.33	116.84±9.17	0.027*

BPD post	62.31±7.66	64.64±8.15	0.274
HR post	84.09±9.49	84.05±11.05	0.539
RR post	18.91±2.29	20.14±3.9	0.232
SPO2 post	98.61±0.93	98.98±0.83	0.108

* Significant at 0.05 level. Data are Mean±SD with P-values derived from Mann-Whitney *U* test or Frequencies and Percentages (%) with P-values derived from Chi Square test.

The table (5) above shows that there is a significant difference at the 0.05 level between the phenylephrine group and the ephedrine group in the postoperative systolic blood pressure (phenylephrine mean=111.31, ephedrine mean=116.84); the p-value = 0.027 < 0.05. On the other hand, the table shows that there are no significant differences between the phenylephrine group and the ephedrine group on the other scales and variables exhibited in the table above at the 0.05 level (the p-values>0.05).

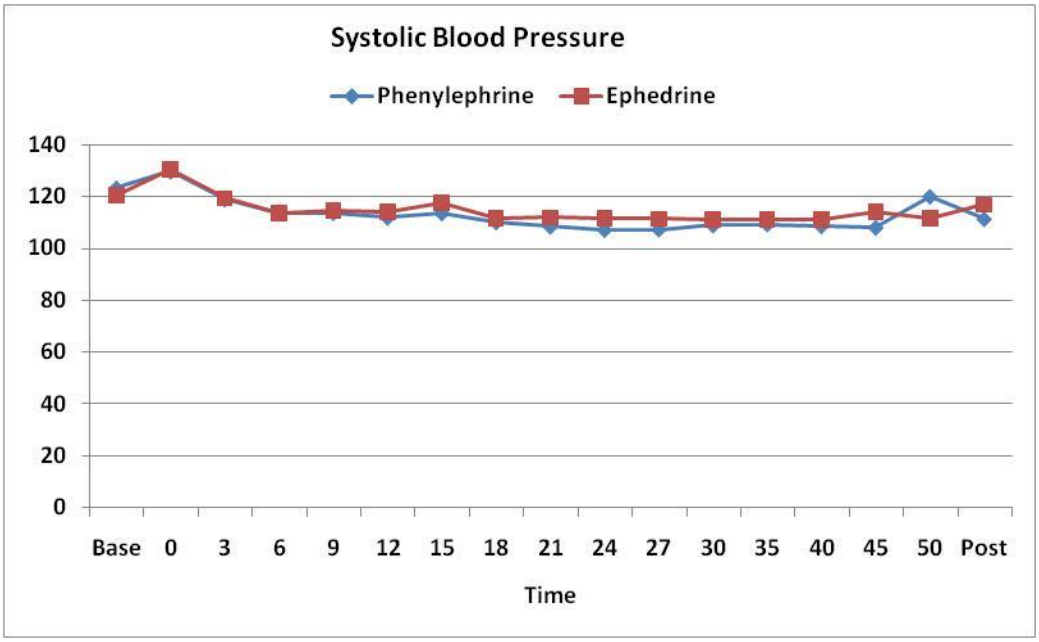

Figure (4): Graphical comparison of changes in mean Systolic blood pressure before and after spinal anesthesia, and after administration of vasopressors.

Figure (4) illustrates that there are no significant differences between the phenylephrine group and the ephedrine group regarding systolic blood

pressure changes before and after spinal anesthesia, and after administration of vasopressors.

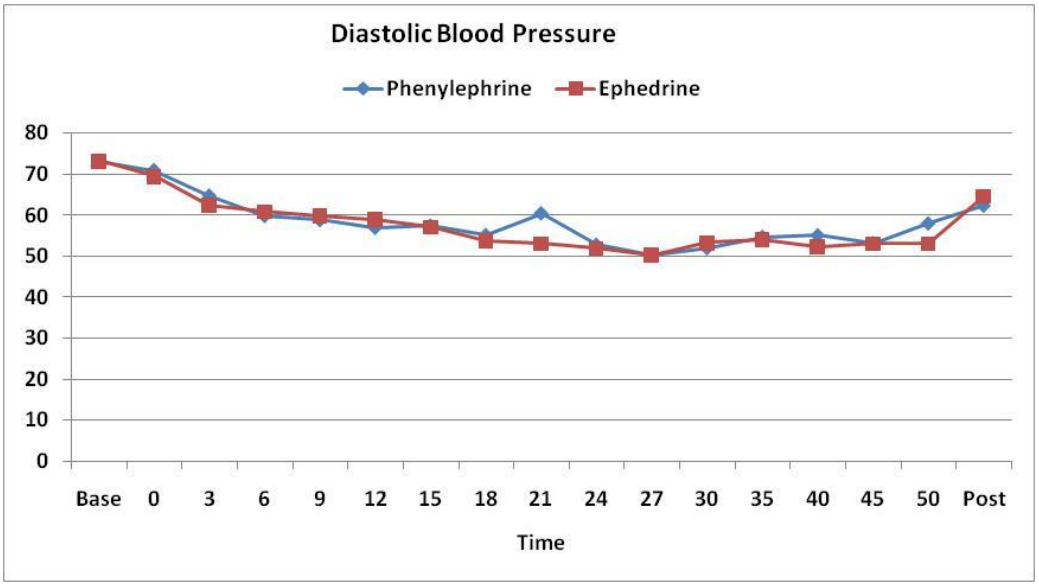

Figure (5): Graphical comparison of changes in mean Diastolic blood pressure before and after spinal anesthesia, and after administration of vasopressors.

Figure (5) illustrates that there are no significant differences between the phenylephrine group and the ephedrine group regarding diastolic blood pressure changes before and after spinal anesthesia, and after administration of vasopressors.

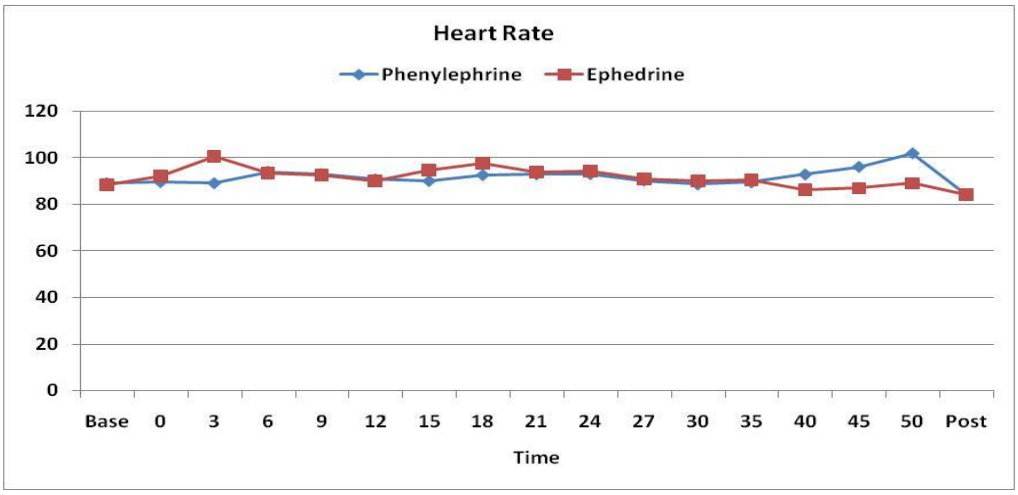

Figure (6): Graphical comparison of changes in mean Heart rate before and after spinal anesthesia, and after administration of vasopressors.

Figure (6) illustrates that there are no significant differences between the phenylephrine group and the ephedrine group regarding heart rate changes before and after spinal anesthesia, and after administration of vasopressors.

Table 6. First time (min) rescue medication drugs given

General characteristics	Phenylephrine (n=28)	Ephedrine (n=27)	P-Value
First time (min) drug given	15.8± 10.55	11.58± 8.92	0.167
	Max=40 Min=3	Max=35 Min=3	

**Significant at 0.05 level. Data are Mean±SD with P-values derived from Mann-Whitney U test or Frequencies and Percentages (%) with P-values derived from Chi Square test.*

The table (6) above shows that there is no significant difference at 0.05 level between the Phenylephrine group and the Ephedrine group in the First time (min) rescue medication drug given (Phenylephrine: Mean =15.8, Ephedrine: Mean= 11.58), the P-Value = 0.005 >0.05.

Null Hypotheses:

H1: There are no significant differences at (α=0.05) between the effect of ephedrine and phenylephrine on the vitality of the newborn baby during spinal anesthesia in cesarean section using an Apgar score.

According to results in tabl (4), we accept H1 since the p-values (0.466, 0.960) >0.05. The table showed that there are no significant differences

between the Phenylephrine group and the Ephedrine group in the two measurements of Apgar score(1 minute and 5 minute).

H2: there are no significant differences at (α=0.05) in Reactive hypertension between Phenylephrine and Ephedrine.

According to results in tabl (3), we reject H2 since the p-value(0.005) <0.05. The table showed that the Phenylephrine group has reactive hypertension less than the Ephedrine group (Phenylephrine =7.7% , Ephedrine=14.5%).

H3: there are no significant differences at (α=0.05) in Nausea and vomiting between Phenylephrine and Ephedrine.

According to results in tabl (3), we reject H3 since the p-value (0.018) <0.05. The table showed that the Phenylephrine group has Nausea and vomiting less than the Ephedrine group (Phenylephrine =10.7% , Ephedrine=37%).

H4: there are no significant differences at (α=0.05) in Restlessness between Phenylephrine and Ephedrine.

According to results in tabl (3), we accept H4 since the p-value (0.068)>0.05. The table showed that there are no significant differences between the Phenylephrine group and the Ephedrine group in Restlessness.

H5: there are no significant differences at (α=0.05) in Heart Rate (Tachycardia episodes, Bradycardia (episodes) between Phenylephrine and Ephedrine.

According to results in tabl (3), we accept H5 since the p-values (0.845, 0.345) >0.05. The table showed that there are no significant differences between the Phenylephrine group and the Ephedrine group in Heart Rate.

H6: there are no significant differences at (α=0.05) in vomiting between Phenylephrine and Ephedrine.

According to results in tabl (IV), we reject H6 since the p-value (0.034)<0.05. The table showed that the Phenylephrine group has vomiting less than the Ephedrine group (Phenylephrine =0.0% , Ephedrine=14.8%).

H7: there are no significant differences at (α=0.05) in Systolic blood pressure intraoperatively between Phenylephrine and Ephedrine.

According to results in table (5), we accept H7 since the p-values (0.501) >0.05. The table showed that there are no significant differences between the Phenylephrine group and the Ephedrine group in systolic blood pressure.

H8: there are no significant differences at (α=0.05) in Systolic blood pressure intraoperatively between Phenylephrine and Ephedrine.

According to results in table (5), we accept H8 since the p-values (0.692) >0.05. The table showed that there are no significant differences between the Phenylephrine group and the Ephedrine group in diastolic blood pressure.

Chapter Five

Discussion

5. Discussion

In the current study, all patients in the two groups were comparable with respect to age and ASA status. The difference observed in baseline parameters, that is, heart rate, systolic, diastolic, and mean arterial pressures between the two groups was statistically insignificant, respectively. There were statistically non-significant differences between surgical times (induction to delivery time and from delivery until the end of surgery) in both groups. Our results coincide with Nazir et al. (2012).

5.1 Techniques to control maternal blood pressure

After subarachnoid block for caesarean section, hypotension can be minimized by the use of IV fluid preload, avoidance of aortocaval compression, and judicious use of vasopressor agent. It has been shown that the percentage decrease in placental perfusion is related to the percentage reduction in maternal arterial pressure *(*Corke,1982*).* For the purpose of this study, hypotension was defined as a decrease in arterial pressure greater than 20% from baseline systolic.

In the present study, parameters associated with post-spinal block hypotension were controlled to evaluate which drug would be more effective in the prevention of hypotension with fewer deleterious consequences to the fetus and mother. Prior studies have presented different methodologies and conflicting results regarding the ideal vasopressor, dose, and administration regimen, as well as the use of other

techniques to control maternal blood pressure with minimal deleterious effects on the fetus (Lee et al., 2002).

In the present study, all patients were hydrated with 20ml/kg of Ringer's lactate, which was instituted prior to the spinal block. In contrast, some studies have demonstrated the inefficaciousness of prior hydration due to rapid redistribution (Ueyama, et al., 1999). However, pre-hydration is commonly administered despite the fact that it has controversial results (Kinsella, 2013; Kubli, et al., 2003). Crystalloids and colloid preload are used to prevent or treat maternal hypotension in addition to vasopressor drugs (Olang, 2010). Also, left uterine displacement is combined with fluid preload to prevent maternal hypotension, but vasopressors are also frequently needed (Maglehaes,2009).

In the present study, the uterus was moved to the left to reduce aortocaval compression, and the blockade was maintained on the same level in all patients. This management is compatible with another study, which confirmed that left uterine displacement is known to decrease the effects of aortocaval compression (Kinsella, 2003). Despite all conservative measures, a vasopressor drug is often required to prevent hypotension during spinal anesthesia (Erler & Gogarten, 2007).

5.2 Maintenance of Blood pressure

In the present study, ephedrine 10 mg and phenylephrine 80 µg were given to maintain systolic arterial blood pressure above 100mmHg. The study shows that phenylephrine is as effective as ephedrine when used in

small incremental bolus injections. Our study is congruent with Moran, et al.(1991)who gave ephedrine 10 mg or phenylephrine 80 µg i.v. bolus to maintain systolic arterial pressure above 100mmHg; it is also congruent with Thomas, et al. (1996). Additionally, our results are consistent with a Prakash et al. (2010) study that confirmed that 100 µg bolus doses of phenylephrine are as effective as 6-mg bolus doses of ephedrine in the treatment of hypotension following spinal anesthesia in term parturient women undergoing caesarean delivery. Our findings are also in agreement with a systematic review of randomized controlled trials conducted by Lee, et al. (2002) that found that ephedrine and phenylephrine have similar efficacy for preventing or treating hypotension. Furthermore, our results coincide with the study of Bhardwai, et al. (2013) in which phenylephrine, ephedrine, and metaraminol were used separately for maintaining maternal BP during spinal anesthesia for cesarean section. They concluded that all three vasopressors were equally effective in maintaining maternal BP without any detrimental effect on maternal or fetal outcomes (Macarthur & Riley, 2007).

The present study is not consistent with the work of a Magalhaes, et al. (2009) study on ephedrine versus phenylephrine for prevention of hypotension during spinal block for cesarean section and effects on the fetus. They concluded that ephedrine was more effective than phenylephrine in the prevention of hypotension. This may have been because a lower dose of phenylephrine was used in their study compared to this study.

On the other hand, clinical trials have shown that phenylephrine can be more beneficial than ephedrine when used to prevent or treat spinal anesthesia-induced hypotension during cesarean section (NganKee, 2006). According to some studies, phenylephrine is the preferred drug for the management of hypotension after spinal anesthesia for elective cesarean delivery (Veeser, 2012), which disagrees with our study.

5.3 Incidence of hypotension

In the present study, spinal anesthesia was associated with hypotension in patients in phenylephrine17 (60.7%), and ephedrine 18(66.7%) groups. The present study is in agreement with the study of Gunda, et al. (2009) who showed that all patients had treatment for hypotension.

Ngan Kee, et al., (2000) studied dose-response effect of ephedrine and showed that the minimal effective dose of ephedrine in the prevention of hypotension following spinal anesthesia is 30 mg. However, this dose does not completely prevent hypertension and in some cases could cause it.

Many studies have compared the effectiveness of phenylephrine and ephedrine in various doses and the administration method. A meta-analysis of four randomized clinical trials by Lee, et al. (2004) showed that ephedrine could not be used as a prophylaxis against hypotension. This is because it cannot prevent hypotension in low doses, and in high doses, it may cause hypertension that might be problematic (Lee, et al., 2004). In other studies, authors showed that prophylactic infusion of phenylephrine

was more effective than other methods in the prevention of spinal anesthesia-induced hypotension (Ngan Kee, et al., 2004).

In the present study, there are no statistical differences regarding systolic and diastolic blood pressure in both ephedrine and phenylephrine groups. This finding is partially in agreement with the study of Brooker et al. (1997) that compared the effect of phenylephrine and ephedrine in maintaining blood pressure in cesarean section following spinal anesthesia. Their results showed that both systolic and diastolic pressures were maintained well, but diastolic pressure was maintained better with phenylephrine than with ephedrine. Mercier, et al. (2001) found that the addition of phenylephrine to ephedrine infusion as a prophylaxis against hypotension resulted in a better prevention of hypotension than ephedrine alone.

5.4 The incidence of bradycardia

In the present study 6 (21.4%) women receiving phenylephrine and 3(11.1%) receiving ephedrine developed bradycardia. This difference was not statistically significant. Magalhaes, et al. (2009) reported comparable numbers of bradycardia with ephedrine and phenylephrine.

Our results are similar to that of a study by Thomas, et al. (1996) of women receiving phenylephrine who were more likely to develop bradycardia than those treated with ephedrine. In this study, 17% of women receiving phenylephrine developed a bradycardia of less than 60 beats/min compared with none in the ephedrine group. This difference was also not

statistically significant. The authors explained that it was probably because the sample size was insufficient (Thomas, et al. 1996; Lee, et al., 2002).

Our results are not compatible with the other studies that found that phenylephrine causes significant reduction in heart rate after the bolus dose (Moran, et al., 1991; Thomas, et al., 1996; Ramanathan, et al., 1988; Hall, et al., 1994; Sahu et al., 2003). Also, our results disagree with the results of the study of Lee et al. (2002) in which they reported higher incidence of bradycardia in patients receiving phenylephrine as compared with patients receiving ephedrine for prevention of hypotension during spinal anesthesia for cesarean section.

In another study of concern conducted by Nazir, 2012), it was found that maternal bradycardia occurred more frequently with phenylephrine than with ephedrine. The authors declared that this is to be expected because of an increase in blood pressure in which an α -agonist may lead to reactive bradycardia. However, this was responsive to atropine treatment without adverse consequences. This result concurs with our results that 6(21%) patients developed bradycardia in the phenylephrine group and were treated with Atropine. The incidence of isolated phenylephrine-related maternal bradycardia (heart rate- 60 bpm) was highest (58%) in one trial when large doses of phenylephrine were used (Thomas et al., 1996)). The authors suggested that maternal bradycardia contributed to cardiac sympathetic denervation because the sensory block was high. Therefore, an ephedrine-phenylephrine combination may help prevent maternal

bradycardia, as the mimetic effect of ephedrine would counteract this mechanism.

5.5The incidence of tachycardia

In the present study, 21(75.0%) patients in the phenylephrine group and 21(77.8%) patients in the ephedrine group developed tachycardia. Our study is unharmonious with the other studies conducted by Gunda, et al (2010) suggesting that the incidence of tachycardia was significantly higher in ephedrine groups;

5.6 Incidence of reactive hypertention

The present study shows that there is a significant difference at the 0.05 level between the phenylephrine group and the ephedrine group in there active hypertension episodes variable (phenylephrine=7.7%, ephedrine=14.5%); the p-value = 0.006 < 0.05. This means that patients in the ephedrine group have significantly more reactive hypertension than the patients in the phenylephrine group. Our findings disagree with the study of Loughery, et al. (2002), which found no cases of rebound hypertension with ephedrine. However, Magalhaes, et al. (2009) reported comparable numbers of reactive hypertension with ephedrine and phenylephrine.

Prior studies have suggested that a bolus of 30 mg of intravenous ephedrine would be more effective in the prevention of hypotension, but with an increased incidence of reactive hypertension (Ngan Kee, et al., 2000). In contrast, a prospective, observational study demonstrated that the

intravenous administration of 15 to 20 mg of ephedrine reduced the incidence of maternal hypotension without increasing the incidence of reactive hypertension (Simon, et al., 2001). A meta-analysis by Lee, et al. (2003) concluded that doses above 14 mg of ephedrine did not reduce the incidence of maternal hypotension, but they caused reactive hypertension in the mother and a small reduction in umbilical cord blood pH. In the study of Magalhães, et al. (2009), a dose of 10 mg of ephedrine was considered to be effective and, at the same time, had little side effects, which is not consistent with our study that a dose of 10 mg ephedrine caused 11(40.7%) patients to develop reactive hypertension. On the other hand, even for patients who were administered 80 μg of phenylephrine, 15 (53.6%) developed reactive hypertension. However, Loughery, et al. (2002) found no cases of rebound hypertension with ephedrine. Reactive hypertension episodes, as observed in the present study for the phenylephrine group, were 26(7.7%) versus the ephedrine group that had 48(14.5%) (p=0.005).This finding corresponds to the findings of the study of Magalhaes, et al. (2009).

5.7 Incidence of nausea and vomiting

The present study shows that there is a significant difference at the 0.05 level between the phenylephrine group and the ephedrine group in the vomiting variable (phenylephrine=0.0%, ephedrine=14.8%); the p-value = 0.034 < 0.05. This indicates that the patients in the ephedrine group had significantly more vomiting than the patients in the phenylephrine group. Also, the present study shows that there is a significant difference at the

0.05 level between the phenylephrine group and the ephedrine group in the nausea and vomiting variables (phenylephrine =10.7%, ephedrine=37%); the p-value = 0.018 < 0.05. This illustrates that the patients in the ephedrine group have significantly more episodes of nausea and vomiting than the patients in the phenylephrine group. Our results are in concurrence with a number of studies indicating a significantly higher incidence of nausea/vomiting with ephedrine usage (Kansal, et al., 2005; Macarthur & Riley, 2007; Loughrey et al., 2002; Gunda, et al., 2010). Nevertheless, Magalhaes, et al. (2009) reported a higher prevalence of nausea/vomiting in patients who received phenylephrine compared to those who received ephedrine. They suggested that in all cases, administration of a second dose of vasopressor resulted in occurrence of nausea and/or vomiting.

5.8 Rescue medication

In the present study, there is a significant difference at the 0.05 level between the phenylephrine and the ephedrine groups in the number of patients who required rescue doses (phenylephrine n= 20/28 (71.4%), ephedrine n= 24/27 (88.9%); the p-value = 0.005 < 0.05. This indicates that the number of patients who required rescue medication in the ephedrine group was significantly more than the number of patients in phenylephrine group.

The present study shows also that there is a significant difference in the number of rescue dose between the two drugs; for the phenylephrine group, there was only one patient (3.6%) that received three rescue doses,

which is less than the expected number, and for the ephedrine group, there were nine patients (33.3%) that received three doses, which is more than the expected number; the p-value=0.033 < 0.05. The present study coincides with the study of Moslemi, et al. (2015), which showed that the need for additional vasopressor doses, especially repeated 3rd and 4th doses for treatment of occurred hypotension following spinal block, was higher in ephedrine than phenylephrine groups. Thus, it seems that phenylephrine infusion is associated with a better blood pressure control and a lower incidence of severe hypotension which needs treatment. The author declared that tachyphylaxis related to repeated doses or continuous infusion of ephedrine is probably responsible for these findings.

5.9Apgar Score

The present study shows that there are no significant differences between the phenylephrine group and the ephedrine group in the two measurements of Apgar scores at 1 minute and 5 minutes. It appears to have no adverse neonatal effects in healthy fetuses. This study is consistent with a Moran, et al. (1991) study that concluded that there were no adverse neonatal effects for fetuses of healthy, non laboring parturient women. Our results also coincide with the study of Prakash, et al. (2010) that showed that Apgar scores at 1 and 5 minutes were similar between the two groups of phenylephrine and ephedrine.

A study demonstrated that even high doses of phenylephrine (above 2,000 μg) were not associated with deleterious effects on the fetus, as

determined by the Apgar scores (Emmett, et al., 2002). In the present study, the dose of 80 μg of phenylephrine was chosen based on a prior study that demonstrated that this was the effective dose when administered as an intravenous bolus, without severe side effects. Our findings is identical with that of a study by Lee (2002).

Evaluation of first- and fifth-minute Apgar scores values revealed that the 5th Apgar score was better in phenylephrine and ephedrine groups than the control group in a study by Moslemi, et al. (2015). According to many studies, neonatal outcome was not affected by prophylactic use of phenylephrine or ephedrine and in some; neonatal condition was maintained well with prophylactic vasopressors (Nazir et al., 2012).

In a systematic review of seven randomized clinical trials, Mercier, et al. (2012) found that although 1st Apgar scores were not different between groups, 5th Apgar scores were higher in phenylephrine and ephedrine groups than the control group. Therefore, prophylactic use of phenylephrine or ephedrine could be effective for neonatal condition and outcome, possibly due to improved control of maternal blood pressure and utero-placental perfusion.

6. Conclusion

We conclude from this study that phenylephrine 80μg had similar vasopressor efficacy to ephedrine 10 mg for preventing or treating maternal hypotension during spinal anesthesia for elective cesarean delivery and there was no difference in clinical neonatal outcome as measured by Apgar

scores. The clinical significance of bradycardia, reactive hypertension and intraoperative nausea and vomiting should not be overlooked. Phenylephrine administration prior to spinal anesthesia is superior to ephedrine in reducing reactive hypertention, nausea, vomiting and the requirement of vasopressors rescue medication. The results of the present study support the use of phenylephrine for maintenance of maternal arterial pressure during spinal anesthesia for elective cesarean section.

7. Nurse anesthetic implications

Phenylephrine 80μg had similar vasopressor efficacy to ephedrine 10 mg for preventing or treating maternal hypotension during spinal anesthesia for elective caesarean delivery and there was no difference in clinical neonatal outcome as measured by Apgar scores. In view of maternal complications, the most important and noticeable complication was brief bradycardia (reflex bradycardia), which was transient and only in a few cases (HR<60 per minute) that needed treatment with 0.5 mg of intravenous Atropine. Nausea and vomiting that responded rapidly to antiemetic medication was slightly high in the ephedrine group. None of the observed complications were serious enough to have a significant impact on either the mothers or newborns, as indicated by the use of the Apgar Score.

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Annexes

Appendix 1

Consent Form

موافقة للإشتراك في البحث العلمي

إسم الباحث: قصي سامي احمد عصبة – طالبماجستير تمريض تخدير . جامعة النجاح الوطنية

د أيسر نصر البرغوثي – اخصائي طب تخدير, استاذ مساعد سريريا – جامعة النجاح الوطنية .

المشرف على البحث : د. عائدة القيسي . عميد كلية التمريض و منسق برنامج ماجستير تمريض التخدير . جامعة النجاح .

عنوان البحث:علاج هبوط الضغط الدموي نتيجة التخدير النصفي (تحت الجافية) للعمليات القيصرية

ايتها السيدة الفاضلة :

أنت مدعو(ة) للمشاركة ببحث علمي سريري . الرجاء أن تأخذي الوقت الكافي لقراءة المعلومات التالية بتأن قبل أن تقرري إذا كنت تريدين المشاركة أم لا. بإمكانك طلب إيضاحات أو معلومات إضافية عن أي شيء مذكور في هذه الإستمارة أو عن هذه الدراسة ككل من الباحث .

يتم عمل التخدير النصفي باستخدام ابرة تحت الجافية بقياس 27 و حقن ادوية التخدير الموضعي بعد حقن دواء افيدرين او فينل افرين في الوريد ولا تاثيرات سلبية حيث ان هذه الطريقة يتم استخدامها دائما .

الهدف من البحث :تجنب مضاعفات التخدير النصفي واهمها وقاية هبوط الضغط الدموي و مضاعفاته للام .

في حال وافقت على المشاركة في هذه الدراسة، سيبقى إسمك طي الكتمان . لن يكون لأي شخص، ما لم ينص القانون على ذلك، حق الإطلاع على ملفك الطبي باستثناء الباحث و الطبيب المسؤول عن الدراسة و مشرف الدراسة من جامعة النجاح الوطنية .

<u>موافقة الباحث:</u>

لقد شرحت بالتفصيل للمشترك في البحث الطبي ل_____ طبيعته ومجرياته وتأثيراته السلبية. ولقد أجبت على كل أسئلته بوضوح على خير ما أستطيع .

الباحث : **الطبيب :**

موافقة المشترك:

لقد قرأت استمارة القبول هذه وفهمت مضمونها. تمت الأجابة على أسئلتي جميعها. وبناء عليه فأنني، حرا مختارا، أجيز إجراء هذا البحث و أوافق على الإشتراك فيه، وإني أعلم ان الباحث و الدكتور سيكونون مستعدين للإجابة على أسئلتي، وأنه باستطاعتي الإتصال بهم على الهاتف 0569486582 . واذا شعرت لاحقا ان الأجوبة تحتاج الى مزيد من الإيضاحفسوف اتصلبهم في اي وقت . كما أعرف تمام المعرفة بانني حر في الإنسحاب من هذا البحث متى شئت حتى بعد التوقيع على الموافقة دون ان يؤثر ذلك على العناية الطبية المقدمة لي. أعلم أني سوف أحصل على نسخة طبق الأصل عن هذه الموافقة.

اسم المشتركة في البحث :

التوقيع :

التاريخ :

Appendix 2

Ephedrine versus phenylephrine study – Data Sheet

Patient name: drug: A or B age : weight :

Hight:

Residency: education: BMI:

Parameter	Yes	No	Frequency	At 0 minute	At 5 minutes
Gestational age					
Bp – pre spinal anesthesia–reference value					
Heart rate pre–spinal anesthesia Reference value					
SpO2 pre spinal anesthesia, reference value					
No. of trials Spinal needle insertion					
Level of the block					
Headache					
Shivering					
Nausea Lickert type scale 0–6 (o no nausea, 6 untolerable					
Vomiting Frequency					
Restlessness					
Arrhythmias ,type					
Reactive hypertension					
Back pain (VAS) 0–10 0 no pain 10 untolerable					
Pain at the surgical incision (VAS) 0–10					
Atropine needed in mg					

Time from spinal puncture to skin incision in minute					
Time to uterine incision In minute					
Time to delivery of the fetus in minute					
Dose of ephedrine 10mg time in min					
Dose of phenylephrine 80μg, time in min					
Rescue dose of ephedrine 5 mg					
Rescue dose of phenylephrine 40μg					
Apgar scores on the first minute of all newborns					
Apgar scores on the fifth minutes of all newborns					

Appendix 3

Ephedrine versus phenylephrine study vital signs and spo2:

Patient name:

Pre op V/S: **BP**: **HR:** **RR:** **SPO_2:** **ECG:**

V/S after drug Administration					
Time	**BP**	**HR**	**RR**	**SPO_2**	**ECG**
Immediate					
3 min					
6 min					
9 min					
12 min					
15 min					
18 min					
21 min					
24 min					
27 min					
30 min					
35 min					
40 min					
45 min					

Post op					
Time	**BP**	**HR**	**RR**	**SPO_2**	**ECG**
Immediate post op					
15 min					
30 min					
45 min					
60 min					
2 hrs					
4 hrs					

Appendix 4

ASA physical status classification system for assessing a patient before surgery.

I. Normal healthy patient .

II. Patient with mild systemic disease .

III. Patient with severe systemic disease .

IV. Patient with severe systemic that is a constant threat to life .

V. Moribund patient who is not expected to survive without the operation .

VI. Patient declared brain dead whose organs are to be harvested for donor purposes .

Appendix 5

Approval of Faculty of Graduate Studies on the topic of the thesis

An-Najah
National University
Faculty of Graduate Studies
Dean's Office

جامعة
النجـــاح الوطنية
كلية الدراسات العليا
مكتب العميد

التاريخ : 2015/10/7

حضرة الدكتورة عائدة القيسي المحترمة
منسقة برنامج ماجستير تمريض التخدير

تحية طيبة وبعد،

الموضوع : الموافقة على عنوان الاطروحة وتحديد المشرف

قرر مجلس كلية الدراسات العليا في جلسته رقم (ملحق 296)، المنعقدة بتاريخ 2015/10/1، الموافقة على مشروع الأطروحة المقدم من الطالب/ قصي سامي احمد عصبة، رقم التسجيل 11356630، تخصص تمريض التخدير، عنوان الأطروحة:

(الاستعمال الوقائي للافدرين مقارنة بالفينيل افرين لتجنب هبوط الضغط الدموي للأم أثناء العمليات القيصرية التي تجرى بالتخدير النصفي)

(Prophylactic Ephedrine Versus Phenylephrine for Preventing Maternal Hypotension in Women Undergoing Spinal Anesthesia for Cesarean Section)

بإشراف: 1- د. عائدة القيسي 2- د. ايسر البرغوثي

تمت الموافقة على ان يقوم الطالب باستبدال كلمة "Patients" بكلمة "Women" في العنوان.

يرجى اعلام المشرف والطالب بضرورة تسجيل الاطروحة خلال اسبوعين من تاريخ اصدار الكتاب. وفي حال عدم تسجيل الطالب/ة للاطروحة في الفترة المحددة له/ا ستقوم كلية الدراسات العليا بالغاء اعتماد العنوان والمشرف.

وتفضلوا بقبول وافر الاحترام ،،،

صادر
جامعة النجاح الوطنية
كلية الدراسات العليا
8. 10. 2015
الرقم المتسلسل

عميد كلية الدراسات العليا
د. احمد الرمحي

نسخة : د. رئيس قسم الدراسات العليا للعلوم الطبية والصحية المحترم
: ق.أ.ع. القبول والتسجيل المحترم
: مشرف الطالب

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* Facsimile 972 92342907 *www.najah.edu - email fgs@najah.edu

Appendix 6
Approval of the Palestine Medical Complex on the study.

14.SEP.2007 16:58 #3715 P.001 /002

بسم الله الرحمن الرحيم

An- Najah National University
Faculty of Medicine & Health Sciences
Department of Nursing

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
دائرة التمريض

التاريخ: 05-04-2015

حضرة الدكتور أحمد البيتاوي المحترم / المدير الطبي لمجمع فلسطين الطبي،،

تحية طيبة وبعد،

تهديكم دائرة التمريض والقبالة في كلية الطب وعلوم الصحه/ جامعة النجاح الوطنية أجمل التحيات ونشكر لكم حسن تعاونكم المستمر معنا، أرجو من حضرتكم التكرم بالموافقة للطالب قصي عصبه باجراء الدراسة البحثيه حيث أنه يدرس ماجستير تمريض التخدير وكمتطلب للتخرج يجب ان ينهي رسالة الماجستير تحت عنوان:

Prophylactic ephedrine versus phenylephrine for maternal hypotension in patients undergoing spinal anaesthesia for caesarean section.

لذا أرجو التكرم بالموافقة للطالب والابعاز إلى رئيس قسم التخدير الدكتور محمد العاجز بالسماح للطالب باجراء دراسته.

وتفضلو بقبول وافر الاحترام والتقدير ، ،

مدررة دائرة التمريض والقبالة

منسقة برنامج ماجستير تمريض التخدير

د. عائدة القيسي

مديرة دائرة التمريض والقبالة
في كلية الطب وعلوم الصحة
د. عائدة أبو السعود القيسي

مرضى صح IRB

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
دائرة التمريض والقبالة

State of Palestine, Palestine Medical Complex

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Appendix 7

The approval of the Palestinian Red Crescent hospital to conduct the study

14.SEP.2007 16:55 #3713 P.002 /002

بسم الله الرحمن الرحيم

An - Najah
National University
Faculty of Medicine & Health Sciences
Department of Graduate Studies

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
دائرة الدراسات العليا

IRB Approval letter

Study title:
Prophylactic ephedrine versus phenylephrine for maternal hypotension in patients undergoing spinal anesthesia for caesarean section .

Submitted by:
Qussai S A Ussbah
Dr . Aisar Albargoti
Dr . Aidah Alkaissi

Date Reviewed:
Fe 8,2015

Date approved:
April 1, 2015

Your study titled: "Prophylactic ephedrine versus phenylephrine for maternal hypotension in patients undergoing spinal anesthesia for caesarean section " with archived number 8/Feb/2015 , Was reviewed by An-Najah National University IRB committee & approved on April 1, 2015 .

Hasan Fitian , MD

IRB Committee Chairman
An-Najah National University

نابلس – ص.ب 7 او 707 هاتف 14/8/7/4/2902342(09)(970) ، فاكسميل 2342910 (09) (970)
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Appendix 8

The approvalLetter

#3713 P.001 /002

بسم الله الرحمن الرحيم

An- Najah
National University
Faculty of Medicine & Health Sciences
Department of Nursing

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
دائرة التمريض

التاريخ: 05-04-2015

حضرة الدكتور عوده أبو نخله المحترم / المدير الطبي لمستشفى الهلال الاحمر الفلسطيني

تحية طيبة وبعد،

تهديكم دائرة التمريض والقبالة في كلية الطب وعلوم الصحه/ جامعة النجاح الوطنية أجمل التحيات ونشكر لكم حسن تعاونكم المستمر معنا، أرجو من حضرتكم التكرم بالموافقه للطالب قصي عصبه باجراء الدراسة البحثيه حيث أنه يدرس ماجستير تمريض التخدير وكمتطلب للتخرج يجب ان ينهي رسالة الماجستير تحت عنوان:

Prophylactic ephedrine versus phenylephrine for maternal hypotension in patients undergoing spinal anaesthesia for caesarean section.

لذا أرجو التكرم بالموافقه للطالب والايعاز إلى رئيس قسم التخدير الدكتور مهدي ملحس بالسماح للطالب باجراء دراسته.

وتفضلو بقبول وافر الاحترام والتقدير ،،

مديرة دائرة التمريض والقبالة

منسقة برنامج ماجستير تمريض التخدير

د. عائدة القيسي

مرفق صلي IRB

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
دائرة التمريض والقبالة

مديرة دائرة التمريض والقبالة
في كلية الطب وعلوم الصحة
د. عائدة أبو السعود القيسي

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Appendix 9

Table for determining sample size for analysis of variance

Justification of sample size:

It is necessary to ensure that the sample sizes are large enough to detect important differences with high probability in both observational and experimental studies. At the same time, the sample sizes should not be so large that the cost of the study becomes excessive and that unimportant differences become statistically significant with high probability. Planning of sample size is therefore an integral part of the design of a study. In this research, we considered the planning of sample sizes with the power approach, which permits controlling the risks of making type I and type II errors. The power approach in planning sample sizes can be implemented by use of the power tables presented in Appendix 9.This table only requires a specification of the minimum range of factor level means for which it is important to detect differences between means with high probability.

The following three specifications need to be made in using Table B12 (Appendix 8):

1) The level α at which the risk of making a type I error is to be controlled, which is 0.05 in our case.

2) The magnitude of the minimum range of the factor level means divided by the standard deviation of the probability distribution of the dependent variable; this ratio (Δ) will be, to the extent possible, equal to 1.

3) The level 1 at which the risk of making a type II error is to be controlled, which is 0.85 in our case.

When using Table B12 for $\alpha = 0.05$, $1-\beta=0.80$, and $\Delta=1$, the table will provide the sample size of 17 for r=2(the number of treatments or groups under study), and the table will provide the sample size = 23 when $1-\beta=0.90$ for r=2, so the necessary sample size for our study will be 20, which means that we shall take at the minimum 20 participants for each group (Kunter, 2005).

TABLE B.12 Table for Determining Sample Size for Analysis of Variance (fixed factor levels model).

Power $1 - \beta = .70$

	$\Delta/\sigma = 1.0$				$\Delta/\sigma = 1.25$				$\Delta/\sigma = 1.50$				$\Delta/\sigma = 1.75$				$\Delta/\sigma = 2.0$				$\Delta/\sigma = 2.5$				$\Delta/\sigma = 3.0$			
	α				α				α				α				α				α				α			
r	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01
2	7	11	14	21	5	7	9	15	4	6	7	11	3	4	6	9	3	4	5	7	2	3	4	5	2	3	3	5
3	9	13	17	25	6	9	11	17	5	7	8	12	4	5	7	10	3	4	5	8	3	3	4	6	2	3	3	5
4	11	15	19	28	7	10	13	19	5	7	9	13	4	6	7	10	4	5	6	8	3	4	4	6	2	3	4	5
5	12	17	21	30	8	11	14	20	6	8	10	14	5	6	8	11	4	5	6	9	3	4	5	6	3	3	4	5
6	13	18	22	32	9	12	15	21	6	9	11	15	5	7	8	12	4	5	7	9	3	4	5	7	3	3	4	5
7	14	19	24	34	9	13	16	22	7	9	11	16	5	7	9	12	4	6	7	10	3	4	5	7	3	3	4	5
8	15	20	25	35	10	13	16	23	7	10	12	17	6	7	9	13	5	6	7	10	3	4	5	7	3	3	4	5
9	15	21	26	37	10	14	17	24	7	10	12	17	6	8	9	13	5	6	8	10	3	4	5	7	3	4	4	6
10	16	22	27	38	11	14	18	25	8	10	13	18	6	8	10	14	5	6	8	11	4	5	6	7	3	4	4	6

Power $1 - \beta = .80$

	$\Delta/\sigma = 1.0$				$\Delta/\sigma = 1.25$				$\Delta/\sigma = 1.50$				$\Delta/\sigma = 1.75$				$\Delta/\sigma = 2.0$				$\Delta/\sigma = 2.5$				$\Delta/\sigma = 3.0$			
	α				α				α				α				α				α				α			
r	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01
2	10	14	17	26	7	9	12	17	5	7	9	13	4	5	7	10	3	4	6	8	3	3	4	6	2	3	4	5
3	12	17	21	30	8	11	14	20	6	8	10	14	5	6	8	11	4	5	6	9	3	4	5	7	3	3	4	5
4	14	19	23	33	9	13	15	22	7	9	11	16	5	7	9	12	4	6	7	10	3	4	5	7	3	3	4	5
5	16	21	25	35	10	14	17	23	8	10	12	17	6	8	9	13	5	6	7	10	4	4	5	7	3	4	4	6
6	17	22	27	38	11	15	18	25	8	11	13	18	6	8	10	13	5	7	8	11	4	5	6	8	3	4	4	6
7	18	24	29	39	12	16	19	26	9	11	14	18	7	9	10	14	5	7	8	11	4	5	6	8	3	4	5	6
8	19	25	30	41	12	16	20	27	9	12	14	19	7	9	11	15	6	7	9	12	4	5	6	8	3	4	5	6
9	20	26	31	43	13	17	21	28	9	12	15	20	7	9	11	15	6	7	9	12	4	5	6	8	3	4	5	6
10	21	27	33	44	14	18	21	29	10	13	15	21	8	10	12	16	6	8	9	12	4	5	6	8	3	4	5	6

TABLE B.12 (*concluded*) Table for Determining Sample Size for Analysis of Variance (fixed factor levels model).

Power $1 - \beta = .90$

	$\Delta/\sigma = 1.0$				$\Delta/\sigma = 1.25$				$\Delta/\sigma = 1.50$				$\Delta/\sigma = 1.75$				$\Delta/\sigma = 2.0$				$\Delta/\sigma = 2.5$				$\Delta/\sigma = 3.0$			
	α				α				α				α				α				α				α			
r	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01
2	14	18	23	32	9	12	15	21	7	9	11	15	5	7	8	12	4	6	7	10	3	4	5	7	3	3	4	6
3	17	22	27	37	11	15	18	24	8	11	13	18	6	8	10	13	5	7	8	11	4	5	6	8	3	4	5	6
4	20	25	30	40	13	16	20	27	9	12	14	19	7	9	11	15	6	7	9	12	4	5	6	8	3	4	5	6
5	21	27	32	43	14	18	21	28	10	13	15	20	8	10	12	15	6	8	9	12	4	5	6	9	4	4	5	7
6	22	29	34	46	15	19	23	30	11	14	16	21	8	10	12	16	7	8	10	13	5	6	7	9	4	4	5	7
7	24	31	36	48	16	20	24	31	11	14	17	22	9	11	13	17	7	9	10	13	5	6	7	9	4	5	5	7
8	26	32	38	50	17	21	25	33	12	15	18	23	9	11	13	17	7	9	11	14	5	6	7	9	4	5	6	7
9	27	33	40	52	17	22	26	34	13	16	18	24	9	12	14	18	8	9	11	14	5	6	8	10	4	5	6	7
10	28	35	41	54	18	23	27	35	13	16	19	25	10	12	14	19	8	10	11	15	5	7	8	10	4	5	6	7

Power $1 - \beta = .95$

	$\Delta/\sigma = 1.0$				$\Delta/\sigma = 1.25$				$\Delta/\sigma = 1.50$				$\Delta/\sigma = 1.75$				$\Delta/\sigma = 2.0$				$\Delta/\sigma = 2.5$				$\Delta/\sigma = 3.0$			
	α				α				α				α				α				α				α			
r	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01	.2	.1	.05	.01
2	18	23	27	38	12	15	18	25	9	11	13	18	7	8	10	14	5	7	8	11	4	5	6	8	3	4	5	6
3	22	27	32	43	14	18	21	29	10	13	15	20	8	10	12	16	6	8	9	12	5	6	7	9	4	4	5	7
4	25	30	36	47	16	20	23	31	12	14	17	22	9	11	13	17	7	9	10	13	5	6	7	9	4	5	5	7
5	27	33	39	51	18	22	25	33	13	15	18	23	10	12	14	18	8	9	11	14	5	6	7	10	4	5	6	7
6	29	35	41	53	19	23	27	35	13	16	19	25	10	12	14	19	8	10	11	15	6	7	8	10	4	5	6	8
7	30	37	43	56	20	24	28	36	14	17	20	26	11	13	15	19	8	10	12	15	6	7	8	10	4	5	6	8
8	32	39	45	58	21	25	29	38	15	18	21	27	11	14	16	20	9	11	12	16	6	7	8	11	5	5	6	8
9	33	40	47	60	22	26	30	39	15	19	22	28	12	14	16	21	9	11	13	16	6	8	9	11	5	6	6	8
10	34	42	48	62	22	27	31	40	16	19	22	29	12	15	17	21	9	11	13	17	6	8	9	11	5	6	7	8

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Appendix 10

Distribution of births in the hospitals of the Ministry of Health according to the type of birth and the hospital in 2014

جدول (138) توزيع الولادات في مستشفيات وزارة الصحة حسب نوع الولادة والمستشفى والمنطقة ، فلسطين، 2014

Annex (138) Distribution of Deliveries in MOH Hospitals by Type of Delivery & Hospital & Region, Palestine, 2014

Hospital	Caesarian قيصرية	Normal طبيعية	Total المجموع	% of C.S	المستشفى
West Bank	8,202	26,416	34,618	23.7	الضفة الغربية
Jenin (Khalil Suliman)	1,498	4,118	5,616	26.7	جنين (خليل سليمان)
Tubas Turkey	29	155	184	15.8	طوباس
Tulkarm (Thabi Thabit)	792	1,714	2,506	31.6	طولكرم (ثابت ثابت)
Rafidia\ Nablus	1,724	4,442	6,166	28.0	رفيديا/ نابلس
Qalqiliya (Darwesh Nazal)	320	1,035	1,355	23.6	قلقيلية (درويش نزال)
Salfit (Yasser Arafat)	335	1,027	1,362	24.6	سلفيت (ياسر عرفات)
Ramallah's Sons Ward	1,441	3,349	4,790	30.1	جناح أبناء رام الله
Jerico	211	744	955	22.1	أريحا
Beit Jala (Al Husein)	399	1,555	1,954	20.4	بيت جالا (الحسين)
Hebron (Alia)	967	5,831	6,798	14.2	الخليل (عالية)
Yatta (Abu Alhasan Al Kassem)	486	2,446	2,932	16.6	يطا (ابو الحسن القاسم)
Gaza Strip	8,635	31,847	40,482	21.3	قطاع غزة
Shifa	4,246	13,051	17,297	24.5	الشفاء
Nasser	2,012	8,382	10,394	19.4	ناصر
Tal El Sultan	1,182	5,405	6,587	17.9	تل السلطان
El Aqssa	1,195	5,009	6,204	19.3	الأقصى
Palestine	16,837	58,263	75,100	22.4	فلسطين

Appendix 11

Distribution of births in the non-governmental hospitals in 2014

جدول (143) معطيات مستشفيات التوليد غير الحكومية، حسب المستشفى، الضفة الغربية، فلسطين، 2014

Annex (143) Non Governmental Maternity Hospitals Utilization by Hospital, West Bank, Palestine, 2014

Hospital	عدد الأسرة No. of Beds	عدد المرضى No. of Patien		معالجون بدون إقامة Treat. without Hospitalization	المواليد Births	العمليات Operations	المستشفى
		الإخراجات Discharges	الإدخالات Admissions				
Shepherrds Field\ Bethlehem	15	1,180	1,180	20,529	578	578	حقل الرعاة/ بيت لحم
Dibs\ Bethlehem	10	376	376		391	25	الديس/ بيت لحم
Naser\ Yatta	14	580	580	3,690	484	99	ناصر/ يطا
PRCS\ Tulkarm	10	1,535	1,535	1,176	711	934	الهلال الأحمر/ طولكرم
Walid El Nazer\ Ramallah	10	441	441		330	111	وليد الناظر/ رام الله
Holy Family\ Bethlehem	60	4,654	4,914	22,262	3,391	566	العائلة المقدسة/ بيت لحم
Shahirah\ Hebron	10	1,092	1,092		1,062	268	شهيرة/ الخليل
Al Mustaqbal\ Ramallah	30	1,974	1,974	6,480	401	1,154	المستقبل/ رام الله
Al Amal\ Jenin	20	2,348	2,348		859	1,494	الأمل/ جنين
Bani Na'em\ Hebron	10	404	404	784	405	15	بني نعيم/ الخليل
Total	189	14,584	14,844	54,921	8,612	5,244	المجموع

جامعة النجاح الوطنية
كلية الدراسات العليا

الاستعمال الوقائي للأفدرين مقارنة بالفينيل افرين لتجنب هبوط الضغط الدموي للام أثناء العمليات القيصرية التي تجرى بالتخدير النصفي

إعداد
قصي عصبي

إشراف
د.عائدة القيسي
د.أيسر البرغوثي

قدمت هذه الأطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في تمريض التخدير، بكلية الدراسات العليا، في جامعة النجاح الوطنية، في نابلس –فلسطين .

2016

الاستعمال الوقائي للأفدرين مقارنة بالفينيل افرين لتجنب هبوط الضغط الدموي للام أثناء العمليات القيصرية التي تجرى بالتخدير النصفي

إعداد

قصي عصبي

إشراف

د.عائدة القيسي

د.أيسر البرغوثي

الملخص

مقدمه :

هبوط الضغط الدموي بعد التخدير النصفي للعمليات القيصرية يكون ثانويا للحصار الودي والضغط على الشريان الابهري من رحم الام الحامل،ويكون مؤذيا للام الحامل وايضا للجنين.لذلك ادويه رافعات الضغط الدموي الافدرينوالفينيل افرين تحافظ على كمية الدم العائد من الاطراف الى القلب بعد الحصار الودي اثناء التخدير النصفي .

هدف الدراسة:

هدف الدراسة الحديثة هو مقارنه الفعالية الدوائية بين الافدرينوالفينيل افرين في حماية وعلاج هبوط الضغط الدموي للأمهات الحوامل أثناء التخدير النصفي.تقييم ألاثار الجانبية للافدرينوالفينيل افرين وكذلك تقييم التغيرات على الجنين باستخدام فحص أبغار .

تصميم الدراسة وطريقتها والمشاركات فيها :

ستون ام حامل،درجة اولى وثانية حسب تصنيف جمعية أطباء التخدير الامريكية،يخضعن للتخدير النصفي بحقندواء الببفاكائين والفينتانيل معا تحت الجافية للعمليات القيصرية تم اختيارهن عشوا ئيا وقسمن الى مجموعتين لاعطائهن جرعة وقائية من الافدرين (عدد:27 بجرعة 10 ملغم) أو فينيل افرين (عدد :28 بجرعة 80 مايكروغرام).

معدل العمر لمجموعة الافدرين 30.48±5.5 مقابل مجموعة ألفينيل افرين 31.64±3.3 .تم تعريف هبوط الضغط الدموي (هبوط الضغط الدموي يساوي أو اقل من 20% عن المستوى

الاساسي.وعولج باعطاء جرعة دوائية من رافعات الضغط الدموي بنسبة 50% من الجرعة الاولية .الضغط الدموي الشرياني للام الحامل وعدد دقات القلب تم قياسها كل 3 دقائق بجهاز قياس الضغط الاوتوماتيكي، اعطيت المشاركات سوائل وريدية رينجر لاكتيت بجرعة عشرون سنتمر مكعب لكل كيلو غرام قبل ثلاثون دقيقة من عمل التخدير تحت الجافية .العلامات الحيوية (ضغط الدم الشرياني / دقات القلب /نسبة اشباع ألاكسجين بالدم) تم تسجيلها أثناء كل عملية، ألمضاعفات للام والجنين أثناء العملية أيضا قد تم تسجيلها، مدى هبوط ضغط الدم الشرياني / ارتفاع ضغط الدم الشرياني التفاعلي / تباطؤ وتسارع دقات القلب / الغثيان و التقيؤ/ فحص أبغار للدقيقة الأولى والخامسة ايضا تم تقييمها وتسجيلها .

النتائج :

أظهرت الدراسة انه لا فرق في المعلومات الجغرافية بين المجموعتين ،معدل جرعة ألافدرين ألتي استخدمت كانت 19.81±5.46 و الفينيل افرين كانت 125.71±35.64 مايكروغرام .تغيرات الضغط الدموي الشرياني تم مقارنتها بين المجموعتين حيث كانت عدد مرات ارتفاع الضغط الدموي التفاعلي بها فرق واضح (مجموعة الافدرين 48(14.5%) و مجموعة ألفينيل افرين 26(7.7 %) p<0.005. لا فرق بين ألدوائين في تباطؤ دقات ألقلب حيث أن مجموعة الافدرين 3(11.1%) مقابله مجموعة ألفينيل افرين 6(21.4 %) على p>0.301 .كذلك كان فرقا واضحا في معدل التقيؤ والغثيان (مجموعة الافدرين: 10(37%) مقابله الفينيل افرين 3(10.7%) ,0.018> .لا فرق أيضا في معدل هبوط الضغط الدموي الشرياني 18(66.7%) لمجموعة ألافدرينو17(60.7) لمجموعة الفينيل افرين علىp<0.646 .عدم انتظام دقات القلب للامهات ظهرت أكثر في مجموعة ألافدرين 10(37%) من الفينيل افرين 7(25%) لكن قيمة p =0.334. عدم الارتياح للام كانت اكثر في مجموعة الافدرين وعددها 8(30.8%) بينما في مجموعة الفينيل افرين 3(10.7%). ايضا انه لا تغيرات في فحص أبغار على الدقيقة الاولى والخامسة .

كذلك اظهرت نتائج الدراسة ان عدد ألامهات اللواتي احتجن الى جرعة تدعيم من الافدرين 24(88.9%) بينما مجموعة الفينيل افرين 20(71.4%) وذلك كان جليا وواضحا على p =0.005. ويظهر ايضا بوضوح في عدد الجرعات التدعيمية للدوائين حيث كان لمجموعة

الفينيلافرين ام واحدة فقط(3.6%) اطيت جرعة ثالثة وفي مجموعة الافدرين كانت9(33.3%) اعطين الجرعة الثالثة p=0.033 .

الخلاصة :

نستنتج من الدراسة ان 80 مايكروغرام من الفينيل افرين تمتلك فعالية 10 ملغرامات من الافدرين في حماية وعلاج هبوط الضغط الدموي الشرياني للامهات الحوامل أثناء التخدير النصفي للعمليات القيصرية المبرمجة ولا تأثيرا سريريا على الجنين باستخدام فحص أبغار.وهذه الدراسة لا تدعم ما هو متعارف عليه بأن دواء الافدرين أفضل خيارا من الفينيل افرين في علاج هبوط الضغط الدموي الشريانياثناء العمليات القيصرية المبرمجة. والاعراض الجانبية كتباطؤ دقات القلب /ارتفاع الضغط الدموي /التقيؤ والغثيان اثناء العملية لا يتم النظر اليها .

اعطاء جرعة فينيل افرين تزامنا معالتخدير النصفي افضل من الافدرينفي تقليل ارتفاع الضغط الدموي الشرياني التفاعلي،التقيؤ،الغثيان، و عدد الجرعات التدعيمية.

نتائج الدراسة الحديثة تدعم نظرية استخدام الفينيل افرين في الحفاظ على الضغط الدموي الشرياني للامهات الحوامل اثناء التخدير النصفي للعمليات القيصرية المبرمجة

توصيات تمريض التخدير :

استخدام 80 مايكروغرام من الفينيلافرين تمتلك فعالية دوائية 10 ملغرامات من الافدرين في وقاية وعلاج هبوط الضغط الدموي للامهات الحوامل اثناء العمليات القيصرية المبرمجة ولا فرق بينهما تاثيرا على الجنين باستخدام فحص أبغار. المضاعفات المهمة جدا التي قد تحدث مثل كتباطؤ دقات القلب اللااردية العابرة في عدد قليل من الحالات (دقات القلب اقل من 60 لكل دقيقة) يتم علاجها باستخدام دواء الاتروبين 0.5 ملغرام وريديا. الغثيان والتقيؤ تستجيب للعلاج لمضادات التقيؤ التي كانت أكثر مع الافدرين. ولم يكن هناك مضاعفات خطيرة على الام والجنين. حيث استخدم فحص أبغارللجنين .

الكلمات المفتاحية: فينيليفرين، الايفيدرين، التخدير الشوكي، هبوط ضغط الأمهات، عملية قيصرية.