Norepinephrine versus Ephedrine Boluses To Treat Spinal-Induced Hypotension in Cesarean Deliveries

Thesis

Submitted for partial fulfillment of the Master Degree in Anesthesiology

By

Mohamed Mohamed Salah El-Din Abo Kamar
M.B., B.Ch. Ain Shams University

Under supervision of

Prof. Dr. Manal Mohamed Kamal Shams
Professor of Anesthesiology, Intensive Care & Pain Management
Faculty of Medicine – Ain Shams University

Dr. Mai Mohsen AbdelAziz
Lecturer of Intensive Care & Pain Management
Faculty of Medicine – Ain Shams University

Dr. Wessam Zaher Selima
Lecturer of Intensive Care & Pain Management
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2019

List of Contents

Title Page No.

List of Tables i

List of Figures ii

Introduction 1

Aim of the Work 4

Review of literature

- **Chapter 1**: Maternal and Fetal Physiology 5
- **Chapter 2:** Spinal Anesthesia in Cesarean Section and Possible Complications 25
- **Chapter 3:** Ephedrine Pharmacological Considerations 36
- **Chapter 4:** Norepinephrine Pharmacological Considerations 44

Patients and Methods 50

Results 55

Discussion 63

Summary 71

Conclusion 74

Reference 75

Arabic summary .....--

List of Tables

Table No.	Title	Page No.
Table (1):	Changes in cardiorespiratory variables with pregnancy, ...	10
Table (2):	Characteristics of fetal development	18
Table (3):	Fetal Functional Development	22
Table (4):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to demographic data.	55
Table (5):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to Surgical time (min), Induction to skin incision (min) and Skin incision to fetal delivery (min).	55
Table (6):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to mean arterial blood pressure.....	56
Table (7):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to heart rate.	57
Table (8):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to number of boluses of vasopressor used.	58
Table (9):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to number of boluses of vasopressors used.	59
Table (10):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to maternal hemodynamic.	60
Table (11):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to maternal complications during the operation.	61
Table (12):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to fetal Apgar score variation.....	62

List of Figures

Figure No.	Title	Page No.
Figure (1):	Fetal circulation	20
Figure (2):	Chemical structure of Ephedrine	36
Figure (3):	Chemical structure of Norepinephrine	44
Figure (4):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to mean arterial blood pressure.	56
Figure (5):	Comparison between group A: Norepinephrine and Group B: Ephedrine according to heart rate.	57
Figure (6):	Bar chart between group A: Norepinephrine and Group B: Ephedrine according to number of boluses of vasopressor used.	58
Figure (7):	Bar chart between group A: Norepinephrine and Group B: Ephedrine according to number of boluses of vasopressors used.	59
Figure (8):	Bar chart between group A: Norepinephrine and Group B: Ephedrine according to maternal hemodynamic.	60
Figure (9):	Bar chart between group A: Norepinephrine and Group B: Ephedrine according to maternal complications during the operation.	61
Figure (10):	Bar chart between group A: Norepinephrine and Group B: Ephedrine according to fetal Apgar score variation.	62

INTRODUCTION

Spinal anesthesia is the preferred method for elective cesarean sections. Cesarean sections normally require an anesthetic block at T4 level, so hypotension is reported to occur in up to 80% of spinal anesthesia cases ***(Hoyme et al., 2015)***.

There is no widely accepted definition of intraoperative hypotension, resulting in different incidences being reported across studies. Many measurements could be analyzed, such as a decrease in SBP or mean arterial pressure (MAP) under a threshold, variation from baseline, combination of parameters, duration of hypotension. In this study we will define hypotension as 20% decrease of MAP from the base line ***(Zwane et al., 2019).***

When maternal hypotension associated with spinal anesthesia for cesarean section is severe and sustained, it can lead to serious maternal complications as well as impairment of the uterine and placental blood flow with consecutive fetal hypoxia, acidosis, and neurological injury ***(Cyna et al., 2006)***. Many approaches have been investigated to prevent spinal hypotension, e.g., fluid loading, vasopressors, or both

(Loubert, 2012). Intravenous fluid protocols have been investigated in many trials to prevent spinal hypotension, but the clinical results were not satisfactory. With this in mind, investigators have turned their attention to vasopressor protocols to prevent spinal hypotension ***(Hasanin et al., 2017)***.

Conventionally, ephedrine was regarded as the first-choice drug to maintain maternal blood pressure ***(Turkoz et al., 2002)***. Its sympathomimetic stimulant activity on α- and β-adrenergic receptors causes positive inotropic and chronotropic effects on the heart and maintains uterine blood flow. However, repeated administration of ephedrine diminishes its vasoconstrictive effect, and its slow onset of action and relatively long duration make accurate titration of blood pressure difficult. Due to ephedrine's slow onset of action, fetal tachycardia may appear rather unexpectedly. If tachycardia appears in concurrence with a preexisting oxygen deficit, it may lead to acidosis ***(Ngan-Kee et al., 2015)***.

Norepinephrine is a weak β-adrenergic and potent α-adrenergic receptor agonist. Therefore, it may be a more suitable option for maintaining maternal blood pressure with

less negative effects on heart rate (HR) and cardiac output ***(Ngan-Kee et al., 2015)***.

One of the main concerns in using α-agonists is a decrease in uteroplacental blood flow. Several studies reported that norepinephrine had no effect on fetal arterial perfusion pressure, and the fetoplacental microcirculation was not compromised ***(Minzter et al., 2010).***

There is limited information available for the use of norepinephrine boluses for the treatment of hypotension during spinal anesthesia in the literature and there are few reports of its use as bolus doses in obstetric patients ***(Ngan-Kee et al., 2015)***.

We hypothesized that using norepinephrine bolus dose 5 μg to raise maternal blood pressure during spinal anesthesia for cesarean delivery provides better hemodynamic stability with subsequent better maternal and neonatal outcomes compared to ephedrine.

AIM OF THE WORK

The aims of this study were to compare the efficacy of bolus norepinephrine and ephedrine regarding the treatment of the decrease of Mean arterial pressure, the number of vasopressor boluses required and number of hypotension episodes following spinal anesthesia in cesarean deliveries.

Secondary objectives included the incidence of tachycardia, bradycardia, and hypertension, maternal side effects, including nausea, vomiting, dizziness and shivering; and neonatal outcome regarding Apgar scores at one minute and five minutes.

Chapter (1)

Maternal and Fetal Physiology

Pregnancy causes anatomical and physiological changes that have implications for the anesthetist not only for intrapartum management but also when surgery is required incidentally to pregnancy. These adaptations primarily occur, so that the metabolic demands of the growing fetus may be met.

1- Cardiovascular

Physiological changes occur very early in pregnancy, leading to an overall hyperdynamic circulation. These early hormonal effects lead to the primary event of peripheral vasodilatation which causes a decrease in the systemic vascular resistance (SVR). This occurs as early as 8 weeks of gestation ***(Chang et al., 2004).***

If arterial pressure (ABP) is to be maintained which is essential for an effective uteroplacental functioning unit, then the cardiac output (CO) has to be increased.

$$ABP = CO\ (HR \times SV) \times SVR$$

This is initially achieved by increasing stroke volume (SV), but as pregnancy progresses, the increase in SV plateaus and there is an increase in heart rate.

The increase in SV occurs secondary to an increase in both end-diastolic volume (EDV) and contractility. Increased pre-load and EDV is a result of the increased blood volume which is progressive from 6 to 8 weeks gestation to a maximum volume at 32 weeks. There is an overall increase of up to 2000 ml in blood volume compared with the non-pregnant individual. As a result of this, the pregnant patient compensates well for blood loss. By the time the classical symptoms and signs of hypovolemia such as tachycardia, hypotension, and oliguria are evident, more than 1500 ml may have already been lost ***(Wong, 2004).***

Despite an increased CO there is an early transient decrease in ABP, resulting in a widened pulse pressure and a reduced mean arterial pressure. This activates the renin–angiotensin system leading to retention of water and sodium and ultimately an increase in plasma volume.

While the increase in plasma volume is approximately 40–50%, the increase in red blood cell mass is only 20% resulting in the dilutional physiological anemia of pregnancy. Central venous pressure and pulmonary capillary wedge pressure are unchanged. ***(Chang et al., 2004)***

Anatomically, the iliac veins join to form the inferior vena cava at a level corresponding to the L4/5 interspace. Once the uterus is at this level, inferior vena cava

compression may occur. By the time enlarging uterus approaches the level of the umbilicus, corresponding to 20 weeks in a singleton pregnancy, the mechanical effects of the enlarging uterus can cause compression of both the inferior vena cava and the descending aorta in the supine position. The combination of these leads to a reduced venous return and decreased CO. ***(Nelson-Piercy, 2002)***

By 38–40 weeks gestational age, there is a 25–30% decrease in CO when turning from the lateral to the supine position. As the uteroplacental circulation possesses no autoregulation properties, this causes a decreased uterine blood flow and reduced placental perfusion. Aortocaval compression can therefore lead to maternal hypotension and a subsequent fetal acidaemia. The maternal compensatory mechanisms for aortocaval compression comprise an increase in sympathetic tone, causing vasoconstriction and tachycardia and diversion of blood flow from the lower limbs through the vertebral plexus and the azygos veins to reach the right heart. In 10% of parturient, this is inadequate to maintain AP in the supine position and hypotension may be severe enough for the mother to lose consciousness. Even if the mother is asymptomatic, uterine blood flow may still be compromised ***(Nelson-Piercy, 2002)***

I.V. and inhalation anesthetic agents, causing a reduction in SV and CO, and neuroaxial block, causing

sympathetic block further increase the risk of supine hypotension. Whenever possible, pregnant patients should adopt a full lateral position. When the supine position is required, they should be tilted to the left or have a wedge inserted under their right hip ***(Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 2011)***

2- Hematological changes

Changes in the coagulation system produce a hypercoagulable state to facilitate clotting at the time of placental separation and prevent bleeding during pregnancy. There is a 10-fold risk of venous thromboembolic disease during pregnancy and a 25-fold increase in the post-partum period. All clotting factors except XI and XIII increase; there is a decrease in natural anticoagulants and a reduction in fibrinolytic activity. All pregnant women should routinely undergo a thromboembolic risk assessment in the antenatal period and again on admission to hospital with appropriate thromboprophylaxis prescribed. As low molecular weight heparins (LMWHs) are being used increasingly in the antenatal period, it is essential that the anesthetist is aware of this and importantly the time the last dose was administered as regional block should not be performed within 12 h of a prophylactic dose of LMWH. ***(Horlocker et al., 2010).***

Platelet production increases, but the platelet count decreases due to increased destruction and haemodilution occurring maximally in the third trimester. The changes that occur are not usually reflected in standard clotting screens.

There is no absolute platelet level that is predictive for development of a neuraxial hematoma; both the number and function of platelets are important ***(Horlocker et al., 2010).***

The leucocyte count is normally elevated during pregnancy (14 000 mm^3). This may increase further during labour and delivery and is not indicative of evolving sepsis. Pregnant patients are however predisposed to the development of sepsis as it is a state of altered immune competence (allowing for paternal antigens in fetoplacental tissue) ***(Horlocker et al., 2010).***

3- Respiratory

Oxygen requirements and carbon dioxide production increase 60 % during pregnancy. Anatomical and physiological changes occur to meet the metabolic demands of mother and fetus. There is an early increase in the tidal volume which gives rise to a maximal increase in minute ventilation of 45% by the second trimester. There is a minimal increase in respiratory rate. ***(Nelson-Piercy, 2002)***

The driving force for this is progesterone which lowers the carbon dioxide response threshold of the respiratory center. ***(Nelson-Piercy, 2002).***

As the uterus expands, the diaphragm gets pushed in a cephalad direction. The functional residual capacity (FRC) is decreased by 20% in the upright position and up to 30% in the supine position (Table 2). The increase in ventilation leads to decreased arterial carbon dioxide tensions with an average PaCO2 of 4 kPa at term. This can reduce further in active labour. Ordinarily, this would lead to a respiratory alkalosis, but a compensatory increase in renal bicarbonate excretion and resulting decrease in serum bicarbonate occurs (HCO_3 18 mEq litre^{-1}) to minimize this. ***(Nelson-Piercy, 2002)***

Table (1): Changes in cardiorespiratory variables with pregnancy, ***(Nelson-Piercy, 2002)***

Cardiorespiratory variable	Alteration in pregnancy
Functional residual capacity: FRC	↓ 30%
Forced expiratory volume in 1 s: FEV1	→ unchanged
FEV1/FVC	→ unchanged
Tidal volume	↑ 45%
Minute volume	↑ 20–50%
Respiratory rate	→ ↑small increase
Cardiac output	↑
Stroke volume	↑
Heart rate	→↑ small increase

The increase in oxygen consumption and decreased FRC mean that parturient become hypoxemic very quickly during episodes of apnea, despite careful preoxygenation. Increased minute ventilation and a reduced FRC facilitates gas exchange at the alveolar level resulting in increased rate of uptake of inhalation agents and more rapid changes in depth of anesthesia. When ventilating a parturient, the lower levels and also the equivalent gradients between end-tidal CO_2 and $PaCO_2$ must be remembered. The lack of gradient is attributed to the reduction in alveolar dead space (increased blood perfusion from an increase in maternal CO). Excessive hyperventilation can lead to severe alkalosis and a left shift of the oxygen dissociation curve resulting in reduced oxygen transfer to the fetus ***(Nelson-Piercy, 2002).***

4- Central and peripheral nervous system

Altered anatomy and responses to pain and pharmacotherapy occur as pregnancy progresses. Increases in venous pressure below the gravid uterus cause blood to flow through the path of least resistance and as such is diverted through the epidural plexus which becomes engorged. The epidural space is bound and a compensatory decrease in cerebrospinal fluid volume occurs. This in addition to enhanced neural susceptibility to local anesthetics and a higher apical level of the thoracic kyphosis result in a 25% reduction in the dose requirement for spinal and epidural