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The University of Southern Mississippi

PHENYLEPHRINE VERSUS EPHEDRINE: SAFEST VASOPRESSOR FOR THE NEONATE DURING CESAREAN SECTION

by

James Stacey Hale Jr.

Abstract of a Capstone Project Submitted to the Graduate School of the University of Southern Mississippi in Partial Fulfillment of the Requirements for the Degree of Doctor of Nursing Practice

ABSTRACT

PHENYLEPHRINE VERSUS EPHEDRINE: SAFEST VASOPRESSOR FOR THE NEONATE DURING CAESAREAN SECTION

by James Stacey Hale Jr.

December 2015

One of the most common side effects of spinal anesthesia is the development of hypotension. Data collected has determined that 80% of parturients that undergo spinal anesthesia for this mode of delivery experience hypotension (Chestnut et al., 2014). Hypotension, if sustained and severe, can lead to fetal hypoxia, neonatal depression or injury, and decreased uteroplacental perfusion. Hypotension can also cause severe health issues for the parturient including apnea, altered level of consciousness, cardiac arrest, and pulmonary aspiration. This systematic review of the literature was conducted to determine whether the administration of phenylephrine or ephedrine was safer for the neonate to administer to a hypotensive parturient during cesarean delivery while undergoing a spinal anesthetic. Inclusion criteria included parturients that were classified as an American Society of Anesthesiologists physical status score of II that experienced hypotension after undergoing spinal anesthesia for elective cesarean section. Exclusion criteria included any parturient classified as an ASA physical status score > 2, any cesarean section classified as emergent, or those parturients that received an epidural as the method of anesthesia for elective cesarean section. A systematic review of the literature was performed and the results of randomized control trials and other studies were analyzed that measured neonatal outcomes following the administration of ephedrine and phenylephrine to the hypotensive parturient. The results of these studies

were disseminated and the conclusions reached were implemented into a white paper change proposal.

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2015

PHENYLEPHRINE VERSUS EPHEDRINE: SAFEST VASOPRESSOR FOR THE NEONATE DURING CAESAREAN SECTION

by

James Stacey Hale Jr.

A Capstone Project Submitted to the Graduate School and the Department of Advanced Practice at The University of Southern Mississippi in Partial Fulfillment of the Requirements for the Degree of Doctor of Nursing Practice

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DEDICATION

I would first like to take the opportunity to thank GOD for giving me the opportunity to achieve my goal of obtaining my Doctorate of Nursing Practice degree.

I would also like to thank my parents, my family, and my friends who have supported me tirelessly throughout the process of achieving this lifelong goal. I could not have done it without your encouragement and love. I dedicate this work to you all for without you this would not be possible.

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TABLE OF CONTENTS

ABSTRACT	ii
DEDICATIO	Niii
ACKNOWL	EDGMENTSiv
CHAPTER	
I.	INTRODUCTION
	Statement of the Problem Clinical Question Purpose of the Project
II.	METHODOLOGY5
	Target Outcome Barriers Populations The Importance of Apgar Scores The Importance of Umbilical Artery pH measurements Preventive Measurements Currently Recommended Comparison of the Vasopressors Ephedrine and Phenylephrine What are clinicians using in practice now?
III.	SYSTEMATIC REVIEW OF LITERATURE
IV.	SUMMARY
	Recommendations Conclusion
DEEEDENCI	24

CHAPTER I

INTRODUCTION

Statement of the Problem

The most commonly performed major surgical procedure in the United States today is cesarean delivery, accounting for more than 1 million procedures each year and approximately 30% of all births (Chestnut et al., 2014). Cesarean delivery is most commonly defined as the birth of an infant through incisions made by the surgeon in the abdomen and uterus. The most common indications for a cesarean delivery in parturients include malpresentation, shoulder dystocia, previous cesarean section, and nonreassuring fetal status. Malpresentation is the presentation of any part of the fetus other than the back of the head during parturition. Shoulder dystocia is a serious complication that occurs during vaginal delivery. After the head is delivered, the baby seems to be pulled back into the perineum due to anterior shoulder being trapped above the pubic symphysis. This complication occurs in as many as 3% of vaginal deliveries (Chestnut et al., 2014). Nonreassuring fetal status is a term used when test results suggest that the fetus's health status may be in jeopardy because the fetus is not getting enough oxygen. This complication usually occurs during labor in the late stages of pregnancy. Complications of cesarean delivery include uterine rupture, infection, hemorrhage, ureteral and bladder injury, abdominal pain, thromboembolism, and death. Thromboembolism is the obstruction of a blood vessel with thrombotic material carried by the blood from the site of origin to plug another vessel. The clot may plug a vessel in the brain, the lungs, the leg, the kidneys, or the gastrointestinal tract.

The most commonly preferred method of anesthesia for elective cesarean section is with a neuraxial technique, which is a spinal, epidural, or a combined spinal epidural (Chestnut et al., 2014). Of these three techniques, spinal anesthesia is the most commonly used technique. Spinal anesthesia is a reliable and simple method that allows for correct needle placement by visual confirmation of the cerebrospinal fluid (Chestnut et al., 2014). This technique is easier to perform than the epidural method of anesthesia. Spinal anesthesia delivers a fast onset of dense neuroblockade that is normally more profound than that which is provided by the epidural technique. This results in a decreased rate of conversion to general anesthesia and the decreased need for supplemental intravenous analgesics. The disadvantage to using the single shot spinal anesthetic method is it has a fixed duration of action and the anesthesia provider does not have the ability to redose without invasively performing the spinal technique again. Additionally, when spinal anesthesia is used as the anesthetic method for cesarean delivery it causes maternal hypotension at a rate of 80% (Chestnut et al., 2014).

One of the most common side effects of spinal anesthesia is the development of hypotension. Hypotension is the medical definition for low blood pressure. Blood pressure is the measure of the pressure in the arteries that is created by the contraction of the heart. The physical process of pregnancy increases dependence on the sympathetic nervous system for the maintenance of systemic vascular resistance and venous return. This dependence coupled with the increased risk of aortocaval compression makes parturients more prone to hemodynamic instability and hypotension from neuraxial anesthesia (Chestnut et al., 2014). Hypotension, if sustained and severe, can lead to fetal hypoxia, neonatal depression or injury, and decreased uteroplacental perfusion.

Hypotension can also cause severe health issues for the parturient including apnea, altered level of consciousness, cardiac arrest, and pulmonary aspiration. Many strategies have been implemented to prevent the incidence of hypotension secondary to spinal anesthesia for cesarean delivery. Some of these strategies are preoperative fluid administration, lower local anesthetic doses, left uterine displacement, vasopressor administration, and leg wrapping or elevation. Left uterine displacement is the act of placing the patient in 15 degrees of left lateral tilt on the operating table. This prevention method is important to minimize aortocaval compression. Aortocaval compression, or supine hypotension syndrome, is caused by compression of the inferior vena cava and aorta by the gravid uterus. This syndrome can comprise uteroplacental blood flow by decreasing cardio output and venous return (Chestnut et al., 2014).

This capstone project will compare the effects of ephedrine versus phenylephrine in mothers undergoing spinal anesthesia during a cesarean delivery. This project will examine the effects it has on neonates by performing a systematic review of the literature by comparing Apgar scores and fetal cord blood pH in cases where parturients received ephedrine and cases where they received phenylephrine. Some deleterious effects can result in the neonate if impaired fetal oxygenation or fetal acidosis occurs.

Deleterious effects in the neonate that can occur are impaired fetal oxygenation with asphyxial distress, fetal acidosis, and decreased uteroplacental blood flow (Lee, Ngan Kee, & Gin, 2002). Although patients undergoing a spinal anesthetic are usually preloaded with intravenous fluids, a vasopressor is often required to treat hypotension after the spinal anesthetic takes effect. Historically, the vasopressor of choice to treat hypotension for obstetric anesthesia has been ephedrine. According to Lee et al. (2002),

this was based on observations researchers had when administering ephedrine to sheep. The study showed that ephedrine maintained and preserved uteroplacental blood flow better than other vasopressors. It also was the most effective in increasing arterial pressure. This effect is rationalized by the β -effect, which causes an increase in arterial blood pressure by increasing cardiac output rather than simply vasoconstriction. Phenylephrine, a pure α agonist, on the other hand, fell into disfavor as a vasopressor in obstetric anesthesia because of the decreased uteroplacental blood flow (Lee et al., 2002). However, controversy exists today because many trials have shown that phenylephrine is just as effective as ephedrine and has shown to possibly be a safer alternative for the neonate.

Clinical Question

In parturients being treated for hypotension during cesarean section, does treatment with phenylephrine or ephedrine produce a higher Apgar score for the neonate while maintaining a normal arterial blood pH?

Purpose of the Project

The purpose of this project was to search the literature to determine whether ephedrine or phenylephrine is safer for the neonate when administered to a parturient with hypotension during elective cesarean section. The outcomes that were measured for this study were Apgar scores recorded at 1 and 5 minutes and umbilical artery pH. These are standard assessments that are performed following the removal of the neonate during cesarean section that determine the current health status of the neonate.

CHAPTER II

METHODOLOGY

After obtaining approval from the institutional review board (IRB) at the University of Southern Mississippi, a systematic search of literature on electronic databases was performed. Databases that were used in this search were the Cochrane Library, Google Scholar, PubMed, and MEDLINE. The search strategy that was incorporated was the search for the following key words in the text: "hypotension", "cesarean delivery", "phenylephrine", "ephedrine", "spinal anesthesia", and "neonatal outcomes after spinal induced hypotension." The outcomes measured were Apgar scores at 1 and 5 minutes and umbilical arterial and venous pH values. These outcomes were measured after the parturient was administered phenylephrine, ephedrine, or both for the treatment of hypotension secondary to spinal anesthesia for elective cesarean section. The results of these studies were compiled and the conclusions reached were utilized in the development of a white paper change proposal. This white paper change proposal was distributed among local clinical sites to prevent the occurrence of fetal acidosis and decreased Apgar scores following the administration of ephedrine and phenylephrine during elective cesarean section.

Target Outcome

The goal of this capstone was to determine whether it is safer for the neonate to administer ephedrine or phenylephrine to the hypotensive parturient during cesarean delivery. The desired outcome was to improve patient safety by developing a practice change policy based upon the findings of the systematic review of the literature. The findings of this systematic review of the literature was implemented into a white paper

change proposal and distributed to local clinical sites to increase knowledge on use of these vasopressors, their effect on neonates and implications for decision-making and clinical practice. This capstone project will hopefully contribute to decreasing the occurrence of fetal acidosis and decreased Apgar scores following the administration of ephedrine and phenylephrine during elective cesarean section.

Barriers

Several barriers were identified while performing this capstone project. There were a limited amount of studies that measured the same neonatal outcomes when comparing the administration of ephedrine versus phenylephrine to hypotensive parturients following the administration of spinal anesthesia for cesarean delivery.

Additional barriers included finding studies that were completed within the last 10 years, time constraints to complete the project, and studies that met the proper inclusion criteria.

Population

The population chosen for this capstone project was women over the age of 18 who were classified as an American Society of Anesthesiologists physical status score of II that experienced hypotension after undergoing spinal anesthesia for elective cesarean section. Anesthesia providers use the ASA scoring system to classify and define relative risk prior to surgical anesthesia and conscious sedation. An ASA physical status score of II is defined as a patient with mild systemic disease with no functional limitations (Butterworth, Mackey, & Wasnick, 2013). Additionally, they had to be treated with ephedrine, phenylephrine, or both. Exclusion criteria included any parturient classified as an ASA physical status score > 2, any cesarean section classified as emergent, or those parturients that received an epidural as the method of anesthesia for elective cesarean

section. An ASA physical status score of III is defined as patients with severe systemic disease with some functional limitations (Butterworth et al., 2013). A total of nine studies met this criteria and were included in this systematic review of the literature.

The Importance of Apgar Scores

The Appar scoring system has been used to access the prognosis and overall condition of the neonate since Virginia Apgar introduced it in 1952 (Casey, McIntire, & Leveno, 2001). Dr. Apgar in her paper A Proposal for a New Method of Evaluation of the Newborn Infant, described a simple and very reliable system for evaluating neonates that revealed a way to detect physiological differences among neonates whose mothers had been anesthetized for cesarean delivery by different techniques (Chestnut et al., 2014). The evaluation method she proposed was based on a 10-point scale that observed and measured five characteristics of newborns after delivery. This method measured the neonate's color, respiratory effort, muscle tone, heart rate, and reflex irritability (Casey et al., 2001). Reflex irritability is the neonate's response to a stimulus that is usually created by oropharyngeal suctioning. The appropriate response is for the neonate to actively cough or sneeze (Chestnut et al., 2014). After each of these easily identifiable characteristics are assessed, they are then assigned a score on a scale from 0 to 2. The scores are then added up to achieve a max score of 10 and that allows the providers an easy way to evaluate the health status of the newborn. Overall, a score of 7 or higher indicates that the neonate's health condition is good to excellent. Apgar scores from 4 to 6 are considered fair for the neonate. The infant's physical status is considered to be poor with Apgar scores less than 4 (Chestnut et al., 2014). The Apgar score rapidly evaluates the physical condition of neonates and is measured at 1 minute and 5 minutes after

delivery. The 5-minute score has commonly been regarded as the best predictor of the neonate's survival in clinical practice (Casey et al., 2001).

The Appar score has come under scrutiny as the standard scoring system for newborns after delivery. Many clinicians and clinical investigators believe that the measurement of pH in umbilical-artery blood is a more objective evaluation tool for assessing neonates. Casey et al. (2001) conducted a retrospective cohort analysis to show that the Apgar score is still as valuable an assessment tool as it was during the last 60 years. The study included 151,891 live-born singleton infants without malformations who were delivered at 26 weeks of gestation or later. The sample was collected from an inner-city public hospital from January 1988 to December 1998. The outcomes measured were paired Apgar scores at 1 and 5 minutes and umbilical-artery blood pH out of 145,627 infants. The study analyzed which test best predicted newborn death during the first 28 days after delivery. The results showed that the risk of neonatal death in term neonates with five-minute Apgar scores of 0 to 3 was eight times the risk in term neonates with umbilical- artery blood pH values of 7.0 or less (Casey et al., 2001). Thus Casey, McIntire, and Leveno concluded that the five-minute Apgar score was a better predictor of neonatal outcome than was the measurement of umbilical-artery blood pH. The investigators determined that the Apgar scoring system is still a vital assessment tool and accurate predictor of newborn survival (Casey et al., 2001).

The Importance of Umbilical-Artery Blood pH Measurements

The umbilical-artery blood pH measurement is a very important measurement and reflects the neonate's physical condition after delivery. According to Omo-Aghoja (2014), the 26th Royal College of Obstetricians and Gynecologists study group on

Intrapartum Fetal Surveillance recommended the measurement of umbilical blood pH and base deficit as a tool to assess the neonate's condition at birth. These measurements can be and are largely considered a more objective indication of a newborn's condition than the Apgar score. Obtaining the blood sample and receiving the results however can be delayed so an assessment of the neonate should immediately be done while awaiting feedback from the umbilical blood gas (Omo-Aghoja, 2014). The American Congress of Obstetricians and Gynecologists has recommended that cord blood pH measurements be obtained in circumstances of low 5-minute Apgar score, abnormal fetal heart rate tracing, severe growth restriction, cesarean delivery for fetal compromise, intrapartum fever, multiple gestation, and maternal thyroid disease.

The major components of the umbilical cord blood that are analyzed are the pH, PCO₂, HCO₃⁻, and PO₂ (Chestnut et al., 2014). HCO₃⁻, or Bicarbonate, is one of the major buffers in the blood of the neonate (Omo-Aghoja, 2014). Another component of the umbilical blood gas that is measured is the base excess or base deficit. The base excess or deficit is basically a measure of the change in the buffering capacity of the neonate's umbilical cord blood. This value can be determined by the HCO₃⁻, PCO₂, and pH. When the obstetrician obtains the umbilical cord sample, it is usually to obtain a sample from both the umbilical vein and the umbilical artery. The umbilical vein measurements reveal the quality of uteroplacental gas exchange and the condition of the parturient (Chestnut et al., 2014). The umbilical artery measurements reflect the condition of the neonate.

According to Omo-Aghoja (2014), small changes in pH can significantly affect the function of various organ systems in the neonate including the cardiovascular system

and the central nervous system. Fetal distress and a low Apgar score often accompany this development. The common pH range for neonatal acidemia in most literature is from 7.00 to 7.2. However, there is a more significant correlation with adverse neonatal outcomes when umbilical cord pH is less than 7.0 (Omo-Aghoja, 2014). According to Omo-Aghoja, the fetal acid-base status correlates well with the Apgar scores of the neonate. Exceptions can occur however in preterm infants, so clinician diligence and the use of multiple assessment tools could be the most beneficial for the neonate.

Several factors can affect the umbilical arterial blood pH measurement. Neonates that endure the stresses of labor tend to have lower pH measurements when compared to neonates who were born via cesarean delivery without experiencing labor (Chestnut et al., 2014). Neonates who are born to nulliparous women also have been documented to have a lower pH than those who were born to parous women. Nulliparous women are women that have not previously had a child. Parous women are those that have delivered at least one child previously (Chestnut et al., 2014). Additionally, some studies have yielded results that suggest that preterm infants have a higher incidence of acidemia when compared to term infants. Preterm infants also routinely receive poor Apgar scores even though their umbilical blood gas measurements are considered normal (Chestnut et al., 2014). This is significant and provides another rationale for more than one method to be used to assess the neonate after delivery.

Preventative Measures Currently Recommended to Prevent Hypotension

The most common preventive strategy used by anesthesia providers today is
intravenous fluid administration (Chestnut et al., 2014). The success of preventing
hypotension intraoperatively during cesarean section depends on the type of fluid

administered whether it is a colloid or a crystalloid, the timing of the administration of fluid, and the rate of fluid administration. A colloid is considered intravenous fluids containing large molecules and proteins that tend to stay within the vascular space. Examples of colloid solutions are Hetastarch, Albumin, and Dextran. Crystalloid intravenous fluids are those that contain various concentrations of electrolytes and tend to diffuse more readily out of the vascular space than colloid solutions. Common crystalloid solutions are Lactated Ringers, Dextrose 5%, and Normal Saline. Some studies conducted on this preventive therapy have determined crystalloids to be minimally effective even administered at volumes of 2,000 milliliters to 3,000 milliliters. A study conducted by Ueyama and others determined that after 30 minutes post administration of a crystalloid solution that only 28% remained in the intravascular space. In contrast, the administration of a colloid solution is a more promising alternative for preventative therapy. The same study conducted by Ueyama on crystalloid administration compared it to the administration of a colloid solution. The researchers discovered that 30 minutes after the administration of a colloid that 100% of the solution remained in the vascular space. However, the side effects to the administration of a colloid solution to parturients make this an unpopular option to many anesthesia providers. Some side effects of colloid administration that have been noted are allergic reactions, pruritus, and coagulation abnormalities. The next step in treating hypotension after intravenous fluid administration and the most successful option is the administration of vasopressors.

Use of Vasopressors

Vasopressors are drugs that are administered that cause the constriction of blood vessels. This desired constriction of blood vessels results in an increase in blood pressure. The main component common to all vasopressors is their ability to mimic some of the sympathetic nervous system actions (Macarthur & Riley, 2007). The basic components that differentiate the vasopressors are each drug's ability to stimulate the alpha or beta-receptor. Sympathomimetics all have the same basic structure, which include the benzene ring based β -phenylenthylamine. According to Macarthur and Riley (2007), the activity of the α and β -receptor is maximized if hydroxyl groups are attached at the third and fourth carbons of the benzene ring. Compounds are considered synthetic noncatecholamines if they do not have the hallmark hydroxyl groups on the third and fourth carbons. The two most commonly used vasopressors in anesthesia practice are ephedrine and phenylephrine and they are both included in the synthetic noncatecholamine group.

Comparison of the Vasopressors Ephedrine and Phenylephrine

Ephedrine is a synthetic noncatecholamine sympathomimetic that stimulates both alpha and beta-receptors directly and causes the release of endogenous catecholamines indirectly that leads to several mechanisms of action (Nagelhout & Plaus, 2014). The indirect effects of ephedrine are due to the stimulation of postganglionic sympathetic nerve endings to release norepinephrine (Macarthur & Riley, 2007). Ephedrine produces increases in blood pressure, heart rate, systemic vascular resistance, and cardiac output. Ephedrine is not metabolized by monoamine oxidase enzyme deamination because it has a α -methyl group. Additionally, catchol-O-methyltranserease enzymes do not metabolize

it because it lacks the traditional hallmark hydroxyl groups. Consequently, its actions are mainly terminated by reuptake in terminal nerve endings. Due to this, ephedrine is primarily excreted relatively unchanged in urine (Macarthur & Riley, 2007). The dosage of ephedrine ranges from 5 mg to 25 mg and has an immediate onset of action when given via the intravenous route. The duration of action has been documented to last from 15 minutes up to 90 minutes usually based on the dosage given. The administration of repeated 5 to 10 mg doses of Ephedrine can lead to tachyphylaxis, which results in a significant decrease in the efficacy of the drug after subsequent dosing.

Phenylephrine is a direct acting pure alpha agonist that is commonly administered to parturients that have episodes of hypotension during cesarean section. Phenylephrine is considered a pure alpha agonist because it has strong alpha stimulating effects with essentially no beta stimulation (Nagelhout & Plaus, 2014). Phenylephrine is metabolized by rapid inactivation by monamine oxidase and catchol-O-methyltranserease. The dosage of phenylephrine commonly administered intravenously is 50 to 200 micrograms and has an immediate onset of action. According to Macarthur and Riley (2007), because of its short duration of action, phenylephrine can also be administered by intravenous infusion of 20 to 50 micrograms per minute. The duration of action of phenylephrine ranges from 5 to 20 minutes. Phenylephrine can cause a sharp rise in blood pressure due to the significant increase in peripheral vasoconstriction by stimulating alpha-1 receptors. A common side effect of phenylephrine is a reflex bradycardia that is produced after baroreceptor stimulation due to the significant increase in peripheral resistance.

What are Clinicians Using in Practice Now?

An electronic survey was conducted by Allen, Muir, George, and Habib that included 292 members of the Society for Obstetric Anesthesia and Perinatology between February and March 2007 to determine their preferences for preventing and treating spinal-induced hypotension. Of the members using vasopressors for prophylaxis, 26% used phenylephrine, 32% used ephedrine, and 33% based their choice on the parturient's heart rate. The group determined that for treatment, 23% used phenylephrine, 32% used ephedrine, and 41% used either based on heart rate. The group concluded that significant variations exist in the prevention and treatment of hypotension due to spinal anesthesia but that ephedrine continues to be a more commonly used vasopressor than phenylephrine.

Clinical Question

The incidence of hypotension is prevalent in parturients undergoing spinal anesthesia for cesarean delivery. Cesarean deliveries account for 30% of all births in the United States. The current anesthetic method of choice for cesarean delivery is spinal anesthesia. Data collected determined that 80% of parturients that undergo spinal anesthesia for this mode of delivery experience hypotension. A clinical question was developed to determine whether the administration of phenylephrine or ephedrine was safer for the neonate to administer to a hypotensive parturient during cesarean delivery while undergoing a spinal anesthetic. In parturients being treated for hypotension during cesarean section, does treatment with phenylephrine or ephedrine produce a higher Apgar score for the neonate while maintaining a normal arterial blood pH?

Research Strategies

To ascertain which vasopressor treatment modality for maternal hypotension is more beneficial for the neonate during elective cesarean delivery, a systematic review of the literature was conducted. A systematic review is a study that focuses on a research question that attempts to identify and appraise research evidence relevant to that question. Inclusion criteria included in this study were parturients that underwent spinal anesthesia for elective cesarean section, were classified as ASA class II, and were treated with either ephedrine or phenylephrine.

CHAPTER III

SYSTEMATIC REVIEW OF LITERATURE

Traditionally, ephedrine has been the drug of choice in obstetrics to treat maternal hypotension following neuraxial anesthesia. The rationale behind this line of thinking from anesthesia providers was it was believed based on previous studies that ephedrine maintains uterine blood flow better than phenylephrine. However, the most recent studies indicated that phenylephrine has now been recommended as the first drug choice following neuraxial anesthesia. The most commonly preferred method of anesthesia for elective cesarean section is with a neuraxial technique, which is a spinal, epidural, or a combined spinal epidural (Chestnut et al., 2014). Of these three techniques, spinal anesthesia is the most commonly used technique. Spinal anesthesia delivers a fast onset of dense neuroblockade that is normally more profound than that which is provided by the epidural technique. Lee et al. (2002) performed a quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during cesarean delivery while under spinal anesthesia. The authors performing the systematic review compared the efficacy and safety of ephedrine and phenylephrine for the treatment and prevention of hypotension during cesarean delivery while undergoing spinal anesthesia. In the study, seven randomized control trials were eligible for use after the systematic search of electronic databases. The outcomes they measured and assessed were maternal hypertension, hypotension, and bradycardia. Neonatal Apgar scores and umbilical cord pH blood values were also studied. The authors determined from the results that there was no difference between ephedrine and phenylephrine in their efficacy for managing maternal hypotension (Lee et al., 2002).

However, maternal bradycardia was more likely to occur with phenylephrine than with ephedrine (relative risk of 4.79; 95% confidence interval, 1.47-15.60). Neonatal umbilical arterial pH values were higher in women who were treated with phenylephrine as compared to those treated with ephedrine. The authors determined from the results that there was no difference between ephedrine and phenylephrine in the incidence of Apgar scores less than 7 at 1 and 5 minutes and true fetal acidosis, which is umbilical arterial pH value less than 7.2 (Lee et al., 2002). Lee et al. did not support the traditional practice that ephedrine is the drug of choice for the management of maternal hypotension during cesarean delivery while under spinal anesthesia.

Magalhaes, Goveia, de Araujo Ladeira, Nascimento, and Cavalcante Kluthcouski (2009) conducted a randomized, double blind, prospective study with 60 women. The women were separated randomly into two groups using sequential, sealed envelopes with random numbers generated by a computer. The group studied the incidence of maternal hypotension, maternal bradycardia, vomiting, Apgar scores at 1 and 5 minutes, and blood gases of the neonatal umbilical cord blood. The 60 patients underwent spinal anesthesia for cesarean section with bupivacaine and sufentanil and were divided into two groups to receive prophylactic phenylephrine (Group P, n = 30, dose = 80 mcg) and ephedrine (Group E, n = 30, dose = 10 mg). According to Nagelhout and Plaus (2014), bupivacaine is traditionally the local anesthetic of choice when administering spinal anesthesia for cesarean delivery. In the United States, it is administered via the intrathecal route, or spinal route, and is formulated in a concentration of 0.75% in dextrose 8.25%. Sufentanil is a narcotic that is commonly administered intrathecally in conjunction with bupivacaine (Nagelhout & Plaus, 2014). The definition of hypotension the group used in their study

was a blood pressure equal or lower than 80% of baseline values. Maternal hypotension was treated with a bolus administration of the participant's vasoconstrictor at 50% of the initial dose. The results from the study determined that the mean dose of phenylephrine used was 186.7 +/- 52.9 and the mean dose of ephedrine used was 14.8 +/- 3.8 mg (Magalhaes et al., 2009). The incidence of hypotension was 70% in the ephedrine group and 93% in the phenylephrine group. The group determined that the Apgar scores in the first minute and the mean arterial pH of the neonatal umbilical cord blood were lower in the Ephedrine group. The group determined that differences in the Apgar score in the fifth minute were not evident. The authors concluded from the study that ephedrine was more effective than phenylephrine in the prevention of hypotension (Magalhaes et al., 2009). However, fetal repercussions were found to be less frequent with phenylephrine and were transitory with the administration of ephedrine.

An updated meta-analysis on ephedrine versus phenylephrine for the management of hypotension during cesarean section while undergoing spinal anesthesia was conducted by Lin, Qui, Ding, Fu, and Li (2012). The aim of this study was to update a systematic literature review that was previously conducted on the same topic in 2002. The group used Medline, the Cochrane Library, and Embase Databases to search for the criteria. The group examined a total of 15 trials and 742 parturients under elective Cesarean Sections. They determined when patients received ephedrine and phenylephrine for prevention of hypotension; results did not significantly differ in the incidence of umbilical arterial pH values, hypotension, or venous pH values. The group determined when ephedrine and phenylephrine were used to treat hypotension that the results indicated both had similar incidence of perioperative hypotension but those

patients receiving phenylephrine had neonates with higher venous pH values and umbilical arterial pH values than those who had received ephedrine (Lin et al., 2012). Thus, the group came to the conclusion that the prophylactic use of ephedrine and phenylephrine were both effective in preventing maternal hypotension during cesarean section under spinal anesthesia, but phenylephrine was superior to ephedrine in treating hypotension which was evidenced by higher umbilical cord arterial and venous pH values.

Adigun, Amanor-Boadu, and Soyannwo (2010) conducted a randomized, double-blind, controlled study of 62 parturients that compared intravenous ephedrine against phenylephrine for the maintenance of arterial blood pressure during elective caesarean section under spinal anaesthesia. The parturients included were those that were classified as American Society of Anesthesiologists' (ASA) class 1 or 2 at term with singleton pregnancy who consented to a subarachnoid spinal block. The patients were injected with 2.5 milliliters of 0.5% hyperbaric Bupivicaine at L3-L4 levels after being preloaded with 10 milliliters per kilogram of crystalloid fluids (Adigun et al., 2010). Phenylephrine 100 micrograms or Ephedrine 5 milligrams was given for the maintenance of arterial blood pressure. The group determined that both vasopressors efficiently restored both the systolic and the diastolic blood pressures and the mean Apgar scores were similar for the two groups. Neither the phenylephrine group nor the ephedrine group had Apgar scores below the value of 8 (Adigun et al., 2010). They concluded that phenylephrine was safe and can be used as effectively as ephedrine.

A randomized, double-blind study was performed by Prakash, Pramanik, Chellani, Salhan, and Gogia (2010) on parturients comparing the effects of bolus

administration of ephedrine and phenylephrine during spinal anesthesia for caesarean delivery. In the study the group administered phenylephrine 100 micrograms or ephedrine 6 milligrams whenever the systolic blood pressure dropped less than 80% of the patient's baseline blood pressure during the spinal block. The group determined that changes in systolic were comparable in the two groups after the administration of the two vasopressors and there were essentially no differences in the incidence of nausea, bradycardia, and vomiting. However, the group determined venous and umbilical artery pH blood values were significantly higher in the phenylephrine group as compared to the ephedrine group. Also, the umbilical artery base excess was significantly less in the ephedrine group than in the phenylephrine group (Prakash et al., 2010). Apgar scores at 1, 5, and 10 minutes were measured as well as neurobehavioral scores at 2-4 hours, 24 hours, and 48 hours and were determined to be similar in the two vasopressor groups.

Simin, Zahra, Pouya, and Reza (2012) conducted a prospective, double-blind, and case-controlled study on 60 parturients. They studied the efficacy of ephedrine and phenylephrine in treatment of hypotension secondary to spinal anesthesia for cesarean section and the effects the two vasopressors had on the neonate. The group randomly assigned the 60 parturients into an ephedrine group, which received boluses of 5 milligrams, and a phenylephrine group, which received boluses of 100 micrograms, for treatment of hypotension after a subarachnoid spinal block during cesarean section. They studied changes in maternal heart rate, maternal blood pressure, and the incidence of nausea and vomiting. Additionally the group measured neonatal umbilical arterial blood gas values and Apgar scores at 1 minute and 5 minutes. The group determined that both vasopressors were efficient at managing hypotension in parturients undergoing cesarean

section with comparable results. Also there were no differences in Apgar scores at 1 minute and 5 minutes after administration of either vasopressor. There were only minimal differences in the umbilical artery pH and base excess values and there were not any incidents of true acidosis, pH less than 7.20, in any of the neonates. Thus, the group concluded that both phenylephrine and ephedrine were both equally efficient at treating hypotension secondary to subarachnoid block during cesarean section and neither vasopressor presented a risk for adverse effects on neonates.

Cooper et al. (2002) performed a randomized, double-blind study on 147 parturients to determine whether ephedrine, phenylephrine, or a combination of the two was the most efficient at treating hypotension secondary to spinal block and whether or not the two vasopressors caused adverse effects to the neonate. The group randomly divided the patient groups into three different groups: a phenylephrine group which received 100 micrograms/milliliter, an ephedrine group which received 3 milligrams/milliliter, and a combination group that received 50 micrograms/milliliter of phenylephrine and 1.5 milligrams/milliliter. These groups were selected by envelope to one of the three vasopressor solutions to maintain maternal systolic pressure during spinal anesthesia. The group determined that fetal acidosis was found to be more frequent in the ephedrine group (10 of 48) and less frequent in the phenylephrine group (1 of 48) and combination group (1 of 47). The group also determined that there is no significance difference among the different vasopressor categories in regards to the measurement of Apgar scores. All vasopressor groups had Apgar scores above 8 and are thus deemed insignificant. The group concluded that administering phenylephrine alone by infusion during spinal anesthesia for cesarean section was associated with a lower incidence of

maternal nausea and vomiting and fetal acidosis than giving ephedrine alone (Cooper et al., 2002). Furthermore, the group determined that it was not advantageous to combine phenylephrine and ephedrine because it increased nausea and vomiting as compared to phenylephrine alone. It also did not improve fetal blood gas values additionally than from administering just phenylephrine.

A systematic literature search was conducted by Veeser et al. (2012) on comparing the administration of phenylephrine and ephedrine to hypotensive parturients after undergoing spinal anesthesia for cesarean section. The outcomes they measured were the maternal and neonatal effects of the two vasopressors. The authors study criteria was fulfilled by 20 trials, which included 1,069 patients. The neonatal outcomes measured were umbilical-artery pH, base excess, and Apgar scores. The investigators determined the relative ratio, or RR, of fetal acidosis was 5.29 (95% CI 1.62-17.25) for ephedrine compared with phenylephrine, which was statistically significant data (P = 0.006) (Veeser et al., 2012). Veeser et al. (2012) also determined that the data accumulated on base excess was significantly lower in the ephedrine group. The weighted mean difference was -1.17 with a 95% confidence interval of -2.01 and P value of 0.006. The number of neonates with Apgar values less than 7 were measured in 11 trials at 1 and 5 minutes after delivery. The only significant score present was a single Apgar value below 7 at 5 minutes in one study. All other Apgar data when comparing phenylephrine to ephedrine was statistically insignificant. The investigators concluded that ephedrine use was associated with an increased risk of true fetal acidosis when compared with phenylephrine. Additionally, ephedrine use also increased the risk for a lower base excess value. The study yielded that the Apgar values did not significantly

differ between the two vasopressors (Veeser et al., 2012). The results of this study are clinically significant for my capstone project.

Loughrey et al. (2005) conducted a randomized control trial of 43 ASA I and II non-laboring women undergoing a planned, elective cesarean delivery. The investigators randomized the 43 parturients into 2 groups. The ephedrine only group received a bolus of ephedrine 10 milligrams intravenously. The ephedrine and phenylephrine combine group received a bolus of phenylephrine 40 micrograms and ephedrine 10 milligrams simultaneously with spinal anesthesia (Loughrey et al., 2005). The group defined hypotension for this study to be a decrease of 20% or greater from the baseline systolic value or any value less than 100 mmHg. Loughrey et al. would give rescue boluses comprised of phenylephrine 20 micrograms and ephedrine 5 milligrams. The results from the study yielded that the mean umbilical artery pH being 7.246 +/- 0.081 for the ephedrine only group and 7.244 +/- 0.106 for the combined ephedrine and phenylephrine group. Apgar scores measured for the two groups were also similar and neither group had one that measured less than 7 (Loughrey et al., 2005). This study determines that there was no significant difference between the groups and that a combination of ephedrine with phenylephrine is not superior to ephedrine alone.

Doctor of Nursing Practice Essentials

DNP Essential I is the scientific underpinning for practice (Chism, 2013). This DNP essential allows the researcher to employ science-based theories and concepts to describe strategies used to improve healthcare delivery, to determine the importance and nature of health and healthcare delivery phenomena, and to evaluate outcomes. The theory I plan to integrate into this capstone project is a middle-range theory. Middle-

range theory is a less abstract, has fewer propositions and concepts than grand theory, and is narrower in scope (Butts & Rich, 2011). The type of theory I plan to integrate into the capstone project is the prescriptive theory or practice theory. This model falls within Ernestine Wiedenbach's model of nursing theory, The Helping Art of Clinical Nursing. The prescriptive theory is fundamentally based on three main factors: the central purpose which the clinical nurse recognizes as crucial to the particular discipline, the realities in the immediate situation that influence the central purpose, and the prescription for the fulfillment of the central purpose. According to Butts and Rich (2011), prescriptive theory is an empirical, experimental theory for practice based on the effects of processes and actions on people and situations. The use of this theory will help to discover whether phenylephrine or ephedrine is safer to administer in obstetric anesthesia.

DNP Essential II is the organizational and systems leadership for quality improvement and systems thinking (Chism, 2013). This DNP essential employs scientific findings in nursing to evaluate and develop care delivery methods that meet the current and future needs of patient populations. This capstone is designed to evaluate research conducted comparing the administration of phenylephrine and ephedrine to hypotensive parturients undergoing spinal anesthesia for cesarean section. The method that will determine the difference between these two vasopressors is by measuring the neonates Apgar scores at 1 and 5 minutes and also by measuring fetal cord blood pH measurements. Both vasopressors appropriately treat hypotension in the parturient but current research is controversial on which one is safer for the neonate. This capstone intends to yield a clear answer on which is more beneficial for the neonate and a clinical practice change will be implemented to improve patient safety.

DNP Essential III is the clinical scholarship and analytical methods for evidence-based practice (Chism, 2013). This DNP essential prepares the nurse researcher to critically and analytically evaluate existing literature and other evidence to determine the best evidence for practice. This essential also aids in evaluating outcomes in practice within populations in various fields. Additionally this essential helps the nurse researcher develop practice guidelines that are based on relevant, best-practice findings. This capstone will systematically review research conducted by other researchers and will gather their results into a systematic review of the literature. The results will then be synthesized into a white paper proposal for the treatment of spinal induced hypotension during cesarean section.

DNP Essential IV is the information systems and technology and patient care technology for the improvement and transformation of health care. This DNP essential is paramount for the researcher in becoming proficient at the skills necessary to evaluate data extraction from practice information databases and systems. This essential also aids the researcher to monitor and evaluate outcomes of care improvement by evaluating, designing, and using programs related to information technologies. Electronic databases will be utilized for this capstone project to conduct my review of literature and to find relevant neonatal outcomes after cesarean delivery to supplement my research findings. Information technologies will also be employed to help synthesize the data into a meta-analysis extracted from research studies.

DNP Essential V is healthcare policy for advocacy in healthcare (Chism, 2013).

This essential is vital for the nurse researcher because it prepares them to provide leadership in the implementation and development of healthcare policy at the institutional

and local levels of healthcare, as well as the state and federal levels. After the results of the capstone have been gleaned, a white paper proposal will be prepared to advocate for policy change at local clinical arenas in regards to obstetric anesthesia. This will improve the quality of care and hopefully improve neonatal outcomes after cesarean section by treating parturient hypotension with the safest vasopressor.

DNP Essential VI is interprofessional collaboration for improving patient and population health outcomes (Chism, 2013). This essential is critical because the DNP prepared nurse must participate in effective collaboration and communication throughout the development of practice guidelines, practice models, health policy, peer review, and standards of care. The DNP prepared nurse must also examine complex organizational or practice issues through leadership of interprofessional teams. Interprofessional collaboration is essential for the implementation of the practice change to be effective and to improve neonatal outcomes. Additionally, communication with all anesthesia providers and department supervisors about the new white paper proposal is imperative for the latest evidenced based practice to be successfully implemented.

DNP Essential VII is clinical prevention and population health for improving the nation's health. According to Allan et al., clinical prevention is defined as reducing risk, illness prevention, and health promotion for families and individuals (Allan, et al., 2004). This essential prepares DNP level nurses to analyze biostatistical, environmental, epidemiological, and occupational data in the development, evaluation, and implementation of population health and clinical prevention (Chism, 2013). The administration of ephedrine as a first line vasopressor for the prevention of hypotension in the parturient following spinal anesthesia for cesarean delivery can potentially lead to

decreased Apgar scores and fetal acidosis in the neonate. Fetal acidosis in the neonate can lead to detrimental health complications like hypoxia, which can then potentially lead to cardiovascular collapse and mortality in the neonate. By implementing the latest evidenced based practice based on the results of this capstone, neonatal complications can be avoided by administering phenylephrine as a first line vasopressor.

DNP Essential VIII is advanced nursing practice (Chism, 2013). This essential is vital and prepares the DNP nurse to systematically assess health and illness parameters while incorporating culturally sensitive and diverse approaches. By utilizing this DNP Essential, the DNP prepared nurse will also evaluate and implement therapeutic interventions based on nursing and other sciences. Additionally, the DNP nurse will be able to utilize advanced critical thinking skills and deliver and evaluate evidence based care to improve patient outcomes. The utilization of this DNP essential will lead the anesthesia provider to utilize the latest evidence based practice provided by this capstone and provide the most optimal care to the parturient during cesarean delivery.

White Paper Change Proposal

The most commonly performed major surgical procedure in the United States today is cesarean delivery, accounting for more than 1 million procedures each year and approximately 30% of all births. The most commonly preferred method of anesthesia for elective cesarean section is with a spinal anesthetic. Spinal anesthesia delivers a fast onset of dense neuroblockade that is normally more profound than that which is provided by the epidural technique. When spinal anesthesia is used as the anesthetic method for cesarean delivery, it causes maternal hypotension at a rate of 80%. Hypotension is the medical definition for low blood pressure. Blood Pressure is the measure of the pressure in the arteries that is created by the contraction of the heart. Hypotension, if sustained and severe, can lead to fetal hypoxia, neonatal depression or injury, and decreased uteroplacental perfusion. Although patients undergoing a spinal anesthetic are usually preloaded with intravenous fluids, a vasopressor is often required to treat hypotension after the spinal anesthetic takes effect.

Historically, the vasopressor of choice to treat hypotension for obstetric anesthesia has been ephedrine. This assumption was based on observations researchers had when administering ephedrine to sheep. In the study, ephedrine showed it maintained and preserved uteroplacental blood flow better than other vasopressors. It also was the most effective in increasing arterial pressure than other vasopressors. This effect is rationalized by the β -effect, which causes an increase in arterial blood pressure by increasing cardiac output rather than simply vasoconstriction. Phenylephrine, a pure α agonist, on the other hand had fell into disfavor as a vasopressor in obstetric anesthesia because of the decreased uteroplacental blood flow seen in the same sheep study. A

systematic review of the literature was performed and the results of randomized control trials and other studies were analyzed that measured neonatal outcomes following the administration of ephedrine and phenylephrine to the hypotensive parturient.

The purpose of this project was to determine whether ephedrine or phenylephrine is safer for the neonate when administered to a hypotensive parturient during elective cesarean section. The desired outcome was to improve patient safety by developing a practice change policy based upon the findings of the systematic review of the literature. The outcomes that were measured for this study to determine this was Apgar scores recorded at 1 and 5 minutes and umbilical artery pH. These are standard assessments that are performed following the removal of the neonate during cesarean section that determine the current health status of the neonate.

One of the major findings of this systematic review of the literature was that there was no significant difference in Apgar scores when comparing the administration of ephedrine and phenylephrine. There were eight studies reviewed in this capstone project that measured Apgar scores comparing ephedrine versus phenylephrine, and seven of them determined that there was no significant difference. The value that was deemed significant in these studies was an Apgar value below seven. In one study, the administration of ephedrine to the parturient during cesarean delivery caused lower Apgar scores at 1 minute, but when the measurement was repeated at five minutes it was above seven and considered normal. The 5-minute score has commonly been regarded as the best predictor of the neonate's survival in clinical practice.

The second neonatal outcome that was reviewed in this systematic review was the measurement of umbilical pH values. The results of the review yielded some significant

and interesting results. There were eight studies in this capstone project that measured neonatal umbilical pH values. After reviewing these studies, five confirmed that ephedrine causes lower umbilical pH values in the neonate when given to the parturient during cesarean delivery. The other three studies deemed the results to be similar or insignificant in their findings. Small changes in pH can significantly affect the function of various organ systems in the neonate including the cardiovascular system and the central nervous system.

Based on the information discovered by this capstone project, phenylephrine is just as safe for neonates as ephedrine and is safer in regards to neonatal umbilical pH values. This capstone recommends the use of phenylephrine over ephedrine as a first line vasopressor to treat maternal hypotension during cesarean delivery secondary to spinal anesthesia. It is also recommended that the proposed changes made with the white paper proposal be tested for accuracy to determine if the results of the studies are significant enough to warrant a wholesale clinical practice change.

CHAPTER IV

SUMMARY

The purpose of this project was to determine whether ephedrine or phenylephrine was safer for the neonate when administered to a hypotensive parturient during elective cesarean section. The outcomes that were measured for this study to determine this was Apgar scores recorded at 1 and 5 minutes and umbilical artery pH. These are standard assessments that are performed following the removal of the neonate during cesarean section that determine the current health status of the neonate. A systematic review of the literature was performed and the results of randomized control trials and other studies were analyzed that measured neonatal outcomes following the administration of ephedrine and phenylephrine to the hypotensive parturient.

Summary of Findings

One of the major findings of this systematic review of the literature was that there was no significant difference in Apgar scores when comparing the administration of ephedrine and phenylephrine. There were eight studies reviewed in this capstone project that measured Apgar scores comparing ephedrine versus phenylephrine, and seven of them determined that there was no significant difference. The value that was deemed significant in these studies was an Apgar value below 7. In one study, the administration of ephedrine to the parturient during cesarean delivery caused lower Apgar scores at 1 minute, but when the measurement was repeated at 5 minutes it was above 7 and considered normal. The 5-minute score has commonly been regarded as the best predictor of the neonate's survival in clinical practice (Casey et al., 2001).

The second neonatal outcome that was reviewed in this systematic review was the measurement of umbilical pH values. The results of the review yielded some significant and interesting results. There were eight studies in this capstone project that measure neonatal umbilical pH values. After reviewing these studies, five confirmed that ephedrine causes lower umbilical pH values in the neonate when given to the parturient during cesarean delivery. The other three studies deemed the results to be similar or insignificant in their findings. This is significant because the majority of the studies determined that there is a correlation between the administration of ephedrine to parturients and lower umbilical pH measurements in neonates. Historically, the vasopressor of choice to treat hypotension for obstetric anesthesia has been ephedrine. However, this capstone has shown that phenylephrine is just as effective as ephedrine and has shown to possibly be a safer alternative for the neonate based on the reviewed measurements of neonatal umbilical pH values.

Recommendations

The review of literature showed that there was little to no significant difference when comparing ephedrine and phenylephrine and the measurement of neonatal Apgar scores. However, the literature review did yield interesting results and the majority determined that ephedrine did cause a lower pH when compared with phenylephrine. This is a significant correlation and one that needs to be studied further for greater accuracy. This capstone project proposes that changes made with the white paper proposal be tested for accuracy to determine if the results of the studies are significant enough to warrant a wholesale clinical practice change.

Conclusion

The goal of this capstone was to determine whether it is safer for the neonate to administer ephedrine or phenylephrine to the hypotensive parturient during cesarean delivery. The desired outcome was to improve patient safety by developing a practice change policy based upon the findings of the systematic review of the literature. The findings of this capstone project may not have proven one vasopressor to be without question safer for neonates than the other. However, this project did provide a correlation between decreased umbilical pH values and the administration of ephedrine to hypotensive parturients following the administration of spinal anesthesia for cesarean delivery. It is my belief that this capstone project will be beneficial in providing local clinical sites with current evidence-based practice on the administration of ephedrine and phenylephrine to hypotensive parturients and the neonatal outcomes that each vasopressor causes.

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