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A Systematic Review Comparing Ephedrine Versus Phenylephrine During Spinal Anesthesia for Cesarean Delivery

Shelby Sullivan

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A SYSTEMATIC REVIEW COMPARING EPHEDRINE VERSUS PHENYLEPHRINE DURING SPINAL ANESTHESIA FOR CESAREAN DELIVERY

by

Shelby Sullivan

A Major Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of

Master of Science in Nursing

in

The School of Nursing

Rhode Island College

2017

Abstract

This systematic review compared the efficacy and safety of ephedrine with phenylephrine for the treatment of hypotension during spinal anesthesia for cesarean delivery. Hypotension during cesarean section delivery can have detrimental effects on both the mother and the neonate. Some vasoactive medications such as ephedrine and phenylephrine have been found to be detrimental to the neonate and divert fetal blood flow. After a systematic search of the electronic database PubMed, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to identify appropriate research. Studies were illustrated in a table to identify key variables and were then critically appraised. Outcomes included oxygen supplementation use, ASA classification, IV fluid prehydration, hypotension incidence after spinal anesthesia, spinal solution and technique, umbilical artery pH, Apgar scores, and nausea and vomiting during the case. Findings revealed no difference in the use of oxygen supplementation, ASA classification, IV fluid prehydration, spinal solution or technique on fetal umbilical artery pH. Women given phenylephrine had neonates with higher umbilical artery pH values than those given ephedrine but there was no significant difference between the two vasopressors in the incidence of true fetal acidosis (umbilical artery pH < 7.20 or Apgar <7 at 1 and 5 min). There was an incidental finding from two studies that additionally examined nausea and vomiting that there was an increase occurrence of nausea and vomiting with ephedrine administration as compared to phenylephrine administration. This systematic review supports the view that ephedrine and phenylephrine have equal efficacy and safety when administered to obstetric patients experiencing hypotension after spinal anesthesia during cesarean sections.

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A Systematic Review Comparing Ephedrine versus Phenylephrine during Spinal Anesthesia for Cesarean Delivery

Background/Statement of the Problem

Hypotension during spinal anesthesia for elective caesarean delivery occurs in about 70-80% of cases (Mercier, Augè, Hoffmann, Fischer & Le Gouez, 2013) and may have detrimental effects on both the mother and the neonate (lee, Kee & Gin 2002). These effects include decreased uteroplacental blood flow, impaired fetal oxygenation with asphyxial stress and fetal acidosis (Lee et al., 2002). Associated effects include maternal symptoms of low cardiac output such as dizziness and decreased consciousness, usually requiring vasoactive drugs as treatment (Lee et al.). Some vasoactive medications have been found to be detrimental to the neonate and divert fetal blood flow, potentially causing more harm than good in pregnant women (Nagelhout, Elisha & Plaus, 2013). Ephedrine and phenylephrine are two vasoactive drugs that reportedly do not change the blood flow to the fetus and therefore are drugs of choice in obstetric patients (Nagelhout et al.). An important clinical question is which vasoactive drug is best for these patients?

Studies have shown that ephedrine can cause fetal acidosis as a side effect and more so than phenylephrine; concerns about the adverse effects of phenylephrine on uterine blood flow have also been reported (Nagelhout et al., 2013). Ephedrine is a mixed acting adrenergic receptor agonist that has both alpha and beta agonist properties (Nagelhout et al.). Ephedrine's predominant beta effect causes an increase in arterial pressure by increasing cardiac output rather than by vasoconstriction (Nagelhout et al.). Phenylephrine is a pure alpha-adrenergic agonist which increases the blood pressure through peripheral vasoconstriction (Nagelhout et al.). A literature review of vasoactive

drugs conducted on animals varies in terms of the safety and efficacy of the two drugs. The results may not apply to the human populations and may not be appropriate because of the species differences (Lee et al., 2002).

The purpose of this paper was to conduct a systematic review to compare the safety and efficacy of the use of ephedrine versus phenylephrine in managing maternal hypotension during spinal anesthesia for cesarean delivery. The effect of ephedrine and phenylephrine on uteroplacental blood flow and fetal outcome will be specifically examined.

Next, the review of the literature will be presented.

Literature Review

A search was conducted using PubMed. Key terms searched were cesarean delivery, cesarean delivery complications, spinal anesthesia, hypotension, maternal hypotension, ephedrine, phenylephrine, vasoactive medications, fetal acidosis, uteroplacental blood flow and impaired fetal oxygenation. The time limit of the search was from January 2001 to January 2017.

Cesarean Deliveries and Spinal Anesthesia

Cesarean sections (C-sections) are the most commonly performed operation in the United States (US) (Gunda, Malinowski, Tegginmath, Suryanarayana & Chandra, 2010). As reported by the Center for Disease Control and Prevention, birth by C-section accounts for over 32% of all deliveries and is performed over 1.2 million times annually in the US. The indications for C-sections include fetal positioning, declining fetal status, the failure to progress, malpresentation, cephalopelvic disproportion (CPD), prematurity, prior cesarean delivery and prior uterine surgery (Nagelhout et al.).

Regional anesthesia in C-sections offers a significant benefit over general anesthesia. Spinal anesthesia provides a rapid onset of dense symmetrical anesthesia and has an endpoint of cerebrospinal fluid as confirmation of placement (Suresh, Segal, Preston, Fernando & Mason, 2012). Spinal anesthetics are relatively inexpensive and have become the preferred anesthetic because of the superior quality of surgical anesthesia, shorter onset time, less patient discomfort, and fewer complications than with epidural and general anesthesia (Suresh et al.).

Although there are several benefits to using spinal anesthesia, it is not without complications. Hypotension is the most common side effect of spinal anesthesia because of the profound sympathectomy produced (Suresh et al.).

Maternal Hypotension: Definition and Contributing Factors

Maternal hypotension is defined as a 20% decrease from baseline or a systolic pressure less than 100 mmHg (Nagelhout et al., 2013). Several factors in pregnancy physiology along with local anesthetic pharmacodynamics can contribute to the high incidence and severity of hypotension under spinal anesthesia: the level of the block; the concentration or density of the sensory block required for the procedure; local anesthetic sympathetic block; the role of aortocaval compression; and a decrease in arteriolar tone (Mercier et al., 2013).

The level of block contributes to maternal hypotension due to the vasodilating effects of the local anesthetic combined with the anatomical position at which the block is being administered and concentration of arteries and veins in the area (Miller & Pardo, 2011). The greater the concentration of the block or denisty of the block, along with the greater presence of arteries and/or veins in the anatomical area, the more likely to result in an increased sympathectomy and therefore hypotension (Miller & Pardo). Local anesthetics also cause a sympathetic block and therefore result in parasympathetic override which can result in hypotension due to a decrease in venous return to the heart, a decrease in cardiac output and a decrease in systemic vascular resistance (Miller & Pardo). Local anesthetics vasodilator effect largely impacts arteries, resulting in a decrease in arteriolar tone which can contribute to the incidence and severity of hypotension in spinal anesthesia (Miller & Pardo). This decrease in arteriolar tone is the

main mechanism and supports why vasopressors are the most important option in the management of hypotension (Mercier et al., 2013).

Aortocaval compression, defined as compression of the vena cava when lying in the supine position due to the gravid uterus, causes a decrease in venous return to the heart and therefore hypotension. This can significantly contribute to the hypotension already caused by local anesthetics vasodilation (Nagelhout, et al., 2013). Aortocaval compression is a major contributor to hypotension in pregnant women based on female physiology and is a syndrome of supine hypotension in term or near-term pregnant women (Nagelhout et al.). The compression of the vena cava can worsen when the abdomen is tense or when the uterus is larger than normal. This decrease in venous return results in a significant reduction in stroke volume and decreases cardiac output. Nagelhout et al. elaborated that the normal physiological response to aortocaval compression is tachycardia and vasoconstriction of the lower extremities. Despite this compensation, uterine blood flow and therefore fetal oxygenation is reduced. Compression of the aorta and vena cava is usually relieved by shifting the uterus to the left. Prevention of aortocaval compression is universally recommended to prevent hypotension and avoid the risk of abrupt fall in venous return and thus decreased cardiac output and blood pressure (Mercier et al., 2013). During patient placement for cesarean delivery, a wedge placed under the right hip or operating room table tilted left is used to relieve aorta or vena cava compression (Mercier et al.).

Maternal Hypotension and Fetal Acidosis with Spinal Anesthesia

Prolonged maternal hypotension may result in uteroplacental hypo-perfusion and therefore fetal acidosis (Gunda et al., 2010). Fetal hypoxia can occur when maternal

perfusion of the placenta is reduced or delivery of oxygenated blood from the placenta to the fetus is impeded (Omo-Aghoja, 2014). When fetal hypoxia is present, metabolism proceeds via an anaerobic pathway and therefore lactic acid is produced, which can accumulate and result in metabolic acidosis (Omo-Aghoja). Umbilical cord blood sampling is performed to examine blood from the fetal umbilical cord to detect fetal abnormalities (Huch, Huch & Rooth, 1994). Blood from the umbilical vein reflects the placental function whereas blood from the umbilical arteries reflects blood coming from the fetus (Huch et al.). Hypo-perfusion on the maternal side can cause a decrease in partial pressure of oxygen (PO2) in the umbilical vein; a low umbilical artery oxygen level (PaO2) indicates a risk of fetal tissue hypoxia (Huch et al.). Umbilical cord blood sampling is indicated when umbilical cord blood gas levels and percent of hydrogen (pH) are needed to aid in the diagnosis of certain conditions such as fetal acidosis (Huch et al.). Fetal acidosis is defined as a pH less than 7.16, with adverse neonatal outcomes occurring with a pH less than 7.0 (Omo-Aghoja, 2014).

The Apgar score provides an accepted and convenient method for reporting the status of the newborn infant immediately after birth (American Academy of Pediatrics, 2015). The Apgar score is comprised of five components including color, heart rate, reflexes, muscle tone, and respirations. Each element is given a score of 0, 1, or 2. The score is reported at one minute and five minutes after birth for all infants and at five - minute intervals after that for infants with a score less than 7, up to 20 minutes (American Academy of Pediatrics). The Apgar score quantifies clinical signs of neonatal depression with free signs of cyanosis, pallor, bradycardia, depressed reflex response to stimulation,

hypotonia and apnea or gasping respirations. All of these symptoms may be present when a neonate experiences fetal acidosis (American Academy of Pediatrics).

Treatment of Maternal Hypotension

Vasopressors are the most important option in the management of hypotension (Mercier et al., 2013). Ephedrine and phenylephrine are two vasoactive drugs that have been reported to not change the blood flow to the fetus and therefore are drugs of choice in obstetric patients (Nagelhout et al., 2013). Until recently, ephedrine was the more favored agent in treating maternal hypotension but several studies have shown that ephedrine risk may outweigh its benefits. As a result, there has been an increase in practitioners' use of phenylephrine to treat maternal hypotension (Mercier et al., 2013). Each drug will be briefly reviewed next.

Ephedrine: Pharmacokinetics and Indications for Treatment of Maternal Hypotension. Ephedrine is a mixed acting adrenergic receptor agonist that has both alpha and beta agonist properties (Nagelhout et al., 2013). The adopted use of ephedrine was initially supported by a study conducted by Ralston and Shnider (1974) that examined sheep to determine uterine blood flow with different vasopressors. Results showed that ephedrine preserved uterine blood flow, while drugs with increasing alpha agonist properties produced potent vasoconstriction of the uterine vascular bed. A landmark study performed by Kang in 1982 showed that a continuous infusion of ephedrine was extremely effective at preventing maternal hypotension during elective caesarean delivery versus a control group that received ephedrine only when hypotension occurred. Ralston and Shnider's study results were reinforced when McGrath et al. (1994) performed a similar study with a randomized design. These authors confirmed that unlike

phenylephrine, ephedrine improved uterine blood flow without increasing uterine vascular resistance when given after epidural anesthesia-induced hypotension. Later studies, which will be reported in the next section, compared the use of ephedrine and phenylephrine.

Phenylephrine: Pharmacokinetics and Indications for Treatment of Maternal Hypotension. Phenylephrine is a pure alpha-adrenergic agonist that increases the blood pressure through peripheral vasoconstriction (Nagelhout et al.). In the 1990s, phenylephrine began to be used more cautiously in clinical practice as a rescue vasopressor to control maternal hypotension, tachycardia and other symptoms when ephedrine had failed (Taylor & Tunstall, 1991). Subsequently, direct comparison of ephedrine and phenylephrine began to challenge the standard use of ephedrine by reporting that the pure alpha agonist produced a better umbilical artery pH (Morgan, 1994). In 2002, Lee et al. performed a meta-analysis of six trials (n=200) comparing ephedrine and phenylephrine used to treat maternal hypotension with spinal anesthesia for cesarean delivery. Results suggested that phenylephrine resulted in better umbilical arterial pH than ephedrine but no difference in the incidence of true fetal acidosis or Apgar score below 7 at 1 minute (RR of 0.77; 95% CI, 0.17-3.51) and five minutes (RR of 1.00; 95% CI, 0.21-4.83) after birth. Pooling the results showed that women given phenylephrine had neonates with higher umbilical arterial pH values than those given ephedrine (WMD = 0.03; 95% CI, 0.02-0.04, mean ephedrine umbilical arterial pH values ranging from 7.27-7.29). Also, women given phenylephrine had neonates with greater venous pH values than those given ephedrine (WMD = 0.02; 95% CI, 0.01-0.03, mean ephedrine venous pH values ranging from 7.29-7.35). The risk of true fetal

acidosis, which was defined as a pH value of <7.20, was similar between the phenylephrine and ephedrine groups (RR of 0.78; 95% CI, 0.16-3.92) (Lee et al.).

Phenylephrine has been demonstrated to be detrimental to the well-being of the fetus, based on numerous animal models (Mercier et al., 2013). When ephedrine began to be reported to cross the placental barrier easily and cause a decrease in umbilical arterial pH or ephedrine failed to treat the maternal hypotension, phenylephrine began to be used cautiously (Mercier et al.). While phenylephrine effectively prevents hypotension and provides a proper neonatal pH, it can cause bradycardia (Mercier et al.). The mechanism is thought to be due to a baroreceptor-mediated response in cardiac afterload due to increased systemic vascular resistance. The response may also be due to cardiac sympathetic denervation associated with spinal blocks which could be masked when ephedrine is used because of its beta-adrenergic chronotropic effect (Mercier et al.). This bradycardia may result in a decrease in cardiac output which can further harm the fetus (Mercier et al.). Further analysis of ephedrine and phenylephrine specific to impact on maternal hypotension and fetal outcomes is indicated.

Next, the frameworks used to guide this review will be presented.

Theoretical Frameworks

Systematic reviews and meta-analyses are a vital component of evidence-based healthcare and as such they support the development of clinical practice guidelines and inform clinical decision-making (Moher et al., 2015). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is used to accurately report high-quality systematic reviews as well as meta-analyses. PRISMA was created in 2009 after the previously used Quality of Reporting of Meta-Analysis (QUOROM) statement (1999) was revised (Atlman et al., 2009). The new PRISMA statement allows for standardization and improvement of the quality of the systematic reviews being produced (Atlman et al.). Although the PRISMA update in 2009 was thought to correct many missing pieces and to promote consistency to systematic review research, there remained the issue of how to include studies with greater than two interventions. To address this issue, experts in research added five more items to the checklist, in the methodology section (Moher et al., 2015). Since this author will only be examining two primary variables, ephedrine and phenylephrine, the 2009 PRISMA checklist, as well as the 2009 flow diagram, will be used. The flowchart was modified to include the number of articles identified, those included as well as those excluded (Moher et al., 2009). The 27-item checklist was created with items thought to be necessary for transparency of data (Moher et al.). The items on the checklist give researchers a step-by-step guide while allowing them to present their research in an accurate and succinct manner (Moher et al.).

The PRISMA statement consists of a 27 item checklist (Table 1) which lays out the requirements for evidence-based studies (Moher et al., 2009). Table 1 can be viewed on the next page. Items on the checklist include seven major sections including title,

abstract, introduction, methods, results, discussion, and funding. Within each heading are subheadings as well as descriptions defining the expectations for each of the sections. The PRISMA checklist will be used to ensure that all items required to complete a systematic review are presented in the completion of the research.

Table 1

PRISMA Checklist

Table 1. **Checklist of Items to Include When Reporting a Systematic Review or Meta-Analysis**

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Along with the checklist is the PRISMA four-phase flow diagram (Figure 1) that helps to dictate the literature search procedure (Moher et al.,). The flow chart illustrated below elucidates the screening and evaluation for eligibility within the research.

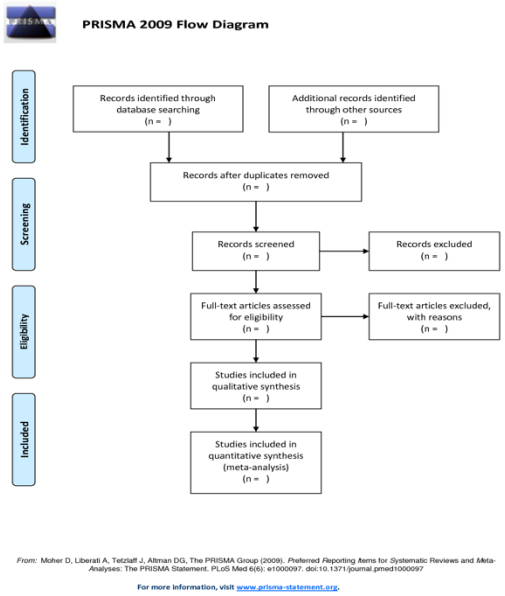

Figure 1. PRISMA Flow Diagram. This figure illustrates the PRISMA statements flow diagram used for the search strategy performed when conducting a systematic review and to evaluate the eligibility of studies.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart supports the attainment of appropriate research. This flowchart also provides a step-by-step set of instructions for articles included for analysis. The flow diagram outlines the records excluded from the study and ask for reasons why to be reported (Moher et al., 2009). It begins with the identification of articles through database searching, the screening of such items for appropriateness and eligibility, and ends with the final articles to be included within the research; the process can be reviewed in Figure

1 (Moher et al., 2009). PRISMA may also be useful for critical appraisal of published systematic reviews but is not a quality assessment instrument (Moher et al.)

The Critical Appraisal for Summaries of Evidence (CASE) worksheet (Table 2) is used to assess the quality of evidence (Foster & Shurtz, 2013) and will be used to critically appraise the studies.

Table 2

CASE Worksheet

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	Yes- Not completely- No-
Summary Methods	
2. Is the authorship of the summary transparent?	Yes- Not completely- No-
3. Are the reviewer(s)/editor(s) of the summary transparent?	Yes- Not completely- No-
4. Are the research methods transparent and comprehensive?	Yes- Not completely- No-
5. Is the evidence grading system transparent and translatable?	Yes- Not completely- No-
Summary Content	
6. Are the recommendations clear?	Yes- Not completely- No-
7. Are the recommendations appropriately cited?	Yes- Not completely- No-
8. Are the recommendations current?	Yes- Not completely- No-
9. Is the summary unbiased?	Yes- Not completely- No-
Summary Application	
10. Can this summary be applied to your patient(s)?	Yes- Not completely- No-

The CASE worksheet is comprised of 10 questions examining specificity, authorship, reviewers, methods, grading, clarity, citations, currency, bias, and relevancy

of each study (Foster & Shurtz, 2013). The researcher must answer these questions as either “yes”, “no”, or “not completely”. Traditionally, the CASE worksheet is utilized to assess the quality of point-of-care tools and treatment modalities that directly effect patient outcomes. The quality assessment data within the studies will be determined through the application of the CASE Worksheet. Each study will be appraised through answering the ten CASE worksheet questions and then all the studies will be compared based on the results and listed from highest to lowest quality, one being the highest quality and five being the lowest quality based on the CASE worksheet results.

Cross study analysis was conducted using a process called descriptive data synthesis, which can be accomplished by both a narrative and a tabulation approach (Evans, 2002). This process will be further described in the methods section.

Next, the methods used to conduct this systematic review will be discussed.

Method

Purpose of Study/Clinical Question

The purpose of this systematic review was to compare the safety and efficacy of the use of ephedrine versus phenylephrine in managing maternal hypotension during spinal anesthesia for cesarean delivery. The effects of ephedrine and phenylephrine on uteroplacental blood flow and fetal outcome was specifically examined.

The question posed was: Is either ephedrine or phenylephrine more effective and safer when used to treat hypotension during spinal anesthesia for cesarean delivery?

Outcomes Examined

The specific outcomes assessed included maternal blood pressure, maternal heart rate, fetal acidosis as measured by neonatal umbilical cord blood arterial and/or venous pH and Apgar score.

Inclusion and exclusion criteria

Inclusion criteria encompassed: studies specific to cesarean delivery with spinal anesthesia that examined: maternal hypotension; ephedrine and phenylephrine; fetal acidosis with or without Apgar scores. Only randomized control trials or systematic reviews published from January 2001 to January 2017 were included. Exclusion included any studies before January 2001 and those not meeting all of the inclusion criteria.

Search Strategy

Applying both the PRISMA flowchart as well as the PRISMA checklist, research articles were obtained from the database PubMed. The search was conducted using the terms cesarean delivery, cesarean delivery complications, spinal anesthesia, hypotension, maternal hypotension, Ephedrine, Phenylephrine, vasoactive medications, fetal acidosis,

uteroplacental blood flow and impaired fetal oxygenation. The results of the search were applied to the PRISMA flow diagram (Figure 1) to support selection for inclusion in the systematic review.

After removing any duplicates located, the investigator then assessed the remainder of the studies for inclusion criteria. Eligibility assessment was performed independently in an unblinded and unbiased standardized manner by the student researcher. Initial steps involved first reviewing both title and abstract for eligibility. The remaining studies were then further screened for eligibility through examination of the entire study and the reasons for exclusion of those that did not qualify was noted. The number of articles being used for data synthesis were identified (PRISMA, 2009).

Data Collection for Each Study

Table 3 served as a data collection table to organize pertinent data from each study. This table was used to organize and summarize information gathered from the research articles included in the study and ensured that all required criteria as stated by PRISMA were captured.

Table 3

Data Collection Tool

Method/Level of evidence & Major Variables Studied	Sample/setting	Intervention	Data Analysis	Results	limitations

Critical Appraisal Tool

The purpose of a critical appraisal is to determine how credible the study is in practice (Fineout-Overholt, Melnky, Stillwell & Williamson, 2010). The quality assessment data within the studies was determined through the application of the CASE Worksheet (Table 2) illustrated earlier in the framework section. All 10 questions examining specificity, authorship, reviewers, methods, grading, clarity, citations, currency, bias, and relevancy of each study were answered. The hierarchy of evidence for assessing healthcare research will also be used to determine the level of evidence of each study (Melnyk & Fineout-Overholt, 2011).

Descriptive data synthesis

Descriptive data synthesis can be attained by both means of a narrative and also a tabulation approach to describe the literature (Evans, 2002). Evans (2002) stated that using both narrative and tabulation data synthesis allows a more comprehensive view of the literature by decreasing limitations than if just one method was used. A narrative was completed to summarize the studies individually as well as across each study in order to identify themes and patterns. The outcome of safety and efficacy of the use of ephedrine versus phenylephrine was examined and further tabulated into more detail in Table 4, illustrated on the next page and then examined for comparisons across the studies.

Table 4

Descriptive Data Synthesis Tool

Study	Oxygen supplementation Used	Intravenous Fluid Prehydration	ASA Classification/patient characteristics	Hypotension incidence after spinal anesthesia	Spinal Solution and Technique	Umbilical artery pH	Apgar scores	N/V during case	Other important findings

Through the descriptive data synthesis and comparison across the studies, the following questions were addressed:

- Which medication causes less umbilical cord arterial and/or venous blood acidosis: phenylephrine or ephedrine?
- Which medication causes the least decrease in infant Apgar scores: phenylephrine or ephedrine?
- Was oxygen administered to the mother during c-section and could this be correlated with fetal acidosis?
- Was the mother administered IV pre-hydration prior to the spinal that could effect the incidence of hypotension seen?
- What were the characteristics of the patient studied?
- Was there a correlation between hypotension after spinal anesthesia and the spinal anesthesia medication used?
- Were there any incidental findings that can be contributed to fetal acidosis?

Next, study results will be presented.

Results

The PRISMA flowchart (Figure 2), illustrated below, along with the inclusion and exclusion criteria aforementioned, were used to further eliminate and select articles for the systematic review. After the database search, a total of 44 non-duplicate citations were screened. The abstracts of these articles were reviewed for evidence of exclusion criteria that would deem them not appropriate for the systematic review. This process eliminated a total of 22 articles. The remaining 22 articles were reviewed in their entirety for relevance and selected for the systematic review based on both exclusion and inclusion criteria. The final elimination process omitted 16 articles, leaving a total of six articles for inclusion within the final systematic review.

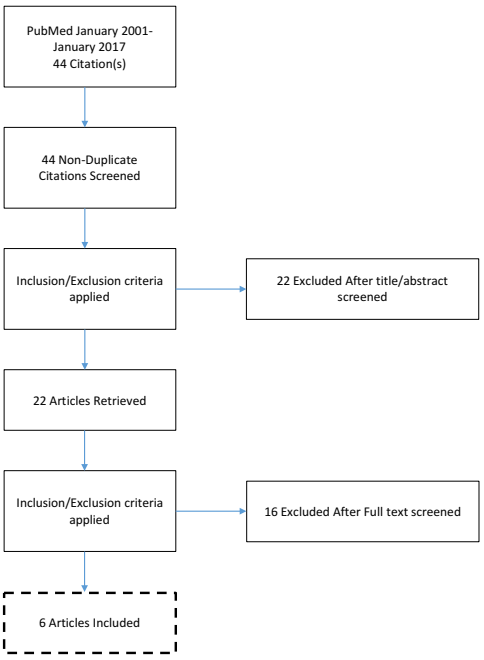

Figure 2. Search Strategy Using PRISMA Flow Diagram. This figure illustrates the search strategy performed and applies the results found to the PRISMA flow diagram.

Of the six articles that remained, five were randomized control trials and one was a retrospective observational and chart review study. The following section summarizes

each individual study as derived from the data collection tool (Appendix A) after the summary of each study, a critical analysis of the study is provided (Appendix B). The retrospective chart review will be reviewed first, followed by the RCTs which will be presented chronologically.

The retrospective observational study and chart review conducted by Cooper et al. (2010) (Appendix A-1) included 385 women with high risk pregnancies that had a cesarean section under spinal anesthesia for singleton delivery where fetal umbilical artery and venous pH were recorded. Charts were reviewed within a four-year period from 2000-2003. Once women for the study were identified, the authors then reviewed the notes, recording maternal and fetal demographic and operative data. Blood gas values, taken from a double clamped segment of umbilical cord at delivery and five minute Apgar scores assessed by a midwife upon admission to the neonatal unit were all recorded. During the study, ephedrine was routinely given as 6mg boluses and phenylephrine as 100 mcg boluses, at the discretion of the anesthetist. Phenylephrine was started at 33 mcg/min immediately following spinal injection and then titrated, aiming to keep systolic blood pressure (SBP) at baseline. The infusion rate was doubled or halved as required. The maximum infusion rate was 67 mcg/min. If there was hypotension despite the prophylactic infusion, 100 mcg boluses of phenylephrine were given. There were no guidelines for ephedrine infusion.

One hundred and twelve participants per group would give the study an 80% chance of detecting a 0.03 difference in umbilical artery pH, at P=0.05, based on a standard deviation of 0.08 for umbilical artery pH for non-elective C-section under spinal anesthesia. Secondary outcomes were the incidence of fetal acidosis (pH <7.20), low 5

minute Apgar score (<7) and admission to the neonatal unit. Mann-Whitney and Kruskal-Wallis tests were used for direct comparison of the groups and subgroups. Forward stepwise multiple regression analysis was used to find which independent variables were associated with umbilical artery pH. Results revealed that there was no difference in umbilical artery pH between the three groups on direct comparison (P=0.21). Following forward stepwise multiple regression analysis, the only variable that was associated with altered pH was non-reassuring fetal heart rate trace (P=0.71).

Critical analysis of the Cooper et al. (2010) study using the CASE worksheet (Appendix B-1) found that the study met six out of 10 criterions. The authors clearly identified the aim of the study as well as the patients that the study applied to. Although the individual authors were identified with their affiliations, their credentialing was not listed. Whether the study was edited or reviewed was also not clearly stated. The inclusion and exclusion criteria and protocol for the study were clearly stated. The study was a retrospective observational chart review study therefore level IV evidence based on the hierarchy of evidence (Melnyk & Fineout-Overholt, 2011). The protocol used in reviewing the charts was clearly stated. Although recommendations for practice were not current, they were clearly stated and multiple options for treatment were provided and could be applied to any setting and population. It was unable to be determined if there was a conflict of interest.

Cooper et al. (2002) (Appendix A-2) conducted a randomized/double blind study including 147 ASA I and II women scheduled for elective C-section of a singleton pregnancy under spinal anesthesia with no other comorbidities. Before entering the operating room, vital signs were taken three times and the lowest of the three was

considered the baseline. Baseline nausea and vomiting scores were also assessed. The participants, anesthetists, nurses and midwives involved were all blinded to the patient grouping. There were three groups: The P group received phenylephrine 100mcg/ml; the E group received ephedrine 3mg/ml; and the C group received a combination of phenylephrine 50mcg/ml combined with ephedrine 1.5mg/ml. One of four spinal anesthetics techniques was used based on provider preference. Immediately before spinal anesthesia, a preload of 10ml/kg of Hartmann solution was rapidly infused. Immediately following spinal injection, the infusion of IV vasopressor solution was started according to protocol. The patient was then positioned supine with a left lateral tilt. Systolic arterial pressure and heart rate were measured every minute. The rate of the solution was doubled or halved if the systolic arterial blood pressure (BP) fell below or above 0.75 times the baseline. Phenylephrine was started at 33mcg/min; ephedrine was started at 1mg/min or half the dose rate for each for the combination solution. The maximum nausea and vomiting score was recorded between spinal and delivery. At delivery, one of the investigators obtained umbilical artery and vein blood samples from a segment of the umbilical cord double clamped before the babies' first breath. No supplemental O2 was given to the mother prior to delivery. The APGAR scores were recorded at one and five minutes by a midwife. The Kruskal-Wallis test was used to compare the three groups. If a difference was found with the Kruskal-Wallis test, pairs of groups were then compared using the Mann-Whitney U test. The Wilcoxon signed-rank test and spearman rank test were also used to analyze data. The Wilcoxon signed-rank test was used to compare data within a group.

All participants were comparable for age, height, weight, gestation, breech presentation, previous c-section, delivery and birth weight. Forty-eight participants in the phenylephrine group (P group), 50 in the ephedrine group (E Group) and 49 in combination of phenylephrine and ephedrine solution group (C group) were studied. Fetal acidosis was less frequent in the P group (1 of 48) and less frequent in the C group (1 of 47) than in the E group (10 of 48), (overall P=0.0007). There was no difference in the incidence of fetal acidosis between the P and C groups (P=0.99). One and five min APGAR scores were normal in all three groups. Blood gas values were similar for the P and C groups; the E group had a lower umbilical artery pH than the P group (P=0.002) or the C group (P=0.009) and a lower umbilical vein pH than the P group (P=0.04) or the C group (P=0.003). There was no difference in the umbilical vein PCO2 between the groups but the E group had a higher umbilical artery PCO2 than the P group (P=0.002). There was no change in the P group from baseline N/V scores (P=0.30) but in the E and C group the N/V scores increased from baseline (E= P<0.0001) (C = P=0.007). The N/V scores were lower in the P group than in the E group (P<0.0001) or C group (P<0.0001) but there was no significant difference between the E and C groups (P=0.09). In the E group, vomiting (n=18) was associated with decreased HR and SABP and increased ephedrine doses. The incidence of fetal acidosis and vomiting at cesarean delivery under spinal anesthesia was reduced by giving phenylephrine alone or in combination with ephedrine versus giving ephedrine alone.

The CASE worksheet was then applied to the study by Cooper et al. (2002) (Appendix B-2). The study was found to meet seven out of ten criteria. The aim of the study was clearly stated as well as the patients that the summary applied to. The

individual authors were listed along with their credentialing and affiliations. It was not clearly stated that the study had been edited and reviewed. The inclusion and exclusion criteria were clearly stated as well as the protocol followed for the study. This study was a randomized double-blinded study which is level II evidence (Melnyk & Fineout-Overholt, 2011). The study stated that randomization was performed by randomly allocating patients by envelope selection to one of three groups and that all participants and investigators were blinded to the group and that unlabeled syringes were used. A third party not involved in the study opened the envelope and handed the appropriate medication to the investigator. The recommendations were clearly stated and multiple options for treatment were provided. The recommendations were from 2002 and therefore not current. It was unable to determine if there was a conflict of interest between the recommendation of the summary and the sponsor for any author. The evidence and setting for this study applies to many populations and settings.

Ngan Kee et al. (2008) (Appendix A-3) performed a randomized double blind study of 204 ASA I and II women with singleton pregnancies scheduled for non-elective C-section for which spinal anesthesia was decided upon for clinical reasons at any point in time. Standard monitoring was applied. No IV prehydration was given. Spinal anesthesia was induced with the patient in the right lateral position at L3-4 or L4-5 with 2.0-2.2 ml of hyperbaric 0.5% bupivacaine (10-20 mg) and fentanyl 15 mcg. The patients were then immediately turned to supine with a left lateral tilt and a rapid IV co-hydration with up to 2 liters of lactated ringer's solution was administered and oxygen of 6-8 L/min delivered by clear facemask until delivery. Participants were randomized to receive an IV bolus of either phenylephrine 100 mcg (group P) or ephedrine 10 mg (group E)

immediately after each episode of hypotension. Umbilical arterial (UA) and umbilical venous (UV) blood samples from double-clamped segments of umbilical cord were obtained. The attending pediatrician assessed APGAR scores at one and five minutes after delivery. Univariate intergroup comparisons were made using the unpaired student's t-test or the Mann-Whitney U-test as appropriate. Nominal data were compared using the Chi-Square test or Fisher's exact test.

The number of doses of vasopressor required was similar between groups. More participants had nausea or vomiting in the E group than the P group (13/102 (12.7%) vs 4/102 (3.9%), P=0.02). There was no difference between groups in the primary outcome, UA pH. In the E group, two cases had a UA pH <7.0 compared with no cases in the P group (P=0.50). The UA PO2 was lower in the P group vs the E group (median difference 0.23 [95% CI of difference 0.20-0.45]; P=0.032) and UV PO2 was lower in the P group vs the E group (Median difference 0.39 [95% CI of difference 0.08-0.70; P=0.012). However, there was no difference between groups in UA or UV oxygen content. There was no difference between groups in the clinical outcome of the neonates. Both phenylephrine and ephedrine are suitable vasopressors for use in non-elective C-sections.

The study by Ngan Kee et al. (2008) was then critically appraised using the CASE worksheet (Appendix B-3). The study met six out of 10 criterions. The aim of the study was clearly stated as well as the patients that the study applied to. Although the individual authors and their affiliations were listed in the study, their credentialing was not. It was not clearly stated that the study was edited or reviewed. The inclusion and exclusion criteria were clearly stated as well as the protocol for the study. The study is level II

evidence being that it is a randomized double-blinded study (Melnyk & Fineout-Overholt, 2011). The study stated that randomization was performed using computer generated codes contained in opaque, sealed and sequentially numbered envelopes as well as medications prepared in identical syringes by someone not involved in the study. Recommendations were clearly stated and multiple options for treatment were provided. The recommendations are not current as the study was completed in 2008. It was unable to determine if there was a conflict of interest between the recommendation of the summary and the sponsor for any author. The evidence and setting for this study applies to many populations and settings.

A randomized double blind study by Prakash et al. (2010) (Appendix A-4) studied 60 ASA I women with singleton pregnancies scheduled for elective caesarean delivery under spinal anesthesia. Standard monitoring was applied. Each patient also received a 10ml/kg IV infusion of Lactated Ringers solution over 15-20 min before spinal anesthesia. With participants in the left lateral position, 2ml 0.5% Hyperbaric Bupivacaine was injected intrathecally at L3-4. Oxygen 6L/min via face mask was given until delivery. Participants were divided into two groups: P group (phenylephrine) and E group (ephedrine). Group E received 1ml bolus of ephedrine 6mg/ml; group P received a 1 ml bolus of phenylephrine 100 mcg/ml. Additional boluses were administered if the systolic pressure remained at or below 80% of baseline. The incidence of nausea and vomiting, arterial and venous blood samples from a double clamped segment of the umbilical cord and Apgar scores at one, five and ten minutes were determined by the attending pediatrician and all were recorded. Descriptive statistics were calculated for

continuous variables as mean and standard deviation and for categorical variables as frequency of distribution and percentage.

The two groups were comparable in age, weight, height, baseline hemodynamic data and dermatomal sensory levels. Apgar scores at one, five and ten minutes were comparable in the two groups with no neonate having an Apgar score < 7 at any time. No umbilical artery pH was less than 7.20. Umbilical artery and venous pH were significantly lower in group E than in group P (p=0.01 and P=0.002). Results showed that 100 mcg bolus doses of phenylephrine were as effective as 6 mg bolus doses of ephedrine in the treatment of hypotension following spinal anesthesia in term parturients undergoing c-section delivery. Neonates of women treated with phenylephrine had higher umbilical cord pH though true fetal acidosis was not seen in any neonate.

The study by Prakash et al. (2010) was also critically appraised using the CASE worksheet (Appendix B-4). The aim of the study was clearly stated as well as the patients that the study applies to were well described. The individual authors and their affiliations were listed but credentialing was not. It was not clearly stated if the study was edited or reviewed. The inclusion and exclusion criteria were clearly stated as well as the study protocol that was followed. This study was a randomized double-blinded study making it level II evidence (Melnyk & Fineout-Overholt, 2011). The randomization was performed by computer generated number allocation and identical syringes prepared by someone not involved with data collection were utilized. Recommendations for practice were clearly stated and multiple options for treatment were provided. The recommendations are from 2009 and therefore not current. It was unable to determine if there is a conflict of interest

between the recommendation of the summary and the sponsor for any author. The evidence and setting for this study applies to many populations and settings.

A randomized double blind study completed by Mercier et al. (2013) (Appendix A-5) included 42 ASA I and II women with singleton pregnancies scheduled for caesarean section delivery under spinal anesthesia. Standard monitors and oxygen via nasal cannula were applied. Baseline vitals signs were obtained. Intravenous preload of 15ml/kg Lactated Ringer's solution was given prior to spinal anesthesia of 11mg of hyperbaric 0.5% Bupivacaine, 2.5 mcg Sufentanil and 0.1 mg morphine at L2/3 or L3/4. A prophylactic vasopressor IV infusion was started at the end of spinal injection. Participants received either 2mg/min ephedrine plus 10 mcg/min phenylephrine (E+P group) or 2mg/min ephedrine alone (E group). Infusions were halved, stopped or doubled based on study protocol. Groups were compared for single parametric, ordinal and nominal variables using unpaired student *t* test, the Mann-Whitney U test, and Fisher exact test, respectively. Hemodynamic values over time were compared using analysis of variance for repeated measures, followed by Dunnett tests.

Participants were all comparable for demographic characteristics, gestational age, neonatal weight, upper sensory level of anesthesia, time from spinal anesthesia to incision, time from spinal anesthesia to delivery and from uterine incision to delivery, baseline SBP and maternal HR. Umbilical venous and arterial pH values were significantly higher in the E+P group. The incidence of arterial pH <7.20 was 31% higher in the E+P group and 63% in the E group (P=0.09). However, Apgar scores at one and five minutes were similar in both groups and were never less than 7. Low venous and arterial pH values were associated only with the E group assignment and spinal

anesthesia to delivery times longer than 33 min. Compared with ephedrine alone, ephedrine plus phenylephrine infusions decreased the incidence of hypotension by approximately 50%, abolished maternal tachycardia and improved venous and arterial pH.

The CASE worksheet was applied to the study by Mercier et al. (2013) (Appendix B-5). The study met seven out of 10 criterion of the CASE worksheet. The aim of the study was clearly stated and the patients that the aim applied to were well described. The individual authors were listed along with their credentialing and affiliations. The inclusion and exclusion criteria were clearly stated and a protocol for the study was stated and followed. This study was a randomized double-blinded study therefore making it level II evidence (Melnyk & Fineout-Overholt, 2011). The study stated that randomization was performed by using numbered, sealed, opaque envelopes ensuring both the patient and investigators were blinded to group assignment and study solutions were prepared by those not involved in the patient's care and according to the group indicated by the envelope. There was an investigator present during the study period to confirm comparability and routine procedures. The recommendations for practice were clearly stated and multiple options for treatment were provided even though the evidence was not considered current. It was unable to determine if there was a conflict of interest between the recommendation of the summary and the sponsor for any author. The evidence and setting for this study applies to many populations and settings.

Moslemi & Rasooli (2015) (Appendix A-6) performed a randomized double blind study which included 83 healthy pregnant women with gestational age of 36 weeks or greater for elective cesarean section under spinal anesthesia. Participants were assigned to

three different groups: phenylephrine (group Ph), ephedrine (group E) and placebo (group P). Standard monitoring was applied. Prior to spinal anesthesia, all participants received a 500 ml crystalloid bolus. Infusion of study drugs were: group Ph received 450 mcg of phenylephrine in 250 ml; group E received 45 mg of ephedrine in 250 ml; and group P received an infusion of only 250 ml normal saline. The participants then received spinal anesthesia in the sitting position at L4/5 or L3/4 with 2.5 ml of Bupivacaine 0.5% (12.5mg) and 2.5 mcg of Sufentanil. After delivery and clamping of the umbilical cord, 1ml of blood was drawn from the umbilical artery for neonatal blood gas analysis. One minute and five minute APGAR scores were recorded as well as the umbilical artery blood gas analysis. Any decrease in BP of about 20% from baseline was treated with 50-100 mcg phenylephrine in pH group or 5-10 mg ephedrine in E and P groups. Data were analyzed using a one-way ANOVA for quantitative variables and Fishers exact probability tests and chi-square for qualitative variables and associations. Multiple comparisons were tested by post-hoc with Turkey technique. Normal distributions of data were evaluated by Kolmogorov-Smirnov normality test.

There was no significant difference in demographic data. Indications for c-section included repeated c-section (n=53), other indications (n=25) and patient preference (n=4). Additional doses required for the treatment of hypotension was higher in groups E (65.2%, n=15) and P (80%, n=20) than in group Ph (28.57%, n=10). There was a significant difference in the 5 min APGAR scores which was better with group Ph and E rather than group P (P=0.002). Umbilical artery (UA) blood gas analysis showed a significant difference in pH and PCO2 between Ph and P groups. Two neonates in the Ph group, seven in the E group and five in the P group had acidosis. Acidosis was

significantly lower in phenylephrine group (P=0.043). Overall results showed that for women who underwent spinal anesthesia for elective c-section, SBPs and neonatal UA pH were best maintained with a prophylactic infusion of phenylephrine compared with those who did not receive it and were even better than those who received prophylactic ephedrine.

Finally, the study by Moslemi & Rasooli (2015) was critically appraised using the CASE worksheet (appendix B-6). The study met eight out of 10 criterion. The aim of the study was clearly stated and the patients that the study applied to were well described. The individual authors were listed along with their credentialing and affiliation. It was not clearly stated if the study was edited or reviewed. The inclusion and exclusion criteria were clearly stated as well as the protocol used. This study was a randomized clinical trial making it level II evidence (Melnyk & Fineout-Overholt, 2011). The study stated that randomization was performed using a table of random numbers and computer generated randomization list. Recommendations for practice were clearly stated and multiple options for treatment were provided; the recommendations were from 2015 making them current. It was unable to appropriately assess if there was a conflict of interest between the recommendation of the summary and the sponsor for any author. The evidence and setting for this study applies to many populations and settings.

Cross Study Analysis

All but one of the studies included in this systematic review were randomized control trials; the Cooper et al. (2010) study was a retrospective chart review study. Descriptive data synthesis of the included studies are illustrated in Appendix C. Key variables were identified and analyzed across the six studies. All six studies had different

intervention groups; some included a combination of medications and some contained a placebo group. The sample size for all six studies were comparable and appropriate to determine statistical significance at the level of $P<0.05$ in all the studies.

The use of oxygen supplementation was determined to be beneficial in the time preceding fetal umbilical clamping and is associated with higher maternal and fetal oxygen levels (Chatmongkolchart & Prathep, 2013). Cooper et al. (2002) reported that they did not use supplemental oxygen at any time before delivery of the neonate, whereas Ngan Kee et al. (2008), Prakash et al. (2010) and Mercier et al. (2013) all administered supplemental oxygen to participants. Mercier et al. (2013) reported an unknown amount of oxygen administered via nasal cannula whereas both Ngan Kee et al. (2008) and Prakash et al. (2010) both reported administration of oxygen via facemask of 6-8 liters. Moslemi and Rasooli, (2015) and Copper et al. (2010) did not report on whether their participants were given any oxygen supplementation. Since this use of oxygen supplementation was demonstrated to be beneficial in other studies (Ngan Kee et al.,2008; Mercier et al. (2013), Prakash et al.,2010), results of the Cooper et al. (2002) study could have provided results of more fetal acidosis when compared to a similar study with the use of supplemental oxygenation. The Cooper et al. (2002) study did find that a lower pH was more frequent with ephedrine (10 out of 48) than with phenylephrine (1 out of 48) or combination of both groups (1 out of 47) (overall $P=0.0007$) but puts into question that if supplemental oxygen was given, would there be as many neonates with a low pH in the ephedrine group?

The use of fluid prehydration before spinal administration has been demonstrated to decrease the incidence of hypotension caused from spinal anesthesia (Riley, Cohen,

Rubenstein & Flanagan, 1995). Cooper et al. (2002), Prakash et al. (2010), Mercier et al. (2013) and Moslemi and Rasooli (2015) all administered some sort of prehydration to their participants. Cooper et al. (2002), Prakash et al. (2010) and Mercier et al. (2013) all administered a weight-based amount of fluid, while Moslemi and Rasooli (2015) only administered a set 500ml boluses of prehydration to participants. Cooper et al (2010) did not report on whether any prehydration was administered. Ngan Kee et al. (2008) did not administer any hydration before spinal anesthesia but instead administered up to two liters of Lactated Ringers solution as needed after spinal anesthesia was given. Although the use of prehydration has been demonstrated to be helpful (Riley et al., 1995) it did not seem to effect the variables in question. For example, in the Ngan Kee et al. (2008) no prehydration was used and only 2 out of 102 neonates in the ephedrine group experienced acidosis versus none in the phenylephrine group.

In 1941 the American Society of Anesthesiologists (ASA) published a booklet for it's members containing the first version of a 'physical status' classification for patients about to undergo surgery (Fitz-Henry, 2011). The function of ASA classifying is to quantify the amount of physiological reserve that a patient possesses at the time of the assessment for a surgical procedure (Fitz-Henry, 2011). This may change before the patient actually undergoes the procedure, either by optimization and improvement of their physical state or because they deteriorate and have less reserve (Fitz-Henry). All of the studies but one included patients that were healthy individuals of ASA classification I or II with similar characteristics (none to mild systemic disturbances). Cooper et al. (2010) examined high risk singleton pregnant subjects with a number of different comorbidities such as prematurity, diabetes, labor problems, pregnancy induced hypertension and

hypotension. High risk parturients have the potential for fetal complications such as fetal acidosis and therefore cannot be compared to non-high risk parturients or healthy ASA class I or II patients. For this reason, the Cooper et al. (2010) study results are not comparable to the other five studies included in this systematic review.

The spinal solution used may effect the incidence of hypotension due to where the site of action of the anesthetic tends to be (Miller & Pardo). Hyperbaric solutions are heavier and tend to be lower within the intrathecal space and therefore may cause less sympathectomy (Miller & Pardo). Since spinal anesthesia height is based on the concentration and solution and not the volume of anesthesia, larger volumes give higher blockade and therefore more sympathectomy leading to increased incidences of hypotension (Miller & Pardo). Moslemi and Rasooli (2015) used 2.5 ml of Bupivacaine 0.5% (12.5mg) with 2.5 mcg of Sufentanil. Mercier et al. (2013) administered 11mg of hyperbaric 0.5% Bupivacaine, 2.5 mcg Sufentanil and 0.1 mg morphine. Prakash et al. (2010) administered 2ml 0.5% Hyperbaric Bupivacaine. Ngan Kee et al. (2008) administered 2.0-2.2 ml of hyperbaric 0.5% bupivacaine (10-20 mg) and fentanyl 15 mcg. Cooper et al. (2010) reported no detail of solutions used but did report they were not consistent. Cooper et al (2002) reportedly used four different techniques which were chosen based on preference by whomever was administering the spinal anesthetic.
As described previously, local anesthetics can cause a sympathetic block, resulting in parasympathetic override. This can produce hypotension due to a decrease in venous return to the heart, a decrease in cardiac output and a decrease in systemic vascular resistance (Miller & Pardo). The height of spinal anesthesia necessary for cesarean section delivery has the increased incidence of hypotension due to this sympathectomy.

Copper et al. (2010) reported the incidence of hypotension to be a systolic blood pressure less than 90 mmHg and was found to be 6.1% in the no vasopressor group 17% in the Ephedrine and 20% in the Phenylephrine group (P=0.005). Cooper et al. (2002) reported that the lowest SABP recorded was higher in the P group (80% [73-88] of baseline) than in the E group (73% [61-87] of baseline) (P=0.02) but the C group (77% [69-86] of baseline) was not significantly different from the P (P=0.14) and E (P=0.25) groups. The proportion of SABP readings below 80% of baseline was lower in the P group (0% [0-8]) (P+0.007) and in the C group (4% [0-10]) (P+0.04) than in the E group (8% [0-20]), but there was no difference between the P and C groups (P=0.55). Ngan Kee et al. (2008) reported an overall incidence of hypotension to be 74/102 (73%) of participants in the P group and 74/102 (73%) of the E group had one or more episodes of hypotension (P=0.52) and required one or more boluses of vasopressor. Prakash et al. (2010) reported that the mean change in systolic pressure was comparable in the two groups with the minimum being 100 in the E group and 93 in the P group (P=0.114) except at 8 minutes where E group was lower (P=0.004). Mercier et al. (2013) reported the incidence of hypotension was halved in the E+P (37%) group when compared with the E (75%) group (P=0.02). SBP values after onset of spinal anesthesia were not significantly different between the two groups. Moslemi, F., & Rasooli, S. (2015) reported SBP after anesthesia every two and every five minutes were different (P>0.050) in the Ph and P groups. Overall, the volume of spinal anesthetic was comparable across the studies as well as the incidence of hypotension after the spinal administration and consequently does not support identifying it as a contributing factor to the outcome of fetal acidosis.

The main focus of this systematic review was to determine if ephedrine or phenylephrine cause more or less fetal acidosis through the diversion of fetal blood flow, potentially causing more harm than good when given to woman experiencing hypotension (Nagelhout et al). . acidosis is determined through the umbilical cord blood pH, specifically the artery. Fetal acidosis is defined as a pH less than 7.16 (some texts state 7.20), with adverse neonatal outcomes occurring with a pH less than 7.0 (Omo-Aghoja, 2014). Cooper et al. (2010) and Cooper et al. (2002) both found there was no true fetal acidosis but Cooper et al. (2002) did find that a lower pH was more frequent with ephedrine (10 out of 48) than with phenylephrine (1 out of 48) or combination of both groups (1 out of 47) (overall P=0.0007). The ephedrine group had a lower umbilical artery pH than the phenylephrine group (P=0.002) or the combination group (P=0.009). Ngan Kee, et al (2008) similarly found no statistical difference between the groups they studied for fetal acidosis (p=0.70). However, in the ephedrine group there were two cases (out of 102 cases) with umbilical artery pH less than 7.0 compared with no cases in the phenylephrine group (p=0.50). Prakash et al. (2010) again found that no umbilical artery pH was less than 7.20 but that umbilical artery and venous pH were significantly lower in the ephedrine group than in the phenylephrine group (p=0.01 and P=0.002) but never reached true acidosis.

Mercier et al. (2013), unlike the other studies, never used phenylephrine alone as an intervention group; instead one group was given a combination of ephedrine and phenylephrine and the other was given just ephedrine alone. They found that umbilical venous and arterial pH values were significantly higher in the ephedrine and phenylephrine combination group (average = 7.24) than in the ephedrine alone group

(average = 7.19) (P=0.05). The incidence of arterial pH <7.20 was 31% in the ephedrine and phenylephrine combination group and 63% in the ephedrine alone group (P=0.09). Interestingly, Moslemi and Rasooli (2015) used three different intervention groups: phenylephrine alone; ephedrine alone; and a placebo group that received no medication. Umbilical artery blood gas analysis showed a significant difference in pH. Two neonates out of 30 in the phenylephrine group, seven out of 27 in the ephedrine group and five out of 26 in the placebo group had acidosis. Acidosis was significantly lower in phenylephrine group (P=0.043).

Overall, out of all groups included in the different studies, the phenylephrine group alone provided a higher pH than any other group alone or in combination but the incidence of true fetal acidosis of a pH less than 7.16 (or 7.20) was extremely low and thus insignificant. In all six studies, Apgar scores at one and five min were similar and there were no statistically significant findings except for Moslemi and Rasooli (2015) who found that there was a significant difference in the 5 min APGAR scores which was better in the phenylephrine and ephedrine groups rather than the placebo group (P=0.002). These findings suggest that the Apgar score does not depict neonatal outcome.

Incidentally, nausea and vomiting were frequently studied. Nausea and vomiting is a side effect of hypotension but the correlation of nausea and vomiting specific to ephedrine or phenylephrine had not been studied. Cooper et al. (2002) and Ngan Kee et al. (2008) both examined nausea and vomiting in the intervention groups and both found that there was more nausea and vomiting in the ephedrine groups. Cooper et al. (2002) found that there was no change in the phenylephrine group from baseline nausea and vomiting (P=0.30) but in the ephedrine and combination of phenylephrine and ephedrine

group the nausea and vomiting increased from baseline (E= $P<0.0001$) (C = $P=0.007$). There was no significant different between the ephedrine and combination groups ($P=0.09$). In the E group vomiting (18 out of 48) was associated with decreased heart rate and systolic blood pressure and increased ephedrine doses.

Next, the summary and conclusions will be presented.

Summary and Conclusions

Hypotension during cesarean section delivery can have detrimental effects on both the mother and the neonate (Lee et al., 2002). These effects include decreased uteroplacental blood flow, impaired fetal oxygenation with asphyxial stress and fetal acidosis (Lee et al.). Some vasoactive medications have been found to be detrimental to the neonate and divert fetal blood flow, potentially causing more harm than good in pregnant women (Nagelhout et al., 2013). Studies have shown that ephedrine can cause fetal acidosis as a side effect and more so than phenylephrine; concerns about the adverse effects of phenylephrine on uterine blood flow have also been reported. Ephedrine is a mixed acting adrenergic receptor agonist that has both alpha and beta agonist properties. Ephedrine's predominant beta effect causes an increase in arterial pressure by increasing cardiac output rather than by vasoconstriction. Phenylephrine is a pure alpha-adrenergic agonist which increases the blood pressure through peripheral vasoconstriction (Nagelhout et al.). A literature review of vasoactive drugs conducted on animals varied in terms of the safety and efficacy of the two drugs. The results may not apply to the human populations and may not be appropriate because of the species differences (Lee et al., 2002).

This systematic review compared these two drugs and their efficacy on fetal and maternal outcomes, specifically examining fetal acidosis through umbilical artery pH testing. Outcomes assessed were maternal hypotension, spinal anesthetic used, supplemental oxygenation, intravenous prehydration, ASA classification and Apgar score. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart assisted in identifying appropriate research by providing a step-by-

step approach with instructions related to those to be included as well as those to exclude (Moher et al., 2009). Each included study was then illustrated in a table in order to identify key variables being researched. The studies were then critically appraised using the CASE worksheet (Foster & Shurtz, 2013). Finally, a cross study analysis was done to examine key outcomes across the studied variables.

No direct conclusion can be drawn from any of the specific variables and their effect on fetal acidosis mainly due to the differences in study design (oxygen supplementation; ASA classification; IV fluid prehydration; hypotension incidence after spinal anesthesia; spinal solution and technique; umbilical artery pH; Apgar scores; nausea and vomiting during the case).

Related to oxygen supplementation, some of the studies reported the use of oxygen supplementation whereas some did not report on the use while others reported no use. Since the use of oxygen supplementation was demonstrated to be beneficial in three studies, (Ngan Kee et al. [2008], Prakash et al. [2010] and Mercier et al. [2013]), studies where no supplemental oxygen was used could have potentially resulted in more fetal acidosis when compared to a similar study with the use of supplemental oxygenation.

High risk parturients have the potential for fetal complications such as fetal acidosis and therefore cannot be compared to non-high risk parturients or healthy ASA class I or II patients. For this reason, results of the Cooper et al. (2010) study, which included all high risk parturients, are not comparable to the other five studies included in this systematic review due to the high risk nature of the patients included.

Cooper et al. (2002), Prakash et al. (2010), Mercier et al. (2013) and Moslemi and Rasooli (2015) all administered some sort of prehydration to their participants. Cooper et

al. (2010) did not report on whether any prehydration was administered. Ngan Kee et al. (2008) did not administer any hydration before spinal anesthesia but instead administered up to two liters of Lactated Ringers solution as needed after spinal anesthesia was given. The late use of IV hydration or none use could have contributed to hypotension experienced during spinal anesthesia.

Overall, the volume of spinal anesthetic was comparable across the studies as well as the incidence of hypotension after the spinal administration. Consequently, this does not support identifying it as a contributing factor to the outcome of fetal acidosis.

In examining umbilical artery pH, Cooper et al. (2002), Cooper et al. (2010), Ngan Kee, et al. (2008), Moslemi and Rasooli (2015) , and Prakash et al. (2010) found that no umbilical artery pH < 7.20; however, umbilical artery and venous pH were significantly lower in the ephedrine group than in the phenylephrine group but never reached true acidosis. In contrast, Mercier et al. (2013) used a different study design and found that umbilical venous and arterial pH values were significantly higher in the ephedrine and phenylephrine combination group (average = 7.24) than in the ephedrine alone group (average = 7.19) (P=0.05).

In all six studies, Apgar scores at one and five min were similar and there were no statistically significant findings except for Moslemi and Rasooli (2015). These researchers found that there was a significant difference in the 5 min APGAR scores, which were better in the phenylephrine and ephedrine groups as compared to the placebo group (P=0.002).

There was no difference between the two vasopressors in the incidence of true fetal acidosis but it is clear that the use of phenylephrine was associated with a better fetal

umbilical artery pH than in those women given ephedrine. Two of the studies included in this systematic review included nausea and vomiting as a variable and found that there was an increased incidence of nausea and vomiting with the administration of ephedrine. Incidentally, Cooper et al. (2002) and Ngan Kee et al. (2008) both examined nausea and vomiting in the intervention groups. Both authors found that there was more nausea and vomiting in the ephedrine groups.

Limitations associated with this systematic review included that not all studies reported on the use of oxygen supplementation in their participants. The dosages, medications used and groups within the studies all varied across the studies, making comparisons difficult. The sample sizes of some of the studies were small and the participants included in five out of the six studies were all healthy women undergoing elective c-section delivery, so extrapolation to situations where fetal compromise is present or to emergency C-section delivery is challenging. The use of IV prehydration may effect the incidence of hypotension and since some studies reported they did use it and some did not, it is difficult to make comparisons across them.

In summary, this systematic review supports the cautioned use of ephedrine over phenylephrine in the obstetric patient experiencing maternal hypotension during spinal anesthesia for elective cesarean section delivery, despite limitations. The use of phenylephrine was associated with better fetal pH status than ephedrine.

Recommendations and implications for advanced nursing practice will be discussed in the next section.

Recommendations and Implications for Advanced Nursing Practice

Systematic reviews provide a succinct review and critical analysis of existing research studies regarding the same subject matter and can therefore offer key information for evidence based practice. Certified Registered Nurse Anesthetists aim to provide the safest care to all their patients and in doing so they rely on current evidence-based knowledge found through thorough research to guide their practice. The incidence of hypotension after spinal anesthesia can not always be prevented but the vasopressor used for treatment can be chosen using critical thinking and evidence-based knowledge found through research.

Although the occurrence of true fetal acidosis could not be determined with the use of either ephedrine or phenylephrine in the reviewed studies, the incidence of a higher pH with phenylephrine should be taken in to consideration when choosing the best vasopressor. Both ephedrine and phenylephrine groups had similar efficacy for preventing or treating hypotension and there was no difference in clinical neonatal outcome as measured by Apgar scores. Nevertheless, the objective of obstetric anesthesia practice is to deliver the fetus in the best condition possible. The studies included reported on the higher incidence of a lower normal pH with ephedrine. Caution should also be taken with the use of ephedrine as the sole vasopressor of choice in obstetric anesthesia and particularly in cases where there is an already increased risk of fetal acidosis.

Continuing education on the indications, dosages and side effects of both phenylephrine and ephedrine should be obtained prior to their use. No vasopressor alone shows benefit over the other but caution should be used based on their side effects.

Ephedrine results in lower pH values but true acidosis has not been seen and phenylephrine's primary alpha agonist properties promote it's side effect of bradycardia. Due to this, patients experiencing bradycardia should not be given phenylephrine as a vasopressor because of the risk of worsening bradycardia. Based on the incidental finding of nausea and vomiting associated with ephedrine use, caution should be taken with the use of ephedrine in patients at high risk for nausea and vomiting or those already experiencing such. Systematic reviews are intended to provide up to date information regarding the latest, safest and most effective methods of anesthesia care. This information can be used not only to improve the practice of existing practitioners, but also become incorporated in the curriculum of institutions training future CRNAs.

No recommendations on policy change can be made when it comes to the use of ephedrine and phenylephrine in choosing one over the other. Based on the conclusion of this systematic review, both medications are acceptable for use in practice. Caution should be taken with the use of ephedrine due to the outcome of lower normal pH than phenylephrine, especially in patients with risk of fetal acidosis.

Further randomized controlled trials need to be conducted with larger sample sizes and and including key variables aforementioned.. Through this research, practitioners may be able to better gauge the use of ephedrine and phenylephrine in their everyday practice. A separate study on the incidence of ephedrine-induced post-operative nausea and vomiting should be completed to determine its role in the matter. These studies would be essential in developing even safer and more effective protocols in obstetric anesthesia.

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Appendix A-1

Data Collection Tool

Cooper, D. W., Sharma, S., Orakkan, P., & Gurung, S. (2010). Retrospective study of association between choice of vasopressor given during spinal anesthesia for high-risk caesarean delivery and fetal pH. *International Journal of Obstetric Anesthesia*, *19*(1), 44-49.

Method/Level of evidence & Major Variables Studied	**Sample/ Setting**	**Intervention**	**Data Analysis**	**Results**	**Limitations**
Retrospective observational study and chart review over a 4-year period from 2000-2003 Level III (Retrospective cohort study) Maternal: blood pressure Fetal: 5 min Apgar score, umbilical	Charts reviewed were those in the 4-year period of 2000-2003, women with high risk pregnancies that had a cesarean section under spinal anesthesia for singleton delivery where fetal umbilical artery and venous pH were recorded and these participants either received ephedrine	Once women for the study were identified, the authors then reviewed the notes, recording maternal and fetal demographic and operative data. Blood gas values, taken from a double clamped segment of umbilical cord at delivery, 5 min Apgar scores assessed by a midwife and admission to the neonatal unit were all recorded. During the period of the study, ephedrine was routinely given as 6mg boluses and phenylephrine as 100 mcg boluses, at the discretion of the anesthetist. Phenylephrine infusion was recommended	Primary outcome was umbilical artery pH. 112 participants per group would give the study an 80% chance of detecting a 0.03 difference in umbilical artery pH, at P=0.05 based on a standard deviation of 0.08 for umbilical artery pH for non-elective C-section under spinal anesthesia. Secondary outcomes were the incidence of fetal acidosis (pH <7.20), low 5 min Apgar score (<7) and admission to the neonatal unit. Mann-Whitney and Kruskal-Wallis tests were used for direct comparison	The no vasopressor, ephedrine and phenylephrine groups were similar for demographic data but there were differences for diabetes (P=0.042), previous C-section (p=0.19), pregnancy induced hypertension (P=0.003), spinal local anesthetic dose (P=0.006) and hypotension (P=0.005). The median total dose of ephedrine given before delivery was 12mg; the median total dose of phenylephrine in given before delivery was 200 mcg. The authors were unable to find accurate records of the dose of vasopressor given by infusion. 13% of the ephedrine group were given a second line vasopressor (median total dose 200 mcg) compared with 5% of the	Low doses of ephedrine used, cofounding variables were not examined. Prematurity and labor may have contributed to the lack of difference between the vasopressor groups in this high risk study by reducing hypotension and therefore, vasopressor requirements. Urgent nature of the surgery for many of the high risk cases may also have reduced the difference between the groups by reducing the spinal delivery interval.

artery and venous pH values	boluses, ephedrine infusion, phenylephrine bolus or phenylephrine infusion for low blood pressures No vasopressor n=115 Ephedrine total n=122 (Ephedrine bolus n=110 Ephedrine infusion n= 12) Phenylephrine total n=148 (Phenylephrine bolus n=51 Phenylephrine infusion n=97)	only to be given according to a standard protocol, which had been developed for a prospective study completed in 2001 at our hospital. Phenylephrine was started at 33 mcg/min immediately following spinal injection and then titrated aiming to keep systolic blood pressure (SBP) at baseline. The infusion rate was doubled or halved as required. The Max infusion rate was 67 mcg/min. If there was hypotension despite the prophylactic infusion, 100 mcg boluses of phenylephrine were given. There were no guidelines for ephedrine infusion. Criteria for admission to the neonatal unit were gestation <34 weeks, weight <1800g or poor condition.	of the groups and subgroups. Forward stepwise multiple regression analysis was used to find which independent variables were associated with umbilical artery pH. The potential explanatory variables entered into the multiple regression analysis were choice of vasopressor, method of administration, time period, maternal age, maternal height, maternal weight, gestational age, fetal weight, previous C-section, spinal dose, spinal delivery interval, hypotension, direct involvement of a consultant obstetrician. Data were analyzed using SPSS version 12. P = <0.05 was regarded as statistically significant	phenylephrine group (all ephedrine boluses, median total dose 9 mg) (P=0.014). There was no difference in umbilical artery pH between the three groups on direct comparison (P=0.21). Following forward stepwise multiple regression analysis, the only variable that was associated with altered pH was non-reassuring fetal heart rate trace (P=0.71). On direct comparison there was no difference in the incidence of umbilical artery pH <7.20 (P=0.21), or 5 min Apgar score <7 (0.089), between the groups, but there was a difference in the incidence of admissions to the neonatal unit (0.040), 37% of patients in the phenylephrine group were admitted, 23% in ephedrine group and 33% in no vasopressor group. The authors observations for umbilical artery pH differ from those in low risk participants which show a higher pH with phenylephrine.	There was no accurate record of maternal oxygen administration which can affect umbilical venous PO2. The ephedrine and phenylephrine groups were not matched for potential confounding variables such as time period of operation, method of vasopressor administration, labor, and bupivacaine dose. This could have biased the univariate analysis. Arterial pressure was documented by hand so there may have been a degree of selective recording or rounding up of readings.

Appendix A-2

Data Collection Tool

Cooper, D. W., Carpenter, M., Mowbray, P., Desira, W. R., Ryall, D. M., & Kokri, M. S. (2002). Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *The Journal of the American Society of Anesthesiologists*, *97*(6), 1582-1590.

Method/level of evidence & Major variables studied	**Sample/ Setting**	**Intervention**	**Data Analysis**	**Results**	**Limitations**
Randomized /Double blind study Level II evidence Maternal: blood pressure and heart rate, Nausea and vomiting scores. Fetal: Apgar score, umbilical artery pH and venous pH	Inclusion: ASA I and II participants scheduled for elective C-section under spinal anesthesia. Singleton pregnancies, with no fetal abnormalities and no history of preeclampsia or diabetes mellitus. Exclusion: ASA >III, non elective C-sections, C-sections requiring	Before entering the anesthesia room, the participants had 3 blood pressure and heart rate readings recorded with an automated oscillometer at 3 min intervals while sitting in bed. The lowest of the 3 readings was recorded as the baseline values. The highest nausea and vomiting score was recorded for 30 min before the spinal (0= none, 1= nausea with no vomiting, 2= vomiting). participants were randomly allocated by envelope selection to one of 3 vasopressor solutions to maintain maternal systolic arterial pressure. The participants, anesthetists, nurses and midwives involved were all blinded to the patient grouping. The P group received phenylephrine 100mcg/ml. the E group received ephedrine 3mg/ml and the C group received a combination of phenylephrine 50mcg/ml combined with ephedrine 1.5mg/ml. These concentrations were based on unpublished pilot work performed at the hospital where the study took place to find solutions of similar potency. A third party not involved with the study opened an envelop	The study was designed to have an 80% chance of detecting a 15% incidence of fetal acidosis (umbilical artery pH <7.20) in the ephedrine group (E Group) and an 80% chance of detecting a difference of 0.03 in the mean umbilical artery pH at P=0.05. The Kruskal-Wallis test was used to compare the three groups. If	48 (n=48) participants in the phenylephrine group (P group), 50 (n=50) in the ephedrine group (E Group) and 49 (n=49) in combination of phenylephrine and ephedrine solution group (C group) were studied. The 3 groups were comparable for age, height, weight, gestation, breech presentation, previous c-section, delivery and birth weight. The groups were well matched for the spinal anesthetics given (P= 0.99), the investigators collecting data (P=0.77) and for the uterine incision to delivery interval (P=0.10). Overall the mean systolic arterial blood pressure (SABP) from spinal until delivery was similar for all three groups as was the SABP over time for the 3 groups. There was a small but statistically significant difference between 20 and 25 min post-spinal when the MAP was lower in the phenylephrine group than in the epidural and combination groups. The incidence of hypotension (SABP <80%) was similar for the 3 groups. However, there was a small	Code had to be broken in two of the ephedrine cases due to hypotension not responding to ephedrine. All participants were healthy women undergoing elective C-section delivery so extrapolation to situations where fetal compromise is present or

	general anesthesia, multiple fetuses, fetal abnormalities or history of preeclampsia or diabetes.	containing the code for the patient group and gave the investigator the relevant unlabeled syringe. The solution was further diluted to to a total of 40ml. One of 4 spinal anesthetics techniques was used based on provider preference. To avoid bias, randomization was stratified by using separate set of randomization envelopes for each of the standard spinal anesthetics techniques. Technique 1: 2.5ml of spinal hyperbaric 0.5% bupivacaine with 20mcg of fentanyl given in sitting position. Technique 2: 2ml of spinal levobupivacaine 0.5% with 20 mcg fentanyl given in the sitting position before an epidural catheter was inserted. Technique 3: 2ml of spinal levobupivacaine 0.5% with 20 mcg, given in the left lateral position before an epidural catheter was inserted. Technique 4: 2.5ml of spinal levobupivacaine 0.5% with 10 mcg of fentanyl, given in the left lateral position before an epidural catheter was inserted. The level of the spinal was measured 10 min post-spinal and at skin incision. Target block height was T5. An epidural top-up, using 0.5% levobupivacaine was only used pre-delivery if neural blockade was not sufficiently high or dense with spinal anesthesia alone. Immediately before spinal anesthesia a preload of 10ml/kg of Hartmann solution as rapidly infused. Immediately following spinal injection, the infusion of IV vasopressor solution was started according to protocol. The patient was then positioned supine with a left lateral tilt. Systolic arterial pressure and heart rate were measured every minute using the same oscillometer as the baseline. The rate of the solution was	a difference was found with the Kruskal-Wallis test, pairs of groups were then compared using the Mann-Whitney U test. The Wilcoxon signed-rank test and spearman rank test were also used to analyze data. The Wilcoxon signed-rank test was used to compare data within a group. P<0.05 was considered significant.	but statistically significant differences between the 3 groups for the lowest SABP recorded and for the proportion of SABP readings below 80% of baseline (P=0.02). The lowest SABP recorded was higher in the P group (80% [73-88] of baseline) than in the E group (73% [61-87] of baseline) (P=0.02) but the C group (77% [69-86] of baseline) was not significantly different from the P (P=0.14) and E (P=0.25) groups. The proportion of SABP readings below 80% of baseline was lower in the P group (0% [0-8]) (P+0.007) and in the C group (4% [0-10]) (P+0.04) than in the E group (8% [0-20]), but there was no difference between the P and C groups (P=0.55). from 5 min onward the HR was higher in the E group than in the P and C groups. Overall the mean HR in the C group was lower than in the E group (P<0.0001) and higher than in the phenylephrine group (P=0.008). The highest HR recorded differed between the groups (P<0.0001): it was higher in the E group (137% [124-156] of baseline) than in the P group (115% [108-128] of baseline) (P<0.0001) and the C group (122% [109-140] of baseline) (P+0.004), but there was no difference between the P and C groups (P=0.051). Fetal acidosis was less frequent in the P group (1 of 48) and less frequent in the C group (1 of 47) than in the E group (10 of 48) (overall P=0.0007). There was no difference in the incidence of fetal acidosis between the P and C groups (P=0.99). 1 and 5 min APGAR scores were good in all 3 groups and no infant required intubation or admission to the special care baby unit.	to emergency C-section delivery may not be valid. All participants were fluid preloaded which could also add to the high baseline blood pressures. The doses of ephedrine and phenylephrine used were based on an unpublished pilot work performed at the same hospital.

		doubled or halved if the systolic arterial blood pressure (BP) fell below or above 0.75 times the baseline. Phenylephrine was started at 33mcg/min; ephedrine was started at 1mg/min or half the dose rate for each for the combination solution. The max infusion rate was 40ml/hr. and min rate was 1.3ml/hr. If more than 40ml/hr. was required 1 or 2ml boluses of trial solution could be given. If the systolic arterial pressure was above 1.25 times the baseline the infusion was stopped and restarted at half the rate when the systolic arterial pressure was below 1.25 times the baseline again. The max nausea and vomiting score was recorded between spinal and delivery. At delivery one of the investigators obtained umbilical artery and vein blood samples from a segment of the umbilical cord double clamped before the baby's first breath. No supplemental O2 was given to the mother prior to delivery. APGAR scores recorded at 1 and 5 minutes by a midwife and the need for tracheal intubation, ventilation or admission to the special care baby unit were recorded.		Blood gas values were similar for the P and C groups. The E group had a lower umbilical artery pH than the P group (P=0.002) or the C group (P=0.009), and a lower umbilical vein pH than the P group (P=0.04) or the C group (P=0.003). There was no difference in the umbilical vein PCO2 between the groups but the E group had a higher umbilical artery PCO2 than the P group (P=0.002). Baseline N/V (nausea/vomiting) scores were similar for all 3 groups. There was no change in the P group from baseline N/V scores (P=0.30) but in the E and C group the N/V scores increased from baseline (E= P<0.0001) (C = P=0.007). The N/V scores were lower in the P group than in the E group (P<0.0001) or C group (P<0.0001) but there was no significant different between the E and C groups (P=0.09). In the E group vomiting (n=18) was associated with decreased HR and SABP and increased ephedrine doses. There was no difference in the block height at 10 min or at skin incision for the E group participants who vomited, compared with the E group participants without N/V (P=0.57 and P=0.36). The incidence of fetal acidosis and vomiting at cesarean delivery under spinal anesthesia was reduced by giving phenylephrine alone or in combo with ephedrine compared with giving ephedrine alone.	

Appendix A-3

Data Collection Tool

Ngan Kee, W. D., Khaw, K. S., Lau, T. K., Ng, F. F., Chui, K., & Ng, K. L. (2008). Randomized double-blinded comparison of phenylephrine vs. ephedrine for maintaining blood pressure during spinal anesthesia for the non-elective Caesarean section. *Anesthesia*, *63*(12), 1319-1326.

Method/level of evidence & Major variables studied	Sample/ Setting	Intervention	Data Analysis	Results	Limitations
Randomized/Double blind study using computer-generated codes contained in opaque seal and sequentially numbered envelopes. Level II evidence Maternal: blood pressure and heart rate and Nausea and vomiting Fetal: Apgar score and umbilical artery blood	204 (n=204) Inclusion: ASA I and II women with singleton pregnancies scheduled for non-elective C-section for which spinal anesthesia was decided upon for clinical reasons at any point in time. Exclusion: participants with pre-existing or pregnancy induced hypertension, cardiovascula	participants were premedicated with 0.3M Na citrate 30 ml on arrival to the OR. Standard monitoring included noninvasive BP measurement, ECG and pulse Oximetry. Fetal HR (heart rate) was monitored by external cardiotocography until surgical prep. No IV prehydration was given. Spinal anesthesia was induced with the patient in the right lateral position. After skin infiltration with lidocaine, a 25-gauge pencil point needle was inserted at what was estimated to be L3-4 or L4-5 vertebral interspace and 2.0-2.2 ml of hyperbaric 0.5% bupivacaine (10-20 mg) and fentanyl 15 mcg was injected intrathecally. The patient was then immediately turned to supine with a left lateral tilt and a rapid IV co-hydration with up to 2 liters of lactated ringer's solution, oxygen of 6-8 L/min was administered by clear facemask until delivery. BP (blood pressure) was measured at 1 min intervals beginning at 1 minute after spinal injection.	85 participants (n=85) per group would be required to have a 90% power at the 0.05 significance level to detect a difference between groups. Primary analysis was performed on an intention to treat basis and a secondary analysis was performed on a per protocol basis to compare only protocol-compliant participants who actually required treatment for hypotension with a vasopressor.	Data collection was completed over a 2-year period. Overall 74/102 (73%) of participants in the P group and 74/102 (73%) of the E group had one or more episodes of hypotension and required one or more boluses of vasopressor (p=0.52). The number of episodes of hypotension and the total volume of IV fluid given in each group was similar. The min recorded HR was lower in the P group vs the E group but there was no difference in max recorded HR or min and max SBP recorded. The number of doses of vasopressor required was similar between groups. More participants had N/V in the E group than the P group (13/102 (12.7%) vs 4/102 (3.9%), P=0.02). There was no difference between groups in the primary outcome, UA pH (p=0.70). In the E group 2 cases had a UA pH <7.0 compared with no cases in the P group (P=0.50). the UA PO2 was lower in the P group vs the E group (Median difference 0.23 (95% CI of	Insufficient amount of UA blood was obtained in 1 patient in the P group and 2 participants in the E group. Insufficient UV blood was obtained for analysis in 2 participants in the E group. 8 UA sample and 1 UV sample was below the min reportable limit range. After the study commenced a study was published by Saravanan et al. reporting that

gases and venous blood gases	r or cerebrovascular disease, multiple gestation, known fetal abnormality or any medical contraindications to spinal anesthesia such as thrombocytopenia or coagulopathy	Hypotension as defined as SBP (systolic blood pressure) <100 mmHg. participants were randomized to receive an IV bolus of either phenylephrine 100 mcg (group P) or ephedrine 10 mg (group E) immediately after each episode of hypotension. The doses of the drugs were chosen based on clinical experience. The upper sensory level of the spinal anesthesia was tested at 5 min after the spinal injection. Skin incision, uterine incision and delivery were all recorded. Vasopressor protocol was continued until the time of uterine incision. The total dose of vasopressor given up to time of uterine decision, the total volume of IV fluid given and any incidence of nausea or vomiting and the number of episodes of hypotension was recorded. Bradycardia was defined as HR <50 bpm. The attending pediatrician assessed APGAR scores at 1 and 5 min after delivery. We recorded the number of neonates admitted to the special care baby unit and neonatal intensive care unit and the duration of stays. Umbilical arterial (UA) and umbilical venous (UV) blood samples from double-clamped segments of umbilical cord were obtained.	Univariate intergroup comparisons were made using the unpaired student's t-test or the Mann-Whitney U-test as appropriate. Nominal data were compared using the Chi-Square test or Fisher's exact test. Analyses were made using SPSS version 10.1.4 and confidence interval Analysis 2.0.0. Values of $p<0.05$ were considered statistically significant.	difference 0.20-0.45) p=0.032) and UV PO2 was lower in the P group vs the E group (Median difference 0.39 (95% CI of difference 0.08-0.70) P=0.012). However, there was no difference between groups in UA or UV oxygen content. There was no difference between groups in the clinical outcome of the neonates. One neonate in the E group had an APGAR score <7 at 1 min and 5 min and one neonate in the P group had an APGAR score <7 at 1 min; all other APGAR score were >7. 17 neonates (17%) in the P group and 21 (21%) neonates in the E group were admitted to the special care baby unit (P=0.045). There was no difference in the duration of stay between groups. In the ephedrine group UA lactate was higher and UV lactate was higher, UA pO2 and UV PO2 were lower in the P group although O2 content was similar. More participants had nausea or vomiting in the E group but there was no other difference in clinical outcome. Both Phenylephrine and Ephedrine are suitable vasopressors for use in non-elective C-sections.	the potency ratio of phenylephrine: ephedrine was approximately 80:1 (Phenylephrine 100 mcg = ephedrine 8mg) when the drugs were given by infusion therefore the doses used in this study were not equipotent. There was a relatively small amount of vasopressors used in this study and that may explain the findings to be not lower in the E group as predicted in multiple previous studies.

Appendix A-4

Data Collection Tool

Prakash, S., Pramanik, V., Chellani, H., Salhan, S., & Gogia, A. R. (2010). Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anesthesia for caesarean delivery: a randomized study. *International Journal of Obstetric Anesthesia*, *19*(1), 24-30.

Method/level of evidence & Major variables studied	**Sample/ Setting**	**Intervention**	**Data Analysis**	**Results**	**Limitations**
Randomized/ Double blind study with computer generated number allocation Level II evidence Maternal: blood pressure and heart rate Fetal: Apgar score and umbilical artery pH and venous pH	A total of 60 women who developed hypotension participated. n=30 in the ephedrine group, n=30 in the Phenylephrine group Inclusion: ASA 1 women with singleton pregnancies scheduled for elective caesarean delivery under spinal anesthesia were recruited.	All women received ranitidine and metoclopramide for antacid prophylaxis. Standard monitoring with on-invasive arterial pressure, electrocardiography and pulse oximetry was established. Women rested undisturbed in the supine position with left uterine displacement for 5 min following which baseline blood pressure and heart rate were calculated as the mean of three successive readings measured 1 min apart. Each patient also received a 10ml/kg IV infusion of Lactated Ringers solution over 15-20 min before spinal anesthesia. With participants in the left lateral position, 2ml 0.5% Hyperbaric Bupivacaine was injected intrathecally at L3-4 via a 25 gauge Quincke needle. participants were then immediately turned supine and positioned with left uterine displacement. Heart rate and blood pressure were recorded at 1 min intervals from the time of induction of spinal anesthesia until delivery. Oxygen 6L/min via face mask was delivered until delivery. Sensory block to the T5 dermatome was considered adequate for surgery.	A total of 23 women per group would have a 90% power at the 5% significance level to detect a difference in umbilical arterial pH of 0.03 between groups. To allow for potential drop-outs a total of 30 participants per group with a SBP <80% of baseline were recruited Descripting statistics were calculated for	The two groups were comparable in age, weight, height, baseline hemodynamic data and dermatomal sensory levels. There were no significant differences in the mean induction to delivery or uterine to delivery intervals between the two groups. Although not significant, induction to delivery times varied, hemodynamic changes were compared up to 20 min after induction of spinal anesthesia, by which time 59 out of 60 women had delivered. The mean change in systolic pressure was comparable in the two groups with the minimum being 100 in the E group and 93 in the P group (P=0.114) except at 8 minutes where E group was lower (P=0.004). The fall in	Sample size was small. All participants were healthy women undergoing elective C-section delivery so extrapolation to situations where fetal compromise is present or to emergency C-section delivery may not be valid. There was a high baseline blood pressure than could of been due to the setting where

	Exclusion: Women with pre-existing or pregnancy induced hypertension, diabetes mellitus, known cardiovascular or cerebrovascular disease, fetal abnormality, or contraindication to spinal anesthesia.	Women were randomly assigned to received one of two vasopressor solutions whenever systolic pressure decreased to 80% of baseline or less. participants were divided into 2 groups: P group (phenylephrine) and E group (ephedrine). Group E received 1ml bolus of ephedrine 6mg/ml, group P received a 1 ml bolus of phenylephrine 100 mcg/ml. Additional boluses were administered if the systolic pressure remained at or below 80% of baseline. Atropine was administered in 0.3mg increments whenever bradycardia was associated with systolic pressure less than baseline or if the heart rate was <45 bpm The incidence of maternal tachycardia (>100 bpm) and reactive hypertension (>20% of baseline) were recorded after the administration of either ephedrine in group E or phenylephrine in group P. The number of vasopressor doses required, total doses of vasopressor administered, time of first administration of vasopressor, requirement for atropine and its relation to vasopressor administration were noted. The time of induction of spinal anesthesia, uterine incision and delivery were recorded. After delivery oxytocin 5 units was given by slow IV injection followed by a 10-unit infusion. The incidence of nausea and vomiting was recorded. Arterial and venous blood samples were obtained from a double clamped segment of the umbilical cord and analyzed within 10 minutes. Apgar scores at 1, 5 and 10 minutes were determined by the attending pediatrician who was unaware of group assignment. Time and onset of sustained rhythmic respiration was noted.	continuous variables as mean and standard deviation and for categorical variables as frequency of distribution and percentage. To assess trend within variables, two-way analysis of variance was used. $P < 0.05$ was regarded as statistically significant. SPSS 14.0 for Windows statistical software was used for analysis.	heart rate below mean baseline in group P was significantly greater than in group E (20± 10 vs 6± 0.6, P<0.001). In all cases, bradycardia developed following phenylephrine administration. Birth weight and Apgar scores at 1 (p=0.739), 5 (p=0.128) and 10 min (p=0.611) were comparable in the two groups. No neonate had an Apgar score <7 at any time. Time to onset of rhythmic respiration was <90s in all cases. No neonate required tracheal intubation or admission to the neonatal intensive care unit. No umbilical artery pH was less than 7.20. Umbilical artery and venous pH were significantly lower in group E than in group P (p=0.01 and P=0.002) Results showed the 100 mcg bolus doses of phenylephrine are as effective as 6 mg bolus doses of ephedrine in the treatment of hypotension following spinal anesthesia in term parturients undergoing c-section delivery. Neonates of women treated with phenylephrine had higher umbilical cord pH though true fetal acidosis was not seen in any neonate.	the baseline was taken that being the OR which is a high stress environment. All participants were fluid preloaded which could also add to the high baseline blood pressures. The doses of ephedrine and phenylephrine used were based on clinical experience of the authors

Appendix A-5

Data Collection Tool

Mercier, F. J., Augè, M., Hoffmann, C., Fischer, C., & Le Gouez, A. (2013). Maternal hypotension during spinal anesthesia for caesarean delivery. *Minerva Anestesiol*, *79*(1), 62-73.

Method/ level of evidence & Major variables studied	**Sample/ Setting**	**Intervention**	**Data Analysis**	**Results**	**Limitations**
Randomized double-blind study using a random table with stratification to allocate participants to each group Level II evidence Maternal: blood pressure	42 parturients (n=42) scheduled for Caesarean section (C-section) delivery using spinal anesthesia. Inclusion: age 18-years or older, weight 90Kg or less, height 152cm or greater, ASA I or II, and term singleton pregnancy. Exclusion: parturients with	Participants were fasted overnight and were given 30 ml of sodium citrate. Oxygen was administered to all participants via nasal cannula. Standard monitors included electrocardiogram, noninvasive BP device and pulse oximetry. After an intravenous (IV) preload of 15ml/kg of Lactated Ringer's Solution (LR) was given, spinal anesthesia was performed at the L2-L3 or L3-L4 interspace with the patient sitting, using a 9 cm 25 gauge whitacre spinal needle. 11mg of hyperbaric 0.5% Bupivacaine, 2.5 mcg Sufentanil and 0.1 mg morphine was injected through the spinal needle. Participants were then immediately placed in the recumbent position with left uterine displacement. A prophylactic vasopressor IV infusion was started at the end of spinal injection. participants received either 2mg/min ephedrine plus 10 mcg/min phenylephrine (E+P group) or 2mg/min ephedrine alone (E group). Study solutions were prepared by an anesthesiologist or a nurse anesthetist not involved in the participant's care and according to the group indicated in a numbered sealed envelope. One of the investigators was present	Data was expressed as mean ± SD unless stated otherwise. Groups were compared for single parametric, ordinal and nominal variables suing unpaired student *t* test, the Mann-Whitney U test, and Fisher exact test, respectively. Hemodynamic values over time were compared using analysis of variance for repeated measures, followed by Dunnett tests. A forward stepwise	Participants characteristics, gestational age, neonatal weight, upper sensory level of anesthesia at 20 min and time intervals from spinal anesthesia to incision, from spinal anesthesia to delivery and from uterine incision to delivery were comparable between the two groups. Baseline SBP and maternal HR were also comparable between the groups. The incidence of hypotension was halved in the E+P (37%) group when compared with the E (75%) group (P=0.02). SBP values after onset of spinal anesthesia were not significantly different between the two groups. Minimal SBP values before delivery were lower in the E group but the difference was no statistically significant (P=0.08). Hypotensive episodes were brief and of similar cumulative duration	Phenylephrine alone group studied would have allowed for a broader knowledge base. Hypotension was found to be very frequent in this study and more prophylaxis should be used.

Fetal: Umbilical cord blood pH and Apgar scores	pregnancy-induced hypertension, cardiac disease, diabetes, or fetal complications, and those in labor	during the study period to confirm comparability of routine procedures. The primary outcome variable was the incidence of hypotension, defined as a systolic blood pressure (SBP) <100 mmHg and less than 80% of baseline before delivery. Baseline SBP and maternal heart rate (HR) were determined by the average of 3 measurements obtained before preloading with LR. After spinal injection SBP and maternal HR were measured every minute for 10 min and every 2 min there after until delivery. A predefined algorithm was used to adjust the syringe rate according to SBP as follows: -maintain rate if SBP within 90-105% of baseline -Rate halved if SBP 105-120% of baseline -Stop if SBP >120% of baseline -Rate doubled if SBP 80-90% of baseline -SBP <100 mmHg and <80% of baseline treated with 6mg ephedrine bolus doses repeated as needed. For each subject, a min and max SBP and HR were recorded before delivery. A back up plan designed to treat several critical situations allowed anesthesiologist to administer epinephrine, addition phenylephrine or atropine as needed. The upper level of sensory changes was determined using an alcohol swab 20 min after spinal injection. Additional data collection included time intervals from spinal anesthesia to incision, from spinal anesthesia to delivery, and from uterine incision to delivery, the dose of vasopressor infused until delivery, venous and arterial umbilical cord pH values, neonatal Apgar scores and neonatal weight.	regression analysis was performed to determine the association between venous or arterial umbilical blood pH with the following five variables: duration of hypotension, total ephedrine dose, time interval from spinal anesthesia to skin incision, time from spinal anesthesia to delivery, and time from uterine incision to delivery. P <0.05 was considered significant. Sample size calculations indicated that including 37 participants in the study would result in an 80% power to detect a decrease from 75 to 37.5% in the incidence of hypotension at a significance level of 0.05	in both groups. Max SBP and Min heart rate were also comparable. Max heart rate before delivery was 15 bpm higher in the E group than in the E + P group (P=0.02). Maternal heart rate after onset of spinal anesthesia was significantly increased in the E group from 3 to 6 min after spinal anesthesia (P<0.05) and remained unchanged in the E+P group. Significantly more ephedrine was infused and supplementation given in the E group. Umbilical venous and arterial pH values were significantly higher in the E+P group (7.24) than in the E group (7.19) (P=0.05). The incidence of arterial pH <7.20 was 31% higher in the E+P group and 63% in the E group (P=0.09). However, Apgar scores at 1 and 5 min were similar in both groups (p=0.7) and were never less than 7. Low venous and arterial pH values were associated only with the E group assignment and spinal anesthesia to delivery times longer than 33 min. Compared with ephedrine alone ephedrine plus phenylephrine infusions decreased the incidence of hypotension by approx. 50%, abolished maternal tachycardia, and improved venous and arterial pH.	

Appendix A-6

Data Collection Tool

Moslemi, F., & Rasooli, S. (2015). Comparison of prophylactic infusion of phenylephrine with ephedrine for prevention of hypotension in elective cesarean section under spinal anesthesia: a randomized clinical trial. *Iranian Journal of Medical Sciences*, *40*(1), 19.

Method/level of evidence & Major variables studied	Sample/ Setting	Intervention	Data Analysis	Results	Limitations
Randomized/Double blind study using a table of random numbers and a computer generated randomization list. Level II evidence Maternal: blood pressure and heart rate Fetal: Apgar score and umbilical artery blood gases	90 women (n=90) for elective c-section under spinal anesthesia were recruited. Inclusion: healthy pregnant women with gestational age of 36 weeks or higher and non-emergency c-section Exclusion: <36 weeks of gestation, emergency c-section, high risk pregnancies (multiple	participants were assigned to 3 different groups: phenylephrine (group Ph), ephedrine (group E) and placebo (group P). Upon arrival to the OR all participants were monitored for basal vital signs (HR, SBP, DBP, and SaO2). Prior to spinal anesthesia all participants received a 500 ml crystalloid bolus. Infusion of study drugs were: group Ph received 450 mcg of phenylephrine in 250 ml, group E received 45 mg of ephedrine in 250 ml and group P received an infusion of only 250 ml normal saline. All solutions were label with numerical codes. The nurses that infused the solutions and monitored the vital signs were blinded to the solutions. The participants then received spinal anesthesia by an anesthesiologist in the sitting position from L4/5 or L3/4 inter-vertebral spaces with 2.5 ml of Bupivacaine 0.5% (12.5mg) and 2.5 mcg of Sufentanil. Immediately after spinal placement all participants were positioned in the supine position with left uterine displacement. BP (blood pressure) was controlled every 2 minutes until	Data was analyzed using a one-way ANOVA for quantitative variables and Fishers exact probability tests and chi-square for qualitative variables and associations. Multiple comparisons were tested by post-hoc with Turkey technique. Normal distributions of data were evaluated by Kolmogorov-	In total 83 participants (n=83) were studied: 30 women in group Ph (n=30), 27 in group E (n=27) and 26 in group P (n-26). There was no significant difference in demographic data. Indications for c-section were: repeated c-section (n=53), other indications (n=25) and patient preference (n=4). There was no significant difference between the 3 groups in basal SBP (systolic blood pressure), how ever SBP after anesthesia every 2 and every 5 minutes were different (P>0.050) in the Ph and P groups. There was no significant difference between groups for HR (heart rate) except for the 1st 3 measurements of every 5 minutes (P=0.006). 38 participants in all groups had severe hypotension and needed additional vasopressor therapy: group Ph=10, group E-15, group P=20. There was a significant difference between group Ph and groups E and P.	Sample size was small. All participants were healthy women undergoing elective C-section delivery so extrapolation to situations where fetal compromise is present or to emergency C-section delivery may not be valid. All participants were fluid preloaded which could also add to

	gestations, intrauterine growth retardation, preeclampsia, maternal cardiovascular or pulmonary diseases), any contraindication of spinal anesthesia (patient refusal, coagulopathy, hemorrhage or hypovolemic shock) and unexpected events during surgery such a hemorrhage or sensory block level higher or lower than T4-T5 after spinal anesthesia	delivery and then every 5 minutes throughout anesthesia as were HR (heart rate) and SaO2 (oxygen saturation). Sensory block was monitored to obtain a T4-T5 level of anesthesia. After delivery and clamping of the umbilical cord, 1ml of blood was drawn from the umbilical artery for neonatal blood gas analysis. Any decrease in BP of about 20% from baseline was treated with 50-100 mcg phenylephrine in pH group or 5-10 mg ephedrine in E and P groups. This was repeated as required. These drugs were prepared in numerical labeled syringes and were given to the nurses blindly. They were instructed to administer 1ml of that drug solution if hypotension was greater than 20% of baseline (1ml of phenylephrine was 50mcg and 1ml of ephedrine was 5mg). HR and rhythm were monitored with ECG and any change from normal (PVC, tachycardia, bradycardia) were recorded and treated as needed. The incidence and degree of hypotension, number of vasopressor therapy and the total dose of injected vasopressor in each group were measured and recorded. 1min and 5 min APGAR scores were recorded as well as umbilical artery blood gas analysis.	Smirnov normality test. Analysis was performed using SPSS 16.0 program. Statistical results were considered significant when $P<0.05$.	Additional doses required for the treatment of hypotension was higher in groups E (65.2%, n=15) and P (80%, n=20) than in group Ph (28.57%, n=10). Overall bradycardia was more significant in the phenylephrine group and ephedrine group than the placebo group ($P<0.001$). There was no significant difference in 1 min APGAR scores between the groups. There was a significant difference in the 5 min APGAR scores which was better with group Ph and E rather than group P ($P=0.002$). UA (umbilical artery) blood gas analysis showed a significant difference in pH and PCO2 between Ph and P groups. 2 neonates in the Ph group, 7 in the E group and 5 in the P group had acidosis. Acidosis was significantly lower in phenylephrine group ($P=0.043$) Overall results showed that women who underwent spinal anesthesia for elective c-section, SBPs and neonatal UA pH were best maintained with a prophylactic infusion of phenylephrine compared with those who did not receive it and even better than those who received prophylactic ephedrine.	the high baseline blood pressures.

Appendix B-1

CASE worksheet

Cooper, D. W., Sharma, S., Orakkan, P., & Gurung, S. (2010). Retrospective study of association between choice of vasopressor given during spinal anesthesia for high-risk caesarean delivery and fetal pH. *International Journal of Obstetric Anesthesia*, *19*(1), 44-49.

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	**Yes-** The aim of the study is clearly stated as well as the patients that the summary applies to are well described
Summary Methods	
2. Is the authorship of the summary transparent?	**No** - The individual authors are listed but their credentialing is not listed. Affiliation is listed.
3. Are the reviewer(s)/editor(s) of the summary transparent?	**No**- It is not clearly stated that the summary has been edited and reviewed
4. Are the research methods transparent and comprehensive?	**Yes-** The inclusion and exclusion criteria is clearly stated. A protocol for the study was Cleary stated and followed.
5. Is the evidence grading system transparent and translatable?	**Yes-** Retrospective observational/chart review study was performed. Protocol used in reviewing charts was clearly stated.
Summary Content	
6. Are the recommendations clear?	**Yes**- recommendations are clearly stated and multiple options for treatment are provided
7. Are the recommendations appropriately cited?	**Yes**- recommendations are appropriately cited
8. Are the recommendations current?	**No**- The recommendations are from 2010 so not within 2 years therefore not updated or current
9. Is the summary unbiased?	Unable to appropriately assess if there is a conflict of interest between the recommendations of the summary and the sponsor for any author
Summary Application	
10. Can this summary be applied to your patient(s)?	**Yes**- This evidence and setting applies to my population and can be translated to any patient within the same population and setting.

Appendix B-2

CASE worksheet

Cooper, D. W., Carpenter, M., Mowbray, P., Desira, W. R., Ryall, D. M., & Kokri, M. S. (2002). Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *The Journal of the American Society of Anesthesiologists*, *97*(6), 1582-1590.

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	**Yes-** The aim of the study is clearly stated as well as the patients that the summary applies to are well described
Summary Methods	
2. Is the authorship of the summary transparent?	**Yes** - The individual authors are listed with their credentialing as well as affiliations.
3. Are the reviewer(s)/editor(s) of the summary transparent?	**No**- It is not clearly stated that the summary has been edited and reviewed
4. Are the research methods transparent and comprehensive?	**Yes-** The inclusion and exclusion criteria is clearly stated. A protocol for the study was Cleary stated and followed.
5. Is the evidence grading system transparent and translatable?	**Yes-** Randomized double-blinded study – stated that randomization was performed by randomly allocating patients by envelop selection to one of three groups all participants and investigators were blinded to the group, unlabeled syringes were used. A third party not involved in the study opened the envelop and handed the appropriate medication to the investigator.
Summary Content	
6. Are the recommendations clear?	**Yes**- recommendations are clearly stated and multiple options for treatment are provided
7. Are the recommendations appropriately cited?	**Yes**- recommendations are appropriately cited
8. Are the recommendations current?	**No**- The recommendations are from 2002 so not within 2 years therefore not updated or current
9. Is the summary unbiased?	Unable to appropriately assess if there is a conflict of interest between the recommendations of the summary and the sponsor for any author
Summary Application	
10. Can this summary be applied to your patient(s)?	**Yes**- This evidence and setting applies to my population and can be translated to any patient within the same population and setting.

Appendix B-3

CASE worksheet

Ngan Kee, W. D., Khaw, K. S., Lau, T. K., Ng, F. F., Chui, K., & Ng, K. L. (2008). Randomized double-blinded comparison of phenylephrine vs. ephedrine for maintaining blood pressure during spinal anesthesia for the non-elective Caesarean section. *Anesthesia*, *63*(12), 1319-1326.

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	**Yes-** The aim of the study is clearly stated as well as the patients that the summary applies to are well described
Summary Methods	
2. Is the authorship of the summary transparent?	**Not completely-** Although the individual authors are listed their credentialing is not listed but their affiliations are. The process to become in author is also not described.
3. Are the reviewer(s)/editor(s) of the summary transparent?	**No**- It is not clearly stated that the summary has been edited and reviewed
4. Are the research methods transparent and comprehensive?	**Yes-** The inclusion and exclusion criteria is clearly stated. A protocol for the study was Cleary stated and followed.
5. Is the evidence grading system transparent and translatable?	**Yes-** Randomized double-blinded study – stated that randomization was performed using computer generated codes contained in opaque, sealed and sequentially numbered envelops as well as medications prepared in identical syringes but someone not involved in the study
Summary Content	
6. Are the recommendations clear?	**Yes**- recommendations are clearly stated and multiple options for treatment are provided
7. Are the recommendations appropriately cited?	**Yes**- recommendations are appropriately cited
8. Are the recommendations current?	**No**- The recommendations are from 2008 so not within 2 years therefore not updated or current
9. Is the summary unbiased?	Unable to appropriately assess if there is a conflict of interest between the recommendations of the summary and the sponsor for any author
Summary Application	
10. Can this summary be applied to your patient(s)?	**Yes**- This evidence and setting applies to my population and can be translated to any patient within the same population and setting.

Appendix B-4

CASE worksheet

Prakash, S., Pramanik, V., Chellani, H., Salhan, S., & Gogia, A. R. (2010). Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anesthesia for caesarean delivery: a randomized study. *International Journal of Obstetric Anesthesia*, *19*(1), 24-30.

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	**Yes-** The aim of the study is clearly stated as well as the patients that the summary applies to are well described
Summary Methods	
2. Is the authorship of the summary transparent?	**Not completely** - The individual authors are listed but their credentialing is not listed. Affiliation is listed.
3. Are the reviewer(s)/editor(s) of the summary transparent?	**No**- It is not clearly stated that the summary has been edited and reviewed
4. Are the research methods transparent and comprehensive?	**Yes-** The inclusion and exclusion criteria is clearly stated. A protocol for the study was Cleary stated and followed.
5. Is the evidence grading system transparent and translatable?	**Yes-** Randomized double-blinded study – stated that randomization was performed by computer generated number allocation, identical syringes prepared by someone not involved with data collection.
Summary Content	
6. Are the recommendations clear?	**Yes**- recommendations are clearly stated and multiple options for treatment are provided
7. Are the recommendations appropriately cited?	**Yes**- recommendations are appropriately cited
8. Are the recommendations current?	**No**- The recommendations are from 2009 so not within 2 years therefore not updated or current
9. Is the summary unbiased?	Unable to appropriately assess if there is a conflict of interest between the recommendations of the summary and the sponsor for any author
Summary Application	
10. Can this summary be applied to your patient(s)?	**Yes**- This evidence and setting applies to my population and can be translated to any patient within the same population and setting.

Appendix B-5

CASE worksheet

Mercier, F. J., Augè, M., Hoffmann, C., Fischer, C., & Le Gouez, A. (2013). Maternal hypotension during spinal anesthesia for caesarean delivery. *Minerva Anestesiol*, *79*(1), 62-73.

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	**Yes-** The aim of the study is clearly stated as well as the patients that the summary applies to are well described
Summary Methods	
2. Is the authorship of the summary transparent?	**Yes** - The individual authors are listed with their credentialing and affiliations.
3. Are the reviewer(s)/editor(s) of the summary transparent?	**No**- It is not clearly stated that the summary has been edited and reviewed
4. Are the research methods transparent and comprehensive?	**Yes-** The inclusion and exclusion criteria is clearly stated. A protocol for the study was Cleary stated and followed.
5. Is the evidence grading system transparent and translatable?	**Yes-** Randomized double-blinded study – stated that randomization was performed by using numbered, sealed, opaque envelopes ensuring both the patient and investigators were blinded to group assignment and study solutions were prepared by those not involved in the patients care and according to the group indicated by the envelope. There was an investigator present during the study period to confirm comparability and routine procedures.
Summary Content	
6. Are the recommendations clear?	**Yes**- recommendations are clearly stated and multiple options for treatment are provided
7. Are the recommendations appropriately cited?	**Yes**- recommendations are appropriately cited
8. Are the recommendations current?	**No**- The recommendations are from 2001 so not within 2 years therefore not updated or current
9. Is the summary unbiased?	Unable to appropriately assess if there is a conflict of interest between the recommendations of the summary and the sponsor for any author
Summary Application	
10. Can this summary be applied to your patient(s)?	**Yes**- This evidence and setting applies to my population and can be translated to any patient within the same population and setting.

Appendix B-6

CASE worksheet

Moslemi, F., & Rasooli, S. (2015). Comparison of prophylactic infusion of phenylephrine with ephedrine for prevention of hypotension in elective cesarean section under spinal anesthesia: a randomized clinical trial. *Iranian Journal of Medical Sciences*, *40*(1), 19.

Critical Appraisal for Summaries of Evidence (CASE) Worksheet **Numbers in evaluation correspond with those assigned to articles in data extrapolation chart**	
Questions	**Evaluation**
Summary Topic	
1. Is the summary specific in scope and application?	**Yes-** The aim of the study is clearly stated as well as the patients that the summary applies to are well described
Summary Methods	
2. Is the authorship of the summary transparent?	**Yes** - The individual authors are listed with their credentialing as well as affiliations.
3. Are the reviewer(s)/editor(s) of the summary transparent?	**No**- It is not clearly stated that the summary has been edited and reviewed
4. Are the research methods transparent and comprehensive?	**Yes-** The inclusion and exclusion criteria is clearly stated. A protocol for the study was Cleary stated and followed.
5. Is the evidence grading system transparent and translatable?	**Yes-** Randomized clinical trial – stated that randomization was performed using a table of random numbers and computer generated randomization list
Summary Content	
6. Are the recommendations clear?	**Yes**- recommendations are clearly stated and multiple options for treatment are provided
7. Are the recommendations appropriately cited?	**Yes**- recommendations are appropriately cited
8. Are the recommendations current?	**Yes**- The recommendations are from 2015, they are current.
9. Is the summary unbiased?	Unable to appropriately assess if there is a conflict of interest between the recommendations of the summary and the sponsor for any author
Summary Application	
10. Can this summary be applied to your patient(s)?	**Yes**- This evidence and setting applies to my population and can be translated to any patient within the same population and setting.

Appendix C

Descriptive Data Synthesis

Study	Oxygen supplementation Used	Intravenous Fluid Prehydration	ASA Classification/ patient characteristics	Hypotension incidence after spinal Anesthesia	Spinal Solution and Technique	Umbilical Artery pH	Apgar scores	N/V during case	Other important findings
Cooper et al., 2010	Not reported	Not reported	High risk singleton pregnant patients	SBP <90 mmHg: No vasopressor group 6.1%, group E 17% and group P 20% (P=0.005)	No detail but reported to be non consistent	On direct comparison there was no difference in the incidence of umbilical artery pH <7.20 (P=0.21),	On direct comparis on there was no difference in 5 min Apgar score <7 (0.089),		Following forward stepwise multiple regression analysis, the only variable that was associated with altered pH was non-reassuring fetal heart rate trace (P=0.71).
Cooper et al., 2002	No supplemental O2 was given to the mother prior to delivery.	Immediately before spinal anesthesia a preload of 10ml/kg of Hartmann solution as rapidly infused.	ASA I and II participants scheduled for elective C-section under spinal anesthesia. Singleton pregnancies, with no fetal abnormalities	The lowest SABP recorded was higher in the P group (80% [73-88] of baseline) than in the E group (73% [61-87] of baseline)	4 different spinal anesthetic solutions/tec hniques were used based on provider presence To avoid bias,	Fetal acidosis was less frequent in the P group (1 of 48) and less frequent in the C group (1 of 47) than in the	1 and 5 min APGAR scores were good in all 3 groups	Baseline N/V (nausea/vomi ting) scores were similar for all 3 groups. There was no change in the P group from baseline N/V scores	

			and no history of preeclampsia or diabetes mellitus.	(P=0.02) but the C group (77% [69-86] of baseline) was not significantly different from the P (P=0.14) and E (P=0.25) groups. The proportion of SABP readings below 80% of baseline was lower in the P group (0% [0-8]) (P+0.007) and in the C group (4% [0-10]) (P+0.04) than in the E group (8% [0-20]), but there was no difference between the P and C groups (P=0.55).	randomization was stratified by using separate set of randomization envelopes for each of the standard spinal anesthetics techniques.	E group (10 of 48) (overall P=0.0007). There was no difference in the incidence of fetal acidosis between the P and C groups (P=0.99). Blood gas values were similar for the P and C groups. The E group had a lower umbilical artery pH than the P group (P=0.002) or the C group (P=0.009), and a lower umbilical vein pH than the P group (P=0.04) or		(P=0.30) but in the E and C group the N/V scores increased from baseline (E= P<0.0001) (C = P=0.007). The N/V scores were lower in the P group than in the E group (P<0.0001) or C group (P<0.0001) but there was no significant different between the E and C groups (P=0.09). In the E group vomiting (n=18) was associated with decreased HR and SABP and increased ephedrine doses.	

						the C group (P=0.003).			
Ngan Kee, et al., 2008	After spinal administration and patient positioned supine oxygen of 6-8 L/min was administered by clear facemask until delivery	No IV prehydration was given After spinal administration and patient positioned supine a rapid IV co-hydration with up to 2 liters of lactated ringer's solution was given.	ASA I and II women with singleton pregnancies scheduled for non-elective C-section for which spinal anesthesia was decided upon for clinical reasons at any point in time.	Overall 74/102 (73%) of participants in the P group and 74/102 (73%) of the E group had one or more episodes of hypotension (P=0.52) and required one or more boluses of vasopressor.	Spinal anesthesia was induced with the patient in the right lateral position. After skin infiltration with lidocaine, a 25-gauge pencil point needle was inserted at what was estimated to be L3-4 or L4-5 vertebral interspace and 2.0-2.2 ml of hyperbaric 0.5% bupivacaine (10-20 mg) and fentanyl 15 mcg was injected intrathecally. The	There was no difference between groups in the primary outcome, UA pH (P=0.70). In the E group 2 cases had a UA pH <7.0 compared with no cases in the P group (P=0.50).	One neonate in the E group had an APGAR score <7 at 1 min and 5 min and one neonate in the P group had an APGAR score <7 at 1 min; all other APGAR score were >7.	More participants had N/V in the E group than the P group (13/102 (12.7%) vs 4/102 (3.9%), P=0.02).	
Prakash et al., 2010	Oxygen 6L/min via face mask was delivered after	Each patient received a 10ml/kg IV	ASA 1 women with singleton pregnancies	The mean change in systolic	With participants in the left	No umbilical artery pH	Apgar scores at 1		

	spinal administration and positioning until delivery	infusion of Lactated Ringers solution over 15-20 min before spinal anesthesia.	scheduled for elective caesarean delivery under spinal anesthesia	pressure was comparable in the two groups with the minimum being 100 in the E group and 93 in the P group (P=0.114) except at 8 minutes where E group was lower (P=0.004).	lateral position, 2ml 0.5% Hyperbaric Bupivacaine was injected intrathecally at L3-4 via a 25 gauge Quincke needle.	was less than 7.20. Umbilical artery and venous pH were significantly lower in group E than in group P (p=0.01 and P=0.002) but never reached true acidosis	(p=0.739) , 5 (p=0.128) and 10 min (p=0.611) were comparable in the two groups. No neonate had an Apgar score <7 at any time.		
Mercier et al., 2013	Oxygen was administered to all participants via nasal cannula of unknown amount.	intravenous (IV) preload of 15ml/kg of Lactated Ringer's Solution (LR) was given	Age 18-years or older, weight 90Kg or less, height 152cm or greater, ASA I or II, and term singleton pregnancy.	The incidence of hypotension was halved in the E+P (37%) group when compared with the E (75%) group (P=0.02). SBP values after onset of spinal anesthesia were not significantly different	Spinal anesthesia was performed at the L2-L3 or L3-L4 interspace with the patient sitting, using a 9 cm 25 gauge whitacre spinal needle. 11mg of hyperbaric 0.5% Bupivacaine,	Umbilical venous and arterial pH values were significantly higher in the E+P group (7.24) than in the E group (7.19) (P=0.05). The incidence of arterial pH <7.20 was 31% higher in the E+P	Apgar scores at 1 and 5 min were similar in both groups (p=0.7) and were never less than 7.		Low venous and arterial pH values were associated only with the E group assignment and spinal anesthesia to delivery times longer than 33 min.

				between the two groups.	2.5 mcg Sufentanil and 0.1 mg morphine was injected through the spinal needle.	group and 63% in the E group (P=0.09).			
Moslemi, F., & Rasooli, S. (2015).	Not reported	Prior to spinal anesthesia all participants received a 500 ml crystalloid bolus.	healthy pregnant women with gestational age of 36 weeks or higher and non-emergency c-section	SBP after anesthesia every 2 and every 5 minutes were different (P>0.050) in the Ph and P groups.	participants then received spinal anesthesia by an anesthesiologist in the sitting position from L4/5 or L3/4 inter-vertebral spaces with 2.5 ml of Bupivacaine 0.5% (12.5mg) and 2.5 mcg of Sufentanil.	UA (umbilical artery) blood gas analysis showed a significant difference in pH between the Ph and P groups. 2 neonates in the Ph group, 7 in the E group and 5 in the P group had acidosis. Acidosis was significantly lower in phenylephrine group (P=0.043)	There was no significant difference in the 1 min APGAR scores between all of the groups. There was a significant difference in the 5 min APGAR scores was shown to be better with group Ph and E than with		

							group P (P=0.002)		